Women’s and Newborn Health Auburn, Blacktown and Westmead Hospitals

Research Report

2016-2018

Published:
January 2019
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Women with GDM at Westmead hospital: birth outcomes in context of country of birth
CONFERENCE PRESENTATIONS
Addressing sexuality concerns during perinatal period: The use of PLISSIT model for midwives and nurses

Presented at Nepean Annual Midwives Conference 2016, Mar 2016, Hawkesbury NSW
Marjan Khajehei

One of the most critical stages in women’s life is the perinatal period. Perinatal women may experience a variety of sexual problems due to the effect of many factors on their sexual function and mental health status. Sexual problem of perinatal women is a sensitive topic. Compared to men, women talk less often about their sexual problems making it more difficult to investigate and treat, especially for those affected by the stereotypes or conventional beliefs.

Midwives and nurses are the health professionals who closely work with the women and can evaluate women’s sexual function at several times: before pregnancy, during pregnancy and at postpartum visits. In order to investigate sexual problem of perinatal women, a comprehensive assessment needs to be done, including physical and psychological assessments, taking detailed sexual history, medical history and laboratory tests.

The next step is to use the PLISSIT model which enables the health professionals to progress from one level to the next. In the “PLISSIT”, the letter “P” stands for “Permission giving”. It is the first step in this model that provides the patients with an opportunity to raise their concerns. To successfully complete this step, the health professionals need to consider rules of effective communication including: being purposeful; not making assumptions; asking straight forward questions; not judging the patient; using the patient’s own words and language; remaining professional; asking for clarity if unsure about a term or activity; and addressing confidentiality, secrecy and privacy.

The letter “LI” stands for “Limited Information”. It is the second step during which the health professionals provide non-expert information on the issue/s. The limited information can be given either verbally or in the form of a leaflet or referring to a website. This step will help indicate that sexuality is an important aspect of your practice, normalise any sexual health concerns that the patient may have, encourage the patient to talk more about their concerns and answer general questions on sexuality.

The letters “SS”, which form the third step, refer to “Specific Suggestions”. The health professionals may use a problem-solving approach and provide more advanced and in-depth advice on each specific sexual problem. This step involves both partners and focuses on sexual and performance anxiety reduction, education and cognitive intervention, mindfulness, conflict resolution, relationship enhancement and relapse prevention training.

The last letters, “IT”, stand for “Intensive Therapy” that is the most advanced stage of the PLISSIT model. If the issue is beyond the competence of the health professional, they may identify further support and refer the patient to appropriate specialists for more intensive therapy.
In summary, midwives and nurses are the first point of contact for many perinatal women and play a fundamental role in addressing the perinatal women’s sexual problems and promoting their quality of lives.

A model of individualised, family focused antenatal care: Findings from the Continuity of Care (CoCo) study
Presented at PSANZ Conference, 2017, Canberra ACT
Susan Heath
[Abstract not available]
Aims: To investigate outcomes of women who experienced severe PPH at Blacktown Hospital, to investigate compliance to the local protocol for severe PPH and to identify potential areas of improvement for the department.

Methods: Data was collected retrospectively from a mix of electronic and paper-based medical records from 100 women who birthed between July 1st 2014 and June 30th 2016 and experienced a PPH of greater than 1500ml.

Results: The incidence of severe PPH was 1.49% (100/6700) or approximately 15 per 1000 births; double that of the reported incidence. Severe PPH was more likely in patients who had undergone an instrumental delivery ($\chi^2(2\text{ df}) = 34.9, P<0.001$) and vaginal trauma was over-represented as the cause in these cases. 48% of cases (48/100) resulted in anaemia, with 8% (8/100) requiring a blood transfusion greater than 4 units, 33% (33/100) required an unplanned return to the operating theatre for an examination under anaesthesia, 14% (14/100) required the insertion of a Bakri balloon and 2% (2/100) required a hysterectomy. There were no deaths. 98% (98/100) of cases had documented regular monitoring of the patient’s vital signs, 76% (76/100) had active management of the third stage of labour and 9% (9/100) required activation of the massive transfusion protocol. 78% (78/100) cases had documentation of medication administration that was according to the local protocol.

Conclusions: The combination of medications used in the management of PPH were quite varied and not always in accordance with the protocol. A system with standardized documentation of management should improve adherence to protocol and may improve patient outcomes.
Bladder dysfunction after treatment for cervical cancer
Presented at NSW Agency for Clinical Innovation Gynaecological Oncology Nurses & Allied Health Seminar, 2016, Sydney
Letitia Lancaster
[Abstract not available]

Career reflections: Mentors, teams, professional organisations and moving out of the comfort zone
Plenary address at the International Conference on Cancer Nursing, 2018, Auckland, New Zealand
Letitia Lancaster
[Abstract not available]

Canberra Taking Heart: Prenatal to Neonatal care for congenital heart disease
Presented at PSANZ Conference, 2017, Canberra ACT
Plenary speaker: Susan Heath
[Abstract not available]
Clinical Practice Guideline for Perinatal Mortality: using the IMPROVE programme to improve midwifery practice

Presented at PSANZ Conference, April 2012, Adelaide NSW

Susan Heath

Background: PSANZ Clinical Practice Guidelines for Perinatal Mortality enables a systematic approach to the investigation and audit of perinatal deaths, and enhances the provision of appropriate care for parents, with the aim of providing better information and in the planning of future pregnancies, and understanding of factors associated with stillbirth which may help in reducing future pregnancy loss. These guidelines are of particular relevance as WSLHD population has diverse cultural and religious practices that demand early burial, which impact on the post-mortem practice, hence maximising the result from investigations parents are willing to consent to is imperative.

Methods: High Risk Pregnancy Clinical Midwifery Consultant attended the PSANZ IMPROVE programme and conducted a review of LHD guidelines and identified where midwifery practice could be improved across LHD. Two areas were identified: placental and cord investigations by clinician and clinical photographs. A “hands on” clinical skills programme and PSANZ guideline introduction across the local health district educated on placental swabs between the amnion and chorion using aseptic technique for aerobic and anaerobic bacterial cultures; and sampling of amnion and placental tissue for karyotyping and clinical photography.

Results: Majority of midwives were not aware of PSANZ techniques for placenta and cord investigations and clinical photography.

Conclusion: WSLHD midwifery staff have improved knowledge of PSANZ Clinical Practice Guidelines, appropriate placental swabbing, karyotype collection, and clinical photography techniques.
Comparing rates of labour interventions amongst low risk women receiving midwifery care at Westmead Hospital using matching

Presented at PSANZ Conference, April 2017, Canberra ACT

Beata Gidaszewski, Emma Gibbs

**Background:** Evidence suggest that continuity of midwifery care improves perinatal outcomes. A Cochrane systematic review of 15 trials involving 17,674 women found that continuity of midwifery care compared favorably with medically led standard models of care. Based on the evidence considerable effort has been made to increase availability of continuity of care at Westmead Hospital. Review of effectiveness of services is an essential aspect of implementation and ongoing sustainability of any service.

**Methods:** This study aimed to compare the effect of model of care on labour and birth outcomes among low risk women who gave birth at Westmead hospital. We used routinely collected data from ObstetriX to identify all primiparous women (n=3,683) that received antenatal care and birthed between May 2011 and November 2014. We used propensity score matching in order to reduce effect of confounding factors. Propensity score matching mimics some of the characteristics of Randomized Control Trial by balancing score of baseline covariates between study groups. The entire cohort of primaparas who were received care from Caseload Midwifery Program (n=500) was matched with equal number of women who received standard midwifery care and low risk women who received GP-shared care. The women in the three groups were matched for age, body mass index (BMI) and country of birth.

**Results:** Our results showed higher rates of normal vaginal birth, lower rates of instrumental birth, as well as lower rates of epistomy and epidural use in labour for women who received care from Caseload Midwifery Program. The differences were statistically significant ($p<0.001$) There was no statistically significant differences in neonatal Apgar’s scores or rates of admission to nursery among the groups.

**Conclusion:** Our study provides further evidence about effectiveness of continuity of midwifery care in reduction of rates of labour and birth intervention.
Comparison of models for estimated fetal weight and performance in detection of small for gestational age in gastroschisis

Ryan A, Melov, SJ, Benjamin S, Kirby A, Alahakoon TI

OP14.07

Introduction

- Obstetric management depends on accurate estimation of fetal weight (EFW) and early identification of small for gestational age (SGA).
- Fetal weight is difficult to estimate in gastroschisis due to the extra abdominal herniation of bowel.
- Identification of SGA changes depending on the population data used as reference.
- Incidence/diagnosis of SGA is 15-80% in gastroschisis and affects the obstetric management.
- Different models for EFW and their accuracy in predicting birthweight and their performance in detecting SGA were compared.

Methods

- 73 cases of gastroschisis (Jan 2011 - Dec 2017) managed at Westmead Hospital were analysed.
- EFW using most recent US data within 14 days of delivery for 5 published models were compared.
- The difference between predicted and actual birthweight for each model was compared.
- SGA were identified using Australian birthweight Intergrowth21(2017) and Nicolaides(2018) datasets.
- McNemar’s test was used to analyze the agreement between the true incidence of SGA at birth and the incidence calculated from the EFW using the different models.
- The sensitivity and specificity in predicting SGA for each formula was calculated in reference to each population study.

Results

### Table 1

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<th>Model</th>
<th>Mean Difference ± SD (g)</th>
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<td>Hadlock et al</td>
<td>168 ± 300</td>
<td>-42 to 755</td>
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<tr>
<td>Hadlock et al</td>
<td>2.5 ± 205</td>
<td>-42 to 664</td>
</tr>
<tr>
<td>Wansof et al</td>
<td>205 ± 306</td>
<td>-393 to 814</td>
</tr>
<tr>
<td>Shepard et al</td>
<td>0.5 ± 344</td>
<td>743 to 005</td>
</tr>
<tr>
<td>Homeyer et al</td>
<td>-108 ± 352</td>
<td>-798 to 583</td>
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Table 1. Both Hadlock models and Shepard demonstrated a mean estimation of fetal weight compared to Birthweight <1000g. Shepard was the most accurate at estimating fetal weight with a mean difference of -65g.

Conclusion

- Shepard et al may be more accurate at EFW in gastroschisis, the difference is not clinically significant compared to Hadlock et al.
- The incidence of SGA, sensitivity/specifcity varies significantly depending on the reference used for fetal weight. Intergrowth21 potentially underestimates SGA and Nicolaides et al overestimates SGA.
- There is potential for an improved model for estimating fetal weight and detection of SGA in gastroschisis. This may include third trimester growth velocity and abdominal circumference in an attempt to distinguish between protein loss through exposed bowel and true utero-placental insufficiency.
Introduction

- Fetal adrenal gland responds to chronic hypoxia and labour by activation of hypothalamic axis leading to adrenal fetal zone enlargement
- Adrenal total gland volume (TGV) and fetal zone (FZ): TGV ratios have been described as potential useful predictors for preterm labour
- Adrenal gland measurements are being described as a novel marker in small for gestational age (SGA) fetuses
- We aim to assess fetal adrenal gland measurement in normal and SGA fetuses as a marker of fetal compromise

Methods

- Prospective cohort study of 50 consecutive SGA fetuses (<10th centile in EFW) and 100 controls (>10th centile in EFW) at 17-34 weeks gestation
- Fetal adrenal gland was measured in 3 orthogonal planes sagittal (S), transverse (T) and coronal (C). Formula for TGV: S * T * C / F7/T6 RATIO: F7/TGV * 100
- Two operator measurements (one blinded) were combined for the analysis
- TGV and FZ/TGV were compared between the normal and SGA (EFW) groups (t test)
- ROC curves were used to assess the performance of FZ/TGV in identifying SGA

Results

- Increase in TGV and FZ/TGV ratio with gestational age in normal pregnancy
- TGV (p = 0.018) and F7/TGV ratio (p = 0.01) were significantly higher in SGA when compared to normal pregnancy
- There is high inter-operator correlation for all adrenal measurements except for transverse fetal zone
- Antenatal FZ/TGV has a moderate ability to identify SGA fetus (AUC 0.7)

Conclusion

- Fetal adrenal TGV and FZ:TGV were significantly different in the two groups (normal growth and SGA)
- Adrenal FZ:TGV has a reasonable sensitivity and specificity for predicting SGA
- Further study in fetal growth restriction is indicated to see the value of the measurements in detecting a compromised fetus
Fetal Double Aortic Arch: A Case Report

Presented at RCOG World Congress, March 2018, Singapore
Stephanie La, Roshini Nayyar, Priscilia Bonura

Introduction: A double aortic arch is a rare cardiac congenital abnormality where the embryonic right aortic arch does not regress, resulting in the presence of both left and right aortic arches and encircling the trachea and oesophagus. The prevalence of a double aortic arch is not well known due to its rarity and it can occur as an isolated abnormality, in association with other congenital cardiac abnormalities or in association with chromosomal abnormalities, such as the 22q11 microdeletion. We present a case of double aortic arch diagnosed prenatally.

Clinical description: A 27-year-old nulliparous female was referred for a tertiary morphology scan after a combined first trimester scan reported high risk for trisomy 21, with a nuchal translucency of 5.2mm. The couple declined invasive karyotyping. A mid-trimester ultrasound revealed a double aortic arch with a dominant right arch and the ductus arteriosus WAS on the left side. The four chamber view of the heart and the outflow tracts were normal. A fetal echocardiogram by THE paediatric cardiologist confirmed these findings. The patient and her family was counselled regarding the potential outcomes of a double aortic arch and appropriate support was provided by both midwifery and medical teams. She was induced at 37 weeks 1 day gestation and proceeded to a normal vaginal delivery of a live female infant.

Discussion: A double aortic arch results in symptoms of a varying degree, depending on the severity of compression of the trachea and oesophagus by the surrounding vascular ring. Most commonly, these include stridor, respiratory distress, apnoea and dysphagia and occur within the first 2 years of life in 72.4% of patients. Surgery is usually required to divide the aortic arches and relieve pressure on the trachea and oesophagus. Without treatment, there may be long-term consequences with persistent trachea-bronchomalacia and progressive airway damage. Therefore, early diagnosis is helpful in the prevention of these potential complications as appropriate medical follow up in the postnatal period can be arranged.

Conclusion: Double aortic arch is an uncommon cardiac anomaly that may have potentially significant consequences if undiagnosed. Early detection during fetal life, as in the case above, will allow both early evaluation and intervention of this anomaly as well as appropriate follow up to avoid potential airway damage in the child.
Background: Foley catheters are a popular tool for cervical ripening prior to induction of labour. Both silicone and latex single-balloon catheters are widely available but no literature exists to compare them.

Methods: Women undergoing Foley catheter cervical ripening were randomized to a silicone or latex catheter. The primary outcome was insertion-related accidental rupture of membranes. Secondary outcomes included catheter insertion failure, need for unplanned hospital admission, insertion-related bleeding and insertion-related discomfort together with general obstetric and neonatal outcomes.

Results: 534 women were recruited, 371 nulliparous and 163 parous. Accidental membrane rupture was significantly more common with a silicone compared to a latex catheter at 7.2% (19/265) versus 1.5% (4/269) (RR 4.8; 95% CI 1.7 – 14.0). Insertion failure was significantly less common in the silicone compared to latex cohort at 2.6% (7/265) versus 9.3% (25/269) (RR 0.3; 95% CI 0.1 – 0.6). Insertion-related hospital admission was higher with silicone at 9.4% (25/265) than latex 4.8% (13/269) (RR 2.1: 95% CI 1.1 – 4.1) with most of the difference due to accidental membrane rupture. All other outcomes were no different between the two groups.

Conclusion: When used for cervical ripening, a silicone Foley catheter is associated with a higher rate of accidental membrane rupture than a latex catheter but a lower rate of insertion failure.
From the womb to the operating room
Presented at Australian Critical Care Nurses Conference, 2016, Sydney NSW

Invited speaker: Susan Heath

[Abstract not available]

Getting the message out: the publishing game
Invited presentation, Introduction to Research Seminar Series, Western Sydney Local Health District Research & Education Network, 2016, Sydney

Letitia Lancaster

[Abstract not available]
High BMI – Impact on the length of labour and mode of birth.

Presented at CCP Westmead Research Forum, August 2018, Westmead NSW

Beata Gidaszewski

Aim: the aim of this research was to describe and compare the length of labour and to estimate the risk of perinatal interventions amongst healthy primiparas with higher than normal BMI who birthed at Westmead hospital between 1st of July 2006 – June 30th, 2017.

Methods: was a retrospective single-centre observational cohort study. We used data routinely collected in ObstetriX database to identify primiparas who gave birth at term, following an uncomplicated pregnancy

Results: 54333 women gave birth during the study period. Data from 15764 primiparas met the study inclusion criteria and were available for final analysis. Amongst them 1182 were had low BMI (less than 18.5), 9982 were identified as having a normal BMI (BMI between 18.5 and 25), 3217 were overweight (BMI 25 to 30), and 1383 were obese (BMI more than 30). Our interim analysis showed no statistically significant difference in the lengths of the first stage of labour for women with high BMI when compared to women with normal BMI. Amongst women who gave birth vaginally, the median length of the first stage of labour was 310, 308 and 300 min, for women with normal, overweight and obese BMI respectively. There is, however, statistically significant difference (p <0.001) in the rate of perinatal intervention and mode of birth between the groups. Obese and overweight women were more likely to need a cervical ripening procedure (13.9% v 11.5% v 8.5%) and oxytocin for labour induction or augmentation (62.4% v 57.6%v52.5%). Furthermore, the percentage of women who required LSCS increased with the increase in BMI from 23.5% for normal BMI to 29.4 % for overweight and 35.9% for obese.

Conclusion: Among healthy women with different BMI who gave birth vaginally there are no clinically significant differences in the length of labour. However, women with overweight or obese BMI experience a significantly higher rate of perinatal intervention, and there is a linear increase in LSCS with increased BMI.
Increasing prevalence of diabetes in pregnant women attending Westmead hospital over a period of 7 years

Presented at Westmead Hospital Week, August 2018, Westmead NSW

Marjan Khajehei

**Aim:** To assess changes in the prevalence and risk factors of diabetes in pregnant women from 2011 to 2017.

**Methods:** In this retrospective study, data from 38,851 pregnant women who attended Westmead Hospital (2011-2017) were considered for evaluation using SPSS for statistical analysis.

**Results:** Out of 38,851 pregnant women, 4,672 (12%) had gestational diabetes and 462 (1.2%) had pre-existing diabetes. There was steady increase in gestational diabetes (from 9% to 14%) and an increase in pre-existing diabetes (from 1% to 2%) (p<0.05) in the general population of pregnant women from 2011 to 2017.

The rate of endocrine diseases, multiparty, and Body Mass Index>35 significantly increased from 2011 to 2017 in pregnant women with diabetes during pregnancy (p<0.05).

After regression analysis adjusting for baseline characteristics, hypertension and endocrine diseases were shown to be significant risk factors for diabetes during pregnancy (p<0.05). The odds of diabetes during pregnancy in women with hypertension increased from 1.86 (95%CI=1.37-2.52) in 2011 to 1.90 (95%CI=1.43-2.53) in 2017. On the other hand, the odds of diabetes during pregnancy in women with endocrine diseases decreased from 1.67 (95%CI=1.32-2.12) in 2013 to 1.28 (95%CI=1.03-1.59) in 2017 (p<0.05).

**Conclusions:** The prevalence of diabetes among pregnant women has increased from 2011 to 2017.

**Implications for practice:** The steadily increasing rates of diabetes in pregnancy indicate the burden of high-risk pregnancies is increasing. Although we have come a long way in improving care for these women, further efforts are needed to reverse the trend toward increased diabetes in women of child-bearing age.

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Maternal and Fetal journey to neonatal surgery

Presented at Susan Ryan Neonatal Seminar, 2016, Sydney NSW

Invited speaker: Susan Heath

*Abstract not available*
Maternal Venous Thromboembolism (VTE) risk assessment

Presented at PSANZ Conference, March 2016, Townsville

Heath S, Goodfellow A

**Background:** VTE remains an important cause of maternal morbidity and mortality. It is recommended that all women should undergo a documented assessment of risk factors in early pregnancy; if there are clinical changes during pregnancy and following birth. A tool for VTE screening was developed, but did not meet the specific needs of a perinatal population, including assessment of bleeding risk. A validated risk assessment tool for obstetric services was required.

**Method:** A 2013 survey across NSW Maternity services by NSW Kids & Families revealed a significant variation in the approach to the management of VTE, recommending that a guideline be developed for use by all maternity services across NSW. A multidisciplinary expert advisory group, including representatives from the Clinical Excellence Committee, developed a pilot risk assessment tool for maternity services. An education package, with a train the trainer approach, accompanied the introduction. A pilot of the tool was undertaken in a variety of services across NSW tiered maternity networks.

Audits of VTE documentation; screening and management and education of women were performed on 60 sets of medical records; 30 pre- and 30 post-introduction of the tool in each pilot site. Tool users completed an issues log.

**Results** Amendments to the tool following the trial and feedback review enabled effective amendments, increasing the clinical effectiveness of the tool in identifying at risk perinatal women.

**Conclusions:** The maternity VTE risk assessment tool is an effective tool for midwives to identify perinatal women at risk of VTE.
Introduction: Point-of-care lactate devices are used worldwide for intrapartum decision making. Current guidelines are based on Lactate Pro (Arkray) but its imminent product discontinuation necessitates determination of an optimal replacement device, and derive scalp lactate cut-offs equivalent to the current intervention trigger of >4.8 mmol/L. Furthermore, the use of paraffin during fetal scalp sampling to aid beading of the sample has been called into question with some lactate device manufacturers advising against its use.

Methods: Paired umbilical cord arterial and venous blood samples were tested on three point-of-care products (two devices each of Lactate Pro, Lactate Pro 2, and StatStrip), cross-compared with the reference method blood gas analyser. The interference of paraffin on lactate measurement was separately assessed by piercing the umbilical cord in two sites (with or without a thin coat of paraffin) and measuring lactate from the resultant drop of blood.

Results: Using 109 cord artery and vein samples, all brands were found to deviate from the blood gas analyser, with Lactate Pro and StatStrip results consistently lower and Lactate Pro 2 consistently higher. Standard deviation from the blood gas analyser was smallest for StatStrip, and largest for Lactate Pro 2. Within-brand variation was similar for all brands (mean absolute difference on cord artery 0.23–0.30 mmol/L). Equivalent values to the 4.8 mmol/L intervention threshold based on Lactate Pro are 4.9–5.0 mmol/L for StatStrip and 5.3–5.9 mmol/L for Lactate Pro 2, calculated by receiver-operating characteristic analysis. Blood samples passing through a paraffin coat did not significantly differ in lactate levels compared to adjacent bare samples.

Discussion: StatStrip appears superior to Lactate Pro 2 to replace the original Lactate Pro. Using StatStrip, the 4.8mmol/L intervention threshold equivalent was 4.9–5.0 mmol/L. The variation in accuracy of point-of-care lactate devices may exceed the small increments (e.g. <4.2 mmol/L versus >4.8 mmol/L) that guide obstetric decisions.
Normal-sized fetal echogenic kidneys – A case report
Presented at Australasian Society for Ultrasound in Medicine, 2018, Auckland
Teo ZQ, Luig M, Arbuckle S, McCarthy H, Nayyar R

Background
Renal abnormalities complicate 1.6 per 1000 births. They include anular tentrant hydrops, anomalies in number and location; and renal size, structure and echogenicity. Hyperechogenic kidneys are diagnosed when the kidneys appear more echogenic than the liver or spleen beyond 17 weeks of gestation.

Case Report
We present a case of a singleton pregnancy complicated by major placenta praevia, which subsequently developed bilateral hyperechogenic kidneys and antihydrarriams. Mrs HH was a healthy 34-year-old G2P, with an uncomplacid obstetric history. Morphology scan at mid-trimester revealed major placenta praevia and no fetal structural abnormality. On subsequent review of the images, the kidneys appeared hyperechogenic although it was not noted at the time.

She presented with ante partum haemorrhage at 24 weeks gestation and ultrasonography demonstrated bilateral hypeechogenic kidneys which were normal in size and normal renal volume.

She remained an inpatient due to recurrent small volumes of perineal antepartum haemorrhage. However, a 26 weeks scan demonstrated slight hydramnios and subsequently at 32 weeks, there was antihydrarriams. There was no evidence of spontaneous rupture of membranes. The parents were counselled regarding the guarded prognosis in view of the kidney disease causing renal failure and antihydrarriams resulting in pulmonary hydrops.

At 37 weeks gestation, she had an uncomplacid caesarean section after being administered two doses of 11.1mg betamethasone 24 hours apart with an estimated blood loss of 700ml. Her postpartum recovery was uneventful.

The baby’s weight was 2120g and was born with Apgar scores of 6, 8 and 10. The baby’s postnatal course was complicated by severe renal failure and bilateral pneumonia. Her urine output remained minimal despite intensive diuretic therapy.

Ultrasound of neonatal kidney: Loss of normal corticomedullary differentiation and increased echogenicity.

In view of the poor prognosis, a decision for palliative care was taken in consultation with the parents. The baby died on day five of life.

Autopsy and histopathology:
- Histology of neonatal kidneys showed diffuse mesangial sclerosis (DMS)
- Ultrasonography of both parents’ abdomen revealed normal kidneys
- Normal corticomedullary differentiation
- Normal renal pelvis and calyces
- No histological evidence of ARPKD
- Kidney histology: (Left) – mesangial sclerosis of glomeruli, segmental and diffuse mesangial hyperplasia, segmental scars, periglomerular fibrosis, tubular atrophy and increased extramedullary haematopoiesis.

Diagnosis
DMS is a histopathological diagnosis of progressive sclerosis of the mesangial matrix. Initially, there is an increase in mesangial matrix without mesangial cellular proliferation eventually in coagulation of glomerular capillaries and then glomerulosclerosis. It is a rare condition with only case reports and series available in the literature since its first description in 1073.

It can be an isolated finding or be a component of the following syndromes associated with the WT1 gene mutation:
1. Denys-Drash syndrome – congenital nephrotic syndrome with DMS, male pseudohermaphroditism or ambiguous genitalia and Wilms’ tumour
2. Frasier syndrome – pseudohermaphroditism, progressive glomerulopathy and risk of genito-urinary tumours (usually gonadal/blastoma)
3. Other genetic mutations associated with DMS are:
   - PLCE1 – encoded for a protein-protein
   - LAMB2 causing Pierson Syndrome – congenital nephrotic syndrome, microtoma and neurodevelopmental defects.

Regarding this case, it is unclear as to the exact nature of the DMS as specific investigations into rare inherited kidney diseases are still ongoing for the couple.

Conclusion
The workup of a pregnancy complicated by fetal hyperechogenic kidneys should include a fetal ultrasound examination, preferably at a specialist centre. Genetic testing, family history and ultrasound examination of the parents’ urinary system. This case of diffuse mesangial sclerosis represents a rare cause of renal abnormality in early postnatal life and unfortunately, a severe form and a poor prognosis.
NSW Fetal cardiac anomalies: providing family focused continuity of midwifery care
Presented at PSANZ Conference, March 2016, Townsville
Susan Heath

**Background:** Cardiac anomalies represent one third of birth defects in children, with heart disease the leading cause of death in infants less than one year old in Australia. The Heart Centre for Children provides a state based fetal cardiac diagnostic and treatment service, including internationally for Pacific Islanders. Recent increasing service provision for complex HLHS, required an equivalent midwifery service and caesarean section at the Children’s Hospital capabilities.

Continuity of midwifery care through pregnancy, birth and the post-natal period is as safe as traditional fragmented hospital care, and NSW Health Toward’s Normal Birth Policy Directive (2010) advises, regardless of risk status, a pregnant woman can access midwifery continuity of care/r across the childbirth continuum, within an interdisciplinary framework.

**Method:** In collaboration with Westmead Perinatal Advice Referral and Liaison Service (PEARLS), a dedicated 1.0 FTE midwife role was developed, and recruited in June 2015, providing continuity of care and private patient shared care. The fetal cardiac midwife’s role “optimises patient care” through the complex patient journey across two tertiary referral campuses, while meeting the primary midwifery care needs.

**Results:** Families in the midwifery model from July to November 2015 (n= 40) Rural/Remote 27.5 %, International 2.5%, Sydney CBD 70%, with fetal cardiac anomalies: Hypoplastic Left Heart Syndrome 17.5%, Structural Defects 67.5%, Conduction defects 2.5%, Rhabdomyoma 2.5% all received targeted continuity of care from diagnosis to postnatal discharge, with individualised care, education and birth planning.

**Conclusions:** Midwifery continuity of care in woman with fetal cardiac anomalies provides optimal family centred care.

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Nutritional assessment in gynaecological cancer patients – are the commonly used tools appropriate in this patient group?
Presented at 17th Biennial Meeting of the International Gynecologic Cancer Society, 2018, Kyoto, Japan
Jamieson A, Carter A, Lancaster L, Brand A

[Abstract not available]

Outcome of extended venous thromboembolic event (VTE) prophylaxis in women undergoing gynaecological surgery for suspected or confirmed malignancy
Presented at 16th Biennial Meeting of the International Gynecologic Cancer Society, 2016, Lisbon, Portugal
Brand A, Lancaster L, Thirunavukarasu A, Hitos K

[Abstract not available]
Outpatient cervical ripening: midwives investigation of discomfort/pain during speculum and Foley catheter insertion

Presented at ACM NSW Conference, September 2018, Wollongong NSW
Beata Gidaszewski, Marjan Khajehei, Terry McGee
Outcomes of pregnancy complicated by gestational diabetes at Westmead hospital

Presented at PSANZ Conference, April 2017, Canberra ACT

Beata Gidaszewski, Emma Gibbs

**Background:** At Westmead Hospital, proportions of women born overseas is steadily increasing with majority of our patients reporting being born overseas. Migrant populations can be remarkably different from general population in terms of prevalence of some health conditions and healthcare outcomes.

**Methods:** We used routinely collected data of 51577 women who birthed at Westmead hospital between July 2006 and June 2016. Data was coded and then analyzed using SPSS software. We have used descriptive statistics to show prevalence of gestational diabetes amongst our population. Our study showed that out of 4978 women who were diagnosed with GDM, majority was born in countries on Indian subcontinent (34%, n=1665) or Asia (24%, n= 1187). Australian born women accounted for 37% of general population of women. However, they represented less than 20% of women with GDM. We have applied a multinomial logistic regression analysis to evaluate the effect of a mother’s country of birth on mode of birth amongst women diagnosed with GDM. In our analysis, we adjusted for maternal age, parity, gestational age, birth weight and use of epidural analgesia.

**Results:** Our results showed statistically significant differences (p values <0.05) in mode of birth and use of oxytocin for labour induction or augmentation for women born in countries on Indian Subcontinent. Our study showed no differences in use of amniotomy, antibiotics or epidural analgesia for labour pain. There was also no differences in rates of postpartum haemorrhage, Apgar scores or neonatal complications amongst different populations of women with GDM.
Aim: To compare perinatal outcomes between women who used assisted reproductive technology (ART) and women with spontaneous conceptions.

Methods: This was a retrospective cohort study. Relevant data from women who gave birth in Westmead Hospital between January 2011 and December 2015 were downloaded from ObstetriX. The data were, then, cleaned, formatted and coded and were analyzed using SPSS software.

Results: The rates of antenatal admission to hospital, antepartum haemorrhage, anaemia, complications of multiple pregnancy, fetal growth restriction and anomaly, abnormal placental site and premature preterm rupture of membrane were higher in ART women compared to women with spontaneous conceptions. In addition, ART women were more likely to receive prostaglandins for cervical ripening and antibiotics during labour along with having higher rate of postpartum haemorrhage. Although the rates of clear liquor and spontaneous vaginal birth were higher in ART women, their newborns were more likely to have complications at birth and be admitted to nursery that was consistent with higher rate of “no feed at birth” among those newborns. According to Multiple Logistic Regression analysis, the odds of complications of multiple pregnancy, fetal anomaly, use of prostaglandin for cervical ripening, antepartum and postpartum haemorrhage and neonatal admission to nursery at birth were 2-3 times greater in ART women (p<0.05). Out of 27,898 women who birthed during period between January 2011 and December 2015, 1474 women used ART to conceive and 26,147 experienced spontaneous conceptions (excluding incomplete and out of range data).

Conclusion: Women with assisted conceptions are at higher risk for adverse perinatal outcomes than women with spontaneous pregnancies. Women with assisted conception should be informed of their increased risks of poor perinatal outcomes and should seek timely support in any unfavourable circumstances. Midwives and other health care professionals that deal with these women need to be aware of their potential adverse outcomes and provide appropriate and timely assistance and support.
Perinatal Venous Thromboembolism State based prevention strategy: Midwifery Risk Assessment tool

Presented at 7th International Symposium on Women’s Health Issues in Thrombosis and Haemostasis, 2017, Barcelona, Spain

Susan Heath

**Background:** VTE is one of the leading causes of preventable death in Australia. Approximately 14,000 Australians develop a VTE each year. Around 5,000 of these cases result in death. Hospitalisation is strongly associated with the development of VTEs - the majority of which are preventable. Effective prevention is achieved through assessment of risk factors and the provision of appropriate prophylaxis.

VTE remains an important cause of maternal morbidity and mortality. The VTE Prevention Program has been established to reduce the incidence of hospital-associated VTE in NSW public hospitals. The aim is to ensure that all patients are assessed for VTE risk and given the appropriate prophylaxis. The program provides local health districts, individual facilities and clinicians with the tools and resources required to address this patient safety issue, as well as the support and advice required to implement the elements into workflow. The VTE Prevention program is a component of CEC's Medication Safety and Quality program.

It is recommended that all women should undergo a documented assessment of risk factors in early pregnancy; if there are clinical changes during pregnancy and following birth. A state based tool for VTE screening was developed, but did not meet the specific needs of a perinatal population, including assessment of bleeding risk. A validated risk assessment tool for obstetric services was required.

**Method:** A 2013 survey across NSW Maternity services by NSW Kids & Families revealed a significant variation in the approach to the management of VTE, recommending that a guideline be developed for use by all maternity services across NSW. A multidisciplinary expert advisory group, including representatives from the Clinical Excellence Committee, developed a pilot risk assessment tool for maternity services. An education package, with a train the trainer approach, accompanied the introduction. A pilot of the tool was undertaken in a variety of services across NSW tiered maternity networks.

Audits of VTE documentation; screening and management and education of women were performed on 60 sets of medical records; 30 pre- and 30 post-introduction of the tool in each pilot site. Tool users completed an issues log.

A state based expert advisory group tested the tool against maternal deaths for 2009-2013. Westmead Hospital, a tertiary referral hospital, piloted the tool in 2016 on all maternity cases (n= 5076). Comments that were provided by the users were examined to determine if changes were required to improve the tool further. During the implementation year staff received state based education on orientation to the workplace, enabled the link to World thrombosis day youtube webinar, Added to the Womens and newborn patient accessible local website – web address given on booking and included in parent education, risk recorded on womans hand held pregnancy record and advised of her risk, VTE prevention
plan added in time out in operating theatre notes, and electronic version of VTE tool on “ematernity” database since December 2016.

**Results:** The tool identified 3 of 5 maternal deaths, and when adjusted to include BMI of 40 following another maternal death, identified all cases.

The initial retrospective clinical record audit, revealed in the first 17 tools audited identified 1 high risk and 1 intermediate risk of VTE that routine antenatal screening had not identified.

A second survey of pilot tool tool users was performed. A total of 25 midwives completed the survey. They were required to rate both the current tool and revised tool in regards to:

1. Ease of use; 2. Layout and flow; 3. Usefulness in guiding the determination of a patient’s VTE risk level; 4. Usefulness in guiding the management of VTE risk; 5. Whether the user would use the tool again.

Users were asked to rate both the current tool and revised version on a scale of 1 to 5 (1 = very poor/no, 3 = neutral, 5 = very good/yes). Results were collated and analysed to determine the number of times the current tool and revised tool rated 4 or 5 on each of the aspects explored revealed regarding ease of use, 12 out of 25 users (48%) rated 4 or 5 for the current tool versus 19 out of 25 (76%) for the revised tool. Regarding layout and flow, 12 out of 25 users (48%) rated 4 or 5 for the current tool versus 15 out of 25 (60%) for the revised tool.

Regarding usefulness in guiding the determination of a patient’s VTE risk level, 14 out of 25 users (56%) rated 4 or 5 for the current tool versus 21 out of 25 (84%) for the revised tool.

Regarding usefulness in guiding the management of VTE risk, 14 out of 25 users (56%) rated 4 or 5 for the current tool versus 17 out of 25 (68%) for the revised tool.

**Conclusion:** Epidemiological data comparison of 2014 pre pilot and post pilot tool introduction revealed a reduction in VTE post pilot tool implementation. The maternity VTE risk assessment tool is an effective tool for midwives to identify perinatal women at risk of VTE, and raise awareness with perinatal women and their families.
Pregnancy and birth outcomes in women with a history of childhood sexual abuse

Presented at ACM NSW Branch State Conference. July 2016, Leura, Blue Mountains NSW

Marjan Khajehei

**Background:** Childhood sexual abuse (CSA) is one of the most traumatising and violent sexual offences that has various long-term consequences on physical and psychological health. Research has shown that 6-36% of pregnant women have a history of CSA and this may influence the quality of obstetrical care they receive. This review of the literature was conducted to critically investigate how CSA affects pregnancy and birth experiences and outcomes.

**Methods:** A search of electronic databases and scholarly journals resulted in identifying English language studies on the association between CSA and pregnancy and birth outcomes. All studies were evaluated regarding predefined criteria.

**Results:** Pregnant women with a history of CSA experience moderate-severe fear of birth and show a desire for caesarean section. They also report more physical and emotional health problems in pregnancy, such as post-traumatic stress symptoms, anxiety, depression, suicidal thoughts and attempts, eating disorders, high BMI, pregnancy terminations and miscarriages, smoking and substance abuse, chronic pain and sexual dysfunction.

Almost half of the laboring women with a history of CSA remember memories from their past traumatic experiences during childbirth, have longer second stage of labour and have higher rate of CS and instrumental delivery. Attending birth preparation and medical decision-making classes, receiving appropriate pain relief during labor and having a trusted person present at birth can remarkably improve birth outcomes in these women. In contrast, extreme labor hours and emergency during labor can have negative impacts on these women and increase their fear and stress.

**Conclusion:** Pregnancy and childbirth following a history of CSA has its own particular challenges. Nurses and midwives should be aware of the link between CSA history and negative pregnancy and birth outcomes. Evaluating individual needs through simple screening questions and providing integrated care can help create a trusting environment and improve quality of life of these women.

Preparing for the birth of a baby with congenital heart disease

Presented at Monash University Hospital, 2018, Melbourne VIC

Invited speaker: Susan Heath

[Abstract not available]
Profile of Gynaecology Surgeries from the Western Province, Solomon Islands

Presented at RANZCOG ASM, September 2018, Adelaide SA
Mandy Wang, Araz S Boghossian, Alan Tong, Angeline Nagu, David Knox

**Introduction:** There is a paucity of data on the profile of gynaecological conditions affecting women in the Solomon Islands, including the availability and quality of surgical management. The country's specialist obstetric and gynaecology services are located in the capital, Honiara, however access to care is impeded by obstacles of cost and transport across the archipelago as over three quarters of the population are rural dwelling.

**Methods:** Prospective study of patients undergoing gynaecological surgery at Gizo Hospital, Western Province, during a 6 day program by volunteer Australian surgeons. Data was collected on pre-operative history, investigations, surgeries, and post-operative recovery. Full blood count, crossmatch, urine analysis, abdominal ultrasound were available in Gizo. Pathology specimens were sent to Brisbane. [Ethics approval HREC/17].

**Results:**

**Surgery performed and pathologies found:**

- **Vaginal surgery (n=12):**
  - Dilatation and curettage (n=8)
    - All benign
  - Diathermy to cervix (n=2)
  - Excision of vaginal wall cyst (n=1)
  - Diathermy to genital warts (n=1)

- **Laparotomy (n=9):**
  - Performed under spinal anaesthesia
  - Total abdominal hysterectomy (TAH)
  - Laparoscopy +/- oophorectomy
    - Adenomyosis
    - Fibroid (p.a, b)
    - Tubal cysts
    - Endometrioma
  - Oophorectomy (n=1): (c)
    - Ovarian teratoma

- **Laparoscopy (n=8):**
  - Performed under general anaesthesia
  - Diagnostic laparoscopy (n=6):
    - Endometriosis
    - Paratubal cyst
    - Subserous fibroids
    - Mesothelial inclusion cyst
    - Chronic pelvic inflammatory disease
  - Operative laparoscopy (n=2):
    - Ovarian cyst, para-ovarian cyst

**Cancellations:**
- 2 cases cancelled due to Dengue fever (thrombocytopenia of 31x10^9/L in one case) - a common surgical challenge in the Pacific Islands, although no published studies exist.

**Estimated blood loss:**
- Median 10 ml (range 5-400ml). No patients required intraoperative or post-operative blood transfusion.

**Laparoscopy in Solomon Islands:**
- Using donated equipment and laparoscopy packs.
- Could replace laparotomy for common procedures, e.g. ovarian cystectomy, and allow resection of endometriosis, and tubal dye studies, with healing, pain, and hospital stay.

**Discussion:** This study demonstrates the feasibility of integrating gynaecological surgery in regional hospital facilities, including the first series of laparoscopic gynaecological surgery in the Solomon Islands, with most patients having surgical outcomes comparable to those in a developed setting. This local data is critical to guiding resource allocation, foreign aid, directing training of health staff for capacity building.

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Reinforcing the connections: translating research findings into practice to improve continuity of care in high risk pregnancies

Presented at PSANZ Conference, March 2018, Auckland, New Zealand
Susan Heath

**Background:** For over a decade professionals providing perinatal services have emphasised the importance of “continuity of care” for pregnant women and their families, described as the degree to which a series of discrete events are experienced by the client as smooth and coordinated over an appropriate time period. However, within the context of antenatal diagnosis of congenital anomalies, this continuity may be disrupted along the “diagnosis to discharge” continuum. Research that addresses the impact on patient outcomes, especially within high risk maternity populations, is lacking.

**Method:** In phase one of this mixed methods study, data from women’s records around the carepathway and processes, and also data from 17 parental interviews were collected. Members of the high risk pregnancy care team were also interviewed. Data was analysed thematically with basic codes initially, organised using a chronological coding framework, based on the phases of the continuum of care mapped for families diagnosed with congenital anomalies. Themes pertaining to continuity of care were then extracted.

**Results:** Relational, managerial and informational continuity were reported by families as contributing to a successful transition across services. Aspects of service provision which contributed to parental perception of discontinuity of care were also identified.

**Conclusions:** Exploring continuity from the perspective of families and professionals resulted in the identification of a variety of existing strategies to support continuity of care. Translation of findings related to discontinuity, resulted in implementation of strategies to improve care and continuity at specific points in the journey for families diagnosed with a congenital anomaly.
Review of perinatal outcome and mode of delivery stratified by severity of antenatally diagnosed fetal cardiac anomaly.

Presented at World Congress on Ultrasound in Obstetrics and Gynecology, October 2018, Singapore

Shetty SP, Melov SJ, Kirby A, Sholler G, Winlaw D, Alahakoon TI
Risk of Venous Thromboembolism Following Postpartum Cultural Rest: A Prospective Study in Migrant Indian and Chinese Women

Presented at 31st ICM Triennial Congress, June 2017, Toronto, Canada
Sarah Melov, Kerry Hitos

**Background:** Many cultures have a set time of traditional rest in the postpartum period. There is limited information on how this activity may potentially increase the risk of venous thromboembolism (VTE). The reported incidence of VTE in pregnancy and postpartum varies between study populations, an Australian study finding the incidence to be 1.14 per 1000 births with estimates in literature ranging 0.6 – 1.88 per 1000 births. Recent targeted strategies have resulted in improved maternal morbidity, mortality and reducing preventable deaths. Inactivity and specifically greater time spent sitting or lying, increases the risk of PE.

**Aim:** To investigate VTE risk by determining the prevalence of the cultural practice of postpartum “lying-in”, quantify activity and determine factors that influence this tradition in women from China and the Indian subcontinent (ISC: India, Bangladesh, Pakistan and Sri Lanka) at an Australian tertiary referral hospital.

**Method:** A prospective cohort study of 150 women (self-identified culturally ISC n=100 or Chinese n=50), who were surveyed at baseline after 32 weeks gestation and at follow-up six to eight weeks postpartum. Demographic details, VTE risk factors (caesarean section, comorbidities and immobility) were collected. Postpartum activities were quantified and factors that might influence inactivity were investigated.

**Results:** Three (2%) women were lost to follow-up and 11 (7.3%) did not meet criteria for assessment of activity. In total there were 91% (n=136) of women who completed the follow up survey. Of these 57% (n=77) were primiparous and 43% (n=59) were multiparous. 85% of women rested postpartum for cultural reasons with 89% of primiparous women planned postpartum rest. A greater proportion of primiparous women 91% (n=70/77) rested compared to 82% (n=41/50) with one child, versus 62.5% (n=5/8) with two children and 0% (n=0/1) with three or more children (P=0.03). There was no statistical difference between the Indian Subcontinent and the Chinese group for characteristics that influenced rest (P=0.330):∙ type of feeding (P=0.784), if a relative stayed (P=0.988) or how many or years she had lived in Australia (P=0.301).

**Discussion:** Resting in women from the ISC and China is strongly embedded within the structure of childbirth rituals. Worldwide VTE is a leading cause of maternal deaths in high resourced countries. In this study there were 85% of women at follow-up who stated they were immobile postpartum, with 51% who rested in bed as much as possible. There is significant inactivity in Indian and Chinese women during the vulnerable postpartum period, increasing the risk for VTE through immobilization. Culturally appropriate postnatal education can be based on the evidence from this research.
Background: Gastroschisis is a congenital anomaly of the fetal abdominal wall, usually to the right side of umbilical insertion. Worldwide reports of increasing incidence are of concern to clinicians and public health workers.

Methods: Five-year retrospective review of gastroschisis cases from January 1st 2011 to December 31st 2015.

Results: There were 56 infants antenatally diagnosed with gastroschisis with no terminations, one stillbirth (2%) and one infant with ‘vanishing’ gastroschisis. The mean maternal age was 23.9 years (range, 15–39 years. The mean gestation at delivery was 36 weeks (range, 25–39+3 weeks). Of the 55 neonates who received surgical management, 62% had primary closure. The median LOS was 33.1 (IQR, 23.2‐44.5) days and the median duration of TPN was 26.0 (IQR, 17.3‐35.7) days. No antenatal variables affected the primary outcomes. Postnatal diagnosis of complex gastroschisis was made in 16% of cases and was predictive of longer LOS (median 88.5 vs 29.8 days) and days on TPN (median 45.6 vs 21.3 days).

Discussion: Data supplied from the NSW Register of Congenital Conditions database for the last ten-year period available (2004-2013), reveals Westmead Hospital cared for more antenatal gastroschisis cases (n = 78, 35.5%) than any other hospital in the state of NSW. In our study cohort we found excellent outcomes for late-gestation infants born with gastroschisis, reporting that all live-born infants survived to discharge from the Children’s Hospital at Westmead.

We found no late-gestation stillbirths and a low overall rate of 1.8%, suggesting the current risk for stillbirth associated with gastroschisis is lower than previously documented. Australia-wide data on reasons for termination and numbers of terminations are unavailable and will continue to confound data on the prevalence of conditions until data are more accurately captured.

For delivery gestation, a range from 30 weeks to 39+3 revealed no predictive outcome, despite other studies identifying early gestation at birth as a predictor of outcome. With improved care, concerns relating to delivery at late preterm gestation may not be significant.

Ongoing funding, support and commitment to a comprehensive national database of birth anomalies will provide valuable information to inform research into the possible causative agents for the rising prevalence of gastroschisis.
Sexual life of women with high-risk pregnancy

Presented at *Perinatal Society of Australia & New Zealand Conference (PSANZ), April 2017, Canberra ACT*

Marjan Khajehei

Sexual life of women can be adversely affected during pregnancy. Women with high-risk pregnancy are, however, at greater risk of impaired sexual function. A systematic review of the literature has shown that while only a small number of women with high-risk pregnancy report better sexual function, a great proportion of the women with high-risk pregnancy experience negative changes in their sexual life. These changes include decreased sexual desire, declined sexual intimacy, less frequent sexual intercourse, sexual pain and discomfort, sexual dissatisfaction and negative body image. More than half of these women that experience sexual problems do not seek help and support from clinicians due to their embarrassment, discomfort in talking about sex, judgmental reactions, negative attitudes and misunderstanding by clinicians, considering sexuality as a private matter, taboos around sexuality during high-risk pregnancy and lack of knowledge on how to seek support and advice. Although these women may not commence a conversation about their sexual problems, they would welcome the opportunity to discuss it with the clinicians, if offered and prompted.

Adverse changes in sexual life of women with high-risk pregnancy is often taken for granted, mainly due to the general value judgment of society. Given that the satisfactory sexual life plays an important role in the quality of life of these women, systematic evaluation of sexuality, discussing their sexual problems and providing appropriate and timely education need to be considered as imperative responsibilities of the clinicians who look after women with high-risk pregnancy.
Social determinants of treatment adherence
Invited presentation, 44th Annual Scientific Meeting of the Clinical Oncological Society of Australia, Nov 2017, Sydney

Letitia Lancaster

[Abstract not available]

Sydney: Discovering the fetal heart
Presented at Discovering the Heart, 2018, Sydney NSW

Invited speaker: Susan Heath

[Abstract not available]

Taking Heart: Prenatal to neonatal care for congenital heart disease
Presented at PSANZ Conference, 2017, Canberra ACT

Susan Heath

[Abstract not available]

The use of vaginal dilators after brachytherapy and radiotherapy for gynaecological cancer
Invited presentation, 25th Australasian Brachytherapy Conference, 2015, Sydney

Letitia Lancaster

[Abstract not available]

Presented at Annual Scientific Meeting of the Australasian Diabetes in Pregnancy Society, August 2018, Adelaide SA

Marjan Khajehei

**Aim:** To assess changes in the prevalence and risk factors of diabetes in pregnant women from 2011 to 2017.

**Methods:** In this retrospective study using women’s records from ObstetriX, data from 38,851 pregnant women who attended Westmead Hospital (2011-2017) were considered for evaluation. The data were transferred from ObstetriX into an Excel datasheet. After cleaning, formatting and coding the data, they were entered into SPSS for statistical analysis. Incomplete or out of range records were excluded from the study.

**Results:** Out of 38,851 pregnant women, 4,672 (12%) had gestational diabetes and 462 (1.2%) had pre-existing diabetes. Assessment of the trend of diabetes in the general population of pregnant women showed a steady increase in gestational diabetes (5%) and an increase of 1% in pre-existing diabetes from 2011 to 2017.

Among pregnant women with diabetes during pregnancy (n=5,134), there were increases in the prevalence of endocrine diseases (by 6%), multiparty (by 5%) and Body Mass Index>35 (by 5%) from 2011 to 2017 (p<0.05).

Despite increases in the prevalence of renal diseases (3%), overseas-born women (2%) and auto-immune diseases (1%) from 2011 to 2017 and a decrease in the prevalence of neurological diseases (1%) among pregnant women with diabetes, changes in the trends were not significant (p>0.05).

After regression analysis adjusting for baseline characteristics, hypertension and endocrine diseases were shown to be significant risk factors for diabetes during pregnancy. The odds of diabetes during pregnancy in women with hypertension increased from 1.86 (95% CI=1.37-2.52) in 2011 to 1.90 (95% CI=1.43-2.53) in 2017. On the other hand, the odds of diabetes during pregnancy in women with endocrine diseases decreased from 1.67 (95% CI=1.32-2.12) in 2013 to 1.28 (95% CI=1.03-1.59) in 2017 (the odds for endocrine diseases were not significant in 2011 and 2012; p>0.05).

**Conclusions:** The prevalence of diabetes among pregnant women has increased from 2011 to 2017 and the odds are higher in women with endocrine diseases and hypertension during pregnancy.
Trends in the prevalence of high BMI in pregnant women and the risk factors: a large, population-based study, 2011-2017

Presented at *CPC Westmead Research Forum*, August 2018, Westmead NSW

Marjan Khajehei

**Aim:** To assess changes in the prevalence and risk factors of high BMI (including overweight and obesity) in pregnant women from 2011 to 2017.

**Methods:** In this retrospective study, data from 38,851 pregnant women who attended Westmead Hospital (2011-2017) were considered for evaluation. The data were transferred from ObstetriX into an Excel datasheet and were then entered into SPSS for statistical analysis. Incomplete or out of range records were excluded from the study.

**Results:** Out of 38,851 pregnant women, 9,622 (28%) were overweight and 6,078 (16%) were obese (mean BMI=25±6.4; ranged 13-125). A steady increase in the prevalence of overweight and obesity were shown from 2011 (22% and 15%, respectively) to 2017 (28% and 16%, respectively) (p<0.001).

Among pregnant women with high BMI (n=15,700), from 2011 to 2017, there were significant increases in the prevalence of overseas-born women (57% vs.64%, respectively), women>35 years old (17% vs. 19%, respectively) and women with endocrine diseases (9% vs. 13%, respectively) (p<0.05); while a significant decrease was shown in the prevalence of smoking (11% vs. 5%, respectively) (p<0.05).

From 2011 to 2017, there was an increase in the prevalence of diabetes and auto-immune diseases and a decrease in the prevalence of hypertension and alcohol consumption during pregnancy among women with high BMI. However, the changes were not statistically significant (p>0.05).

After regression analysis adjusting for baseline characteristics, being Australia-born (OR=1.59, 95% CI=1.53, 1.67), older age >35 years (OR=1.49; 95% CI=1.41, 1.58), smoking (OR=1.27, 95% CI=1.17, 1.39) and endocrine diseases (OR=1.08, 95% CI=1.01, 1.15) were shown to be significant risk factors for high BMI during pregnancy (p<0.05).

**Conclusions:** The prevalence of high BMI among pregnant women has increased from 2011 to 2017 and the odds are higher in Australia-born, older and smoking women as well as women with endocrine diseases.
Vascular Ehlers Danlos Syndrome in Pregnancy: Case & Management Considerations

Presented at RANZCOG NSW/Qld Regional Scientific Meeting, July 2018.

Yu M, Nayyar R, Sillence D

INTRODUCTION

Vascular type 4 Ehlers-Danlos Syndrome (vEDS) is a severe form of EDS, characterised by abnormal type III collagen synthesis and is associated with high risk of pregnancy related complications. This case explores obstetric management considerations with multidisciplinary involvement (Figure 1) throughout to optimise maternal fetal outcomes.

CASE REPORT

We present the case of a 21 year old primigravida female with vEDS and 3 previous early miscarriages. She has cutaneous and ligamentous manifestations requiring multiple hospital admissions. She is a known carrier of COL3A1 gene mutation with autosomal dominant inheritance pattern and 50% inheritance risk, however patient declined invasive testing. Maternal MRA showing 5mm internal carotid artery aneurysm (Figure 2). She had regular antenatal care and fetal growth ultrasound at 27 weeks demonstrated a SGA fetus. There was a detailed intrapartum plan formulated with precautions for both vaginal delivery and caesarean section (LSCS).

At 37 weeks gestation, IOL was commenced for SROM and she was GBS positive. LSCS was performed under spinal anaesthesia for FTP and non-reassuring CTG. Delivery of infant was routine with EFW 2.28kg and ApgarS normal. Her postoperative recovery was unremarkable.

DISCUSSION

Currently there are no standardised obstetric management guidelines for vEDS due to the spectrum of clinical manifestations. The type and severity of EDS is important in guiding assessment and planning for potential complications that may occur in each stage of pregnancy. Literature reports vEDS pregnancy related mortality at 5% and a high risk of morbidity mainly due to potential spontaneous arterial dissection, uterine rupture and surgical complications. However the most common complications are perineum lacerations and preterm delivery. More research is required regarding pregnancy decreasing the life expectancy of women with vEDS.

Although it is generally accepted that pregnancy avoidance can prevent the risk of pregnancy-specific complications such as uterine rupture. Multi-disciplinary considerations include pre-pregnancy counselling involving maternal-fetal medicine specialists, geneticists to advise on risk of potential complications, planning mode of delivery including anaesthetics and vascular surgeons if required for a vascular emergency. Pregnancy in women with vEDS raises several considerations including recurrence risk, maternal risk of pregnancy related morbidity and mortality, maternal or fetal risk with prenatal diagnosis, influence of mode of delivery on maternal and fetal mortality and surveillance of maternal vasculature.

Further research is required to determine optimum mode of delivery and whether its timing affects risk of life-threatening complications.

CONCLUSION

Multidisciplinary care involving genetics, anaesthetics and vascular surgery is important to plan for potential challenges associated with vEDS. There is no consensus in literature on timing and mode of delivery for pregnant women with vEDS.

REFERENCES

When less is more: The effect of syntocinon (synthetic oxytocin) on health and well-being of women and infants

Presented at Westmead Women’s and Newborn Health Conference, May 2017, Westmead NSW

Marjan Khajehei

Background: Syntocinon is one of the most common drugs used in labour. While endogenous oxytocin (EOT) and syntocinon are similar in terms of binding to oxytocin receptors in the uterus, they are different in the way they affect brain and body.

Aim: To systematically review the effects of syntocinon on health and wellbeing of women and infants during labour, birth and postpartum.

Methods: Using selected keywords, a search of electronic databases and reference lists resulted in identifying peer reviewed research on syntocinon, transition to motherhood and sexuality. All studies were evaluated regarding predefined criteria.

Results: Syntocinon hampers normal function of the central nervous system and interferes with the release of its hormones. Syntocinon contributes to ‘tocolphobia’ through creating longer and stronger contractions with less interval and results in reduced blood flow to the placenta, low oxygen supply, abnormal foetal heart rates and fetal distress. The strong contractions put remarkable pressure on the occipital portion of foetus’s head and increases the risk of cranial molding, asymmetry and cranial base misalignment. These changes result in lower Apgar scores at birth and negatively affect the function of the six cranial nerves that are involved in sucking and swallowing during breastfeeding. High doses of syntocinon administered during labour and after birth are also associated with breast engorgement (antidiuretic effects), hyperbilirubinemia, neonatal resuscitation and admission to NICU that can contribute to unsuccessful breastfeeding and impaired mother-child bonding.

Exposure to syntocinon during birth changes infant’s DNA methylation, dysregulates the infant’s brain neuropeptide systems, leads to atypical brain development and increases odds of attending specialised educational programs for children with special needs.

Use of syntocinon in labour inhibits pulsatile secretion of EOT and disturbs hormonal physiology resulting in postpartum loss of sexual desire, arousal and orgasm. Since inhibitory effects of syntocinon on hormones can last years, the impaired sexual function of women can remain until years after childbirth.

Conclusion: Syntocinon administered during labour has lasting effects such as increased pain, impaired breastfeeding, disturbed maternal behaviours, poor foetal and neonatal outcomes, infant’s developmental issues and sexual problems.

Implications for practice: The widespread use of syntocinon is not justified considering its short-term and long-term adverse effects. Childbirth professionals should encourage and support a natural birth free of interventions and pregnant women should be informed about the potential effects of syntocinon in order to make informed decision about how to manage their labour in consultation with childbirth professionals.
Writing for publication

Invited Workshop presentation, 21st Annual Congress of Cancer Nurses Society of Australia, June 2018, Brisbane

Letitia Lancaster, Stephens M, Chan R

[Abstract not available]
JOURNAL PUBLICATIONS
A bump inside the bump: a case report of a chorionic bump

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1 | INTRODUCTION

The “chorionic bump” was first described in 2006 by Harris et al1 as “an irregular, convex bulge from the choriodecidual surface into the first trimester gestational sac.” The prevalence of chorionic bumps appears to be2 between 1.5 and 7 per 1000 pregnancies,3 although data are limited. The aetiology of the chorionic bump is uncertain; however, the evolution of the radiological features on ultrasonography and magnetic resonance imaging has suggested they are likely haematomas4 and there is some histopathological evidence to support this.4,5 Harris et al3 also postulated that the chorionic bump may represent a resorbing blighted pregnancy; however, there is at present, no evidence for this theory. The chorionic bump can be distinguished from the subchorionic haemorrhage because they bulge from the choriodecidual surface into the gestational sac; in contrast, the subchorionic haemorrhage separates the chorionic membrane from the decidua.6

The pilot study conducted by Harris et al1 suggested that pregnancies with the finding of chorionic bump was associated with a lower live birth rate; however, subsequent studies2,3,7 have not supported those earlier findings. The rarity of this sonographic finding creates a challenge for large scaled studies and a need for individual cases to be reported. Our case provides another small piece of evidence that the finding of the chorionic bump does not always lead to a poor outcome in pregnancy.

1.1 | Case presentation

A 30-year-old primigravida was referred for an obstetric ultrasound to our maternal–fetalm medicine laboratory at 8 + 4 weeks of gestation. Subsequently, three ultrasounds were performed throughout this pregnancy at our laboratory. The first scan reported a single live intrauterine pregnancy corresponding to 9 + 2 weeks gestation. In addition, an avascular hyperechoic mass, arising from the chorion, was seen measuring 24 mm × 19 mm. This mass was in close proximity to the umbilical cord insertion and bulged into the gestational sac (Figures 1 and 2).

A progress scan was performed at 10 + 3 weeks gestation, and the findings remained unchanged (Figures 3 and 4). At 12 + 4 weeks gestation, a cell free fetal DNA test was performed, and the results were low risks for trisomy 13, 18, and 21. At the 19 + 3-week morphology scan, the mass appeared largely anechoic with a few hyperechoic areas within and measured 51 mm × 26 mm (Figure 5). The relationship of the mass with the umbilical cord insertion was still maintained. Fetal biometry and morphology were within normal limits.

The pregnancy progressed without complications. At term, a live baby girl, who weighed 3.1 kg, was born in good condition by an elective caesarean section. A cyst was identified at the amniotic surface of the placenta and histopathology confirmed it was a septal cyst of the placenta (Figure 6).

2 | DISCUSSION

The association between the finding of the chorionic bump and pregnancy prognosis is still not known for certain. One limitation of attempts to investigate this association is the presence of confounding factors. In the pilot study conducted by Harris et al.1,2 2178 sonograms were reviewed, and 15 pregnancies with the chorionic bump between 5.8 to 9.3 weeks of gestation were identified. Within this cohort of 15 cases, six patients had received infertility treatment in the index pregnancy and three in prior pregnancies. The pregnancy outcome was compared with two control groups; each had 15 patients: a “healthy” control group, from the general pregnant population, and an “infertility” control group from the infertility clinic. The maternal age and gestational age of the control groups were matched to the study group. The results were that the study group had a live birth rate of 47% (7 of 15), and the healthy control group had a statistically significant higher live birth rate of 87% (13 of 15); however, there was no statistically significant difference between the live birth rate of the study group and the infertility control group (11 of 15 live births). This data may suggest that infertility was a confounding factor that contributed to the poorer pregnancy outcome in the study group. Another potential confounder in this pilot study was that 6 out of 15 women in the study group experienced vaginal bleeding. Subsequently, four of these
women had first trimester miscarriages, one a second-trimester miscarriage, and one progressed to a live birth at term. Of the nine women who did not have vaginal bleeding, only one pregnancy resulted in a first trimester miscarriage and one in a second trimester miscarriage. Therefore, from this study, it is difficult to isolate the true prognostic impact of the chorionic bump independent of infertility treatment and vaginal bleeding.

In 2015, Arleo and Troiano\(^3\) published a prospective observational study on the prognosis of pregnancies with the chorionic bump. Over a 4-year period, 52 pregnancies with one or more chorionic bumps were identified at their centre, where an estimated 7280 to 10 400 first trimester scans were performed during that time. Thus, they estimated the prevalence of the finding of the chorionic bump to be five to seven per 1000 pregnancies. A subset analysis was performed on pregnancies in which the gestational sac, yolk sac, and an embryo with a heartbeat were seen and found that in this group the live birth rate was 83\% (34 of 41). Furthermore, in 91\% of cases, the chorionic bump resolved by 12 weeks of gestation (31 of 34). Unlike the findings of Harris et al\(^1\) where two of the 15 women had second trimester losses, all 18 pregnancy losses occurred in the first trimester. Another
Progress ultrasound at 10 + 3 weeks of gestation showed the chorionic bump to be 24 mm × 22 mm.

3D reconstruction of the fetus, umbilical cord (UC) and the chorionic bump (CB) from the ultrasound scan at 10 + 3 weeks of gestation.
possible prognostic indicator Arleo et al\(^3\) identified in this study was that four pregnancies in the study group had more than two chorionic bumps, and these pregnancies all resulted in demise. They also noted that four patients had a history of coagulation disorder, and three of them went on to have live births. This data suggested that the chorionic bump is not necessarily associated with poor outcome in pregnancies with otherwise normal first trimester sonographic findings.

Later that year, Arleo, Dunning, and Troiano\(^7\) published a systematic review and meta-analysis that combined the data from the two studies previously described, and another retrospective case-control study by Sana et al.\(^2\) which included 57 cases with the chorionic bump. In this meta-analysis, a subset analysis was conducted on pregnancies that were otherwise normal and found the live birth rate was 83%.\(^7\)

Wax, Cartin, Litton, Pinette, and Lucas\(^8\) performed a retrospective cohort study that included 690 singleton pregnancies between 2010 and 2015, where both ultrasound and chromosomal testing were performed. Since it was not their practice at the time to report the finding of the chorionic bump on the ultrasound report, two examiners who
were blinded to all patient information (including chromosomal testing result and pregnancy outcomes) retrospectively reviewed all patients’ ultrasound images for the presence or absence of chorionic bumps. A chorionic bump was identified in 16 patients, and there was good intraobserver and interobserver agreement for the diagnosis. 117 (17%) fetuses were aneuploidy, of which five had a chorionic bump (4%). The risk of aneuploidy in the presence of a chorionic bump was higher than in its absence; however, this was not statistically significant.

There are several unique and interesting features in our case. First, the chorionic bump persisted throughout the pregnancy, which continued to term. Second, a healthy baby was born despite the persistence of the chorionic bump. Third, the chorionic bump developed into a cyst.

At the caesarean section, a large cyst of the placenta was seen, but unfortunately, no macroscopic measurement was obtained because the cyst was no longer intact upon arrival at the histopathology laboratory. Histopathological examination did confirm that the ruptured cyst was a septal cyst of the placenta. This differs from what has been previously reported for the histopathology of the chorionic bump and the current hypothesis that they are haemorrhagic lesions. In 2010, Tan et al\(^5\) reported a case study of a pregnancy with three chorionic bumps that demised at 6 weeks gestation. Histopathological examination of the abortus reported haematoma remnants, and this concurred with the appearances of their serial ultrasonographic findings, which also suggested that the lesion was a haematoma. It is however difficult to compare our case with that of Tan et al since the duration of the pregnancies were markedly different. This demonstrates again that our case is indeed unique in its ability to help us understand the potential progress and prognosis of the finding of a chorionic bump.

3 | CONCLUSION

The current data suggests that given the presence of normal first trimester sonographic findings (yolk sac, gestational sac, fetal heart motion), the presence of only one chorionic bump, and the absence of fertility treatment and vaginal bleeding, we can offer reassurance to our patients that the chorionic bump is likely to resolve by 12 weeks of gestation and there is a high chance of live birth. However, to understand the true prognosis of pregnancies with the first trimester ultrasound finding of the chorionic bump, prospective data from the general population are needed.

ACKNOWLEDGEMENTS

The patient consented to the publication of her case and ethics approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee.

FUNDING

None.

CONFLICT OF INTEREST

None.

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REFERENCES


Case Report
A Case of Placenta Percreta Managed with Sequential Embolisation Procedures

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Received 30 October 2017; Revised 23 December 2017; Accepted 23 January 2018; Published 15 March 2018

Academic Editor: Akihide Ohkuchi

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Background. The incidence of morbidly adherent placenta, including placenta percreta, has increased significantly over recent years due to rising caesarean section rates. Historically, abnormally invasive placenta has been managed with caesarean hysterectomy; however, nonsurgical interventions such as uterine artery embolisation (UAE) are emerging as safe alternative management techniques. UAE can be utilised to decrease placental perfusion and encourage placental resorption, thereby reducing the risk of haemorrhage and other morbidities. Case. We describe one of the very few reported cases of placenta percreta which was successfully treated primarily with sequential artery embolisation. Our patient underwent four embolisation procedures over a period of 248 days, with no major morbidity or complications. Conclusion. Repeat UAE may be a beneficial primary management modality in cases of placenta percreta with bladder involvement.

1. Introduction

Placenta percreta is a serious obstetric complication where the placental villi penetrate through the myometrium into the uterine serosa and possibly adjacent organs. There are three degrees of morbidity adherent placenta (MAP): placenta accreta, increta, and percreta. Placenta percreta is the most severe but least common form of this condition, accounting for 7% of abnormally implanted placentas; however it is associated with a significantly higher maternal morbidity than the other varieties [1, 2]. The incidence of morbidity adherent placenta, including placenta percreta, has increased significantly over recent years, which has been attributed to increasing rates of caesarean delivery, although the mechanism remains speculative [3]. The most appropriate management for this life-threatening condition is debated. We report a case that presented at the end of the first trimester with successful conservative management and detailed angiographic and ultrasound imaging.

2. Case Presentation

A 38-year-old female, G7P3 (three previous lower segment caesarian sections and 3 prior surgical terminations), presented to our hospital with a massive haemorrhage after surgical termination of pregnancy. The gestational age estimate was 14 weeks based on biparietal diameter on bedside ultrasound performed preoperatively at a private clinic. No formal ultrasound had been performed during her current pregnancy. A dilation of cervix and suction curettage were performed. Significant haemorrhage occurred with the loss exceeding 1000 ml. Syntocinon was administered intramuscularly and a Foley catheter was inserted into the uterus for
range of management options are presented in the literature, there is a lack of good quality data to indicate which management option is preferable, largely due to the paucity of such cases. These can be broadly categorised into hysterectomy with placenta in situ, placental resection, and conservative management modalities with or without a planned interval hysterectomy.

Conservative management, where the placenta is left in situ, can include expectant management, methotrexate administration, uterine artery embolisation (UAE), or a combination of these modalities. Conservative management offers the main advantages of minimising the risk of haemorrhage and other significant surgical morbidities at the time of delivery, as well as preserving fertility. One review (n = 407) found that 85.7% of women conceived following conservative treatment in all forms of morbidly adherent placenta (MAP); however in cases of placenta percreta specifically only 10% (1/10) had a subsequent pregnancy [4, 5]. It is also important to consider the significant recurrence risk of MAP, which has been reported to be as high as 29% [4]. Serious complications such as secondary haemorrhage, sepsis, and the need for emergency hysterectomy may occur with conservative management, and have been reported up to many months after delivery; thus this approach requires close surveillance.

In one of the largest case series of conservatively managed placenta percreta (n = 119), 61% of patients experienced at least one postoperative complication, compared to 12% in placental resection and caesarean hysterectomy groups [6]. The most common complications were emergency hysterectomy (50%) (even up to 9 months after caesarean section), haemorrhage (44%), sepsis (25%), and bladder injury (17%) [6]. Management with methotrexate has been described in some small case series and reports, with results ranging from successful placental resorption without complications [7–10] to significant complications including coagulopathy, haemorrhage, and need for secondary hysterectomy or placental removal [11–14]. Uterine artery embolisation has been used to manage placenta percreta primarily and in cases of postpartum haemorrhage; however a significant proportion of these (18–62%) may still require hysterectomy [5, 15–17]. For cases managed successfully with expectant management alone, reports of complete resorption range from 8 months to 3 years postpartum [18, 19]. It has been suggested by a number of case reports and series that leaving the placenta in situ at the time of delivery with a planned interval hysterectomy at a later date may be a safe management option, as there may be markedly decreased vascularity, allowing for technically easier hysterectomy with a reduced rate of peri- and postoperative complications [20–23]. However, this requires extensive planning and multidisciplinary input and there is insufficient consistent evidence to suggest an appropriate timeline before which a definitive interval hysterectomy should be offered. The unpredictability of complications with conservative management and associated morbidity necessitate taking a cautious, individualised approach with each case given the lack of robust evidence.

Local placental resection has also been presented as a conservative surgical alternative in cases of placenta percreta with bladder involvement; however there have been mixed
Table 1: A timeline summary of the management of this patient.

<table>
<thead>
<tr>
<th>Days after surgical uterine evacuation</th>
<th>Events and Images</th>
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| **Day 22**                            | (i) Ultrasound showed persistent retained placental tissue with significant vascularity and extension into bladder with no overlying myometrium, suggestive of placenta percreta with bladder involvement (See Figure 3)  
(ii) Multidisciplinary discussion between gynaecologist, urogynaecologist, maternal fetal medicine specialist, and patient  
(iii) The options of management discussed included expectant management, abdominal hysterectomy, or uterine artery embolisation  
(iv) Uterine artery embolisation was decided                                                                 |
| **Day 33**                            | (i) Initial angiogram showed very large, tortuous, abnormal uterine arteries, particularly on the left side; thus it was decided to proceed with initial embolisation with the view that multiple procedures would be required to adequately devascularise the retained placental tissue  
(ii) This decision was based on attempting to minimise undue ischemia and pain to the patient, and therein any hospital admissions, as well as minimising the radiation exposure to this young patient by spreading the embolisation over multiple sessions  
(iii) Left sided arterial embolisation performed via microcatheter, using Boston Scientific Helical pushable metal coils (4 mm + 6 mm) and Boston scientific contour embolisation particles (250–350 microns) (See Figures 4, 5, and 6) |
| **Day 36**                            | (i) Ultrasound showed persistence of retained placental tissue with significant vascularity             |
| **Day 54**                            | (i) Pelvic angiogram showed persistent uterine vascular abnormality with some regression since the initial embolisation procedure  
(ii) Further embolisation of two arterial branches of the left internal iliac artery  
(iii) Regression of persistent PV bleeding and return of regular menses                                     |
| **Day 57**                            | (i) Serum beta HCG 7                                                                                 |
| **Day 107**                           | (i) Angiogram showed further improvement of the uterine vascular abnormality  
(ii) Further embolisation of a branch of the right internal iliac artery                                 |
| **Day 177**                           | (i) Pelvic angiogram showed a single abnormal feeding vessel to the vascular anomaly off the right internal iliac artery, which was successfully embolised  
(ii) No further abnormal vessels, including intraperitoneal feeding vessels, were identified (See Figure 7) |
| **Day 241**                           | (i) Ultrasound showed persistent uterine mass (16 × 15 × 10 mm); however this was avascular and significantly reduced in size as compared to earlier ultrasound images (See Figure 8) |
| **Day 248**                           | (i) Hysteroscopy was performed which showed no evidence of residual placental tissue over the anterior uterine wall. Endometrium overlying possible remnant placental tissues could not be ruled out. A uterine septum was identified which was divided with scissors (See Figure 9) |
| **Day 283**                           | (i) Patient was well, continuing to have regular menstrual periods with no abnormal bleeding           |

results depending on the resection method utilised. In one prospective study \((n = 68)\), local resection was performed via retrovesical and parametrial dissection with subsequent repair of the anterior wall defect, with 26% of patients requiring secondary hysterectomy, the majority due to extensive uterine destruction, and two cases of inadvertent ureteric ligation \([24]\). In a retrospective review of local resection \((n = 17)\), there were no reported cases of urological complications and only two cases of haemorrhage, neither requiring hysterectomy \([6]\). One small cohort study \((n = 19)\) has proposed a method of local resection involving myometrial excision leaving the area of placental involvement of the bladder intact and uterine artery balloon occlusion, which has shown a reduced rate of postpartum haemorrhage, secondary hysterectomy, and duration of hospital stay when compared to leaving the placenta in situ \([25, 26]\). A systematic review found that partial resection resulted in a subsequent pregnancy in 19/26 (73%) cases of morbidly adherent placenta \([5]\).

Caesarean hysterectomy has historically been the treatment of choice for abnormally invasive placenta, where the placenta along with the uterus is removed at the time of delivery. This minimises the risk of long term complications, such as sepsis, haemorrhage, and need for emergency hysterectomy. However, there is considerable morbidity associated with this procedure, with significant intraoperative and
Figure 3: Ongoing evidence of adherent placenta (P) with likely bladder (B) invasion (arrowed) and dilated vesical and uterine vessels.

Figure 4: Pelvic angiogram—early arterial phase. Both internal iliac arteries (arrowed) show extensive abnormal arterial supply to the uterus, more evident on the left.

Figure 5: Pelvic angiogram—late venous phase. Early venous drainage to internal iliac veins (arrowed).

Figure 6: Microcatheter metal coil embolisation of the abnormal left internal iliac arteries.

Postoperatively complications, including maternal death (up to 5%) [27]. Urology involvement preoperatively has been shown to reduce the rates of urological complications [28]. A large retrospective review ($n = 66$) found that 30% of cases managed with caesarean hysterectomy resulted in some form of complication, with 17% suffering a bladder injury and 7.6% postoperative haemorrhage [6]. Conversely, one prospective case series ($n = 58$) had only 6.9% of patients enduring a bladder injury and 1.7% requiring reoperation due to haemorrhage; however, almost one-third (29.3%) received more than 4 units of red blood cells [29]. There have been a number of case reports presenting modified caesarean hysterectomy methods, with techniques such as intentional cystotomy and resection of the affected bladder wall with subsequent bladder repair [30], subtotal hysterectomy with invasive portion of placenta left in situ [31], and retrograde caesarean hysterectomy [32]. These methods have been proposed in an attempt to minimise urological complications and intraoperative blood loss; however they lack sufficient supporting evidence and do not seem to result in a significant reduction of morbidity. Caesarean hysterectomy in conjunction with arterial embolisation and/or arterial balloon occlusion has been shown to reduce intraoperative blood loss and transfusion requirements when compared to caesarean hysterectomy alone [6, 33, 34].

This is one of the first reported cases of serial embolisation for the primary management of placenta percreta. While there have been other case reports of sequential arterial embolisation, to our knowledge, this is the first report of so many embolisation procedures, utilised as the only management method [8, 35]. Given the fact that our patient did not have a progressing pregnancy and that she had completed her family but was eager for uterine conservation and also very compliant, we were able to try this uterine sparing method. In a retrospective review including nine cases managed with primary arterial embolisation, 78% (7/9) did not experience major morbidity, with only two requiring hysterectomy [36] and resorption of placental tissue has been
Figure 7: Pelvic angiogram following serial embolisation shows no persisting abnormal uterine vessels.

Figure 8: Avascular echogenic mass (16 × 15 × 10 mm) at the site of caesarean scar (arrowed).

Figure 9: Uterine septum (S). Otherwise normal uterine cavity.

the range of 4–12 months as reported by other similar case studies in the literature [5, 8, 35, 37, 38].

4. Conclusion

While the incidence of morbidly adherent placenta, including placenta percreta, is sure to increase in the years to come, there is a lack of robust evidence regarding the most appropriate management; thus management must be individualised. We present a case of a successfully managed placenta percreta with serial arterial embolisation procedures over a period of nine months, which resulted in placental regression and uterine preservation without significant morbidity.

Consent

The patient described in this case has provided written consent for its publication.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Acknowledgments

The authors would like to thank Priscilla Bonura, Westmead Hospital Maternal Fetal Medicine Unit, for performing the ultrasound examinations.

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CASE REPORT

Acinic cell carcinoma of the parotid gland in pregnancy: an approach to cancer in pregnancy

Philip Peter Cellich,1 Roshini Nayyar,2 Eva Wong3

SUMMARY
A 27-year-old woman presented with an enlarging painless right preauricular mass at 28 weeks’ pregnant. The mass had been stable for more than 10 years, but showed rapid growth during pregnancy. Imaging and biopsy were consistent with parotid gland malignancy, with surgical resection undertaken at 33+4 weeks’ gestation. Histopathology confirmed acinic cell carcinoma. Labour was induced without complication at 36+6 weeks’ gestation and adjuvant radiotherapy commenced 2 weeks postpartum. At 9 months follow-up, both mother and baby were well, with no signs of disease recurrence. Rapid progression in pregnancy, of a previously stable salivary gland mass, is a common feature among reported cases and was also observed in the current case. This suggests an aetiological link between pregnancy and salivary gland tumour progression. We demonstrate successful management of a parotid gland malignancy in pregnancy and review guiding principles for cancer management in pregnancy.

BACKGROUND
Cancer complicates approximately 1:1000 pregnancies.1 This rate is increasing as maternal age increases. Cancer in pregnancy presents complex medical, ethical and psychological challenges and should be managed by a multidisciplinary team.2 The most common cancers seen in pregnancy include: breast cancer, cervical cancer, lymphoma, ovarian cancer and melanoma.1 Cancer of the salivary glands is rare, with an incidence of 1.3 per 100 000 people per year.3 The coincidence of salivary gland cancer with pregnancy is even more rare, with only a handful of cases reported internationally.4–6 Rapid progression in pregnancy, of a previously stable salivary gland mass, is a common feature of these cases,3,5,7 suggesting an aetiological link. We report a case of parotid gland acinic cell carcinoma which demonstrated rapid progression in pregnancy and describe its successful multidisciplinary management.

CASE PRESENTATION
A 27-year-old East-Asian non-English speaking woman presented with an enlarging painless right preauricular mass at 28 weeks’ pregnant. The mass had been stable in size and asymptomatic for more than 10 years and had not previously been imaged or biopsied, but showed rapid growth during pregnancy.

INVESTIGATIONS
Ultrasound and MRI were undertaken, demonstrating an 18×22×34 mm heterogeneous right parotid mass (figure 1). Fine needle aspiration biopsy suggested high grade primary salivary gland malignancy.

TREATMENT
Following multidisciplinary team assessment, superficial parotidectomy and selective cervical lymph node dissection was undertaken at 33+4 weeks’ gestation (figure 2). Histopathology confirmed dedifferentiated acinic cell carcinoma that was oestrogen and progesterone receptor negative, with no nodal involvement. Labour was induced close to term (36+6 weeks’ gestation), to facilitate timely commencement of adjuvant radiotherapy, which had been delayed due to pregnancy. Labour progressed to normal vaginal delivery of a 2985 g term female infant, with no maternal or neonatal complication. Adjuvant radiotherapy directed to the right parotid bed was commenced 2 weeks post-partum, within 6 weeks of surgery.

OUTCOME AND FOLLOW-UP
At 9 month follow-up, 6 months post radiotherapy, the patient was disease free, the surgical wound had healed well and there was no evidence of any adverse effect of radiotherapy. A mild facial nerve neurapraxia present in the initial postoperative period resolved completely. The 8-month-old female infant was healthy and meeting developmental milestones.

DISCUSSION
Cancer in pregnancy
The management of cancer in pregnancy requires consideration of the effect of (1) pregnancy on the cancer; (2) the cancer on the pregnancy and (3) cancer investigation and treatment on the pregnancy.6 It raises complex moral and ethical issues, as the goals of preserving both maternal and fetal well-being are often in direct conflict. Given the relative rarity of these cases, an individualised, multidisciplinary management approach should be adopted, taking into account the type and location of tumour; grading, staging and prognosis of disease; sensitivity to chemotherapy and radiotherapy; gestational age at presentation; pre-existing pregnancy complications and patient wishes.2 The principles of management of cancer in pregnancy include1 2.

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Accepted 2 July 2018
Pregnancy should be continued to close to term in the majority of cases.

Ultrasonography and MRI are preferred imaging modalities.

Surgical management is possible throughout pregnancy, but preferred in the second trimester.

Chemotherapy is possible in the second and third trimesters, but should be ceased 3 weeks prior to delivery.

Radiotherapy of the upper body is possible, with shielding of the abdomen, in the first and second trimesters.

Salivary gland tumours in pregnancy
Rapid progression during pregnancy, of a previously stable salivary gland mass, is a common feature among the small number of cases of salivary gland tumour in pregnancy reported in the literature. This observation suggests an aetiological link between pregnancy and salivary gland tumour progression, which could reflect physiological changes of pregnancy, such as increased immune tolerance or represent an hormonal influence on tumour progression. Our study adds to the body of evidence for the association between pregnancy and salivary gland tumour progression.

Due to the small number of reported cases, there are no established risk factors for salivary gland tumour progression in pregnancy. In addition, the epidemiology of salivary gland malignancy, and salivary gland tumour progression in general, is not well documented due to the heterogeneity of tumour types and sites and the inconsistencies in data gathering internationally. Exposure to ionising radiation is a known risk factor for salivary gland tumour. Females are more commonly affected, but this is dependent on tumour type. There is some evidence for predisposition based on ethnicity, association with viral infection (such as Epstein-Barr virus and cytomegalovirus) and association with certain occupational exposures, but none of these have been demonstrated conclusively.

There are several lines of evidence hinting at a role for sex hormones in the progression of salivary gland tumours. Studies have shown the presence of oestrogen and progesterone receptors in a proportion of normal and neoplastic salivary glands. There is some evidence to suggest that salivary gland malignancy in women may share risk factors with endometrial, ovarian and breast cancers, such as early menarche and nulliparity. A more recent, larger case–control study did not bear this out, except for a non-significant relationship between salivary gland cancer and older maternal age at first birth, a trend shared with endometrial and ovarian cancers. In the face of this evidence for an hormonal influence on salivary gland tumour progression, our case demonstrated rapid progression in pregnancy despite being oestrogen and progesterone receptor negative.

We demonstrate successful multidisciplinary management of a salivary gland malignancy, with definitive surgery during pregnancy, delivery at close to term with good neonatal outcome and minimal delay to adjuvant therapy. We suggest that the obstetrician should be a full and active member of the multidisciplinary team, a factor that was critical to the optimal management of our case.

**Learning points**

- There is a possible aetiological link between pregnancy and salivary gland tumour progression.
- This link may relate to increased immune tolerance or hormonal changes in pregnancy, but occurred in our case despite oestrogen and progesterone receptor negativity.
- Cancer can be managed successfully in pregnancy (including judicious use of surgery, chemotherapy and radiotherapy), without unnecessary risk to maternal or fetal well-being, by respecting certain guiding principles.

**Contributors**  PPC contributed to the literature review, analysis and drafting of the manuscript. RN contributed to conception of the work and data analysis. EW contributed to conception of the work. All authors contributed to the data collection and revision of the manuscript.

**Funding**  The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests**  None declared.
Patient consent  Obtained.

Provenance and peer review  Not commissioned; externally peer reviewed.

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Topical Review

Advanced analyses of physiological signals in the neonatal intensive care unit

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Received 28 May 2017, revised 30 August 2017
Accepted for publication 4 September 2017
Published 21 September 2017

Abstract

Management and monitoring of infants within the neonatal intensive care unit represents a unique challenge. It involves an array of life-threatening diseases, procedures with potentially lifelong impacts, co-morbidities associated with preterm birth and risk of infection from prolonged exposure to the hospital environment. With the integration of monitoring systems and increasing accessibility of high-resolution data, there is a growing interest in the utility of advanced data analyses in predictive monitoring and characterising patterns of disease. Such analyses may offer an opportunity to identify infants at high risk of certain conditions and to detect the onset of disease prior to manifestation of clinical signs. This allows caregivers more time to respond and mitigate any abnormal or potentially fatal changes. We review techniques for variability analysis as they have been or have the potential to be applied to neonatal intensive care, the disease conditions in which they have been tested, and technical as well as clinical challenges relevant to their application.

Keywords: signal processing, variability analysis, neonatal, intensive care, time series analysis

(Some figures may appear in colour only in the online journal)
1. Introduction

The management and monitoring of neonates within the neonatal intensive care unit (NICU) presents many unique challenges, given the prematurity of the patients admitted as well as the criticality and range of conditions observed. The human body is a complex system, comprising numerous interacting components. True to such systems, it is more than the sum of its parts (Kane and Higham 2015), i.e. the interactions between the components results in behaviour that is far more complex than expected by simply adding the behaviour of the individual components. The state of complex systems can be characterised by monitoring changes in patterns over time (Volpe 1989b, Seely and Macklem 2004). This becomes particularly relevant in monitoring critical care environments where changes are often abrupt and life threatening.

In recent years, there has been growing interest in modelling and characterising deviations from normal physiological patterns, made possible by improved capabilities to process large amounts of data. In medicine, particularly in the critical care setting, the analyses of variability and physiological patterns over time have shown promising results in predictive monitoring for critical illness and the opportunity to adjust healthcare and potentially improve outcomes and mortality (Moorman et al 2011 and Sullivan and Fairchild 2015). The work by Griffin and Moorman (2001) has demonstrated the potential for early detection of neonatal sepsis with the HeRO monitoring system. It uses a proprietary heart rate characteristic (HRC) index to characterise both variability and transient decelerations in heart rate which occur during systemic inflammation (Griffin et al 2005). The HRC index becomes increasingly abnormal prior to abrupt clinical deterioration or other recognisable clinical indicators suggesting sepsis (Griffin and Moorman 2001). In a randomised trial across 9 neonatal intensive care units, Moorman et al reported a reduction in mortality by more than 20% compared to settings where this information was not displayed (Moorman et al 2011). Such an approach to monitoring offers the opportunity to precede abrupt or catastrophic deterioration which may be life-threatening, with conventional diagnosis of sepsis often not confirmed until after significant haemodynamic compromise (Sullivan and Fairchild 2015).

There have been a number of recent reviews in this area. These range from those with a focus on the variability analysis techniques available and their underlying assumptions (Seely and Macklem 2004, Bravi et al 2011) to the range of applications in clinical settings, including but not limited to predictive monitoring, early detection and improving clinical outcomes (Ahmad et al 2009b, ChuDuc et al 2013, Billman et al 2015, Sullivan and Fairchild 2015). The majority of applications reviewed pertain to the adult population, following successful prediction results in mortality after myocardial infarction (Voss et al 1996, Schmidt et al 1999) and the onset of sepsis in adult bone marrow transplant patients (Ahmad et al 2009a, 2009b). This paper offers an overview of variability analysis as applied to the neonatal population, or more specifically neonatal intensive care, taking into account its unique challenges and conditions. This follows recent promising results in mortality reduction (Moorman et al 2011), the clinical interest in identifying patterns of critical illness and the potential to respond in a more timely manner to critical conditions that have long-term, even lifelong impacts.

1.1. The neonate

The neonatal period refers to the first 4 weeks of life following term birth delivery at 40 weeks gestation (Robertson and Rennie 1992). Survival is possible with extreme prematurity as early as 23 weeks gestation, and time between neonatal admission and discharge can be as long as 17 to 20 weeks in total. For preterm infants, this period is particularly critical; many are admitted to the NICU with congenital abnormalities and other conditions such as patent
ductus arteriosus (PDA) or may develop an array of conditions ranging from sepsis, necrotising enterocolitis (NEC) to intraventricular haemorrhage (IVH), where treatment, interventions and management can have significant and long-term impacts. Table 1 provides an overview of certain NICU-relevant conditions and their current diagnosis. To further complicate their management, these conditions may occur concurrently and exhibit similar clinical signs, with diagnosis often taking place after significant deterioration or compromise. They are often interrelated with factors leading to preterm birth (Villar et al. 2006) such as infection and poor placental function (acute = asphyxia, chronic = intrauterine growth restriction). Importantly, lifelong injury of tissues such as the retina, brain, kidneys and gastro-intestinal can be related in part or wholly to recurrent pathological deviations in the physiological state in preterm newborns. Recurrent hypocarbia can be associated in a dose dependent manner with severity of brain damage (Collins et al. 2001, Erickson et al. 2002). There is thus difficulty in characterising the precise and long-term impact of a patient’s stay in the NICU, where assessment of developmental outcomes, from physical to neurological, require longer term studies.

1.2. The neonatal intensive care environment

The NICU provides life-saving support for newborns born prematurely. The length of stay in the NICU varies with survival, gestational age, birthweight, intrauterine growth restriction and use of antenatal steroids (Lee et al. 2013). Over this time, management and monitoring of the neonate in this environment presents a combination of challenges, from the need for intubation and mechanical ventilation to intravenous catheterisation—all the while, risk of infection increases with every day of exposure to the hospital environment (Taeusch et al. 2005). Administration of care in and the introduction of new systems to this environment requires consideration of noise and light exposure levels as well as the existing framework for monitoring and life-saving support. It also presents the opportunity to initiate individualised treatment. A recent report from Moody et al. demonstrated the potential for reducing length of stay in the NICU through early initiation of developmental care (Moody et al. 2017).

1.3. Current monitoring approaches and limitations

Physiological parameters monitored in these units range from oxygen saturation (SpO2) using pulse oximetry, heart rate derived from temporal distances between consecutive R peaks in the electrocardiogram (ECG) signal, and arterial blood pressure which is measured invasively using an umbilical or peripheral arterial catheter. Other parameters include cerebral oximetry which is monitored using near-infrared spectroscopy and respiration rate which can be derived from chest electrical impedance monitoring.

Conventional monitoring of these physiological parameters involves a limit-based approach, where deviations from the set thresholds may trigger alarms to which healthcare providers can respond. This approach requires patient-customisation for effective use, such as gestational age and birthweight-adjusted limits for arterial blood pressure. Even with appropriate limits set, false alarms persist. An excess of alarms contributes to desensitisation or alarm fatigue, especially when a high proportion of these may be false or not clinically important. Examples include those triggered by instances of excessive tidal volume from deep spontaneous breaths during weaning from mechanical ventilation or by motion and other artefacts (Imhoff and Kuhls 2006). Addressing alarm overload may also come with a trade-off, with McClure et al. showing that while longer time windows for averaging SpO2 signals may reduce the number of alarms, it may underrepresent the number and severity of events (McClure et al. 2016).
Table 1. Overview of prevalent conditions, their incidence rates and the potential for early prediction in the NICU. Signals of use include electrocardiogram (ECG), electroencephalography (EEG), arterial blood pressure (ABP) and tissue oxygenation index (TOI).

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>Definition</th>
<th>Current diagnosis</th>
<th>Clinical signs</th>
<th>Incidence rates</th>
<th>Signals of use</th>
<th>Interventions initiated at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset sepsis</td>
<td>Systemic infection occurring after 3 d of life (Boghossian et al 2013)</td>
<td>Positive blood cultures</td>
<td>Frequent apnoea episodes, increase in desaturations and apnoea episodes, temperature instability, lethargy, feeding intolerance as well as abdominal distension, Hypotension and/or shock, acidosis, multi-system organ failure.</td>
<td>Incidence ranges from 0–30% (Boghossian et al 2013, Lahra et al 2009, Tröger et al 2014) and is inversely proportionate to birthweight (Stoll et al 2002)</td>
<td>ECG, ABP and pulse oximetry as measures for shock (Bohanon et al 2015, Funk et al 2009)</td>
<td>Antibiotics, haemodynamic support</td>
</tr>
<tr>
<td>Intraventricular haemorrhage (IVH)</td>
<td>Bleeding, originating from the germinal matrix and possibly extending to the ventricular area</td>
<td>Cranial ultrasound</td>
<td>Falling haemoglobin, shock, bleeding disorders, seizures, apnoea bradycardia, pupillary and cranial nerve abnormalities, changes in levels of consciousness, movement or tone.</td>
<td>Over 20% in infants &lt;30 weeks gestation Heuchan et al (2002)</td>
<td>ECG, ABP, TOI, respiratory signals</td>
<td>Haemodynamic and respiratory support, monitoring for hydrocephalus, supportive care</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1. (Continued)

<table>
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<tr>
<th>Clinical conditions</th>
<th>Definition</th>
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<th>Incidence rates</th>
<th>Signals of use</th>
<th>Interventions initiated at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotising enterocolitis (NEC)</td>
<td>Disease of the gastrointestinal tract, possible mucosal injury</td>
<td>Abdominal radiography and ultrasound</td>
<td>Frequent apnoea episodes, increase in desaturations and apnoea episodes, temperature instability, lethargy, feeding intolerance as well as abdominal distension (Bell et al 1978). Blood-stained or bilious gastric aspirates, blood in stools, pneumatosis intestinalis.</td>
<td>1–5% of all newborns admitted to the NICU (Lin and Stoll 2006), 7–14% of very low birthweight (&lt;1500 g) infants (Luig and Lui 2005, Neu et al 2008)</td>
<td>ECG, ABP and pulse oximetry</td>
<td>Antibiotics, bowel rest and decompression</td>
</tr>
<tr>
<td>Patent ductus arteriosus (PDA)</td>
<td>Persistence of the ductus arteriosus connecting systemic and pulmonary circulation</td>
<td>Doppler echocardiography</td>
<td>Widened pulse pressure, failure to wean ventilator pressures, long systolic murmurs and distinct peripheral pulses (Evans et al 2004)</td>
<td>30% of very low birthweight infants (Lemons et al 2001)</td>
<td>ABP</td>
<td>Intravenous ibuprofen or indomethacin (Ohlsson et al 2013)</td>
</tr>
</tbody>
</table>
Furthermore, abnormal signals may fail to trigger an alarm and/or a response, as demonstrated by an analysis of nurse-recorded as well as monitor and algorithm detected apnoea events. Of the algorithm-detected prolonged apnoea events, only 26% had nurse documentation within 1 hr and only 23% activated the monitor’s apnoea alarm (Vergales et al 2014). There is also an under-utilised potential to display trends in the data over various timescales and make this available for review, which is highlighted by the more recent promising work in predictive monitoring (Fairchild et al 2013, Sullivan and Fairchild 2015).

2. Variability analysis techniques

The prevailing notion in variability analysis of biological signals is that illness itself usually causes a reduction in system variability Goldberger (1997), though the opposite can also occur. The available methods for this can be broadly classified into time domain, frequency domain or a combination of the two.

2.1. Time domain analysis

These are measures which describe the signals of interest in terms of their variation over time. One example are moments, which are statistical quantities that characterise the variability of a series: \(x_1, x_2, x_3, \ldots, x_n\). The \(r\)th sample moment is denoted by \(\mu_r = \frac{1}{n} \sum_{i=1}^{n} x_i^r\). For a mean-centred series, the moments from \(n = 2\) onwards are referred to as central moments, with the second central moment denoting variance, the third skewness, and the fourth kurtosis. Standard deviation (SD), that is the square root of the variance, is often used to quantify variability. Like the mean, these features are most informative for Gaussian-distributed data, where cases which deviate from this may not be discerned or characterised based on time features alone (Stanley et al 1999).

In relation to HRV, these parameters are the basis for calculating SDANN, the standard deviation of average NN (normal sinus to normal sinus) interbeat intervals of an ECG calculated for 5 min segments across a 24h recording, and RMSSD which represents the root mean square of differences between adjacent NN intervals (Shaffer et al 2014).

The Poincaré plot is derived from the time domain signal, whereupon a signal is plotted against a version of itself shifted by a time log. It offers a visual representation of self-similarity, where reduced variability manifests as increased elongation of the ellipse fitted to the data points. This can also be characterised using SD1 and SD2, which represent the standard deviation perpendicular and parallel to the line of identity. These two parameters have been shown to be highly correlated with other statistics such as SDANN (Brennan et al 2001).

Using HRV as an example, with ECG derived RR\(_n\) on the x-axis and RR\(_{n+1}\) on the y-axis, figure 1 displays examples of regular (a) and irregular (b) neonatal HRV, respectively. Note that figures 1 and 2 were generated from data collected as part of a study approved by the Sydney West Area Health Service Human Research and Ethics and conducted according to the World Medical Association Declaration of Helsinki.

2.2. Frequency/time-frequency domain analysis

Transformations, that is the reproducible and reversible mapping of one set of values to another using a function, is at the core of frequency or time-frequency domain analysis. The Fourier transform represents one such function, simplifying a given time series as sinusoidal waves of varying periods superimposed on one another. This is often applied as the short-time
Fourier transform where this transform is applied to the window of interest. Most frequency-domain features involve the total power over a given frequency band (a–b Hz) and denoted by

\[
\int_a^b |F(t)|^2 dt
\]  

(1)
where $F(t)$ represents the fast Fourier transform (FFT). The validity of this approach rests on assumptions of periodicity and stationarity (Seely and Macklem 2004), that is, where statistical properties such as mean and SD remain constant over time. The latter description is not often accurate for physiological data such as heart rate and blood pressure signals, which may exhibit local or intermittent fluctuations.

The wavelet transform is another such function, where the time series is expressed in terms of correlation at varying scales and times to a reference signal or mother wavelet. The process is described in further detail elsewhere (Ivanov et al. 1996, Torrence and Compo 1998), though can also be used to define similar components over a range of frequencies. These techniques assume stationarity and periodicity of the signal (Mansier et al. 1996) and are sensitive to artefacts, introducing bias in the calculated low frequency or high frequency components. The ranges are also not definitive and may vary depending on the individuals and other factors (Furlan et al. 1990).

2.3. Fractal analysis and power law behaviour

Fractal analysis deals specifically with self-similarity across various scales. This can manifest geometrically, as observed in many biological structures such as in the human airways (ER 1962, Horsfield and Cumming 1968), though can also manifest as statistically identical properties over time (Thamrin and Stern 2010). Any given section of a self-similar signal, when scaled to the original signal, would exhibit an identical mean and standard deviation, as demonstrated in figure 2.

Developed by Peng and co-workers, detrended fluctuation analysis (DFA) is a method used to quantify long range power-law correlations (Peng et al. 1995). It has since been applied to

Figure 3. Application of detrended fluctuation analysis, showing the divisions of the integrated mean-centred signal into various box sizes (a) and (b). (c) shows the linear trend determined for a single box, which is subsequently removed to determine the root mean-squared fluctuation. (d) shows the logarithmic plot of this fluctuation $F(n)$ against the box size $n$, the slope of which is defined as the scaling exponent $\alpha$. 

various clinical contexts, given its capacity to mitigate the effects of non-stationarities. This view has developed since the introduction of this technique, with studies to caution the risk of introducing bias in the presence of non-linear trends as well as the need for appropriate pre-processing (Bryce and Sprague 2012). Its application also requires a substantial number of data points (Seely and Macklem 2004).

The application of DFA involves several steps for a given time series $x(k)$:

(i) Integration of the mean-centred signal

$$y(k) = \sum_{j=1}^{k} x(j) - \bar{x}$$

(ii) Division of the integrated signal into boxes of equal length $n$ and each box is detrended by subtracting the local linear trend

(iii) The root mean square (RMS) fluctuation of the time series is determined using the following expression

$$F(n) = \left( \frac{1}{N} \sum_{k=1}^{N} [y(k) - y_n(k)]^2 \right)^{1/2}$$

![Figure 4](image-url)  

**Figure 4.** Illustration of approximate entropy matches and non-matches. A template pattern is defined according to pattern length $m$ which is defined by continually shifting along the window of analysis. For each of these templates, matches between the template and signal are counted when differences between the two do not exceed the defined tolerance $r$. This parameter $r$ is often expressed as a function of the standard deviation. Once the fraction of matches from all possible windows of analyses is determined for each $m$-length template, $C_m$ represents the mean of these fractions. This process is then repeated for a template of pattern length $m+1$, and the approximate entropy determined from the natural logarithm of the ratio between $C_m$ and $C_{m+1}$.
where \( y_n(k) \) is the local linear trend per box of length \( n \)

(iv) The process detailed in (2) to (3) is repeated for varying box sizes \( n \)

(v) A linear trend is fit to the log-log relationship between box size \( n \) and the RMS fluctuation \( F(n) \) to determine scaling exponent \( \alpha \)

\[
F(n) = An^\alpha.
\]  

This process is illustrated in figure 3. The scaling exponent \( \alpha \) is thought to represent stability in the system and is thus deranged in disease. There is some suggestion that either a low or high \( \alpha \) value may represent pathology (Rojo-Álvarez et al 2007), though clinical interpretation may be difficult, especially in attributing it to specific pathophysiological causes (Glass 1999). Power laws governing the distribution of inter-breath intervals, which are related to the scaling exponent \( \alpha \), have been associated with maturation in preterm and term infants (Frey et al 1998).

2.4. Approximate and sample entropy

We can also approach variability characterisation using entropy or the rate of information generated. The work of Grassberger and Procaccia (Grassberger and Procaccia 1983) on the extraction of correlation exponent \( v \) from time series data served as a precursor for subsequent entropy measures (Eckmann and Ruelle 1985). With respect to time series analysis of physiological signals, it is commonly used in the form of approximate entropy (ApEn) or sample entropy (SampEn).

ApEn was originally presented by Pincus and is a measure of logarithmic likelihood that similar patterns will be further followed by similar patterns (Pincus 1991). A time series with a low ApEn is often interpreted as having predictable or deterministic fluctuations. This statistic denotes the conditional probability that a given template pattern of length \( m \), will not be followed by a similar pattern in the proceeding time epoch, within a tolerance of \( r \). This is expressed as a fraction of the SD (Pincus 1991), as illustrated in figure 4. Discussions surrounding its use and reliability have targeted the inherent bias towards regularity as it takes into account self-matches (to avoid the possibility of \( \ln(0) \)) (Richman and Moorman 2000).

ApEn is defined according to the following equation:

\[
\text{ApEn} = \ln \frac{C_m(r)}{C_{m+1}(r)}
\]  

where \( C_m \) represents the mean fraction of matches for all possible templates of length \( m \).

In addressing the limitations of ApEn, SampEn was developed, denoting the likelihood that two similar sequences for a given window of length \( m \), remain similar at the proceeding time epoch, within a tolerance of \( r \) (Richman and Moorman 2000). The definition of SampEn also displays relative consistency. Put simply, where one record has a lower SampEn than another, this observation will be consistent for any given definition of \( m \) and \( r \) (Lake et al 2002). The application of these statistics assume stationarity (Pincus and Singer 1996) and thus requires appropriate interpretation. Reduced entropy estimates were largely due to the presence of non-stationarities (such as spikes in the data, inflating the SD and thus the tolerance for identifying matches) and not necessarily an indication of underlying complexity changes (Moorman et al 2006, 2011). Analysis is also affected by parameter selection and data length.
2.5. Cross-correlation and multi-signal approaches

The above techniques can also be extended to incorporate multiple sources of information in a single feature. Linear dependency between two simultaneously measured time series can be quantified with the linear correlation coefficient, $r$ with bounds of $-1$ and $1$, representing perfect negative and positive correlation, respectively. Running correlation coefficients can also be calculated for short window definitions, forming the basis for studies on synchronisation and functional connectivity. Cardiorespiratory synchronisation or coupling represents a more signal-specific approach, where a parameter $\lambda$ indicates the strength of synchronisation between heart rate and respiratory signals. This was found to characterise early changes in breathing control in infants (Nguyen et al. 2012).

Existing variability statistics such as ApEn and SampEn can also be extended to account for multiple signals, as in their cross-entropy counterparts, cross-ApEn and cross-SampEn. These were introduced to quantify the degree of asynchrony of two time series, where the more asynchronous the series, the higher the statistics (Pincus and Singer 1996, Pincus et al. 1996, Richman and Moorman 2000). More complex measures include multiscale entropy (Costa et al. 2002, 2005) and multiscale cross-sample entropy (Xia and Shang 2012). Interpretation of these measures needs to account for underlying dynamics and the potential influence of sampling time and selected time scales (Thuraisingham and Gottwald 2006).

The detrended cross-correlation coefficient, $\rho_{DCCA}$ (Zebende 2011), is the fractal analysis counterpart to the linear correlation coefficient that can quantify correlations in non-stationary signals (Kristoufek 2014). Extensions of this work, such as the generalised detrended cross-correlation coefficient, have been described elsewhere (Oświęcimka et al. 2014, Kwapien et al. 2015, Shen et al. 2015).

2.6. Considerations in technique selection and data collection

Technique selection ought to take into consideration the underlying assumptions of each technique, data requirements (how many data points are required, how large a dataset is required) and the impact of deviations from these assumptions. Most of the techniques described above depend strongly on assumptions of stationarity, being susceptible to bias when this does not hold. An exception to this is DFA, which was originally presented as a means of addressing non-stationarities (Peng et al. 1995), mainly through the linear detrending step. While this may be true of certain non-stationarities, there is also the potential to introduce bias in the presence of non-linear trends (Bryce and Sprague 2012). Other assumptions include those of periodicity, permitting valid transformation of a signal to the frequency domain.

Signal availability and the nature of their collection may also impose restrictions on the techniques applied. This is certainly the case for EEG, which may not be routinely monitored in the NICU environment, as well as for ECG, where sufficient separation of the electrodes may not be possible in a small-sized preterm infant, given other monitoring devices and potential irritation (Baird et al. 1992). Blood pressure can be particularly helpful, though its continuous measurement requires an invasive (umbilical or peripheral) arterial catheter. Temperature measurements, though continuously available, are not necessarily useful as deviations from the normal range may be masked by temperature-controlled incubator environments. The routine collection of oxygen saturation data from pulse oximetry and its signal availability renders it a good candidate for analysis, though acute changes in oxygen saturation have not been specifically investigated in the context of neonatal conditions such as sepsis or NEC (Sullivan and Fairchild 2015).
The use of plethysmography-derived signals within the NICU context has been limited predominantly to time domain techniques, though with varying degrees of effectiveness. Renner et al. evaluated the usefulness of respiratory variations in velocity time integral, peak flow velocity as well as the plethysmography variability index (Cannesson et al. 2008) for predicting fluid responsiveness in infants (Renner et al. 2011). There is also potential for exploring features extracted from the raw plethysmography signal, such as respiration rate or those pertaining to cardiovascular and neural fluctuations. The fluctuations from each manifest in this plethysmography signal at different frequencies, allowing each to be distinguished by their sinusoidal components (Nilsson 2013). This would be particularly beneficial for cases where ECG signals may not be available.

The presence of artefact may also confound clinical interpretation, from movement of the patient, mains contamination to the detachment of electrodes. Signal quality measures can thus help to contextualise the interpretation of these analyses. These can be applied in the form of a threshold for analysis of the selected window or as a means of adjusting the probability of prediction, as was used in a neonatal apnoea detection algorithm (Monasterio et al. 2012). Pre-processing may also play a key role, where removal of cardiac artefact from the CI signal improved neonatal apnoea detection (Lee et al. 2011) and the removal of non-linear trends facilitated valid interpretation of fluctuation analyses (Bryce and Sprague 2012). Removal of baseline wander from ECG similarly allows for accurate heart rate acquisition.

Nyquist’s theorem stipulates that the sampling frequency must be at least 2 times the highest frequency component of the signal, though the sampling frequency required for accurate and non-biased variability analysis may be higher. Motivated by computational efficiency, which is especially pertinent for real-time applications, a considerable number of studies have investigated the influence of sampling frequency on variability analysis (Merri et al. 1990, Garcia-Gonzalez et al. 2004, Ziemssen et al. 2008, Bhatia et al. 2010, Ellis et al. 2015, Choi and Shin 2017). Some have proposed analysis-driven minimum bounds for sampling frequency, such as the >25 Hz for pulse rate analysis from photoplethysmographic signals (Choi and Shin 2017), >100 Hz for frequency-domain blood pressure variability (Bhatia et al. 2010) and the caution against sampling at <12 Hz for HRV spectral analysis (Garcia-Gonzalez et al. 2004).

3. Clinical applications

Clinical applications of variability analysis are often aimed at predicting the onset of critical conditions, leveraging technology and signal processing to assist healthcare providers (Griffin et al. 2005) as well as prompting further bedside evaluation and consideration of appropriate tests or treatments (Fairchild et al. 2013). A summary of these conditions and their current incidence rates is provided in table 1.

The above techniques have been applied to a range of neonatal intensive care applications, from HRV analysis for the prediction of sepsis (Griffin and Moorman 2001, Griffin et al. 2003, Moorman et al. 2006, Sullivan and Fairchild 2015) to early developments in IVH and mortality risk prediction (Gilmore et al. 2011, da Costa et al. 2015) to ECG and EEG analysis for seizure detection (Greene et al. 2007, Greene de Chazal et al. 2007). The following sections offer an overview of variability analysis that has been applied in the context of the NICU-relevant conditions summarised in table 1.

3.1. Neonatal sepsis and necrotising enterocolitis

Neonatal sepsis is a systemic infection which remains an important cause of morbidity and mortality in preterm infants (Stoll et al. 2002). Prolonged hospitalisation may predispose
preterm infants to late-onset sepsis due to indwelling vascular catheters and incompletely developed immunity (Moorman et al. 2011). Late-onset sepsis, hereinafter sepsis, is characterised by an onset of at least 3 d following birth, often originating from the hospital or NICU environment (Boghossian et al. 2013). Risk of sepsis increases with decreasing birthweight and gestational age (Stoll et al. 2002) and is associated with PDA, prolonged mechanical ventilation, NEC and bronchopulmonary dysplasia (Neu et al. 2008).

It is diagnosed via blood culture, though this may be limited by the low sampling volume (<0.5 – 1 ml) for neonates (Goldstein et al. 2005, Connell et al. 2007) and has been associated with false positives and negatives (Volante et al. 2004, Dong and Speer 2014). Diagnosis may also not occur until after substantial deterioration or haemodynamic compromise (Sullivan and Fairchild 2015). Antibiotics are generally administered in response to confirmed sepsis or suspected sepsis on the basis of concerning signs such as increased apnoea episodes, inactivity or feeding intolerance (Sullivan and Fairchild 2015). These signs are neither very sensitive nor specific to the disease, overlapping with other conditions such as NEC.

Necrotising enterocolitis (NEC) affects the gastrointestinal tract, occurring most commonly in the small and large bowel (Henry and Moss 2009). In preterm infants, bacterial colonisation of the gut is abnormal and often delayed, which, in combination with external stressors and ischemic or hypoxic insults, may lead to mucosal injury. This may also be exacerbated by the invasion of certain pathogens, amplifying the inflammatory response (Papillon et al. 2013). Key risk factors include prematurity and formula feeding though its pathogenesis is not well-understood (Caplan 2008, Neu et al. 2008). Clinical stages can be defined according to Bell’s criteria (I to III), with the latter two stages involving significant intestinal distension and ileus as confirmed via abdominal radiography (Bell et al. 1978).

The premise for the early detection or prior to manifest clinical signs lies in the elevated levels of the cytokines which initiate sepsis or sepsis-like illnesses. These were reported by Kuster et al. to be present up to 2 days preceding clinical diagnosis (Küster et al. 1998). The general trend observed in these disease states has been a reduction in regularity, a term used interchangeably with complexity. Lake et al. observed a reduction of SampEn in the lead up to clinical diagnosis of neonatal sepsis, while acknowledging its susceptibility to noisy or large spikes in the data (Lake et al. 2002). In response to this, it was suggested that regularity based on the SampEn statistic requires interpretation alongside additional measures of complexity and non-stationarity (Lake et al. 2002).

Griffin and Moorman observed a reduction in HRV and transient decelerations in heart rate (HR) in association with neonatal sepsis and sepsis-like illnesses which preceded clinical signs and abrupt deterioration. In some cases, this lead time was as much as 24h (Griffin et al. 2005), motivating further exploration of this approach. An earlier publication of this work explored the use of time domain techniques such as the skewness of the asymmetrical RR interval histograms in discerning sepsis cases. A multicentre randomised trial using a novel HRC monitoring system was conducted, detecting both variability and transient decelerations in heart rate. Moorman et al. reported a significant reduction in mortality rates from 10.2% to 8.1% when this variability information was displayed alongside other signals (Moorman et al. 2011). A retrospective review of this study was also conducted on NEC cases in a subset of infants, with reports of significant increases in the HRC index prior to clinical diagnosis of NEC (Stone et al. 2013). This elevation from the patient-specific baselines were observed from 16 hours prior to diagnosis of NEC cases requiring surgical intervention and from 6 hours for the remaining cases (Stone et al. 2013).

Recent work in this area has also demonstrated the potential utility of cross-correlation of vital signs in early detection of sepsis and NEC (Fairchild et al. 2017). The cross-correlation between HR and SpO2 was one of the best independent predictors of sepsis and NEC,
increasing prior to diagnosis. This increase was also reported to be greater in NEC cases than in those with sepsis. The reported model including this statistic, was combined with HRC index from the HeRO monitor and found to significantly improve predictive ability (Fairchild et al 2017).

3.2. Intraventricular haemorrhage

Intraventricular haemorrhage (IVH) stands as the most prevalent intracranial haemorrhage in preterm neonates and remains a major concern in extremely preterm infants. The severity of the haemorrhage is defined by Grades I to IV of the Papile system, reflecting whether the area of bleeding is confined to the subependymal germinal matrix (I) or extends to the ventricular system (II to IV) (Papile et al 1978). Along with IVH, periventricular haemorrhagic infarction (PVHI) and cerebellar infarction are also important conditions for neurodevelopmental prognosis. With increasing survival of infants born preterm, there is a growing number of those at risk of permanent brain injury, cerebral palsy or adverse neurodevelopmental outcomes (Volpe 2008, 2009).

The preferred method for imaging the neonatal brain is cranial ultrasonography (van Wezel-Meijler et al 2010); it is highly sensitive in the detection of IVH and/or PVHI and cerebellar infarction. It allows the location and extent of the injury to be visualised (Volpe 1989a). Currently, no treatment for IVH exists, though studies identifying risk factors and pathophysiology help to guide clinical care for prevention. One such study identified a strong association between improvements in blood pressure and increased low-frequency variability in blood pressure within infants exposed to inotropes, often administered to improve mean arterial blood pressure (Vesoulis et al 2017). This variability was quantified using spectral analysis of certain low-frequency (0.005–0.16 Hz) components of the blood pressure signal and may be used as an adjunctive measure of response to these medications and potentially mitigating risk of hypertension-induced IVH (Bel et al 1987) through more optimal titration (Vesoulis et al 2017).

Pressure passivity has been observed in cases of intraventricular haemorrhage, where the cerebral circulation is affected by fluctuations in system circulation. This autoregulation was quantified by Gilmore et al (2011) using COx, a cerebral oximetry index calculated from a running window correlation of between the arterial blood pressure (ABP) and cortical reflectance oximetry. A similar approach was employed by da Costa et al (2015) in their definition of TOHRx, the running correlation between the tissue oxygenation index (TOI) as measured from near-infrared spectroscopy and heart rate (HR). Reduced complexity, as characterised by SampEn calculations over multiple time scales (multiscale entropy) was also observed in preterm infants who subsequently developed IVH (Sortica da Costa et al 2017).

In retrospective analyses of premature infants following IVH, altered autonomic functions have been observed (van Ravenswaaij-Arts et al 1991, Hanna et al 2000), as reflected by HRV analysis. The potential for predicting IVH has been explored using DFA to quantify the fractal dynamics of heart rate (Tuzcu et al 2009) as well as beat-to-beat mean arterial and systolic blood pressure (Zhang et al 2013). Both reported on increased short-term scaling exponent $\alpha_1$ in infants who subsequently developed IVH.

The impact of impaired cerebral autoregulation associated with IVH and long-term neurodevelopmental outcomes has been reported in literature (Futagi et al 2006, Bolisetty et al 2013). The dynamic nature and multiple-time-scale (MTS) properties (Zhang et al 1998, 2000) of cerebral autoregulation has recently been characterised using MTS correlation analysis of the mean arterial pressure and regional cerebral tissue oxygen saturation measured using
NIRS. Chalak et al reported associations of both in-phase short-term (15 mins) and long-term antiphase (4h) time scales with abnormal neurodevelopmental outcomes in a small number ($n = 5$) of newborns (Chalak et al 2016).

3.3. Patent ductus arteriosus

Patent ductus arteriosus (PDA) is characterised by persistence of the ductus, resulting in shunting from the systemic to the pulmonary circulation. Though this is normal at birth, functional closure of the foetal ductus generally occurs within 24 to 48h of birth (Schneider and Moore 2006). Diagnosis is usually through cardiac ultrasound, allowing the degree of constriction and nature of the shunt to be characterised. Observational studies of PDA have shown a consistent association with various adverse outcomes such as NEC and IVH. Other studies have also reported on associations with neonatal chronic lung disease and death (Evans and Kluckow 1996, Kluckow and Evans 2000, Noori et al 2009).

Several studies have been focused on how and when to treat PDA (Laughon et al 2004, Benitz 2010, Evans 2015), more so than its effect on physiological parameters such as HRV. Although the overarching question of treatment continues, variability analysis of PDA-specific data may help to characterise other conditions with which it is correlated.

3.4. Neonatal apnoea and seizures

Apnoea, the cessation of breathing, is highly prevalent among very low birthweight infants (<1500g) and often accompanied by bradycardia (HR < 100 beats per minute) and/or oxygen desaturation ($\text{SpO}_2 < 80\%$). They are considered clinical events if cessation of breathing exceeds 20s or 10s in the presence of one of the above (Finer et al 2006). An assessment of central apnoea in preterm infants supported the inverse relationship between apnoea events and gestational and postmenstrual age (Fairchild et al 2016). This study also reported an increase in apnoea events in the presence of bradycardia and desaturation prior to diagnosis of sepsis and NEC. Interestingly, such events were not more frequent in infants with IVH after adjustment for gestational age (Fairchild et al 2016).

Two main signals pertinent for neonatal apnoea detection are the chest impedance (CI) signal and the pulse-oximeter derived signal for oxygen saturation, with previous studies exploring the relationship between desaturation and apnoea (Haider et al 1995, 1996). Effective detection of apnoea based on respiration rate has often been confounded by inaccuracy of the CI signal, the presence of cardiac artefact and the fact that many infants are on mechanical ventilation (Lee et al 2011, Sullivan and Fairchild 2015). It thus depends on the capacity to identify and filter out these artefacts as well as the algorithm for classification of relevant events. Validation of one such algorithm showed over 90% agreement with clinical experts (Lee et al 2011). This approach involved both the CI and ECG signals, where cardiac artefact was filtered from the CI interval and residual fluctuations were subsequently analysed using a running standard deviation (SD). Cessation of breathing was identified in excerpts below a defined variance threshold (Lee et al 2011). Reduced HRV was also reported for preterm infants with apnoea of prematurity compared with term neonates (Henslee et al 1997).

Seizures frequently occur within the neonatal period and are often characterised by rapid changes in heart rate, respiration rate and blood pressure (Bassan et al 2008). Other subtle seizure phenomena can include altered behaviour, motor manifestations such as peculiar limb movements and apnoea. Although there have been small-scale studies on the detection of seizures based on variability, specifically using heart rate based features, the precise nature of these effects have not been clarified. Vaugh et al observed a reduction in mean heart rate
during seizure (Vaughn et al. 1995), while the converse was reported by Greene et al. in their investigations (Greene de Chazal et al. 2007). The approaches to ECG-based seizure detection have utilised features spanning multiple domains (Greene de Chazal et al. 2007, Malarvili and Mesbah 2009). These included the conventional time domain features such as mean, SD, coefficients of variation and Hjorth parameters for quantifying activity, mobility and complexity (Hjorth 1973, Malarvili and Mesbah 2009, Oh et al. 2014). Various frequency domain coefficients of power spectral density were also extracted (Greene et al. 2008, Temko et al. 2011).

Although EEG-based approaches have been explored for adult seizures (Gardner et al. 2006, Srinivasan et al. 2007), similar studies have only recently been conducted on the neonatal population, with EEG not routinely monitored in the NICU. An example of this is the early work by Lommen et al. in developing an algorithm for automated neonatal seizure detection. They used frequency analysis for identifying artefacts and reported a rise in the lower boundary of the amplitude-integrated EEG signal during seizures in the studied newborns \( n = 13 \) (Lommen et al. 2007). Continuous changes inherent in the developing brain may render EEG results difficult to interpret at this stage and there are additional technical considerations when recording from a neonatal (therefore, small) scalp, ranging from skin resistance to the pathologically-bound states of activity.

There also remains the question of treatment and early interventions following detection, with potential neurotoxic risks of commonly used seizure medications (Bittigau et al. 2002), especially given the lack of definitive evidence linking reduced seizure burden with neurodevelopmental outcomes (Glass et al. 2012).

4. Remaining questions and future directions

A summary of the parameters relevant for each condition and evidence for observed patterns in variability is presented in tables 1 and 2.

4.1. Multidimensional approaches for identifying key features and classifying disease

Studies and reviews on variability analysis techniques continue to emphasise the need for multiple techniques rather than a consensus on the use of a single approach (Seely and Macklem 2004). Once these individual features have been extracted, it is necessary to evaluate their relevance (feature selection) as well as consider approaches for combining this information (feature classification).

Feature selection methods can be employed to improve model performance as well as mitigate risks of overfitting to the data. These algorithms can be broadly categorised as filter, wrapper and embedded approaches which have been reviewed in detail elsewhere (Saeyes et al. 2007, Hira and Gillies 2015). Their use must also take into consideration computational efficiency, specificity to the selected classification algorithm as well as the nature and number of features extracted.

In terms of classification, approaches range from multivariable logistic regression models and Bayesian models to decision trees, support vector machines and artificial neural networks, the details of which have been extensively reviewed (Michie et al. 1994, Kotsiantis et al. 2007).

At this stage, a considerable proportion of NICU-specific variability analysis has focused on single-parameter models, with an expanding breadth of application for HRV analysis. This is particularly true of approaches to identifying sepsis, NEC and IVH cases. A natural path for development and improved robustness in this area lies in multivariate models and the combination of features which have independently been shown to be predictive of such conditions.
Table 2. Parameters and their use in intensive care and predictive monitoring. Use of various signals including arterial blood pressure (ABP), tissue oxygenation index (TOI) and electroencephalography (EEG).

<table>
<thead>
<tr>
<th>Technique</th>
<th>Parameter</th>
<th>Signals applied to</th>
<th>Physiological interpretation; clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple statistical measures</td>
<td>Standard deviation (SD)</td>
<td>HRV (RR intervals)</td>
<td>Reduced SDRR interpreted as reduced variability of RR</td>
</tr>
<tr>
<td></td>
<td>Percentage of absolute difference between consecutive RR &gt; x ms</td>
<td>HRV (RR intervals)</td>
<td>Reduced pNNx indicates lower variability; used to monitor cardiac parasympathetic activity (Ewing et al 1984)</td>
</tr>
<tr>
<td>Hjorth parameters</td>
<td>Variance of the time domain or signal power in the frequency domain ($\sigma^2$)</td>
<td>HRV, EEG (Malarvili and Mesbah 2009, Oh et al 2014)</td>
<td>Measures activity; used in neonatal seizure detection from ECG-based HRV (Malarvili and Mesbah 2009)</td>
</tr>
<tr>
<td></td>
<td>Ratio of SDs from the first derivative and original signal ($\sigma_d/\sigma$)</td>
<td>HRV, EEG (Malarvili and Mesbah 2009, Oh et al 2014)</td>
<td>Measures mobility; used in neonatal seizure detection from ECG-based HRV (Malarvili and Mesbah 2009)</td>
</tr>
<tr>
<td></td>
<td>Change in frequency ($\sigma_{dd}/\sigma_d$)</td>
<td>HRV, EEG (Malarvili and Mesbah 2009, Oh et al 2014)</td>
<td>Measure complexity as deviation from pure sinusoidal wave; used in neonatal seizure detection from ECG-based HRV (Malarvili and Mesbah 2009)</td>
</tr>
<tr>
<td>Poincaré/ recurrence plots</td>
<td>Standard deviations perpendicular to and along the line of identity, reflecting short and long-term variability (SD1, SD2)</td>
<td>HRV (RR intervals)</td>
<td>Ratio between SD1/SD2 possible surrogate measure of sympathovagal balance (Hoshi et al 2013)</td>
</tr>
<tr>
<td>Frequency/ power spectrum</td>
<td>Integral of the power spectrum from Fourier or wavelet transform, partitioned into very low (VLF), low (LF) and high frequency (HF) power bands</td>
<td>HRV</td>
<td>VLF of HRV associated with mortality (Bigger et al 1992); LF with both sympathetic and parasympathetic inputs; HF of parasympathetic activity</td>
</tr>
<tr>
<td>Entropy</td>
<td>Approximate entropy (ApEn) quantifying likelihood that similar patterns remain close in adjacent comparisons (Pincus 1991)</td>
<td>HRV, EEG (Beuchée et al 2009, Srinivasan et al 2007)</td>
<td>In HRV, decreased ApEn used in identifying sepsis in premature infants (Richman and Moorman 2000, Beuchée et al 2009), though with reference to other parameters</td>
</tr>
</tbody>
</table>

(Continued)
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Parameter</th>
<th>Signals applied to</th>
<th>Physiological interpretation; clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample entropy (SampEn)</td>
<td>quantifying self-similarity in matches; similar to ApEn but excluding self-matches (Richman and Moorman 2000)</td>
<td>HRV (Lake et al 2002)</td>
<td>In HRV, SampEn observed to decrease prior to clinical signs of neonatal sepsis (Lake et al 2002), though may be reflective of increased non-stationarity (Cao et al 2004)</td>
</tr>
<tr>
<td>Detrended fluctuation analysis</td>
<td>Scaling exponent ($\alpha$) quantifying fractal-like self-similarity in fluctuations across time scales</td>
<td>HRV, ABP (Tuzcu et al 2009, Zhang et al 2013)</td>
<td>Fractal patterns demonstrated in heart rate and blood pressure variability (Tuzcu et al 2009, Zhang et al 2013, Fairchild et al 2014)</td>
</tr>
<tr>
<td>Running correlation</td>
<td>Correlation coefficient ($r$) between two signals applied on a running window basis</td>
<td>ABP and oximetry (Gilmore et al 2011), TOI and HR (da Costa et al 2015), MAP and cerebral tissue oxygenation saturation (Chalak et al 2016)</td>
<td>In oximetry, used to characterise cerebral autoregulation changes, associated with IVH (Gilmore et al 2011). In TOI versus HR, used to define optimal, patient-specific blood pressure ranges for potentially identifying morbidity/mortality risk (da Costa et al 2015). In MAP versus cerebral tissue oxygenation saturation, used to characterise cerebral autoregulation over time (Chalak et al 2016)</td>
</tr>
<tr>
<td>Phase synchronisation</td>
<td>Degree to which two signals oscillate together ($\lambda$)</td>
<td>HRV and respiratory rate variability (Nguyen et al 2012)</td>
<td>Used to characterise cardiorespiratory coupling/decoupling, possible indicator of stability in critical conditions (Nguyen et al 2012)</td>
</tr>
</tbody>
</table>
This is further motivated by the understanding these conditions are systemic and manifest in ways that are not limited to a single physiological parameter, spanning cardiac signals to respiration rate, arterial blood pressure and oxygen saturation. Their application however is not without unique consideration—respiration rate, for example, may be confounded by mechanical ventilation in the NICU context.

HRV and respiration rate variability have been independently shown to offer predictive potential in the NICU context and may offer improved prediction performance through combination with each other or other informative features. This approach was adopted by Green et al in the discernment of adult organ dysfunction cases and severity characterisation (Green et al 2013). ECG and EEG-based features were also combined and reported to improve automatic neonatal seizure detection (Greene et al 2007).

From a classification standpoint, multiclass classifiers also present opportunities to characterise the severity of these conditions. IVH for example, is a suitable candidate for such classification, given the staged approach to its diagnosis using the four-grade Papile system (Papile et al 1978). Similar approaches to identifying the severity of septic shock in the case of neonatal sepsis may also be possible. Among the available approaches for classification, there are also varying degrees of complexity. These range from simpler logistic regression models to the integration with support vector machines (Temko et al 2011, 2012) and neural networks (Srinivasan et al 2007).

4.2. Clinical interpretation

There are a number discussion points surrounding the clinical applications of variability analysis. Although variability studies may have demonstrated potential to distinguish or classify disease states on this basis, there remains the challenge of physiological interpretation of these differences. Changes in indices of variability may not necessarily indicate a physiological change in system control.

One such example is found in the interpretation of the frequency components of HRV which was highlighted early on by the task force paper (Malik 1996). The higher frequency component has been associated with parasympathetic input, though there remains conjecture around the interpretation of the lower frequency component. It is thought to be reflective of both sympathetic and parasympathetic activity (Eckberg 1997, Longin et al 2005, Billman 2007, Shaffer et al 2014) by some, and an indicator of sympathetic excitation by others (Malliani et al 1991, Montano et al 2009), though this evidence mostly stems from investigations of orthostatic tilt effects on HRV (Reyes del Paso et al 2013). The interpretation of such HRV changes also requires consideration that these components may be influenced by both non-neural and autonomic mechanisms and their valid interpretation may be reliant on controlled studies and specific populations (Lombardi 2011).

Another example is the scaling exponent $\alpha$ from DFA, which can be defined for short and long-term ($\alpha_1$ and $\alpha_2$, respectively) ranges. Modelling has aided the understanding of how changes in sympatho-vagal activity can impact these exponents calculated for HRV (Rojo-Álvarez et al 2007), while studies using vagal blockade by atropine have demonstrated an increase in the short-term scaling exponent of blood pressure fluctuations (Castiglioni et al 2011).

These studies have helped to clarify the mechanisms that may influence parameters from advanced analyses, although in practice, clinical application and interpretation is often difficult. Associations between variability parameters and respective pathophysiology may be confounded by external influences, such as medically-induced interventions altering the underlying dynamics of the data or mechanical ventilation in the interpretation of respiratory
variability parameters. Another factor is limitations in the data acquired, e.g. lack of precision in heartbeat detection for HRV or air flow or breath timing for respiratory variability analyses, missing data or insufficient length of monitoring, presence of artefacts, linear or non-linear trends or violation of assumptions behind the analysis techniques. Finally, there is also the possibility that these techniques are simply unable to capture the underlying mechanisms for changes in pathophysiology.

Although the exact mechanisms of influence may be unknown and under investigation, we may continue to develop an understanding of how variability patterns and their links to the onset of conditions such as neonatal sepsis, seizures and IVH.

4.3. Other emerging applications

Characterising physiological variability can also extend beyond neonatal conditions and the onset of diseases; it has also been applied in the prediction of extubation-readiness in neonates, with Kaczmarek et al reporting significant HRV reductions in those who failed extubation (Kaczmarek et al 2013). This becomes particularly important when considering the increased incidence of neurodevelopmental problems linked to prolonged mechanical ventilation (Walsh et al 2005). A cardiorespiratory approach was also used in this area (Precup et al 2012), where frequency-based features of HRV and parameters measured using respiratory inductive plethysmography were combined for training support vector machine classification.

Several monitoring systems and software have been developed, grounded in the work on clinical/physiological variability analysis. The previously described HeRO monitor represents a more neonate-specific development, although recent years have seen the introduction of continuous individualised multiorgan variability analysis (CIMVA) software. This computes features (such as HRV and respiratory rate variability) using a range of variability analysis techniques and accepting input from multiple physiological waveforms (Bravi 2013). Systems such as these highlight the potential to support clinical decision-making and risk assessment, though there remains the question of the extent to which they impact and are responsible for the final decision. While specific medical claims are not made in relation to these technologies, they may still be introduced to these settings as objective tools for clinicians to improve prognostication and guide interventions (Seely and Macklem 2004).

5. Conclusion

The neonatal intensive care environment presents many unique challenges to monitoring and management of its patients, from the criticality of the conditions faced, the abrupt and sudden nature of changes in system state as well as the long-term implications of the treatments done at this stage of life. The availability of physiological signals and monitoring systems in the NICU establishes a foundation for further signal processing. Variability analysis techniques can be utilised to capture short- and long-term data trends, develop markers for risk as well as assist understanding of the patterns associated with the onset of illness and other critical conditions. In an appropriate context and with sufficient validation, these techniques offer caregivers more time in responding to and treating critically-ill patients.

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Original Article

Age-stratified trends in 20 years of stress incontinence surgery in Australia

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Background: Stress urinary incontinence (SUI) is a common, debilitating condition in Australian women. Since its introduction in 1998–1999, the less invasive mid-urethral sling (MUS) procedure has become the new standard for surgical correction of SUI and overall numbers of continence procedures increased. Trends since 2009 have not been analysed.

Aims: To identify patterns in the surgical treatment of women with SUI in Australia from January 1994 to December 2014 stratified by age.

Materials and Methods: Gender- and age-specific data from Medicare Australia between January 1994 and December 2014 were extracted and the patterns of SUI surgery analysed for the 20-year period. Data on gynaecologists and urologists performing MUS and colposuspension were collected from Department of Human Services.

Results: Following the introduction of MUS, total SUI operations increased with the peak in 2002, a plateau between 2006 and 2011, and a new decline from 2012 onwards. There has been a sustained 51.7% increase in total SUI operations in 75- to 84-year-old women, and a 105.2% increase in women aged over 84. However, SUI operations in 45- to 64-year-olds decreased below pre-MUS baseline in 2014.

Conclusions: Mid-urethral sling has become the standard SUI procedure being performed in Australia since its introduction in 1999. SUI operations have increased each year for patients aged over 65, with the greatest increase seen in patients aged over 84 – indicating expanded eligibility for SUI surgery in older women. However, since 2010, there has been a fall in SUI operations to below the pre-MUS baseline.

Key words: Burch colposuspension, incontinence surgery, mid-urethral sling, pelvic floor surgery, stress urinary incontinence.

Introduction

Surgical correction is a key solution to treating stress urinary incontinence, which has not responded to conservative treatment. Since the introduction of the mid-urethral sling (MUS) operation to Australia in late 1998, it has superseded more complex approaches as the new standard of care.1 The relative simplicity and improved risk profile of this less invasive option contributed to its overwhelming adoption and to an increase in total stress incontinence procedures internationally.2–4

In Australia, a previous audit of Medicare data between 1994 and 2009 found that Stress urinary incontinence (SUI) procedures performed in Australia almost doubled with the introduction of MUS, with the greatest increase in women aged over 55.5 This would suggest that patients previously felt to be unsuitable for an open abdominal continence procedure, such as the Burch colposuspension, were now being offered this minimally invasive surgical option. However, this does not necessarily account for the significant increase in the rate of continence surgery in the 35- to 54-year age group and could indicate other factors at play, such as patient and surgeon enthusiasm.

Audits in Australia and abroad5–8 charted an initial spike in SUI operations following the introduction of the MUS, with the years following reaching a plateau slightly above the previous pre-MUS baseline. The aim of our study was to further monitor patterns in SUI surgery in Australia and to consider possible contributory factors.

Materials and Methods

Data of stress incontinence procedures between January 1994 and December 2014 were extracted from Medicare Australia. Australian population data for women aged over 24 years for the years during the study period were sourced from the Australian Bureau of Statistics and

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Received 3 December 2015; accepted 9 January 2016.
stratified in age brackets 25–34, 35–44, 45–54, 55–64, 65–74, 75–84 and greater than 84. Trends were further assessed by ‘operations per 100 000 population’, to account for population growth and ageing between 1994 and 2015. This was calculated by dividing annual operations by population in each age bracket.

Surgery rates were divided into MUS and ‘other continence procedures’, which included all non-MUS surgical options for stress incontinence treatments (excluding periurethral bulking injections). Total continence procedures per year were also analysed by age.

Data on gynaecologists and urologists performing MUS and colposuspension were collected from the Department of Human Services for period 1998–2013 inclusive.

Data were imported and analysed with IBM SPSS Statistics 20 statistical software, and results were examined for statistical significance.

As this study conforms to the standards established by NHMRC for ethical quality review, ethics approval was not sought.

Results

Trends in SUI procedures between 1994 and 2014

Figure 1 shows the overall trend in all female SUI operations from 1994 to 2014, across all age brackets. There was an initial increase in the rate per 100,000 population relative to that in 1999 in the first few years (2000 through 2002). However, this relative increase in operation rate peaked in 2002 (41% higher than in 1999, [95% CI 36% to 46%]). Since then, the annual operation rate has declined over time, and by 2012, there was no statistically significant difference from the rate observed in 1999 when sling operations were introduced ($P = 0.111$) which persisted into 2014.

Since the initial peak in continence procedures in 2002 following the introduction of MUS, there has been a consistent decline in the rate of operations per 100 000 population in the 45–54 and 55–64 age brackets (Fig. 2). In 2014, rates of SUI operations in 45- to 54- and 55- to 64-year-old patients had fallen below pre-MUS introduction rates (21.1% and 23.5% less, respectively, when compared with 1998) – following the 2002 peak increase of 33% in 45- to 54- and 42% in 55- to 64-year-olds. A significant drop was observed in 2014 in SUI operations being performed in 25- to 34-year-olds, 39.8% less than in 1998.

In contrast, total continence procedures have either increased or remained steady since the 2002 peak in patients 34–45 years and greater than 65 years, and stayed above the pre-MUS introduction baseline. In particular, there has been a 51.7% increase in total SUI operations in 75- to 84-year-old women, and a 105.4% increase in women aged over 84, since the introduction of MUS in 1999.
Figure 3 charts the absolute number of total continence procedures in each age group, not as a proportion of per 100,000 population, since the introduction of the MUS in 1999. The peak in total operations peaked in 2006 for 45- to 64-year-old women, rather than 2002 when viewed in proportion to population. It should be noted that population growth was significantly higher in 45- to 64-year-old women between 1998 and 2014 in comparison with other age groups and therefore helps to explain the difference. Otherwise, absolute figures steadily increased for patients 65 years and over.

**Trends in specialist performance of SUI procedures between 1994 and 2014**

Gynaecologists and urologists have traditionally both treated female urinary incontinence. Any change in surgical practice by one of these craft groups could explain changes in the rate of surgical procedures. Figure 4 shows the ratio of MUS and colposuspension procedures performed by gynaecologists compared to urologists, each year between 1998 and 2013. There has been a persistent increase in the ratio of MUS performed by gynaecologists since it was introduced, peaking in 2008. In comparison, a variable pattern can be observed in colposuspension of the same period, with an overall increase, but marked spikes in 2010 and 2012.

While overall numbers of colposuspension procedures declined over the study period, the proportion performed by gynaecologists remained between 80 and 95%. There was no consistent change in any of the age brackets. The percentage of MUS procedures performed by gynaecologists vs. urologists increased initially as MUS became the primary SUI procedure and has remained at just over 90%. This pattern is consistent across each age bracket other than for patients over 84.

These data demonstrate that the absolute and population-adjusted increase in stress urinary incontinence surgery was driven predominantly by an increase in procedures performed by gynaecologists.

**Discussion**

Mid-urethral sling has become the standard SUI procedure being performed in Australia since its introduction in 1999. This is consistent with similar trends in the USA, UK and Asia.6–8 In the years following introduction of the MUS, there was a peak in total SUI operations in 2002, a plateau between 2006 and 2011, and a new decline from 2012 onwards. Traditional SUI operations such as the Burch colposuspension and pubovaginal sling have been all but replaced by the less invasive MUS.

Since 2012, the overall rate of SUI operations in Australia has begun to decrease towards the pre-MUS baseline. Interestingly, this decrease is not consistent across all age groups. The greatest relative increase in SUI operations (although absolute numbers remains small) is...
Figure 3 Total continence procedures stratified for age, per year since 1998.

Figure 4 Mid-urethral sling and Colposuspension – ratio performed by gynaecologists and urologists between 1998 and 2013.
seen in patients aged over 84, while total SUI operations in patients aged between 45 and 64 have fallen below pre-MUS introduction levels.

**MUS caused a dramatic spike in total SUI operations in Australia**

The introduction of the MUS operation in Australia created a dramatic peak in SUI operations across all age groups by 2002. This pattern is accounted for by a progressive rise in MUS operations being performed on top of the steady rate of other continence procedures, which was relatively unchanged between 1999 and 2002 (prior to being largely replaced by MUS in 2006). This indicates that MUS alone increased the number of patients undergoing surgical treatment for SUI.

Surgeons appear to have become more enthusiastic to treat SUI patients surgically once MUS was introduced. It was a new, exciting technology which, unlike traditional continence surgery, was comparatively easy to learn. So, the initial spike in SUI operations following the introduction of the MUS may have represented a rush to operate on ‘low-hanging fruit’. That is, women diagnosed with SUI that was not severe enough to warrant more major abdominal surgery but where both patient and surgeon were happy to proceed with less invasive surgery once MUS was available. This is consistent with an American study showing there had been a 27% increase in the rate of surgical management of SUI since 2000 in women aged 18–64.11 It is important to note that in Australia, the steepest rate of increase in the 5–6 years after introduction of the MUS was in the 45- to 64-year age group who would in most cases have easily tolerated a retropubic surgical approach. Analogous to the slightly more recent situation with vaginal mesh repairs, it is noteworthy that over 8000 Australian women had undergone a MUS procedure before the first randomised trial comparing colposuspension with the MUS was published in 2002.12

**Gynaecologists perform the majority of SUI procedures**

We also investigated the practice patterns of the two groups traditionally performing continence surgery – gynaecologists and urologists – for any change contributing to these trends. Throughout the observation period, gynaecologists have always performed more SUI procedures than urologists. While urologists initially performed just under 30% of MUS in the immediate period following introduction, within five years, over 90% of MUS were being performed by gynaecologists and it has stayed at that level since. Conversely, while the majority of colposuspension is also performed by gynaecologists, there appears to be no specific pattern in annual fluctuations – this is likely due to the limited number of procedures performed. Overall, the data and that the spike in SUI procedures after 1998 were due to an absolute increase in MUS surgery performed by gynaecologists. Given the numbers involved, it is most likely that this was because of the rapid adoption of the new MUS procedure by surgeons not previously performing significant numbers of continence procedures. A recent audit in Taiwan demonstrated that gynaecologists performed more MUS operations compared with urologists,13 despite urologists likely seeing more SUI patients.

**Introduction of the MUS has increased SUI operations in older patients**

Our results also demonstrate that the introduction of the less invasive MUS has allowed treatment of older patients, who were much less likely to be candidates for traditional procedures such as Burch colposuspension or pubovaginal fascial slings. The sustained increase on pre-MUS baseline for patients aged over 65 (rather than a peak and fall pattern) represents a new group of patients who were previously not suitable for more invasive SUI surgery but are candidates for MUS. Most notably, women aged over 84 experienced the greatest relative increase in SUI procedures since the introduction of the MUS (135.2%) although overall numbers remain small. Recent literature found MUS to be safe in patients older than 80 years.14,15 However, there is ongoing debate as to whether the risk of postoperative complications is greater in patients aged over 65 (or due to the increased presence of comorbidities).16,17

**SUI operations have declined below pre-MUS baseline in 45- to 64-year-olds**

However, despite an increase in total SUI operations for older age groups, the overall number of SUI operations has begun to decline from the post-MUS baseline since 2010. This decrease is almost exclusively due to a decline in SUI operations in women aged between 45 and 64 (where SUI has the highest prevalence18), while rates in other age groups remain more steady. SUI operations in women aged between 45 and 64 have in fact dropped below pre-MUS figures. This fall has occurred in MUS procedures without any corresponding increase in other continence procedures.

Initial thoughts may conclude that this fall is due to patients being operated on earlier than they otherwise would be, due to greater eligibility for the MUS operation. That is, patients are now being treated at 44, as opposed to 54, and therefore, there are less women to operate on between 45 and 64. However, examination of the absolute SUI operation figures in patients under 45 (to account for population shifts across age groups) does not reveal enough of an increase to confirm this hypothesis.

This pattern may be accounted for by recent recommendations for early SUI to be treated conservatively, and often in primary care.19 Nonsurgical management of SUI has been demonstrated to be

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beneficial, cost-effective and have minimal side effects in the years since the introduction of the MUS. Since 2010, NICE,22 the Canadian Urological Association23 and American College of Obstetrics and Gynaecology24 have amended their guidelines for SUI to emphasise the role of conservative and pharmaceutical management in low-risk patients prior to offering surgery. Conservative treatment (such as pelvic floor exercises) and lifestyle modifications are now recommended as first line treatment for women with SUI and can temporarily or permanently delay surgical management.20,25 As a result, patients with a mild first presentation of SUI are likely to be treated nonsurgically initially, and only escalated to MUS once these measures have failed.26 Recent literature also confirms the increasing role of primary care in the management of early SUI in young women over immediate referral to a specialist gynaecologist,27,28 which could also explain the concurrent increase in SUI operations in older age groups, who have failed first line nonsurgical options. However, it is unclear why this should disproportionately affect women in the 45- to 64-year age group.

Another factor may be the negative publicity around surgical mesh placement for pelvic organ prolapse, which may have confused patients who were offered MUS. The FDA issued a public statement warning of the risks of mesh repair for pelvic organ prolapse in 2011, amid widespread international news coverage.29 This negative publicity spread in Australia29 since 2011 and has led to a class action against mesh manufacturer Johnson and Johnson. Personal injury litigation firms have broadcast the dangers of mesh pelvic surgery without distinguishing this from slings. Although difficult to confirm, the fall in SUI operations from in 2010–2011 coincides with the beginning of the media coverage surrounding the dangers of surgical mesh for pelvic organ prolapse. Therefore, it is reasonable to expect that the negative press has affected public perception of SUI surgery in general leading to a decrease in demand for elective procedures such as MUS.

Limitations of study

The use of Medicare data introduces limitations to the results of our study. Medicare data only record trends in the private sector, which may differ from trends in the public sector (where less elective procedures are performed). Equally, Medicare data do not offer any insight into the different types of MUS being used across the age groups or whether patients were previously unsuitable for traditional procedures. However, it is likely that private practice represents a significant proportion of elective SUI operations and is therefore a reliable measure of SUI surgery trends.

Conclusion

It is clear that MUS is the new standard in SUI surgery and has undoubtedly brought about major quality of life improvement for hundreds of thousands of women worldwide. In particular, its introduction appears to have increased access to surgical correction of SUI for older patients who were poor candidates for more invasive traditional procedures. This audit is the first Australian study to demonstrate a falling trend towards pre-MUS baseline levels for SUI operations, and further monitoring is required. However, the rapid adoption of the MUS procedure before strong clinical data, the early significant increase in surgical treatment and the recent decline in SUI operations (at least for women between 45 and 64 years) may have lessons for us about how and why we incorporate changes into our surgical practice.

Acknowledgement

None.

References


A low intensity dietary intervention for reducing excessive gestational weight gain in an overweight and obese pregnant cohort

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Received: 13 June 2018 / Accepted: 15 August 2018 © Springer Nature Switzerland AG 2018

Abstract

Purpose Excessive gestational weight gain is associated with detrimental outcomes to both the mother and baby. Currently, the best approach to prevent excessive gestational weight gain in overweight and obese women is undetermined. The present study aimed to evaluate the effectiveness of a group-based outpatient dietary intervention in pregnancy to reduce excessive gestational weight gain.

Methods In this retrospective study, overweight and obese pregnant women who attended a single 90-min group education session were compared to women who received standard care alone. Total gestational weight gain, maternal and neonatal outcomes were compared between the intervention and control groups. Data were analysed using Student t, Mann–Whitney and Chi-squared tests as appropriate. A 24-h dietary recall was analysed and compared to the Australian National Nutrition Survey.

Results A significant reduction in gestational weight gain was observed with this intervention (P = 0.010), as well as in the rate of small for gestational age births (P = 0.043). Those who attended the intervention had saturated fat and sodium intake levels that exceeded recommendations. Intake of pregnancy-specific micronutrients including folate, calcium and iron were poor from diet alone.

Conclusions A low-intensity antenatal dietary intervention may be effective in reducing excessive gestational weight gain, although multi-disciplinary interventions yield the best success. Further research is required to identify the optimal modality and frequency to limit excessive gestational weight gain. Dietary interventions tailored to ethnicity should also be explored.

Level of evidence Level II, controlled trial without randomization.

Keywords Gestational weight gain · Maternal health · Nutrition therapy · Obesity · Pregnancy

Introduction

Overweight and obesity have been deemed a major public health issue in Australia [1]. The group at greatest risk for weight gain is young female adults and pregnancy can further modify women’s future weight gain trajectory [2]. Rates of overweight and obesity in women of a reproductive age are reported to be approximately 50% in Australia and other developed countries and the prevalence of obesity in all classes amongst pregnant women has increased [3]. Furthermore, 45% of the population in the Western Sydney Local Health District are of culturally and linguistically diverse backgrounds, with 22% being of Southern Asian descent [4, 5]. These individuals have an increased susceptibility to central adiposity and cardio-metabolic complications, adding to the likelihood of adverse health outcomes [6].

The Institute of Medicine (IOM) recommends a weight gain of 7–11.5 kg for overweight and 5–9 kg for obese pregnant women, based on pre-pregnancy BMI [7]. Substantial evidence has documented the link between excessive gestational weight gain (GWG) and poor maternal and neonatal outcomes [8–10]. The prevalence of excessive GWG in Australia is reported to be 38% [11]. There is worrying evidence that the obesogenic intrauterine environment programs the
offspring to be at risk of overweight or obesity and chronic diseases during childhood, adolescence and adulthood [9, 10, 12]. Women who limit their excessive GWG reduce the risks of these detrimental outcomes. Prenatal care providers are most effective in reducing excessive GWG [13] and the antenatal period is an ideal stage for intervention, as this period is when women are more receptive to health messages and are in regular contact with health practitioners [14].

Evidence is contradictory on the efficacy of interventions to limit GWG. While some studies conclude that the effects of intervention are unclear [15], others, including a recent Cochrane review, support notion that diet and exercise can decrease the rate of excessive GWG [7, 8, 16, 17]. Of related importance, little data exists on the macronutrient composition of diets associated with excessive GWG. A systematic literature review has highlighted the need for further research on this topic [18]. Adequate micronutrient intake preconceptionally and antenatally is of importance due to its influence on fetal growth and birth outcomes, with previous research indicating that obese pregnant women demonstrate poor dietary compliance to key micronutrients for pregnancy (calcium, iron, folate and vitamin D) [19]. In addition, micronutrient status may be further compromised by the impact of obesity itself on metabolic pathways, such as by reducing plasma folate levels [20].

The primary aim of this study was to evaluate the effectiveness of a group-based outpatient dietary intervention to reduce excessive GWG, poor maternal and neonatal outcomes were also explored. The secondary aim was to examine the nutritional composition of the diet of the intervention group and compare the results to published national data.

Materials and methods

This retrospective study was designed and conducted with ethics approval from the institution’s human research ethics committee and was performed in accordance with the declaration of Helsinki [21]. The study comprised of overweight or obese pregnant women who attended an antenatal clinic at a large tertiary hospital, between January and December 2015. Women were included in the study if they were aged 18 or older, between 10 weeks and 18 weeks gestation, and were overweight (BMI 25–29.99 kg/m²) or obese (BMI of ≥ 30 kg/m²). Women were excluded from the study if they had pre-existing diabetes, a diagnosis of gestational diabetes before the education session or a self-reported medical or psychiatric condition. The women’s BMI was calculated at the first antenatal appointment, occurring between 10 weeks and 16 weeks gestation. Midwives and obstetricians referred eligible women to the intervention. Gestational weight gain was defined as weight at final pregnancy antenatal visit minus the self-reported pre-pregnancy weight. The participants were classified as having excessive GWG if they exceeded the IOM guidelines for overweight (7–11.5 kg) or obese (5–9 kg) women [7]. Based on earlier studies conducted at the site, a sample size of 111 in each group will have 90% power to detect an average difference at 3.5 kg in GWG between the intervention vs the control arm, assuming a common standard deviation of 8 kg for observed weight gain (two sample t test, 5% two-sided significance level).

The intervention group received a single 90-min antenatal group dietary education session run by a dietitian. This included recommendations such as appropriate pregnancy nutritional requirements (based on the Australian Guide to Healthy Eating), strategies to limit sugar and fat consumption, how to deal with non-hungry eating and how to meet physical activity requirements. The control group being those who did not attend, received standard care and no intervention by a dietitian. Medical and obstetrical history of all patients was obtained from patient charts. Active tobacco use in the first half of the pregnancy was self-reported using questions from the 5A’s framework for smoking cessation [22].

A trained senior clinical dietitian collected a 24-h food recall once at the time of the intervention and analysed data for the first 50 patients in the intervention group using Foodworks nutrient analysis program (Xyris Software Australia). A 24-h food recall was used as the dietary collection method due to time constraints in a group setting and having limited communication with participants prior to and post intervention. The nutritional profiles of the participants were compared to the pregnancy category nutrient reference values (NRV) for Australia and New Zealand, which is a set of recommendations for nutrient intake based on currently available scientific knowledge. Estimated average requirement (EAR) is a daily nutrient level estimated to meet the requirements of half the healthy individuals of a population. The acceptable macronutrient distribution range (AMDR) is the recommendation for the proportion of energy derived from for protein, carbohydrate and fat in an individual’s diet believed to reduce risk of chronic disease. Adequate intake (AI) is a daily nutrient intake level, based on lower level evidence than EAR, above which daily nutrient intake is assumed to be adequate. EAR, AMDR and AI were used to identify the prevalence of inadequate nutritional intake within this group [23]. After the analysis of dietary data, micronutrient supplementation was added into Foodworks and the intake of those who attended the intervention was compared to the Australian National Nutrition Survey (NNS) 2011–2012 results of women who were aged 19–50 years old [24].

IBM SPSS version 23 (IBM Corporation, New York) was used to analyse the data. Two-tailed tests with a significance level of 5% were used throughout. Continuous variables were summarised using mean±standard deviation (SD) or,
for skewed distributions, median and lower to upper quartile (Q1–Q3). Student $t$ or Mann–Whitney tests were used as appropriate to test for differences in the distribution of continuous variables between groups. Chi-squared or Fisher’s exact tests as appropriate were used to test for association between categorical variables. The potential confounding variables, parity, country of birth and tobacco use, showed substantial imbalance between intervention and control groups. General linear models for continuous outcomes and multiple logistic regression models for dichotomous outcomes were used to adjust for the effects of these potential confounders. Both unadjusted and adjusted $P$ values are reported.

**Results**

A total of 231 women participated in the study, 118 women in the intervention group and 113 in the control group. Baseline maternal characteristics of the intervention and control groups can be seen in Table 1. Nearly half the intervention groups were nulliparous compared to one-third of controls. Baseline imbalances presented in country of birth, 11% more women born in Australia and New Zealand elected not to attend the education session and a disproportionate number of Southern Asian born women chose to attend the session. Active tobacco use in the first half of the pregnancy was 12.6% greater in the control group in comparison to the intervention group (Table 1).

Table 2 summarises the maternal and neonatal outcomes for the intervention and control groups. Both the unadjusted effect of intervention vs control and the effect adjusted for the potential confounding variables, parity and country of birth, are presented. In the intervention group, 25 (26%) women gained less than the IOM guidelines and 48 (49%) gained more, while in the control group 15 (16%) gained less and 52 (54%) gained more. Of the 40 women who gained less weight than the IOM recommendations, only 2 (5%) had babies born SGA. Gestational diabetes mellitus (GDM) occurred in 16% of cases overall, with no significant difference in rate whether attending the intervention or not (21 vs 15, respectively, $P=0.27$).

Table 3 summarises the nutritional intake of the subsample. In a majority of participants whose dietary data were analysed, the energy, carbohydrate and fat intakes were less than reported by the NNS [24]. The intervention group consumed more than the EAR recommended for protein and the AMDR recommended for saturated fat [23]. Micronutrient compliance of the women that attended the clinic was adequate only after adjusting for the use of supplementation. Based on dietary intake alone of those who attended the intervention, 20% met the folate EAR requirement, 2% met the iron EAR and 34% met the EAR for calcium. Sodium intake also exceeded the AI with 98% consuming above recommendations [23].

<table>
<thead>
<tr>
<th>Table 1 Maternal baseline characteristics</th>
<th>Intervention ($n=118$)</th>
<th>Control ($n=113$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal weight, mean (SD) (kg)</td>
<td>93.7 (17.2)</td>
<td>95.3 (18.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Height, mean (SD) (cm)</td>
<td>164.0 (7.0)</td>
<td>164.5 (7.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>BMI, mean (SD) (kg/m$^2$)</td>
<td>34.8 (5.6)</td>
<td>35.1 (5.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Maternal age, mean (SD) (years)</td>
<td>30.6 (4.9)</td>
<td>29.9 (4.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Tobacco smoker</td>
<td>3.50%</td>
<td>16.10%</td>
<td>0.001**</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>8.80%</td>
<td>13.60%</td>
<td>0.26</td>
</tr>
<tr>
<td>History of endocrine disease$^a$</td>
<td>22.10%</td>
<td>22.00%</td>
<td>0.99</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
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<tr>
<td>Parity of 0</td>
<td>47.80%</td>
<td>32.20%</td>
<td>0.04*</td>
</tr>
<tr>
<td>Parity of 1</td>
<td>33.60%</td>
<td>39.80%</td>
<td></td>
</tr>
<tr>
<td>Parity of ≥ 2</td>
<td>18.60%</td>
<td>28.00%</td>
<td></td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>47.80%</td>
<td>58.50%</td>
<td>0.04*</td>
</tr>
<tr>
<td>Southern Asia</td>
<td>31.00%</td>
<td>16.90%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21.20%</td>
<td>24.60%</td>
<td></td>
</tr>
</tbody>
</table>

SD Standard deviation, BMI body mass index

$^a$Endocrine disease consists of gestational diabetes from previous pregnancy, thyroid disease and pituitary disease

$^*P < 0.05$, $^{**}P < 0.001$
The present study has evaluated the effectiveness and nutritional intake of a group intervention for reducing excessive GWG in overweight and obese pregnant women. The results indicate that the current dietary intervention may be effective in restricting excessive GWG, as the women who did not attend the education session gained 2.9 kg more gestational weight than those who did attend.

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The use of tobacco is known to be associated with the incidence of SGA, and we found significantly higher use of tobacco in the control group [29]. After adjusting for this confounder, a significant decrease in the prevalence of SGA in the intervention group compared to the control group was observed.

### Table 2  Maternal and neonatal outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n = 118)</th>
<th>Control (n = 113)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjustedb OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>15.00%</td>
<td>14.40%</td>
<td>1.05 (0.51–2.18)</td>
<td>0.891</td>
<td>1.46 (0.48–2.27)</td>
<td>0.910</td>
</tr>
<tr>
<td>Antenatal admission</td>
<td>13.30%</td>
<td>16.90%</td>
<td>0.75 (0.36–1.55)</td>
<td>0.437</td>
<td>0.80 (0.37–1.70)</td>
<td>0.556</td>
</tr>
<tr>
<td>Pre-labour intervention</td>
<td>39.30%</td>
<td>34.50%</td>
<td>1.23 (0.71–2.12)</td>
<td>0.467</td>
<td>0.97 (0.53–1.77)</td>
<td>0.928</td>
</tr>
<tr>
<td>Antibiotic use in labour</td>
<td>22.10%</td>
<td>19.50%</td>
<td>1.17 (0.62–2.21)</td>
<td>0.622</td>
<td>1.04 (0.53–2.01)</td>
<td>0.917</td>
</tr>
<tr>
<td>Total GWG, mean (SD) (kg)</td>
<td>9.8 (6.9)</td>
<td>12.2 (8.2)</td>
<td>−2.89 (1.1)</td>
<td>0.026*</td>
<td>−2.88 (1.1)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Postnatal length of stay, mean (SD) (days)</td>
<td>2.19 (0.98)</td>
<td>1.93 (0.98)</td>
<td>0.25 (0.13)</td>
<td>0.050</td>
<td>0.85 (0.13)</td>
<td>0.504</td>
</tr>
<tr>
<td><strong>Neonatal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>0.90%</td>
<td>6.00%</td>
<td>0.14 (0.02–1.16)</td>
<td>0.068</td>
<td>0.99 (0.11–0.93)</td>
<td>0.043*</td>
</tr>
<tr>
<td>LGA</td>
<td>18.60%</td>
<td>15.40%</td>
<td>1.25 (0.63–2.5)</td>
<td>0.519</td>
<td>1.32 (0.63–2.734)</td>
<td>0.451</td>
</tr>
<tr>
<td>Manoeuvre for shoulder dystocia</td>
<td>12.40%</td>
<td>13.60%</td>
<td>0.90 (0.42–1.95)</td>
<td>0.792</td>
<td>0.80 (0.35–1.83)</td>
<td>0.602</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>11.50%</td>
<td>12.70%</td>
<td>0.89 (0.40–1.98)</td>
<td>0.779</td>
<td>0.69 (0.30–1.61)</td>
<td>0.391</td>
</tr>
<tr>
<td>Neonatal complication at birth</td>
<td>15.90%</td>
<td>16.90%</td>
<td>0.93 (0.46–1.86)</td>
<td>0.834</td>
<td>0.81 (0.39–1.67)</td>
<td>0.057</td>
</tr>
<tr>
<td>Prematurea</td>
<td>7.10%</td>
<td>7.60%</td>
<td>0.92 (0.34–2.48)</td>
<td>0.873</td>
<td>0.83 (0.30–2.31)</td>
<td>0.714</td>
</tr>
<tr>
<td>Formula use</td>
<td>14.10%</td>
<td>26.10%</td>
<td>0.47 (0.22–0.97)</td>
<td>0.041*</td>
<td>0.71 (0.32–1.58)</td>
<td>0.400</td>
</tr>
<tr>
<td>Gestational age, mean (SD) (weeks)</td>
<td>39.2 (1.9)</td>
<td>38.9 (30)</td>
<td>0.29 (0.33)</td>
<td>0.374</td>
<td>0.28 (0.35)</td>
<td>0.421</td>
</tr>
<tr>
<td>Birth weight, mean (SD) (g)</td>
<td>3521 (576)</td>
<td>3402 (739)</td>
<td>118.9 (87.0)</td>
<td>0.173</td>
<td>160.6 (91.74)</td>
<td>0.810</td>
</tr>
</tbody>
</table>

SD Standard deviation, GWG gestational weight gain, SGA small for gestational age, LGA large for gestational age, CI confidence interval, SE standard error

a<37 weeks gestational age
bAdjusted for country of birth and parity
pc < 0.05
**pc < 0.01

**Discussion**

The present study has evaluated the effectiveness and nutritional intake of a group intervention for reducing excessive GWG in overweight and obese pregnant women. The results indicate that the current dietary intervention may be effective in restricting excessive GWG, as the women who did not attend the education session gained 2.9 kg more gestational weight than those who did attend.

Similar to our findings, some lifestyle interventions have reported a reduction of 2.1–3.0 kg in GWG in overweight and obese women [25], although other studies have shown low-intensity dietary interventions to be limited in preventing excessive GWG in obese women [9, 15]. One study proved intensive dietary intervention to be beneficial, showing patients who attended multiple appointments with a dietitian to have significantly low excessive GWG [26]. Total GWG, however, did exceed the IOM recommendation of 9 kg in both the intervention and control groups (9.8 kg vs 12.2 kg, respectively), indicating a dietary approach alone may not be sufficient to facilitate appropriate weight gain, as found previously [27]. Use of a multi-disciplinary approach with prenatal care providers who have counselling experience in nutrition and physical activity has demonstrated greater success in limiting excessive GWG [13, 28], while this evidence is suggestive, the optimal modality and frequency is yet to reach consensus in the literature [13].

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Table 3 Nutrient intake of the intervention group compared to the national intake

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>NNS resultsa</th>
<th>Intervention (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>NRV</td>
<td>RI</td>
</tr>
<tr>
<td>Energy (kJ)</td>
<td>7701</td>
<td>7330</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>1841</td>
<td>1747</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>79</td>
<td>95</td>
</tr>
<tr>
<td>%TE</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Carbohydrate (g/day)</td>
<td>205</td>
<td>201</td>
</tr>
<tr>
<td>%TE</td>
<td>58</td>
<td>45</td>
</tr>
<tr>
<td>Sugar (g/day)</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td>%TE</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Total fat (g/day)</td>
<td>68</td>
<td>58</td>
</tr>
<tr>
<td>%TE</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>SFA (g/day)</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>%TE</td>
<td>N/A</td>
<td>12</td>
</tr>
<tr>
<td>MUFA (g/day)</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>%TE</td>
<td>N/A</td>
<td>11</td>
</tr>
<tr>
<td>PUFA (g/day)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>%TE</td>
<td>N/A</td>
<td>5</td>
</tr>
<tr>
<td>Fibre (g)</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Sodium (mg/day)</td>
<td>2229</td>
<td>1923</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>762</td>
<td>754</td>
</tr>
<tr>
<td>Iron (mg/day)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Vitamin A (RE) (µg /day)</td>
<td>773</td>
<td>703</td>
</tr>
<tr>
<td>Vitamin D (µg /day)</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Folate (µg /day)</td>
<td>533</td>
<td>494</td>
</tr>
</tbody>
</table>

NNS National Nutrition Survey, TE total energy, SFA saturated fatty acids, PUFA polyunsaturated fatty acids, RE retinol equivalents, N/A not available, NRV nutrient reference value, RI recommended intake, AMDR acceptable macronutrient distribution range, AI adequate intake

*aNNS values based on women aged 19–50

was present (0.9% vs 6%). A large body of evidence suggests that the prevalence of SGA decreases with increased excessive GWG and all classes of overweight and obesity [3, 10]. Supporting this, a systematic literature review has indicated that obese women who failed to meet the IOM minimum guidelines of 5 kg had a higher risk of SGA infants than those who met the 5–9 kg IOM recommendations (OR 1.28) [30]. The literature postulates poor fetal growth may occur in this population due to altered insulin function and maternal hypertension [31]. However, a recent study found no increase in SGA neonates in obese women with weight gain less than the IOM guidelines [32]. Furthermore, a study in the same demographic area as this study demonstrated an increased incidence of SGA (16%) amongst obese women compared to women with normal weight (11%) [33]. The relationship between gestational weight gain and SGA requires further clarification in the literature.

With respect to the incidence of GDM (16%), an incidence of GDM of 12% was found in a similar demographic in an obese population by Cheung et al. [33] and an incidence of 15.1% has been reported in an obese population in Western Australia [26].

Women of Southern Asian decent were more likely to attend the dietary intervention, while women of Australian and New Zealand decent were less likely to attend. The reasoning for this is unknown, further investigation is necessary. As South Asians are at higher risk of developing central adiposity than Europeans [34], and have higher Caesarean section, stillbirth and maternal death rates [6], exploration of ethnicity tailored interventions is warranted.

The energy intake of the intervention group being lower than the NNS suggests the likelihood of underreporting, which is common within this population group [35]. Our results indicate that 68% of the women who reported their intake exceeded the AMDR for saturated fat. Evidence linking saturated fat to chronic disease is conflicted within the literature with more recent high-quality cohort data showing little effect of saturated fats on cardiovascular and metabolic health. These data need to be further substantiated before being incorporated into current guidelines [36]. The women in the subsample derived 21% of total energy intake from sugar, exceeding the World Health Organisation guidelines for free sugars of less than 10% of total energy [37]. Unfortunately, this study did not include free sugars alone although regular intake of sugar-sweetened beverages did contribute to these values, which have been linked to an increased risk of GDM [38]. Dietary intakes of key pregnancy micronutrients including folate, iron and calcium were inadequate in those who attended the nutrition education session, consistent with previous findings [19]. After adjusting for multivitamin supplementation, intakes of these micronutrients were replete, though timing of intake should be taken into consideration to ensure optimal micronutrient utilisation. This study supports the current practice of supplementing key pregnancy micronutrients in combination with adhering to the Australian guide to healthy eating. Of the women who had their dietary intake analysed, 98% exceeded the AI for sodium. The excessive salt intake does not include salt added to food, but emanates from food sources, in particular fast food and processed meats. To address mild iodine deficiency in Australia, mandatory fortification of iodised salt in bread was implemented in 2009.

Excessive sodium intake has been previously related to compromised cardiac and renal function in the offspring of laboratory animals [39], furthermore, evidence also suggests that, in humans, excessive sodium predisposes offspring to hypertension [40].

The strengths of this study included adding to the evidence base for simple low cost, group-based dietary interventions for limiting GWG, which can be widely applied to
tertiary hospital outpatient settings; the effectiveness of this intervention in a culturally and linguistically diverse population; the controversial findings of reduced incidence SGA in the intervention group, and increased formula use in this population. The small sample size, self-reported pre-pregnancy weight and lack of randomisation were limitations of the dietary analysis. In addition, women who attended the intervention had increased motivation for weight loss and this may have introduced bias. The dietary analysis quality was compromised by the use of a 24 h recall, only being administered once during 9 months of pregnancy. In addition, the reported energy intake of the intervention group, being lower than the NNS, likely represents underreporting; this has been shown to occur in approximately 45% of overweight or obese pregnant women [35]. The external generalisability of these results may be limited given the cultural variation of the baseline characteristics in the participants.

This study has revealed that a single 90-min group dietary education session may be effective in reducing excessive GWG. This study further substantiates evidence for use of dietary intervention, although multi-disciplinary interventions yield the best success. Further research is required to identify the optimal modality and frequency to limit excessive GWG. Dietary interventions tailored to ethnicity should also be explored.

Acknowledgements We would like to thank all study participants and staff in Women’s and Newborn Health at Westmead Hospital that contributed to the project.

Author contributions The authors responsibilities were as follows: CB, AW and TM contributed to study design, BD, AW and CB conducted the research, BD, KB and CB analysed the data, BD wrote the paper; TM, CB and KB edited the final manuscript.

Funding None.

Compliance with ethical standards

Conflict of interest On behalf of all the authors, the corresponding author declares that there is no conflict of interest.

Ethical approval This study was approved by Western Sydney Local Health District Human Research Ethics Committee [SAC2017/4/6.2 (5643) QA]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this retrospective study, formal consent was not required.

References

ANTENATAL COUNSELLING FOR FOETAL HEPATIC HAEMANGIOMA

Zaynab El-Hamawi1*, Roshini Nayyar2
1Maternal Fetal Medicine, Women’s and Newborn Health, Westmead Hospital, the 2Westmead Institute of Maternal Fetal Medicine

Background: Foetal and neonatal hepatic haemangiomas are rare, with current literature documenting an incidence of approximately 5% of tumours in infants. Antenatal identification of these lesions is becoming more possible with routine ultrasound surveillance in pregnancy.

Method: A database search was conducted for case reports in the literature pertaining to diagnosis and management foetal hepatic vascular lesions.

Results: There is debate in the literature regarding the true diagnosis of vascular hepatic lesions identified on ultrasound antenatally. The suggestion is that it is difficult to classify foetal hepatic vascular lesions prior to birth, as it requires differentiation between benign hepatic haemangioma, pre-malignant hepatic haemangioendothelioma, and hepatic arterio-venous malformation.

Therefore, antenatal surveillance of these lesions aims to monitor for foetal compromise. Initial evaluation includes assessment of the size, number, location, and vascularity of the lesion. The majority of haemangiomas will follow a classical course of short-term proliferation followed by involution, mainly after birth. However, a small subgroup have been documented to develop complications antenatally. These haemangiomas are larger, greater than 40 mm, and may have identifiable feeding vessels and high flow velocity that could result in significant arterial-venous shunting. There are reports of complications such as cardiac failure with hydrops, thrombocytopenia, haemolytic anaemia and consumptive coagulopathy.

Conclusion: Hepatic haemangiomas are rare lesions which may be identified antenatally on routine ultrasound surveillance, though limitations on accuracy of diagnosis make antenatal management challenging. Therefore, ongoing antenatal ultrasound monitoring has been recommended. The majority of these lesions will remain asymptomatic and regress in early childhood.
Antenatal diagnosis of isolated infracardiac infradiaphragmatic total anomalous venous connection – Pictorial essay and discussion

Usha Nandhini1, Monique Atkinson1, Mani Ram Krishna2 and Thushari Indika Alahakoon1,3

1Westmead Institute of Maternal and Fetal Medicine, Westmead Hospital, Westmead, New South Wales, Australia
2Department of Paediatric Cardiology, The Children’s Hospital Westmead, Sydney, New South Wales, Australia
3Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

Abstract

Introduction: Antenatal diagnosis of isolated infracardiac total anomalous pulmonary venous connection (TAPVC) is rare. Making the diagnosis antenatally is critical as delayed management could result in neonatal deterioration and poor outcome after surgery.

Method: A multipara at 29 weeks of gestation was referred to our tertiary unit for ultrasound review. The fetal growth and biophysical profile were normal. A fetal echocardiogram revealed normal cardiac position with atrioventricular and ventriculoarterial concordance. There was a mild discrepancy in size of the right and left chambers of the heart. A connection between the pulmonary veins and the left atrium could not be established. A pulmonary venous confluence was noted posterior to the left atrium, from which a descending vertical vein emerged traversing the diaphragm and draining into the left portal vein into the liver.

Results: A diagnosis of infracardiac infradiaphragmatic total anomalous pulmonary venous connection was made. The pregnancy was delivered at 39 weeks by lower segment caesarean section. The antenatal findings were confirmed by postnatal echocardiogram. Successful sutureless repair of the pulmonary veins was performed.

Conclusion: Isolated infracardiac total anomalous pulmonary venous connection can be diagnosed antenatally. This ensures early postnatal evaluation and successful repair.

Keywords: antenatal ultrasound, congenital heart disease, total anomalous pulmonary venous connection.

Introduction

Total anomalous pulmonary venous connection (TAPVC) constitutes 0.2–2% of congenital heart disease (CHD). In TAPVC, all four pulmonary veins drain into the systemic venous system instead of the left atrium. This condition can be isolated or associated with other CHDs, most commonly as part of a heterotaxy syndrome. Antenatal diagnosis of isolated TAPVC is very challenging. Antenatal detection along with appropriate stabilisation of the neonate and early surgical repair results in a good long-term prognosis.

Methods and patients

A 32-year-old multiparous woman was referred to our tertiary unit at fourteen-week gestation in view of returning a high-risk result for Trisomy 21 (1:22) in a combined first-trimester screen. The nuchal translucency thickness was increased at 5.8 mm. Amniocentesis was performed, and the result was normal (46XY). A routine fetal morphology scan was reported as normal. She was again referred at 29-week gestation to our tertiary centre for an ultrasound review. The growth and liquor were normal. Written consent from the patient and ethics approval was obtained to publish this case.

Results

On cardiac examination, the left atrium (LA) appeared to be smaller than the right atrium. There was mild asymmetry of the right and left heart ventricles. The mitral valve measured 4.75 mm (z-score: −2.82), and the tricuspid valve measured 8.1 mm (z-score: −1.16). The foramen ovale showed unrestricted flow, and the outflow tracts were unobstructed. The normal connection between the pulmonary veins to the LA
could not be established. The LA to descending aorta (DAo) distance was noted to be increased. A pulmonary venous confluence was noted posterior to the left atrium (Figure 1a and b). On tracing the confluent vessel, a descending vertical vein (VV) was noted coursing towards the abdomen and draining into the left portal vein (Figures 2a, b and 3). Pulse wave Doppler study showed an abnormal pulmonary venous pattern with biphasic continuous flow and no significant obstruction of the descending VV at the draining point (Figure 4b). The ductus venosus was normal. A diagnosis of infracardiac TAPVC to the portal vein was made and confirmed by a paediatric cardiologist using fetal echocardiography.

The pregnancy was continued till term and electively delivered at 39 weeks by lower segment caesarean section, due to her history of having a previous caesarean section. Postnatal echocardiogram confirmed the diagnosis of infracardiac TAPVC as well as drainage of the pulmonary vein confluence into the left portal vein. There was mild obstruction at the site of entry into the liver. The baby underwent repair of the TAPVC at five hours of life. The pulmonary veins were re-anastomosed to the LA by a sutureless technique. The post-operative course was uncomplicated. The baby was discharged home 2 weeks after surgery.

**Discussion**

TAPVC is the fifth most common critical congenital heart disease. A delay in diagnosis of TAPVC and hence surgical repair leads to high rates of neonatal morbidity and mortality. Without surgical repair of an obstructed VV in TAPVC, the neonate will suffer from progressing pulmonary oedema, pulmonary artery hypertension and cardiac failure. The neonate usually presents with low oxygen saturation. Oxygen therapy may worsen the lung damage. Prostaglandin therapy to maintain a patent ductus arteriosus is contraindicated in TAPVC. Antenatal diagnosis of isolated TAPVC is challenging. There are no data available on the antenatal detection of TAPVC.
rates of TAPVC and the literature are limited to isolated case reports.

Anomalous pulmonary venous connection collectively refers to conditions where some or all of the pulmonary veins return blood to the systemic venous system and eventually to the right atrium, instead of the left atrium. This can be total (TAPVC) or partial (PAPVC). The latter is clinically less severe, and neonates are usually asymptomatic. The ultrasound features of TAPVC are listed in Table 1. The abnormal drainage may either be directly into the right atrium, or through a connecting venous structure, known as the vertical vein (VV), to the superior vena cava (SVC) or inferior vena cava (IVC). Based on the drainage pattern, TAPVC is anatomically classified as supracardiac, cardiac, infracardiac or mixed type (Figure 5).

Supracardiac TAPVC is the most common type of TAPVC, accounting for 45–55% of cases. In this type, the pulmonary venous confluence connects to an ascending VV that in turn connects to the innominate vein. This drains all pulmonary venous blood into the SVC and right atrium. The cardiac type of TAPVC accounts for 25–30% of cases. It is defined by drainage of the pulmonary venous confluence into the coronary sinus or directly to the right atrium. Infracardiac cases of TAPVC (13–25% of cases) have the pulmonary venous confluence connecting to a descending VV that courses through the oesophageal hiatus, and usually drains into the portal venous system. Mixed types of TAPVC are rare and account for less than 5% of cases.

The pathophysiology of TAPVC depends mostly on the degree of obstruction to pulmonary venous flow. Infracardiac TAPVC is more likely to be obstructed, with the tortuous course of the pulmonary venous return through the liver. Patients with supracardiac TAPVC are less likely to have obstruction. Cardiac TAPVC, with connection of the pulmonary venous return to the coronary sinus, is least likely to be obstructed. Obstruction of the pulmonary venous return leads to severe pulmonary venous congestion, pulmonary oedema and pulmonary arterial hypertension which results in severe cyanosis and respiratory distress in the first few hours of life. Hence, significant obstruction requires immediate neonatal surgery.

The degree of functional obstruction is also influenced by the size of any interatrial communication, with a smaller communication associated with more severe symptoms. If the interatrial communication is large, however, it allows flow of blood into the left heart reducing pulmonary hypertension. Infants with TAPVC who are not obstructed, or who have an adequate atrial septal defect, may escape diagnosis in the neonatal period and present later in childhood.

There are direct and indirect ultrasound markers which should raise the suspicion of TAPVC antenatally (Table 1). In a four-chamber view, there may be an increase in the distance between the descending aorta (DAo) and LA (Figure 1b). The LA wall may appear smooth suggesting the absence of pulmonary vein ostia or there may be an additional vessel seen between the LA and descending aorta, representing the
atrial pressure changes (Figure 4a). In TAPVC, this pattern is lost. The abnormal waveform may be biphasic/pulsatile (Figure 4b), biphasic/continuous, monophasic/pulsatile or monophasic/pulsatile.

Doppler studies can also be used to investigate the degree of obstruction. High velocity and turbulent flow at the drainage site would suggest obstruction.

The ISUOG guidelines for routine second-trimester evaluation suggest imaging the four-chamber view, outflow tract view and three-vessel-trachea view as part of an extended cardiac scan, but do not mention about visualisation of the pulmonary veins. However, the guidelines on fetal heart examination recommend visualisation of at least two pulmonary veins when technically feasible during cardiac examination. The AIUM guidelines recommend imaging four-chamber view, right and

**Table 1**: Ultrasound features of total anomalous pulmonary venous connection.

<table>
<thead>
<tr>
<th>Cardiac view</th>
<th>Ultrasound feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-chamber view</td>
<td>Diagnostic feature: Lack of connection between LA and pulmonary veins</td>
</tr>
<tr>
<td></td>
<td>Additional vessel behind LA (representing the pulmonary venous confluence)</td>
</tr>
<tr>
<td></td>
<td>Increased LA–DAo distance</td>
</tr>
<tr>
<td></td>
<td>Smooth wall LA (suggesting absence of PV ostia)</td>
</tr>
<tr>
<td></td>
<td>Dilated coronary sinus (cardiac type)</td>
</tr>
<tr>
<td></td>
<td>Chamber asymmetry (right larger than left)</td>
</tr>
<tr>
<td></td>
<td>Small left atrium</td>
</tr>
<tr>
<td>Three vessel view</td>
<td>Dilated SVC (supracardiac)</td>
</tr>
<tr>
<td></td>
<td>Additional vessel–ascending VV (supracardiac)</td>
</tr>
<tr>
<td>Abdomen view</td>
<td>Additional vessel–descending VV (infracardiac)</td>
</tr>
</tbody>
</table>

LA, left atrium; DAo, descending aorta; SVC, superior vena cava; PV, pulmonary veins; VV, vertical vein.

**Figure 5**: Classification of Cases of Anomalous Pulmonary Venous Connection. Patients with Anomalous Pulmonary Venous Connection may have a Total (All Four Pulmonary Veins Effected) or Partial (One to Three Pulmonary Veins Effected) Abnormality. The Cases with Total Anomalous Pulmonary Venous Connection may be Classified Based on their Anatomical Configuration, or their Physiology. This Classification Impacts Upon the Severity of the Condition and Subsequent Management Required.
left ventricular outflow tracts in the second- and third-trimester fetal examination. However, considering the technically difficulty, the ASUM guideline does not include visualisation of pulmonary veins in their ‘statement of Mid Trimester Obstetric Scan’ guidelines.

During routine cardiac screening, failure to establish a connection between the pulmonary veins and left atrium should raise suspicion of TAPVC and hence referral for detailed fetal echocardiography. Asymmetry between right and left heart chambers may occur later in gestation and hence should not be used as primary feature to rule out TAPVC. Other indirect markers act as clues to diagnosis but are subjective. The visualisation of pulmonary veins during routine fetal screening ultrasound will aid in increasing antenatal diagnosis of this often missed cardiac anomaly. In our patient, the diagnosis was missed despite a comprehensive anomaly evaluation in a tertiary care centre. This highlights the challenges in establishing the diagnosis and the need for dedicated fetal echocardiography in high-risk cases.

Conclusion
Antenatal diagnosis of TAPVC is challenging, but identification is crucial if optimal perinatal management is to be performed. Suspicion of TAPVC can be raised during a standard fetal cardiac ultrasound examination in the second or third trimester. Diagnosis of TAPVC in the fetus can lead to planning delivery in a tertiary centre with appropriate neonatal cardiac surgical capabilities.

References
Antenatal diagnosis of midgut volvulus with successful immediate post-natal management

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\section*{ARTICLE INFO}

\textbf{Keywords:}
Volvulus  
Antenatal diagnosis  
Tissue plasminogen activator  
Congenital anomalies

\section*{ABSTRACT}

Fetal volvulus of the midgut occurs when the bowel twists around the axis of the superior mesenteric artery. It is usually diagnosed postnatally but with improving ultrasonography, there have been increasing number of cases reporting antenatal diagnosis that had allowed planning of obstetric intervention and prompt surgery in the postnatal period. We present a case of dichorionic diamniotic twin pregnancy wherein Twin A had multiple anomalies, which included an Ivemark heterotaxy syndrome with a double outlet right ventricle. This twin developed dilated bowel loops at 33 weeks of gestation. The pregnancy continued to have regular antenatal surveillance and was managed by a multidisciplinary team. At 36 weeks of gestation, these bowel loops were found to have absence of peristalsis compared to previous ultrasounds. An emergency caesarean section was performed, which was uncomplicated and Twin A weighing 2760g was born with Apgars of 6\textsuperscript{1} and 8\textsuperscript{2}. The diagnosis of volvulus in Twin A was confirmed during its emergency laparotomy along with a Type IV jejunal atresia and was successfully treated surgically with resection and administration of tissue plasminogen activator (TPA). This is the first description of a case treated with TPA after fetal diagnosis.

\section*{1. Case report}

This case report describes a spontaneous dichorionic diamniotic twin pregnancy in a 32-year-old multipara with increased BMI of 36.5 but no other medical history. The patient was an international transfer to our facility for multidisciplinary care due to the diagnosis of complex fetal anomalies including Ivemark heterotaxy syndrome with a double outlet right ventricle in Twin A. Dilated bowel loops were then noted in Twin A at 33 weeks of gestation with extensive constant peristalsis but no significant increase in amniotic fluid volume.

At 36 weeks of gestation, ultrasound again revealed extensively dilated loops of bowel but in a C shape (Fig. 1) suggestive of a volvulus as well as continuous distension of the bowel in the following distal loops (Fig. 2). In contrast to previous ultrasounds, there was no peristalsis noted, and vascularity could not be demonstrated in the superior mesenteric artery. An antenatal diagnosis of acute volvulus of the gut with bowel ischemia was made, the pediatric surgeon was consulted, and delivery was organized by emergency caesarean section. Twin A was born with Apgar's of 6\textsuperscript{1} and 8\textsuperscript{2} and weighed 2760g.

Immediate transfer to the pediatric surgical facility and an urgent laparotomy within 4 h of birth confirmed the diagnosis of malrotation of the intestine with a torted ischemic midgut volvulus (Fig. 3) and a Type IV jejunal atresia. The intestine had twisted around a very narrow mesenteric pedicle resulting in ischemia to the entire small bowel. The first atresia was seen approximately 60 cm from the duodenal jejunal flexure. There were six other small atretic segments of bowel of lengths varying from 1 to 2 cm distal to this with an intact ileo-caecal valve. After untwisting the bowel, the proximal bowel was decompressed. Tissue plasminogen activator (TPA) was injected directly into the superior mesenteric artery to break microthrombi and to facilitate perfusion to the gut to aid gut recovery. The proximal bowel was brought out as a stoma. Two of the six isolated segments were excised.

Systemic TPA was administered for 18 h using the protocol described by Kiely et al. (7) for ischemic mid gut volvulus. The abdomen

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https://doi.org/10.1016/j.epsc.2018.01.005

Received 5 January 2018; Accepted 8 January 2018

Available online 11 January 2018

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Total parenteral nutrition (TPN) was started. On subsequent laparotomy, the entire gut looked pink and had fully recovered (Fig. 4). Proximal bowel dilatation had reduced and caliber discrepancy between distal and proximal bowel was minimal. The child had a total of 100 cm of small bowel with the ileocecal valve.

Feeds were gradually introduced, and the child could feed on full enteral feeds with full withdrawal of TPN 4 weeks after surgery. The neonate recovered well progressing to normal feeds and is awaiting cardiothoracic review for her heterotaxy syndrome. Informed consent from patient was obtained for publication.

2. Discussion

Midgut volvulus from malrotation is usually reported in the first month after birth or in late childhood [8,9]. Several ultrasound findings have been reported to suggest the diagnosis of volvulus but only two were present in our case. The ‘whirlpool’ sign is demonstrated when the superior mesenteric vein and the mesentery swirl around the axis of the superior mesenteric artery whereas the ‘coffee bean’ sign refers to the appearance of dilated bowel loop which has a thick inner wall and a thin outer wall owing to double wall and single wall thickness respectively [2,5]. Other signs include absence of peristalsis on real-time ultrasound [5] and ascites [10] which suggest bowel perforation. The ultrasound features critical to the diagnosis of bowel ischemia in this case were the inability to demonstrate vascular flow to the bowel and absence of peristalsis.

3. Conclusion

The immediate diagnosis and management of this acute catastrophic complication resulted in a good outcome for the fetus. The previous use of TPA for ischemic bowel associated with midgut volvulus has been described on neonates with postnatal diagnosis [7]. This is the first description of a case treated with TPA after fetal diagnosis. The immediate use of TPA for resolution of mesenteric thrombus as well as the ongoing infusion was likely life saving for this neonate.

Declarations of interest

None.
Funding source

None.

Acknowledgements

We would like to gratefully acknowledge the parents of the neonate presented in this paper for permission to share their story.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References


CASE REPORT

Antepartum uterine rupture at 29 weeks gestation following unilateral salpingectomy and review of literature

Yu-Ting Huang, Stephen Li-Yen Yim, Supuni Kapurubandara, Anbu Anpalagan

SUMMARY
Antepartum uterine rupture following salpingectomy is a rare condition and is associated with high fetal and maternal mortality and morbidity. We illustrate a 33-year-old primigravida who presented with abdominal pain at 29 weeks of gestation. Her previous obstetric history included a ruptured right ectopic pregnancy for which she underwent laparoscopic salpingectomy with no breach of uterine cavity. Her antenatal care had otherwise been unremarkable. Following admission for undetectable fetal heart, ultrasound and CT demonstrated an extrauterine fetus at the right adnexal region with free fluid consistent with intra-abdominal haemorrhage. An exploratory laparotomy was performed which revealed a uterine rupture at the right cornua with the extruded fetus en caul. The fetus was delivered and the uterus repaired in three layers. The patient made an uneventful postoperative recovery and was discharged 5 days following surgery. We review the current literature including the evaluation and management of this rare condition.

BACKGROUND
Uterine rupture is defined as a disruption of the integrity of the uterine myometrium, often with catastrophic maternal and fetal consequences.

Spontaneous uterine rupture is a rare obstetric event, usually associated with prior surgical or traumatic disruption to myometrium, including labour. In the absence of labour, the risk after one lower segment caesarean section has been described as 1.6 per 1000 deliveries. The risk rises at the onset of labour (5.2–24.5 per 1000 deliveries), depending on the nature of the labour. The risk of uterine rupture after a classical caesarean section is significantly higher (40–90 per 1000 deliveries).

Many obstetricians have viewed myomectomy to be associated with an increased risk of uterine rupture. However, there is still paucity of high-level data regarding this complication. One study by Gyamfi-Bannerman showed that there were no differences in rupture rate compared to a patient who had had a previous lower segment caesarean section. However, in that study, all women with a prior myomectomy delivered by repeat caesarean section (with or without labour) and were significantly more likely to be delivered at an earlier gestational age. Another study reported a rupture rate of 2 per 1000 births. However, a small Canadian survey showed obstetricians were more likely to draw parallels between a myomectomy where there has been a breach of the uterine cavity during the procedure with a classical caesarean section and therefore recommended repeat caesarean section for the increase perceived risks.

Thus far, there have only been three case reports of uterine rupture after a salpingectomy. Inovay reported one such case of a cornual dehiscence in a patient after salpingectomy. This follows reports of the same by Lizan in 1986.

CASE PRESENTATION
A 33-year-old gravida three nulliparous woman of Southeast Asian decent with a history of first trimester spontaneous miscarriage, complete without intervention. Subsequent pregnancy was a ruptured right ectopic pregnancy at 5 weeks gestation at the right tubal isthmus requiring emergency laparoscopic right salpingectomy bipolar energy. Ectopic pregnancy was excised and uterine cavity was not breached. Bipolar energy source was used. The third pregnancy was essentially uncomplicated apart from gestational diabetes that was well-controlled by diet alone. Her pregnancy ultrasound scans including nuchal translucency, morphology and 27-week growth scan were all unremarkable.

At 29 weeks, she presented to hospital overnight with non-specific lower abdominal pain with one in 10 minutely contractions. There was no history of premature rupture of membranes, antepartum haemorrhage or trauma. She had reported normal fetal movements. Cardiotocography was reassuring. Examination revealed a soft abdomen; cervix was not breached. Bipolar energy source was used. The third pregnancy was excised and uterine cavity was not breached. Bipolar energy source was used. The third pregnancy was essentially uncomplicated apart from gestational diabetes that was well-controlled by diet alone. Her pregnancy ultrasound scans including nuchal translucency, morphology and 27-week growth scan were all unremarkable.

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On examination, there was tenderness on the right side of the pelvis. Vaginal examination revealed an empty uterus (figures 1 and 2) with the extrauterine pregnancy in the right adnexal region, and confirmed fetal demise. There was considerable free fluid in the pelvis suggestive of intra-abdominal haemorrhage. A CT abdomen and pelvis was also performed to obtain more information regarding bowel and placental involvement (figure 3). The CT examination revealed an intra-abdominal
pregnancy secondary to uterine rupture in the mid-upper abdomen in the transverse oblique plane. Gas bubbles were noted within the fetus consistent with fetal demise. Placenta was anterior, centred at the level of the umbilicus. Patient was transferred to a tertiary centre for explorative laparotomy.

**Laparotomy findings:**
- ruptured uterus at the right cornua
- haemoperitoneum 200 mL
- placenta complete
- normal ovaries bilaterally
- normal left fallopian.

Postoperative recovery was uneventful. Postmortem was declined by the patient.

**OUTCOME AND FOLLOW-UP**
Histopathology findings of the placenta were unremarkable and chromosome microarray of the umbilical cord revealed a normal fetal karyotype. Patient was discharged day 5 with follow-up at first and sixth week to debrief events and counsel regarding future pregnancies.

**DISCUSSION**
Traditionally, uterine rupture refers to the disruption of all uterine layers including the serosa. Dehiscence of the uterine scar, on the other hand, refers to the separation of all uterine layers except the serosa. The most common cause of such disruption of uterine integrity is a history of uterine surgery, including caesarean sections (lower segment or classical incision) and/or myomectomies with or without breach of the uterine cavity. Surgical technique, operator experience and suture material used are all factors that can contribute to such disruption of the uterine scar. Other predisposing factors to uterine rupture include anatomical uterine anomalies and abnormal implantation of pregnancies such as those within the rudimentary horn of uteri.

Less commonly are other non-uterine gynaecological surgeries that can affect the integrity of the uterus tissue, such as salpingectomies. Our literature review has only identified three other case reports of uterine rupture post salpingectomy. One case reported a previous elective laparoscopic bilateral salpingectomy without cornual resection prior to in vitro fertilisation (IVF) as
This patient subsequently underwent imaging that suggested the need for surgery. MRI can be used to diagnose uterine rupture especially in the context of maternal trauma in order to identify the extent of fetal and maternal injuries. The limiting factor with the use of CT scan is maternal and fetal exposure to radiation. MRI is another imaging modality that has been mentioned in the literature which has the advantage of demonstrating soft tissue contrast, the ability to highlight myometrial defect along with spatial relations of the placenta, uterus, fetus and pelvic structures. MRI can be used to diagnose or confirm suspicion of uterine rupture and thereby assist with counselling and meticulous surgical planning of this potentially life-threatening emergency.

Current practice is at the discretion of the specialist to monitor myometrial thickness and integrity in patients at risk of uterine rupture using ultrasound or MRI in the absence of robust evidence to support their use. To date there is no reliable data of what the benchmark ‘norm’ of myometrial thickness should be or how thin the myometrium can become to prompt early delivery.

Current salpingectomy techniques can be performed by laparoscopic or laparotomy approach. Laparoscopic salpingectomy can be described by using surgical loop, surgical clips, carbon dioxide laser or electrosurgical excision. Laparotomy techniques mainly involve ‘clamp, cut and tie’ of the pedicle. Resection of the fallopian tube can be partial or complete. The techniques used are at the discretion of the surgeon.

The discussion lies whether the use of electrocautery is ideal in salpingectomies when there are known potential lateral diathermy injuries to the myometrium, which is avoidable considering there are other techniques available to achieve the same result. However, as uterine rupture post salpingectomy is a rare obstetric event, there is insufficient data to support this conclusion to justify change in practice. Mindfulness is recommended when using electrocautery to perform the salpingectomy in order to prevent inadvertent lateral thermal tissue damage particularly to the myometrium. A prospective randomised control trial looked at the outcomes of using pretied surgical ligatures (ENDOLOOP, Ethicon) versus electrocautery techniques for salpingectomy, which demonstrated comparable surgical outcomes; however, long-term implications were not reviewed in this study. A prospective or retrospective cohort study comparing laparoscopic salpingectomy performed using pretied surgical ligatures versus electrosurgery to explore the short-term and long-term outcomes further. This will be challenging given the rate of complications are so small; a very large sample size is required to adequately power such a study.

**Learning points**

- Uterine rupture post salpingectomy is a very rare adverse obstetric event.
- Currently there is insufficient evidence to recommend one laparoscopic salpingectomy technique over others.
- This case raises the need to be attentive when performing salpingectomy using electrosurgery especially near myometrium of the uterus.

**Acknowledgements** We would like to thank the patient for allowing us to publish this case so that the wider community may benefit from our findings.
We would also like to thank Dr Imad Mahmoud who was involved in the clinical management of this patient for his guidance and expertise.

Contributors All authors have contributed to the design, data collection and analysis of this article. Namely, Y-TH, SL-YY and SK were the contributors to literature review and the writing of the piece including technical support in editing the piece as required by publisher. AA oversaw the process and provided guidance in putting the above together.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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A perinatal review of singleton stillbirths in an Australian metropolitan tertiary centre

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\textsuperscript{1} Westmead Institute for Maternal and Fetal Medicine, Westmead Hospital, Sydney, New South Wales, Australia, \textsuperscript{2} University of Sydney, Sydney, New South Wales, Australia, \textsuperscript{3} Liverpool Hospital, Sydney, New South Wales, Australia, \textsuperscript{4} Nepean Hospital, Sydney, New South Wales, Australia

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Abstract

It is estimated that everyday 7000 women worldwide have their pregnancy end with a stillbirth, however, research and data collection on stillbirth remains underfunded. This stillbirth case series audit investigates an apparent rise in stillbirths at a Sydney tertiary referral hospital in Australia. A retrospective case series of singleton stillbirths from 2005–2010 was conducted at Westmead Hospital. Stillbirth was defined as per the Perinatal Society of Australia and New Zealand classification as a death of a baby before or during birth, from the 20th week of pregnancy onwards, or a birth weight of 400 grams or more if gestational age is unknown. A total of 215 singleton stillbirths were identified in a cohort of 28 109, a rate of 7.6 per 1000 singleton births. There was a significant increase in annual stillbirth rate at our institution; the rate exceeded both Australian national and state singleton stillbirth rates. After pregnancy terminations over 20 weeks were excluded from the data, there was no statistical change in the stillbirth rate over time. Congenital anomalies (27%) and unexplained antepartum death (15%) remained as major causes; fetal growth restriction (17%) was also identified as an increasingly important cause, particularly in preterm gestations. Termination of pregnancy after 20 weeks was found to be the cause of rising stillbirth rate at our institution. Local and national data collection on stillbirth should be standardised and should include differentiation of termination of pregnancy as a separate entity so as to accurately assess stillbirth to target appropriate research and resource allocation.

Introduction

There are more than 2.6 million stillbirths worldwide every year beyond 28 weeks gestation, with estimates of over 7000 women experiencing stillbirth every day.\textsuperscript{[1–3]} The majority (98%) of stillbirths occur in low and middle income nations, many of which are under-reported.\textsuperscript{[4]} However this significant burden on families has improved from estimates of 24.7 per 1000 births in the year 2000 to currently 18.4 per 1000 births,\textsuperscript{[1]} which has remained stable over
the last five years. [5] Stillbirth is still the largest contributor to perinatal death rate and is ten times more common than sudden and unexpected infant deaths. [6]

Overall there has been a decline in the rate of stillbirths in high income countries, however Australia has not reflected these trends. [2, 7, 8] In 2013 there were 2,191 stillbirths in Australia, a stillbirth rate of 7 per 1000, [9] stable from a stillbirth rate of 6.7 per 1000 births in 2002. [10]

The cause of majority of stillbirths in high income countries remain unexplained, accounting for 27–75% of all cases, varying according to the classification system used. [10, 11] Congenital anomaly has been documented as the leading cause of known stillbirths in Australia. [12, 13] The Australian Institute of Health and Welfare (AIHW) 2013 [9] report found a rising rate of stillbirths amongst the 20–23 week gestational age group in Australia, stating that terminations were unable to be distinguished from all stillbirths in this subgroup.

Despite the high prevalence of stillbirth globally, the UN Millennium Development Goals did not address stillbirth as a significant public health concern. This significant omission to an essential public health tragedy is readdressed in the 2014 Every Newborn Action Plan (ENAP) that is coordinated by UNICEF and the World Health Organisation (WHO) and aimed at reducing preventable newborn and fetal deaths. [14] ENAP sets the difficult world goal of a stillbirth rate of 10 per 1000 by 2035. [15] Despite the prominence placed to this significant global issue, there remains a lack of substantial research in this area. [16, 17] A recent review for an effective global stillbirth and neonatal classification system, documented and compared 81 different systems used with no method satisfying more than 7 of 17 expert-determined domains for effective classification. [18] The lack of adequate standardised methods of investigating, collecting and reporting data is critical for the prevention, management and understanding of stillbirth. [19–21] Perinatal Society of Australia and New Zealand (PSANZ) stillbirth clinical practice guideline was developed in order to standardise the investigations, data collection, classifications and reporting of perinatal deaths and to enable analysis of such data but needs effective implementation. [22] PSANZ Perinatal Death Classification (PSANZ-PDC) defines stillbirth as the death of a baby before or during birth, from the 20th week of pregnancy onwards, or a birth weight of 400 grams or more if gestational age is unknown. [23] Across Australia there is inconsistent reporting on termination of pregnancy and exclusion or inclusion of terminations from stillbirth records. Hence it has not been possible to reliably separate terminations from other causes of stillbirth in Australia. [12]

In 2013 Westmead Hospital, a major tertiary teaching hospital had a catchment population of 876,500 with approximately 43% being born overseas, compared to only 27% across the state of New South Wales. [24] The literature suggests that ethnicity and country of birth are risk factors for stillbirth. [25–27]

The primary aim of the study was to review the incidence, causes of singleton stillbirth and any recent trends at our institution in the context of a demographically diverse obstetric population over a six-year period.

**Materials and methods**

A retrospective case series review was conducted using data extracted from the hospital obstetric database. All singleton stillbirths over a six-year period from January 1st 2005 to December 31st 2010 at our institution were included in the study. Multiple pregnancies were excluded from this analysis. Local and regional designated referral pathways based on place of residence were consistent during the study period.

The review was conducted in accordance to PSANZ perinatal mortality audit guidelines. The standard pro forma was completed individually for each stillbirth after careful review of
hospital records. The pro forma was modified to incorporate consanguinity, which was relevant to the study population.

A total of 235 singleton stillbirths were identified. Subsequently 20 were omitted from analysis, due to missing medical records (n = 4), incorrect classification of stillbirth (n = 6) and patient transferred to our institution following stillbirth occurring at another hospital prior to transfer (n = 10).

A team of specialists in maternal fetal medicine analysed 215 files that were available for review to ascertain the cause of stillbirth according to the PSANZ Perinatal Death Classification system (PSANZ-PDC). Fetal growth restriction was defined as per the PSANZ-PDC category 8, inclusive of birth weight of <10th percentile of gestational age in a non-macerated stillbirth and or confirmed diagnosis of growth restriction by antenatal ultrasound. [23]

Data collected and used for analysis included primary cause of stillbirth, gestational age, maternal demographics, antenatal complications and postpartum maternal outcomes. Investigations for stillbirth and follow-up data according to PSANZ perinatal guidelines were also collected.

The statistical software package SPSS, version 21 (SPSS Inc. Chicago Illinois) was used to analyse the data collected. Cross-tabulation between stillbirth and different covariates was performed in order to define the characteristics of the study population. Descriptive analysis of stillbirth and antenatal care received, stillbirth investigations and postpartum follow up were also performed. Univariate logistic regression analysis was used to calculate the odds ratio (OR) and the 95% confidence interval to determine the trend in stillbirth rate over the study period. Overall cause of stillbirth and analysis of cause stratified by type of stillbirth (antepartum or intrapartum) and three gestational ranges (term ≥37 weeks, preterm 28–36+6 weeks and early preterm 20–27+6 weeks) were also performed.

Approval for the study was obtained from the Western Sydney Local Health District Human Research Ethics Committee.

Results
During the study period, 2005–2010, 28 109 singleton deliveries were recorded at our hospital, this comprised 215 stillbirths for analysis. The overall singleton stillbirth rate varied from 6.2 to 9.4 per thousand singleton births over the study period (Table 1), with an overall rate of 7.6/1000 births. We noted a statistically significant rising trend in the singleton stillbirth rate (OR per year = 1.08, 95%CI 1.001 to 1.171, p = 0.048). However, after excluding termination of pregnancy (TOP n = 40) this was not significant (OR per year = 1.03, 95%CI 0.945 to 1.124, p = 0.49).


<table>
<thead>
<tr>
<th>Year</th>
<th>Australian Births</th>
<th>National SBR*</th>
<th>National singleton SBR*</th>
<th>Westmead Births</th>
<th>Westmead singleton SBR*</th>
<th>Westmead singleton SBR *#</th>
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<td>2005</td>
<td>272 419</td>
<td>7.3</td>
<td>6.9</td>
<td>4 504</td>
<td>6.2</td>
<td>5.3</td>
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<td>2006</td>
<td>282 169</td>
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<td>7.4</td>
<td>7.0</td>
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<td>2008</td>
<td>296 925</td>
<td>7.4</td>
<td>6.9</td>
<td>4 688</td>
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<td>299 220</td>
<td>7.5</td>
<td>7.4</td>
<td>4 790</td>
<td>9.4</td>
<td>6.5</td>
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<td>2010</td>
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<td>7.4</td>
<td>7.0</td>
<td>5 206</td>
<td>8.6</td>
<td>6.5</td>
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</tbody>
</table>

National stillbirth rate without TOP is not available
* Per 1,000 Singleton Births
# without TOP

doi:10.1371/journal.pone.0171829.t001
In our study group of 215 mothers, 90 were Australian born and 125 were overseas born.
The maternal ethnicity data was not available for the general obstetric population. Demo-
graphic data from the stillbirth population are presented in Table 2.
A majority of women (84%) in this study who had a stillbirth were non-smokers and we
were not able to assess smoking as a risk factor for stillbirth.

Table 2. Demographics and clinical characteristics of women with stillbirths.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Stillbirths</th>
<th>Percentage of Stillbirths (%)</th>
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<tbody>
<tr>
<td>Maternal Age</td>
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<td>85.58</td>
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<td>12.09</td>
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<tr>
<td>&gt; 34</td>
<td>5</td>
<td>2.33</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primipara</td>
<td>201</td>
<td>93.49</td>
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<tr>
<td>1–3</td>
<td>12</td>
<td>5.58</td>
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<td>&gt; 3</td>
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<td>0.93</td>
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<td>Gestational Age</td>
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<tr>
<td>Early (20–27 weeks)</td>
<td>115</td>
<td>53.49</td>
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<tr>
<td>Preterm 28–36</td>
<td>59</td>
<td>27.44</td>
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doi:10.1371/journal.pone.0171829.t002
Parental consanguinity was a feature in 28 of 184 stillbirths (15%), with 31 (14%) cases missing this data. Between 2005 and 2010, consanguinity rate amongst those who had a stillbirth increased (Fig 1).

Thirty seven percent of the study group reported decreased fetal movement in the week preceding the stillbirth. Within this sub group, the predominant causes of stillbirth was due to unexplained antepartum death (27%) followed by fetal growth restriction (22%) and congenital anomalies (20%). Five percent of women had not booked for antenatal care prior to their diagnosis of stillbirth.

The most common causes of singleton stillbirth were congenital abnormality (27.4%), intrauterine growth restriction (IUGR; 16.7%), threatened preterm labour (14.9%) and unexplained stillbirth (14.9%). The majority of the stillbirths (78%) occurred in the antepartum period (Fig 2). There were a total of 46 stillbirths classified as intrapartum death. Of these 15 were due to termination of pregnancy, 8 were at gestations of extreme prematurity (<24/40) and 7 were due to congenital anomalies as a cause of death. This results in an intrapartum stillbirth rate of 9% (16/175) which included 3 cases of stillbirth classified as hypoxic peripartum death.

The causes of stillbirth varied according to gestational age. At term, the most common cause of stillbirth was unexplained antepartum death (39%), perinatal infections (13.9%) and congenital abnormalities (13.9%). In preterm gestations (28–36+6 weeks), congenital abnormalities (32.8%), intrauterine growth restriction (17.2%) and antepartum haemorrhage (15.5%) were the most common causes. In early preterm gestations (20–27+6 weeks) congenital abnormality (29.3%), preterm labour (26.7%) and IUGR (19.8%) were the top three causes of stillbirth. Disorders such as hypertension are classified as per criteria set in PSANZ-PDC section 7 (https://www.psanz.com.au/assets/Uploads/Section-7-Version-2.2-April-2009.pdf) with expert consensus that the condition was the primary issue that resulted in stillbirth.

Uptake of stillbirth investigations was analysed after the exclusion of terminations of pregnancy (n = 40). Although postmortem was offered in 87% of the cases, the uptake was only 42%. Of the unexplained antepartum stillbirths, 53% had a postmortem performed.
Complete maternal blood testing, as recommended by PSANZ guidelines (Perinatal Society of Australia and New Zealand, 2009 https://www.psanz.com.au/assets/Uploads/Section-5-Version-2.2-April-2009.pdf), was undertaken in 50% of women with stillbirth and partial tests in 38%. Other investigations included ultrasound prior to delivery (45%), placental histopathology (93%) and amniocentesis (5%). There were 159 placental histopathology results available, excluding the 33 pregnancy terminations reports. Only 17% (n = 27) of placental histopathology results were reported as normal; 30% (n = 47) showed evidence of placental insufficiency, 33% (n = 52) showed changes associated with infection while 16% (n = 26) had pathology associated with the umbilical cord.

The reason given for termination of pregnancy (n = 40) were varied with, 40% (n = 16) were for fetal anomaly, genetic cause 28% (n = 11), 4 terminations were for maternal indication (hypertension and preeclampsia), some of these conditions were considered fatal and no terminations were for social reasons.

Medical records documented medical follow-up in 64%, midwifery follow-up in 85% and bereavement counselling in 85% after discharge.

Fig 2. Cause of stillbirth using PSANZ perinatal death classification- comparison of Westmead Hospital singleton data and national data.

doi:10.1371/journal.pone.0171829.g002
Discussion

The data presented from our review demonstrated a rising annual singleton stillbirth rate, a trend beyond the Australian national rate between 2005 and 2010 (Table 1). However, the stillbirth rate was found to be stable after terminations were identified and excluded from the cohort. Varying inclusion of termination of pregnancy in stillbirth figures throughout Australia and internationally provides a challenge to interpretation of stillbirth figures.

Bythell et al. [28] found there was a consistent overestimation of the real stillbirth rate due to termination of pregnancy. A Canadian study also revealed the need to have clear data as the rising stillbirth rate in their study group was the result of an increase in late termination of pregnancy. [29] The rising trend in Australian national stillbirth rate at an earlier gestation [12] may reflect an increase in termination as was uncovered at our institution. A large linked data study in Western Australia [30] from 1986–2010, found an increase in late termination of pregnancy had significant influence on stillbirth rates, concluding that disaggregated data was desirable for accurate analysis of trends in perinatal statistics. Flenady et al. [19] also called for standardised stillbirth data parameters, inclusive of details of termination to ease comparative studies between countries.

In the national data, 71.9% of confinements in 2010 were to Australian born mothers. [13] This is a significant contrast to our obstetric population with 41% born in Australia. Ethnicity and in particular the Indian subcontinent, has been identified to be associated with an increase in stillbirth rates [25–27], the contribution of this factor to stillbirth in our cohort is unknown and warrants further investigation.

Ethnicity is not recorded in the obstetric database and country of birth was the only relevant parameter available for our study. The literature suggests that recording ethnicity along with country of birth is needed for accurate appraisal of pregnancy outcomes in Australia and should be incorporated into obstetric/midwifery data collection. Further study into genetic differences and susceptibility to pregnancy complications as well as relevant cultural factors should be investigated to understand the risk of stillbirth in a multicultural obstetric population. We have identified consanguinity as a potential important risk factor for stillbirth in our population. Consanguinity as a risk factor for stillbirth has been suggested in other studies. [31–34] A previous study at this hospital during the same time period, revealed an overall consanguinity rate of 5.5%, less than the 15% found in this stillbirth case series. [34] Further investigation with a larger cohort is warranted into the clinical implications of consanguinity for stillbirth.

It is of interest that 5% of women in our audit were unbooked (i.e. had not booked-in hospital for antenatal care prior to presentation with stillbirth). Women that are unbooked and present late for antenatal care are known to be at greater risk for adverse fetal outcome. [34–36]

Our tertiary centre has a state-wide role in managing and delivering babies with surgical and congenital abnormalities due to its proximity to a large tertiary Children’s Hospital. The disparity between our institution and national stillbirth rates was not accounted for by this factor alone. The study demonstrated that stillbirth due to congenital abnormalities accounted for 27% of all cases, which was only marginally different to the national rate of 25.8% in 2010. [13] Interestingly, there was a difference in the rates of IUGR between the national and our hospital data. IUGR has emerged as one of the leading causes of singleton stillbirth in our hospital over this period accounting for 16.7% of stillbirths which is higher than the national rate of 8.8% in 2010. [13] Further study into ethnicity and causes of stillbirth such as IUGR may be beneficial to explore the higher rate of stillbirth associated with IUGR in our multicultural
population. Growth restriction as a cause of stillbirth accounted for 20% of early preterm (<28 weeks), 17% of preterm (28–36\textsuperscript{6} weeks) and 5.6% of term stillbirths (≥37 weeks). These results highlight the necessity to improve antenatal screening, detection and surveillance of IUGR, particularly in the preterm gestations. Recent publications have demonstrated that detection of IUGR can be accomplished by improved antenatal surveillance.\textsuperscript{[37, 38]} This is of particular significance to our antenatal care framework, as low risk women are often not seen between 20 and 28 weeks of pregnancy.

Unexplained antepartum stillbirth remained in the top three causes of stillbirth despite 42% postmortem examinations and 93% having placental histological examinations (termination of pregnancy excluded). This study found that extra information was gained in 77% of cases through placental histopathogy uptake.\textsuperscript{[13]} However of the 32 cases where no cause of death was found 31 had placental histopathology completed.

During this study universal placental examination was recommended but there was poor compliance with recommendations. Since this case review placental examination process at this hospital has improved, guidelines are adhered to and valuable information that can be gained from placental review are now more readily available. Postmortem examination is considered gold standard for stillbirth investigation as a cause might be found in 20–86% of all stillbirths.\textsuperscript{[39, 40]} The postmortem rate is marginally higher than the state reported rate of 37.2%. This study also highlighted areas where clinical management can be improved with respect to completing all recommended investigations for stillbirth according to the PSANZ guidelines.

The importance of ongoing and persistent education with respect to the significance of fetal movement amongst pregnant women and obstetric staff was highlighted in this study by the fact that 37% of stillbirths had decreased movements in the week preceding adverse outcome. Additionally, this emphasises the need for clear protocols for management of decreased fetal movements. Set protocols for management of decreased fetal movements based on NSW health policy guideline, have been adopted at our institution since the study was undertaken.

Limitations of this study can be attributed to the retrospective methodology, which may lead to reporting and data collection bias. Recall bias may have effected some women who reported reduced fetal movement preceding stillbirth, due to the retrospective nature of the study it is difficult to delineate women who presented for assessment due to reduced fetal movement and those that may have been given leading questions on fetal movement after presenting for another reason. Consanguinity data collection on extent of relatedness is poor, with related or not related the only definition. Well-designed prospective studies, such as the Auckland Stillbirth study, would improve data quality to investigate the risk factors of stillbirth.\textsuperscript{[41]} Variations in data collection throughout Australia and proven quality control of the data limits comparisons.

**Conclusion**

In high income countries stillbirth still remains an ongoing tragedy for women and their families with little or no reduction in overall rate. Our study confirms that termination of pregnancy has to be clearly delineated from stillbirth data. Appropriate resources can then be allocated to researching unexplained stillbirth and any modifiable risk to reduce stillbirth such as fetal growth restriction. In the setting of a changing multicultural population, with increasing patient numbers and limited resources, prospective data collection and review will assist in improving clinical outcomes. This will enable institutions to review allocation of resources, clinical practice, improve guidelines, identify areas for research and ultimately reduce the rate of stillbirth.
Following this study our institution has implemented a formal perinatal review process of all stillbirths and a standardised stillbirth care plan. However further prospective and ongoing research and analysis is crucial to recognise the variables and trends associated with stillbirths to manage and prevent adverse perinatal outcomes in our population.

Acknowledgments

We thank Dr. Karen Byth, senior biostatistician at the Western Sydney Local Health District Research & Education Network and Emma Gibbs the biostatistician for Women's and Newborn Health Division, Westmead Hospital for their assistance with statistical analysis.

Author contributions

Conceptualization: SK TIA RN.

Data curation: SK SJM ERS MM SY ZB NK RN TIA.

Formal analysis: SK.

Investigation: SK SJM ERS MM SY ZB NK RN TIA.

Methodology: SK.

Project administration: SK TIA SJM.

Supervision: SK TIA SJM.

Validation: SK SJM ERS MM SY ZB NK RN TIA.

Visualization: SK SJM ERS MM SY ZB NK RN TIA.

Writing – original draft: SK SJM ERS NK TIA.

Writing – review & editing: SK SJM ERS NK TIA.

References


A RARE CASE OF CHRONIC LYMPHOCYTIC LEUKAEMIA IN PREGNANCY

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**Background:** Chronic lymphocytic leukaemia (CLL) is one of the commonest leukaemias in the western world however is rare with pregnancy, as the median age of diagnosis is 72 years with a male to female ratio of 2:1. CLL is commonly associated with an increased risk of immunocompromise and infection.

**Method:** Case study and review of the management of CLL in pregnancy.

**Results:** A 29 year old woman was diagnosed with CLL 3 years prior to pregnancy. Her karyotype reported a deletion in 11q which confers a poor clinical outcome. She underwent 4 rounds of chemotherapy with Fludarabine, Cyclophosphamide and Rituximab and was clinically well.

She was advised against pregnancy by her treating team as this is a condition where the risk of relapse is high and she has a poor prognosis condition. During the pregnancy she experienced recurrent genital herpes infections and anaemia. Her Immuno-globulin A remained low and she received monthly intravenous immunoglobulin as well as blood transfusions every 3 weeks. Fetal monitoring revealed a small for gestational age fetus and she was carefully monitored by a multidisciplinary team. The risks and benefits of chemotherapy during pregnancy were care-fully discussed however this was not required during the pregnancy.

**Conclusions:** CLL is rare in pregnancy but our case illustrates that with careful monitoring, pregnancy can be safely achieved for these women.
Case Report

A Vaginal Angiomyofibroblastoma as a Rare Cause of a Prolapsing Vaginal Mass: A Case Report and Review of the Literature

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Received 27 December 2017; Accepted 21 March 2018; Published 29 April 2018

Academic Editor: Yoshio Yoshida

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Introduction. Angiomyofibroblastoma (AMFB) is a rare, benign, mesenchymal cell tumour which presents as a slow-growing mass. It is most commonly seen in the vulva and is often mistaken for Bartholin’s abscess. It is histologically diagnosed by the presence of stromal cells intermingled with small blood vessels. It is morphologically similar to cellular angiofibroma and aggressive angiomyxoma, the latter of which is locally invasive and has a possibility of metastasis and a high risk of local recurrence. There is one reported case of an AMFB undergoing sarcomatous transformation. Case Report. We report a case of a multiparous, 36-year-old woman with an anterior vaginal mass which was inappropriately treated as a vaginal prolapse prior to definitive surgical management. This is only the second reported case of an AMFB presenting as a prolapsing mass.

1. Introduction

Angiomyofibroblastoma (AMFB) is a rare, benign, mesenchymal tumour that most commonly occurs as a slow-growing mass in the vulva, first described in 1992 [1]. It is often misdiagnosed as Bartholin’s gland cyst [1, 2].

This type of solid tumour has also less commonly been described in the vagina and the inguinoscrotal region of men. It is most prevalent in women in the reproductive age group with a mean age of 45 and varies in size (from 0.5 to 23 cm) but is usually less than 5 cm [1–4].

Histologically, it has a defined border and is characterised by alternating hypo- and hypercellular areas with numerous blood vessels [1, 5].

2. Case Report

We describe a case of a 36-year-old multiparous (G3P2) woman who presented with an acute episode of pelvic pain. She was referred to a general gynaecological clinic after ultrasound findings revealed a 4.1 cm complex left ovarian cyst suggestive of an endometrioma.

She also reported a 2-year history of a bulge that protruded from her vagina and was associated with discomfort and dyspareunia and occasionally required digital reduction especially with tampon use. She had been diagnosed with a vaginal prolapse by a gynaecology clinic at another institution.
Her past medical history consisted of migraines with aura, exercise induced asthma, and a family history of breast cancer (half-sister). She had never had a PAP smear.

On bimanual examination, a well-delineated solid mass was found on the anterior vaginal wall in the midline, measuring 5 cm by 5 cm. There was no evidence of pelvic organ prolapse with good support of the uterus, posterior wall, and anterior wall above the mass. The cervix was visualised anteriorly and there was no evidence of cervical excitation. A routine PAP smear was performed with difficulty secondary to the vaginal mass.

With respect to investigations, Ca125 was 29 U/mL giving a low relative malignancy index. A repeat ultrasound scan demonstrated a 2.9 cm left ovarian cyst, suggestive of an endometrioma and a solid mass inferior to the uterus and anterior to the vagina, displacing the bladder (Figure 2).

On Magnetic Resonance Imaging, a 45 mm × 50 mm solid mass in the vesicovaginal septum with a well-defined margin was demonstrated (Figure 1). The mass was displacing the bladder anteriorly and displacing the urethra towards the left of the midline. T2 imaging showed a predominantly hypointense, heterogeneous signal with areas of hyperintensity. There was mild enhancement after gadolinium injection. Close to the external urethral orifice, the interface between the mass and the urethra was ill defined. Evidence of a left ovarian endometrioma and endometriosis deposits were seen elsewhere in the pelvis.

These MRI findings suggested that the mass was either endometriosis with surrounding reactive fibrous and smooth muscle proliferation, neoplasm, or an infection relating to a urethral diverticulum. After a multidisciplinary meeting with a urogynaecologist, the patient underwent an examination under anaesthesia, diagnostic laparoscopy, cystoscopy, excision of endometriosis, and excision of the vaginal mass.

The vaginal mass was removed with laparoscopic assessment via a midline incision on the anterior vaginal wall with lateral dissection around the cystic structure (Figures 3–6). A cystoscopy and urethroscopy suggested no involvement and the cyst was enucleated. Multiple haemostatic sutures were needed with surgical snow to achieve haemostasis and the defect was closed. A repeat cystoscopy and urethroscopy showed no injury.

Histopathological macroscopic assessment of the mass showed pale tan tissue surrounded by a thin capsule and on sectioning a homogeneous whorled tan tissue (Figure 6). Microscopically the low power photomicrographs showed a well-circumscribed border. It comprised collagenised areas of epithelioid to spindled cells with small to thin walled arborizing vessels. Aggregation of cells around vessels was noted and there were no atypical mitoses, necrosis, or atypia (Figures 7 and 8).

The immunohistochemistry showed positive desmin, SMA, CD34, and vimentin. The cells displayed high intensity nuclear positivity for progesterone and oestrogen receptors. These findings were consistent with a diagnosis of angiomyofibroblastoma.

3. Discussion

AMFB is a very rare benign, mesenchymal tumour with less than 100 cases previously having been reported in the literature. There has been a reported age range of 17–86 with a mean age at presentation of 45 [2, 6, 7].

It commonly presents as a painless, slow-growing, vulval mass and is most commonly diagnosed as Bartholin’s cyst or abscess (46%) or a lipoma (15%) [2]. There is only one other reported case of it presenting as a prolapsing vaginal mass [8]. There is often a delay in diagnosis with a mean duration of 29 months between initial symptoms and diagnosis [2, 6].

AMFB is morphologically similar to other invasive mesenchymal cell tumours such as aggressive angiomyxoma (AAM) and cellular angiofibroma and they share many
are often found in the periphery [10]. Vulvovaginal myofibroblastomas characteristically contain ovoid, spindle, or stellate cells in a variety of architectural patterns. They also do not have the perivascular aggregates seen in AMFB [10]. Both cellular angiofibromas and myofibroblastomas exhibit the loss of RB1 and FOXO1A1 genes due to the deletion of the 13q14 chromosomal region. This typical loss of genetic material is not found in AMFB [13].

Immunohistologically, AMFB tumours have been found to be strongly positive for vimentin, positive for desmin, and to a lesser degree alpha-smooth muscle actin. Staining is rarely useful in differentiating between tumour types [13]. The stromal cells are characteristically positive for oestrogen and progesterone receptors, suggesting a hormonal role in the development of the tumour [14].

There have only been 5 previous reports of MRI findings of an AMFB. All report a mass with well-defined margins and as in our case they have been found to appear as a heterogeneous signal intensity on T2-weighted MRI. All other cases reported fast and persistent enhancement on dynamic gadolinium-enhanced MRI whereas ours showed only mild enhancement [15, 16].

The other studies found a mass with homogeneous intermediate signal intensity on T2-weighted MRI [7, 17, 18]. Ultrasound has been reported to be useful in assessing heterogeneity, vascularity, and delineating infiltration and relation to surrounding structures [7, 19].

It is widely accepted that AMFB can be treated with wide local excision with clear margins. There has only been one case report of a benign local recurrence. This was a pedunculated mass 5 × 3 cm arising from the vaginal vault which was excised with clear margins. Upon follow-up 14 months later 3 small, nodular growths were found close to the site of excision on the anterior and posterior vaginal walls which, when excised, showed the same features as the previous tumour with no transformation [8].

There has also been reported one case of previously diagnosed AMFB undergoing sarcomatous change. A 13 cm vulval mass was resected which showed many accepted features of an AMFB however did show focal sarcomatous change at the resected margin. At 2 years, the mass had recurred at the same site and resection demonstrated a 14 cm mass comprised of only the high-grade sarcomatous component with vascular invasion that was not previously present [20].

Another reported case of a locally invasive recurrence of AMFB at 2 years after resection was due to a misdiagnosed AAM on the original specimen [21]. The local recurrence rate of AAM after clear margin resection has been reported to be up to 47% [22–25].

4. Conclusion

The majority of AMFB occur in the vulva, most commonly presenting as a painless mass.

Vaginal AMFB are rarer and may present later with dyspareunia, awareness of a vaginal mass, or an incidental finding on exam [26–28]. Wide local excision is the recommended treatment, with enough surrounding tissue to enable

overlapping immunohistochemical and structural features [9, 10].

It is diagnostically challenging to differentiate between AMFB and AAM but important due to the latter’s locally invasive nature, the possibility of metastasis, and the high risk of local recurrence [11, 12]. AMFB can be diagnosed by a higher cellularity, distinct border, plump stromal cells, increased presence of small blood vessels, and a lesser degree of stromal myxoid change [6]. Other differential diagnoses include cellular angiofibroma and vulvovaginal myofibroblastoma. Cellular angiofibromas are uniformly cellular with thick-walled, hyalinised blood vessels without surrounding aggregation of epithelioid or plasmacytoid cells. Adipocytes

overlapping immunohistochemical and structural features.

overlapping immunohistochemical and structural features [9, 10].
infiltrative AAM. The pathologist to differentiate between AMFB and the locally slender collagen fibrils with no evidence of necrosis.

Figure 7
(a) Low power photomicrographs of the angiomyo-
ofibroblastoma with prominent thin walled vessels surrounded by clusters of epithelioid to spindle shaped cells (arrows)
(b) Low power photomicrographs of the angiomym-
ofibroblastoma with prominent thin walled vessels surrounded by clusters of epithelioid to spindle shaped cells (arrows)

Figure 8: Cross section showing alternating hypercellular areas around blood vessels (H) and hypocellular (O) areas containing slender collagen fibrils with no evidence of necrosis.

MRI and US can be useful imaging modalities depending on location of the tumour. Due to the rarity of cases, there are no recommendations on long-term monitoring but due to the reported instances of tumour recurrence and sarcomatous transformation we suggest that follow-up should be considered until at least 2 years postoperatively [8, 20].

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Case Reports in Obstetrics and Gynecology


Birth Outcomes, Intervention Frequency, and the Disappearing Midwife—Potential Hazards of Central Fetal Monitoring: A Single Center Review

James Brown, MBBS, BA, MPH, Andrew McIntyre, MBBS, Robyn Gasparotto, and Therese M. McGee, MD RANZCOG

ABSTRACT: Introduction: Many birth units use central fetal monitoring (CFM) under the assumption that greater surveillance improves perinatal outcomes. The unexpected loss of the CFM system at a tertiary unit provided a unique opportunity to evaluate outcomes and staff attitudes toward CFM. Methods: This retrospective cohort study compared patient data from 2,855 electronically monitored women delivering over a 12-month period, where CFM was available for the first 6 months but unavailable for the following 6 months. Primary outcomes relating to neonatal morbidity and secondary outcomes relating to intrapartum interventions were examined. Additionally, birth unit staff members were surveyed about aspects of care related to CFM. Results: There were no significant differences in perinatal outcomes between the cohorts. While unadjusted analysis suggested a lower spontaneous vaginal birth rate (55.4% vs 60.3%) and a higher cesarean delivery rate (25.1% vs 22.0%, \( p = 0.026 \)), together with higher epidural (53.0% vs 49.2%, \( p = 0.04 \)) and fetal blood sampling (11.8% vs 9.4%, \( p = 0.03 \)) rates in the presence of CFM, these differences were lost when adjusted for prostaglandin ripening. Over half of the staff (56.0% of midwives, 54.0% of obstetricians) reported spending more time with the laboring woman in the period without CFM. Conclusions: This single institution’s experience indicates that in birth units staffed for one-to-one care in labor, central fetal monitoring does not appear to be associated with either a benefit on perinatal outcomes or an increase in cesarean delivery and other interventions. However, it is associated with a reduction in the time a midwife spends with the laboring woman. (BIRTH 43:2 June 2016)

Key words: cesarean delivery, central fetal monitoring, continuous fetal monitoring, epidural, fetal heart rate monitoring, fetal scalp blood sampling, perinatal outcomes

Many birth units have incorporated central fetal monitoring (CFM) as an adjunct to continuous electronic fetal monitoring during labor, under the assumption that greater surveillance will improve perinatal outcomes (1). CFM allows health care workers to survey the electronic fetal monitoring of multiple patients simultaneously from a remote location such as a staff station.

While electronic fetal monitoring is an easy to use, comprehensive surveillance tool, with a beneficial influence on neonatal morbidity and mortality rates demon-
Stratified in several large cohort studies (2), national guidelines and systematic reviews continue to highlight a lack of evidence to support its superiority over intermittent auscultation in improving outcomes such as perinatal death and cerebral palsy; they also document the increase in cesarean delivery and instrumental birth rates associated with its use (3–6). The additional influence of CFM is unclear.

CFM has widespread and growing use with a large number of available systems (7). Despite this, little is known about its role (5). There have been only two studies examining the effect on perinatal outcomes of electronic fetal monitoring with CFM versus electronic fetal monitoring without CFM. Both found no significant difference (1,8), while one found an increase in the cesarean delivery rate with CFM.

CFM provides the potential benefit of having several "back-up" clinicians overseeing fetal monitoring as second or third line screeners for worrying trends that may have been overlooked by the primary carer. Alternatively, the midwife/doctor in the labor room may feel pressured to undertake potentially unnecessary interventions by the comments of colleagues in the staff room who can see the CFM but otherwise know nothing about the labor management already in place. Additionally, the possibility exists that midwives may attend the laboring woman less frequently in the presence of CFM (9). This may negatively influence the known benefits of one-on-one care in labor (5). No study has yet examined the influence of CFM systems on staff behavior or opinions (7).

CFM units are expensive to implement and maintain. With growing pressure on the efficient allocation of health care resources, budgets need to be directed at providing adequate staffing (10) and infrastructure that materially and cost-effectively benefits the patient (8). It is unknown whether CFM is a cost-effective intervention. The substantial initial cost may possibly be offset by minimizing adverse events or by needing fewer staff to oversee the monitoring of many patients (although the ability to identify abnormal patterns can be compromised if allocated staff are too few or the screens suboptimal) (11,12). Alternatively CFM may lead to more intervention without improved outcomes as a result of inappropriate over-surveillance.

Now that CFM is standard practice in perinatal care in many high-resource countries, it is increasingly difficult to compare birth care and outcomes with and without its availability. Westmead Hospital (New South Wales, Australia) delivers over 5,500 births per year. It caters to an ethnically diverse population and is a tertiary referral centre for high-risk pregnancies because of its large neonatal intensive care unit (NICU) and adjoining Children’s Hospital. For over 10 years, the birth unit used CFM for all women having electronic fetal monitoring during labor, until the system unexpectedly failed on April 7, 2014. Over the ensuing weeks, it was deemed irreparable and replacement was indefinitely deferred for financial and technological reasons pending further review.

This unexpected loss provided a unique opportunity to evaluate birth outcomes, intervention rates, and staff attitudes with and without the availability of CFM, and to contribute to the limited existing body of knowledge about the efficacy of a technology used increasingly across birth units worldwide.

Methods

This retrospective cohort study compared patient data from women delivering in the birth unit at Westmead Hospital over a 12-month period, during which time CFM was available for 6 months (from October 7, 2013 to April 6, 2014) and was unavailable for 6 months (from April 7, 2014 to October 6, 2014). The unit is consciously staffed to provide one-to-one midwifery care for women in established labor at most times; midwives undertake nearly all spontaneous vaginal births.

Inclusion criteria for the study were live singleton pregnancies with cephalic presentation, in either spontaneous or induced labor, and requiring continuous electronic fetal monitoring for any standard indication as per national guidelines (13). Multiple pregnancies, malpresentations, and women who presented in labor before their planned elective cesarean delivery date were excluded.

Patient demographic and birth outcomes data were collected from the Westmead Hospital perinatal database (Obstetrix).

The primary outcomes assessed were neonatal welfare: umbilical cord arterial lactate between 5.2–10 mmol/L and greater than 10 mmol/L, 5-minute Apgar score less than 7 and less than 4, and admission to the NICU. Cord lactate testing was discretionary rather than routine, but was performed with a low threshold for any deviation from usual intrapartum practice or where there was any concern about fetal or neonatal welfare. It was performed using a Lactate Pro test meter and strips (Arkay Inc., Kyoto, Japan). The secondary outcomes assessed were labor intervention rates: cesarean delivery, instrumental birth, fetal scalp blood sampling (FBS), and epidural rates.

Potential confounding factors considered with respect to these clinical outcomes include parity, maternal age, race, maternal weight, medical conditions, tobacco use, gestational age, birthweight, induction of labor, oxytocin use, and cervical ripening. Those characteristics significantly different between the study periods in the
univariate analyses \((p < 0.05)\), in addition to parity, were analyzed using multivariate analysis.

In addition to clinical outcomes, consultant and trainee obstetricians, and senior (team leader) and junior qualified midwives who had worked for at least 3 months during each of the CFM and non-CFM periods were surveyed about aspects of CFM in early November 2014. The birth-related statistics for the non-CFM period were unknown to staff at that time. A senior midwifery educator oversaw the paper-based survey and ensured each eligible staff member received a survey form. The staff members then completed the survey anonymously and deposited it into a locked box in the birth unit. Staff status but not identity was ascertainable from the survey response. The time staff spent with a patient was self-reported. Staff rosters were reviewed to confirm equivalence of staffing numbers and seniority across both time periods.

Data were exported into a comma separated values file which was then sorted and analyzed using SPSS software using chi-square test and logistic regression analysis.

**Results**

**Demographics**

A total of 5,588 births occurred during the 12-month study period. After applying the exclusion criteria, a total of 2,855 births with continuous electronic fetal monitoring in labor were eligible for analysis (Fig. 1), with 1,385 births during the period receiving CFM and 1,470 in the period without. Background and other characteristics were similar between the two groups except for induction of labor (more common in the non-CFM group) and cervical ripening and prostaglandin \(E_2\) vaginal gel use (more common in the CFM group) (Table 1). The difference in induction rates is unexplained. The lower cervical ripening rates in the non-CFM period are at least partly explained by a change in hospital induction policy. In mid 2014, overlapping the time period of the study, the Bishop score warranting ripening was lowered from “less than 8” to “less than 7” and a move from prostaglandin \(E_2\) vaginal gel to balloon catheters was encouraged.

**Neonatal Outcomes**

There was no significant difference in any perinatal outcome measure, with umbilical cord lactate, Apgar scores and admission to the NICU being similar across both cohorts (Table 2). There were no perinatal deaths in either group. Cord arterial lactate was performed in 50 and 49 percent of patients in the CFM and non-CFM cohorts, respectively. Mild acidosis, taken as arterial lactate between 5.2 and 10 mmol/L occurred in approximately 20 percent of those tested in both cohorts, while more significant acidosis, lactate more than 10 mmol/L, occurred in 1–2 percent of those tested in both cohorts. The above results did not change when prostaglandin use was accounted for.

**Mode of Delivery and Other Intervention Rate**

In univariate analysis, there was a significant difference in mode of delivery patterns with and without CFM.
Compared with the non-CFM period, the intrapartum cesarean delivery rate in continuously electronically monitored women was significantly higher in the CFM period being 25.1 percent (348/1,385) compared with 22.0 percent (324/1,470). Conversely, spontaneous vaginal births were lower at 55.4 percent (767/1,385) compared with 60.3 percent (887/1,470) (Table 3). However, when cesarean delivery is examined as a single variable, it is not significant, having an odds ratio of 1.19 (95% CI 1.00–1.41). In addition, logistic regression analysis for possible confounding as a result of parity, induction, prostaglandin use and epidural, confirms the cesarean delivery rate to be no different between the cohorts (Table 4).

The rates of epidural and FBS utilization in the time period without CFM were found to be significantly lower than with CFM. The epidural rate during the period with CFM was 53 percent compared with 49.2 percent without CFM (OR 1.17 [95% CI 1.01–1.35]). Likewise, the performance of FBS was higher with CFM being 11.8 percent compared with 9.4 percent without CFM (OR 1.31 [95% CI 1.01–1.35]) (Table 3).

The increased epidural and fetal blood sampling rates persisted after correction for nulliparity and induction, but lost significance after adjustment for prostaglandin (Table 4).

**Survey Results**

Here 83 staff who had worked for at least 3 months during each of the 6-month periods completed the survey on their impressions about the impact of the

---

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With CFM</th>
<th>Without CFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19</td>
<td>25 (1.8)</td>
<td>32 (2.2)</td>
</tr>
<tr>
<td>20–24</td>
<td>165 (11.9)</td>
<td>196 (13.3)</td>
</tr>
<tr>
<td>25–29</td>
<td>481 (34.7)</td>
<td>487 (33.2)</td>
</tr>
<tr>
<td>30–34</td>
<td>491 (35.5)</td>
<td>521 (35.4)</td>
</tr>
<tr>
<td>35–39</td>
<td>192 (13.9)</td>
<td>207 (14.1)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>31 (2.2)</td>
<td>27 (1.8)</td>
</tr>
<tr>
<td>Gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 27 weeks</td>
<td>5 (0.4)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>28–32 weeks</td>
<td>29 (2.0)</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td>33–36 weeks</td>
<td>90 (6.5)</td>
<td>91 (6.2)</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td>1,261 (91.0)</td>
<td>1,350 (91.8)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>775 (56.0)</td>
<td>825 (56.1)</td>
</tr>
<tr>
<td>1 or greater</td>
<td>610 (44.0)</td>
<td>645 (43.9)</td>
</tr>
<tr>
<td>Early pregnancy BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19.9</td>
<td>196 (14.2)</td>
<td>201 (13.7)</td>
</tr>
<tr>
<td>20–24.9</td>
<td>652 (47.1)</td>
<td>674 (45.9)</td>
</tr>
<tr>
<td>25–29.9</td>
<td>317 (22.9)</td>
<td>383 (26.0)</td>
</tr>
<tr>
<td>30–34.9</td>
<td>137 (9.9)</td>
<td>134 (9.1)</td>
</tr>
<tr>
<td>≥ 35</td>
<td>83 (6.0)</td>
<td>78 (5.3)</td>
</tr>
<tr>
<td>Australian-born</td>
<td>461 (34.9)</td>
<td>497 (33.8)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>93 (6.7)</td>
<td>101 (6.9)</td>
</tr>
<tr>
<td>Preexisting diabetes, or IDGDM†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (all categories)</td>
<td>91 (6.6)</td>
<td>107 (7.3)</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>483 (34.9)*</td>
<td>580 (39.5)</td>
</tr>
<tr>
<td>Oxytocin in labor</td>
<td>823 (59.4)</td>
<td>908 (61.8)</td>
</tr>
<tr>
<td>Amniotomy performed</td>
<td>843 (60.9)</td>
<td>879 (59.8)</td>
</tr>
<tr>
<td>Any cervical ripening‡</td>
<td>254 (18.3)*</td>
<td>216 (14.7)</td>
</tr>
<tr>
<td>Cervical ripening with prostaglandin</td>
<td>231 (16.7)*</td>
<td>157 (10.7)</td>
</tr>
<tr>
<td>Cervical ripening with balloon catheter</td>
<td>32 (2.3)*</td>
<td>67 (4.6)</td>
</tr>
<tr>
<td>Birthweight [mean]</td>
<td>[3,293 g]</td>
<td>[3,278 g]</td>
</tr>
<tr>
<td>Birthweight ≥ 4,000 g</td>
<td>137 (9.9)</td>
<td>124 (8.4)</td>
</tr>
<tr>
<td>Birthweight ≤ 2,500 g</td>
<td>101 (7.3)</td>
<td>93 (6.3)</td>
</tr>
</tbody>
</table>

*Statistically significant at p < 0.05 level. †Insulin-dependent gestational diabetes mellitus. ‡A few women received cervical ripening with both prostaglandin and balloon catheter. CFM = central fetal monitoring.

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Table 2. Neonatal Outcomes with and without Central Fetal Monitoring (CFM) at Westmead Hospital, New South Wales, Australia, 2013–2014

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With CFM</th>
<th>Without CFM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>111 (8.0)</td>
<td>114 (7.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>No</td>
<td>1,274 (92.0)</td>
<td>1,356 (92.3)</td>
<td></td>
</tr>
<tr>
<td>Apgar score (5 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 and above</td>
<td>1,366 (98.6)</td>
<td>1,451 (98.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt; 7</td>
<td>14 (1.4)</td>
<td>16 (1.3)</td>
<td></td>
</tr>
<tr>
<td>&lt; 4</td>
<td>5 (0.4)</td>
<td>3 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Cord arterial lactate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performed</td>
<td>694 (50.1)</td>
<td>719 (49.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Not performed</td>
<td>691 (49.9)</td>
<td>751 (51.0)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5.2 mmol/L</td>
<td>544 (78.4)</td>
<td>567 (78.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>5.2–10 mmol/L</td>
<td>136 (19.6)</td>
<td>142 (19.7)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 mmol/L</td>
<td>14 (2.0)</td>
<td>10 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>

CFM = central fetal monitoring; NICU = neonatal intensive care unit.
absence of CFM (Table 5). Excluding staff on leave during the week of the survey, responses were received from 93 percent (28/30) of eligible obstetric staff and 95 percent (55/58) of eligible midwifery staff.

Overall, 55 percent of staff (56% of midwives, 54% of obstetricians) reported spending more time with the patient, 4 percent less time, and 40 percent the same amount when the CFM system was no longer available.

Most staff reported unchanged confidence in their own fetal monitoring interpretation with the absence of CFM, while 13 percent felt increased confidence and 16 percent felt decreased confidence. These differences were more marked among junior midwives (more confident) and consultant obstetricians (less confident).

While the majority of respondents across all groups believed perinatal outcomes would be unchanged, almost one-third (30%) expected a worsening of outcomes with the loss of the CFM. This expectation was highest among obstetric trainees (44%).

While the majority of respondents overall believed the intrapartum cesarean delivery rate would be

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With CFM No. (%)</th>
<th>Without CFM No. (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>348 (25.1)</td>
<td>324 (22.0)</td>
<td>0.026</td>
</tr>
<tr>
<td>Spontaneous vaginal</td>
<td>767 (55.4)</td>
<td>887 (60.3)</td>
<td></td>
</tr>
<tr>
<td>Instrumental</td>
<td>270 (19.5)</td>
<td>259 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Indications for cesarean delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructed labor</td>
<td>73 (21.0)</td>
<td>59 (18.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>203 (58.3)</td>
<td>199 (61.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>72 (20.7)</td>
<td>66 (20.4)</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>229 (29.5)</td>
<td>210 (25.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>Noninstrumental vaginal</td>
<td>334 (43.1)</td>
<td>399 (48.4)</td>
<td></td>
</tr>
<tr>
<td>Instrumental</td>
<td>212 (27.4)</td>
<td>216 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>119 (19.5)</td>
<td>114 (17.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Noninstrumental vaginal</td>
<td>433 (71.0)</td>
<td>488 (75.7)</td>
<td></td>
</tr>
<tr>
<td>Instrumental</td>
<td>58 (9.5)</td>
<td>43 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>734 (53.0)</td>
<td>723 (49.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>651 (47.0)</td>
<td>747 (50.8)</td>
<td></td>
</tr>
<tr>
<td>Fetal blood sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>164 (11.8)</td>
<td>138 (9.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>No</td>
<td>1,221 (88.2)</td>
<td>1,332 (90.6)</td>
<td></td>
</tr>
</tbody>
</table>

CFM = central fetal monitoring.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Observed OR (95% CI)</th>
<th>OR adjusted for nulliparity only</th>
<th>OR adjusted for induction of labor only</th>
<th>OR adjusted for prostaglandin use only</th>
<th>OR adjusted for epidural only</th>
<th>Combined multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean delivery</td>
<td>1.19 (1.00–1.41)</td>
<td>1.19 (1.00–1.42)</td>
<td>1.19 (1.00–1.41)</td>
<td>1.16 (0.98–1.38)</td>
<td>1.17 (0.98–1.02)</td>
<td>1.16 (0.97–1.38)</td>
</tr>
<tr>
<td>Epidural</td>
<td>1.17 (1.01–1.35)</td>
<td>1.18 (1.01–1.37)</td>
<td>1.20 (1.04–1.39)</td>
<td>1.13 (0.97–1.31)</td>
<td>–</td>
<td>1.19 (1.02–1.38)</td>
</tr>
<tr>
<td>Fetal blood sampling</td>
<td>1.30 (1.02–1.65)</td>
<td>1.31 (1.03–1.67)</td>
<td>1.33 (1.05–1.69)</td>
<td>1.24 (0.97–1.58)</td>
<td>1.24 (0.97–1.58)</td>
<td>1.26 (0.98–1.61)</td>
</tr>
</tbody>
</table>

*Includes nulliparity, induction of labor, prostaglandin use, and epidural. CFM = central fetal monitoring.
unchanged, one-third (33%) believed the cesarean delivery rate would be lower with the loss of the CFM. This expectation was the highest among senior midwives (46%).

**Discussion**

Our study builds on the findings of the two earlier reports (1,8). At the same time, it adds the unique perspective afforded by the staff survey which, with a high response rate across all levels of practitioner, provides a window into staff beliefs and practices around CFM.

**Presence of CFM Does Not Appear to Decrease Adverse Perinatal Outcomes**

The intention of CFM is to allow simultaneous remote viewing of all electronically monitored patients for enhanced surveillance and therefore safety. The staff survey reflects this faith in enhanced safety, with 30 percent believing perinatal outcomes would be poorer with the loss of the CFM. In fact, the actual results do not support this belief. In line with earlier reports (1,8), our study demonstrates that perinatal outcomes are not compromised by the absence of the CFM. It must, however, be acknowledged that the study is underpowered to detect rare intrapartum events and that the one-to-one staffing ratio allowed continuous surveillance of each electronic fetal monitor even without CFM.

**Presence of CFM Does Not Appear to Influence Mode of Delivery**

The possibility that decision-making about a laboring woman can be influenced by pressure for intervention from uninvolved colleagues who can, nevertheless, see the CFM, is reflected in the survey finding that one-third of staff (and nearly half of senior midwives) believed the intrapartum cesarean delivery rate would be lower with the loss of CFM. However, the results do not confirm this belief.

Univariate analysis suggests a significant fall in the cesarean delivery rate in the non-CFM period in keeping with the findings of the earlier CFM study by Weiss (8); similarly, there was an increase in both epidural and FBS utilization. However, the differences in cesarean, epidural, and FBS rates are lost when multivariable analysis includes the variations in prostaglandin use between the groups. While the prostaglandin variation may simply reflect the change in ripening policy that coincided with the study period (especially given that overall induction rates were actually higher in the non-CFM period) and while large randomized controlled trials have not shown a difference in cesarean rates between these ripening techniques (14–16), its confounding influence cannot be discounted. Overall

<table>
<thead>
<tr>
<th>Your confidence in electronic fetal monitoring interpretation</th>
<th>Junior midwives (n = 31)</th>
<th>Senior midwives (n = 24)</th>
<th>Obstetric trainees (n = 16)</th>
<th>Obstetric consultants (n = 12)</th>
<th>Total (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased with absence of CFM</td>
<td>8 (26%)</td>
<td>3 (12.5%)</td>
<td>0</td>
<td>0</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Decreased with absence of CFM</td>
<td>5 (16%)</td>
<td>3 (12.5%)</td>
<td>1 (6%)</td>
<td>4 (33%)</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>No change</td>
<td>18 (58%)</td>
<td>18 (75%)</td>
<td>15 (94%)</td>
<td>8 (67%)</td>
<td>59 (71%)</td>
</tr>
<tr>
<td>Amount of time you spend with the patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased with absence of CFM</td>
<td>18 (58%)</td>
<td>13 (54%)</td>
<td>10 (63%)</td>
<td>5 (45%)*</td>
<td>46 (56%)</td>
</tr>
<tr>
<td>Decreased with absence of CFM</td>
<td>0% (0)</td>
<td>1 (4%)</td>
<td>1 (6%)</td>
<td>1 (9%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>No change</td>
<td>13 (42%)</td>
<td>10 (42%)</td>
<td>5 (31%)</td>
<td>5 (45%)</td>
<td>33 (40%)</td>
</tr>
<tr>
<td>What influence do you think absence of CFM has on intrapartum cesarean delivery rate?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased with absence of CFM</td>
<td>5 (16%)</td>
<td>3 (12%)</td>
<td>2 (12.5%)</td>
<td>1 (8.3%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Decreased with absence of CFM</td>
<td>10 (32%)</td>
<td>11 (46%)</td>
<td>2 (12.5%)</td>
<td>4 (33.3%)</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>No change</td>
<td>16 (52%)</td>
<td>10 (42%)</td>
<td>12 (75%)</td>
<td>7 (58.3%)</td>
<td>45 (54%)</td>
</tr>
<tr>
<td>What influence do you think absence of CFM has on perinatal outcomes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved with absence of CFM</td>
<td>4 (13%)</td>
<td>2 (8%)</td>
<td>0</td>
<td>0</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Worsened with absence of CFM</td>
<td>8 (26%)</td>
<td>7 (29%)</td>
<td>7 (44%)</td>
<td>3 (25%)</td>
<td>25 (30%)</td>
</tr>
<tr>
<td>No change</td>
<td>19 (61%)</td>
<td>15 (63%)</td>
<td>9 (56%)</td>
<td>9 (75%)</td>
<td>52 (63%)</td>
</tr>
</tbody>
</table>

*One consultant did not respond to the survey question. CFM = central fetal monitoring.
Presence of CFM Is Associated with Reduced One-On-One Patient Care Even in Optimally Staffed Units

The potential hazard that CFM may reduce staff presence in the birthing room (9) is confirmed by the study. Labor is a time of physical and psychological distress for women, and of potential risk to both mother and her baby. Accordingly, women in established labor should have one-to-one or near-continuous midwifery care (4,10). Continuous support in labor also appears to improve outcomes and reduce interventions (17). While the availability of CFM may be expected to reduce the time the obstetrician spends with a laboring woman, it should not influence the attention the midwife gives to the woman under her care in units like ours which are staffed for one-to-one support and where midwives perform almost all spontaneous vaginal births. Even so, 56 percent of midwives reported spending more time with the woman in the non-CFM period.

Limitations

Our study has some limitations. First, by its nature, it is retrospective with the intervention and control groups across different time periods, as is the case for the two earlier studies (1,8). The policy change in cervical ripening that coincided with the study period has been discussed above; there were no other changes in practice while staffing numbers and skill mix were the same across the time periods. The women cohorts appear to be similar although potential unexplored confounders include the indication for induction and where midwives perform almost all spontaneous vaginal births. Even so, 56 percent of midwives reported spending more time with the woman in the non-CFM period.

Conclusion

In conclusion, our data suggest that in birth units staffed for one-to-one care in labor, central fetal monitoring does not appear to be associated with either a measurable benefit on perinatal outcomes or an increase in cesarean delivery or other interventions. However, it is associated with a reduction in the time a midwife spends with the laboring woman under her care.

References

Background: A blood pressure profile (BPP) is often used to diagnose and manage hypertension in pregnancy. However, there is no consensus on the number and interval of blood pressure (BP) readings required.

Aims: To ascertain whether BP readings at 15-min interval over one hour yields clinically equivalent results to readings at 60-min interval over three hours.

Materials and methods: Eighty unique women were recruited to this prospective study. Automated BP machines were used to take readings at 15-min interval over one hour and at 60-min interval over three hours. The mean systolic and diastolic BPs obtained using each regimen were calculated and compared. Women also completed a questionnaire to evaluate the psychosocial and financial impact of a prolonged outpatient investigation.

Results: BP readings from 67 patients were included for analysis. Clinical equivalence was assessed using the British Hypertension Society (BHS) validation criteria for comparing nonmercury devices to the gold-standard calibrated mercury device. Mean SBP readings for 54% (36/67), 90% (60/67) and 97% (65/67) and mean DBP readings for 73% (49/67), 94% (63/67) and 100% (67/67) were within 5, 10 and 15 mmHg agreement across the two time regimens which achieved grade B and grade A validation, respectively. A BPP was costly and stressful for women and affected their ability to attend work and look after other children.

Conclusions: A BPP performed over one hour compared to over three hours yields clinically equivalent results, yet has psychosocial and financial advantages.

Key words: blood pressure profile, diagnostic techniques and procedures, hypertension, patient experience, pregnancy.

Introduction

Hypertensive disorders in pregnancy are common and are associated with increased maternal and perinatal mortality and morbidity. However, while there is concern not to overlook hypertension, there is also theoretical concern about a possible reduction in placental perfusion through the injudicious use of antihypertensives.1,2 The accurate detection and management of hypertension is therefore one of the key purposes of antenatal care.

In all patients, both pregnant and nonpregnant, blood pressure (BP) fluctuates with respiration, eating, laughing, physical activity, temperature, caffeine/tobacco, alcohol, pain and emotions. Variations in individual systolic blood pressure (SBP) readings can be as large as 50–60 mmHg over a 24-h period; anxiety alone can cause a rise of 30 mmHg.3 Therefore, national guidelines require that the patient be seated and relaxed, ideally for several minutes in a quiet room, and without having exercised for 30 min or consumed caffeine or tobacco for at least two hours before BP is taken.4

BP fluctuations can also be introduced by inter- and intra-observer error related to digit preference (rounding up or down to end in a 0 or 5) and observer prejudice (altering readings up or down towards the clinician’s prior expectation).4 In some patients, the BP measurement process itself can induce an increase in BP known as the white-coat effect, which is more common in pregnancy4 and when BP is taken by a doctor rather than other staff.5 Alternatively, up to 15% of nulliparas have ‘masked’ hypertension where a single clinic reading underrepresents the true BP level.6

However, when a series of individual readings is averaged, then apart from the fall of 10–20 mmHg while asleep, there is little diurnal variation in the mean BP from hour to hour during the day.7

In addition, an average of several BP readings is more reflective of the true BP status and more predictive of
end-organ damage or adverse outcome than individual clinic or office BP readings in both nonpregnant and pregnant patients. Consequently, multiple national guidelines recommend using an average of BP readings. Averaged readings can be obtained with patient-initiated home BP monitoring (HBPM), automated 24-h ambulatory BP monitoring (ABPM) or extended outpatient review via a blood pressure profile (BPP) in a pregnancy day assessment unit (DAU). HBPM is becoming popular but accuracy and interpretation of results can be suboptimal in some patient cohorts. ABPM has been investigated in some pregnant populations and appears a reasonable technique to identify hypertensive women at risk of adverse pregnancy outcomes, but is complex to provide and its role in pregnancy has yet to be properly defined. A DAU BPP therefore remains a popular model of extended BP review in pregnancy, both to further assess possible hypertension and to monitor women with established hypertension, including those on treatment. SOMANZ recommends that elevated BP results be confirmed by repeated readings ‘over several hours’ but the optimal number and interval of measurements to characterise BP in pregnancy is unknown.

At Westmead Hospital, a tertiary level teaching hospital in Sydney with almost 5500 births per annum, our usual BPP is one reading per hour over three hours (four readings). Other units and the literature report shorter intervals, including readings taken only minutes apart.

The time commitment required for an outpatient pregnancy BPP can be considerable with implications both for patients and the service. We hypothesised that since mean awake BP generally fluctuates little, the mean of four 15 minutely BP readings taken over one hour would be similar to the mean of four 60 minutely BP taken over three hours and that, as a result, the time taken for the BPP could be reduced to one hour. We also hypothesised that our patients would welcome this. A time period shorter than one hour was not explored since a CTG and blood tests are also usually performed necessitating assessment of that duration.

Materials and Methods

Multiple BP readings taken over one hour versus multiple over three hours

Women attending the DAU at Westmead Hospital for the purposes of obtaining a BPP were invited to participate in the study. These women had been identified as needing a BPP to investigate a suspected new diagnosis of hypertension following a one-off antenatal visit reading of ≥140/90 mmHg or as part of the ongoing monitoring of existing hypertension in pregnancy. Medicated and unmedicated women were included. Each individual woman was only included once. Women were allowed to exit the study at any stage.

BP readings were obtained using two new Spacelab 90207 automated sphygmomanometers. These were calibrated by the hospital’s biomedical engineering department after six months, exceeding the manufacturer’s recommendation of calibration on an annual basis. Automated cuffs were used to eliminate inter-observer variability. The cuff was placed on the woman’s right arm. A cuff of appropriate size was used for each woman.

The automatic BP cuffs were programmed to take BP readings every 15 min for three hours. If an error occurred, such as that caused by excessive movement during cuff inflation, the machine automatically re-inflated to take a repeat reading. During the BPP, women were allowed to ambulate but were instructed to remain stationary at the time of the BP cuff inflation. The measurements at zero, one, two and three hours were taken seated in the DAU as per usual practice. At the completion of the BPP, all measurements stored in the automated machines were uploaded for analysis.

Data analysis compared the BP readings obtained over the first hour at 15-min interval to those obtained over the three hours at 60-min interval.

To be considered for inclusion in the analysis, women had to meet strict criteria, namely having at least three consecutive BP readings taken at 15-min interval and at least three consecutive BP readings taken at 60-min interval. The other readings collected every 15 min after the first hour were not used.

The outcomes used to compare the two regimens were the mean BP and the standard deviation of the difference in mean BP readings obtained by each regimen.

The standard used for assessing clinical equivalence was the British Hypertension Society (BHS) validation criteria for comparing nonmercury devices to the gold-standard calibrated mercury device. To be judged equivalent, the mean difference must be no greater than 5 mmHg ± 8 mmHg. In addition, 60/85/95% (Grade A Validation) or 50/75/90% (Grade B Validation) of mean BP results using the nonmercury device must be within 5/10/15 mmHg of the mercury device, respectively.

The impact of a lengthy BP profile on women

Women also completed a questionnaire regarding the impact of a prolonged outpatient investigation had on their finances, mental health and family life. The information collected through these questionnaires was analysed independently of the BPP data and was not linked to individual patients.

Approval for the study was obtained via the Western Sydney Local Health District Human Research Ethics Committee. HREC approval number HREC2013/5/6.4 (3717)AU RED LNR/13/WMEAD/122.
Results

The study population

Eighty women agreed to participate in the study. The BP data from thirteen women were excluded due to insufficient available readings meeting the strict inclusion criteria. These women either did not quite reach the third of the hourly readings because of early discharge home (six women), had readings in the first hour that were not strictly 15 min apart (four women) or had most of their 15 minately readings in the second and third hours rather than the first hour (three women) because of initial issues adjusting to the automated cuff. These women were not excluded due to complications or need for admission. This left data obtained from 67 women for analysis. The patient population represented women with mild-to-moderate hypertension (Table 1).

Difference between the BP readings obtained using the two regimens

For each woman, the mean systolic (SBP) and diastolic (DBP) blood pressures were calculated. The mean SBP obtained during the one-hour regimen was 2.7 mmHg lower (SD 6.1) than the mean SBP obtained during the three-hour regimen (P < 0.01) (Table 2, Fig. 1a). Mean SBP readings for 54% (36/67), 90% (60/67) and 97% (65/67) were within 5, 10 and 15 mmHg agreement across the two time regimens (Table 3). The seven women whose mean SBP readings differed by more than 10 mmHg had mean SBP readings ranging across the SBP spectrum, from 116 to 162 mmHg. Of the seven, six had a higher mean reading obtained with the three-hour BP profile while one had a lower reading (Fig. 1a).

Table 1 The study population included for analysis

<table>
<thead>
<tr>
<th>Number of women</th>
<th>Total number recruited</th>
<th>Number excluded with &lt; three readings over either time period</th>
<th>Total number included</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-hour BP</td>
<td></td>
<td></td>
<td>Three-hour BP</td>
</tr>
<tr>
<td>Four readings available</td>
<td>61 (91%)</td>
<td>53 (79%)</td>
<td></td>
</tr>
<tr>
<td>Three readings available</td>
<td>6 (9%)</td>
<td>14 (21%)</td>
<td></td>
</tr>
<tr>
<td>Minimum SBP (mmHg)</td>
<td>110.3</td>
<td>110.0</td>
<td></td>
</tr>
<tr>
<td>Maximum SBP (mmHg)</td>
<td>156.5</td>
<td>169.7</td>
<td></td>
</tr>
<tr>
<td>Minimum DBP (mmHg)</td>
<td>59.8</td>
<td>59.8</td>
<td></td>
</tr>
<tr>
<td>Maximum DBP (mmHg)</td>
<td>107.3</td>
<td>113.0</td>
<td></td>
</tr>
<tr>
<td>Mean SBP (SD)</td>
<td>132.6 (10.4)</td>
<td>135.3 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Mean DBP (SD)</td>
<td>86.6 (10.1)</td>
<td>87.2 (10.1)</td>
<td></td>
</tr>
</tbody>
</table>

BPP, blood pressure profile; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

There was a statistically insignificant difference of 0.51 mmHg between the mean DBP obtained using the two regimens (Table 2, Fig. 1b). Mean DBP readings for 73% (49/67), 94% (63/67) and 100% (67/67) were within 5, 10 and 15 mmHg agreement across the two time regimens. Four women had a mean DBP which differed by more than ±10 mmHg across the two regimens. Their mean DBP readings ranged from 86 to 96 mmHg. Three of the four women had mean DBP readings 10.5 to 14.3 mmHg lower with the three-hour versus one-hour BPP, while one woman had a mean DBP 12 mmHg higher with the three-hour profile (Fig. 1b).

Survey data

A total of 60 women completed the psychosocial/financial impact survey, although not all answered every question (Table 4). BPP attendance was associated with considerable work disruption (28% for patients, 53% for partner/family) and loss of income (13% for patients, 35% for partner/family) with the mean reported loss of income being $230 per patient and $206 per other family member. In addition, almost half spent over $20 and one in eight spent over $40 on direct expenses (transport, refreshments) associated with the three-hour attendance. About 57% felt that a shorter BPP assessment would allow them or their family member to return to work, which they saw as a positive outcome. About 60% of women reported that attendance for a BPP was a stressful event.

Discussion

Duration of BP profile

While SOMANZ advises repeated BP readings over several hours to investigate suspected hypertension, there is no evidence to guide the ideal duration of review. Very short periods of BP assessment may be reasonable and highly desirable. Some researchers consider 30–60 s adequate between cuff inflations to avoid venous congestion and minimise blood pressure variability.\(^{10,14}\)

In our own study, there was no difference in the mean of the DBP readings obtained at three hours versus one hour while the mean SBP was 2.7 mmHg higher over the three-hour BP profile (Table 2). While this is statistically
significant, it falls well within the BHS acceptable range of 5 mmHg and is also unlikely to be clinically significant. The DBP readings were within BHS criteria for a Grade A validation while the SBP readings achieved a Grade B validation, falling slightly short of having 60% of readings within 5 mmHg (54%) but exceeding validation criteria for the clinically more important readings that were within 10 mmHg (90%) and 15 mmHg (97%) across the two time periods.

While well within acceptable correlation, the small trend towards a slightly higher mean BP over the longer regimen seen in six of the seven women with more than 10 mmHg difference between regimens was unexpected. Blood pressure tends to trend down slightly with repeated testing such that the first one (or several) BPs are often discounted as unrepresentative. It is less usual to demonstrate a small increase in SBP over time. This result may have been due to the direct pressor effect of the

Figure 1 Bland–Altman plots illustrating the within patient differences in mean (a) systolic BP and (b) diastolic BP. Each circle identifies a single woman. The dashed line indicates the mean of the differences in mean BP readings obtained between the one hour and three hour of regimens. The dotted lines indicate the limits of agreement (equivalent to 2SD of within patient differences).
automatically inflating ambulatory device, exercise (women could gently ambulate around the DAU environs), caffeine/tobacco, or anxiety about work, family or rising costs as the monitoring session progressed. In addition, since the DAU operates from 07:30 hours, the small rise could also be detecting the tail end of the BP ‘morning surge’ after the BP fall during sleep. Further study may clarify this issue.

**Women’s experience of the BP profile**

Our survey of patient experience supports a shorter period of assessment for a BPP. A lengthy assessment negatively impacts upon a woman’s ability to attend work and manage other family commitments such as looking after young children. The large indirect costs (loss of income for patient/family member) and direct costs (transport/refreshment), which affect a considerable number of BPP attendees (Table 4), would be reduced by a shorter stay.

The literature has previously identified that women are more satisfied with an outpatient than an inpatient model of care for managing hypertension in pregnancy. However, ours is the first study to investigate the impact on women of the length of time spent undertaking this common antenatal outpatient assessment.

**Strengths and limitations of the study**

One strength of the study is that all BP readings were taken using a calibrated automated blood pressure device. This eliminated interobserver error, digit preference and observer prejudice. The Spacelabs device has been extensively studied and is acceptable for use in pregnant women although not in women with established pre-eclampsia. However, it has been recognised previously that an ambulatory device can have a small pressor effect on blood pressure over the first few hours and this could be considered a limitation in our study. The use of a single dedicated nurse using one manual BP

### Table 3 Mean BP agreement between one and three hour of BPP regimens

<table>
<thead>
<tr>
<th>Mean BP agreement (mmHg)</th>
<th>Number of women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 5</td>
<td>Systolic BP</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
</tr>
<tr>
<td>Within 5</td>
<td>36 (54)</td>
</tr>
<tr>
<td>Within 10</td>
<td>60 (90)</td>
</tr>
<tr>
<td>Within 15</td>
<td>65 (97)</td>
</tr>
</tbody>
</table>

### Table 4 The disruption a BPP places on women’s lives as assessed by patient survey

<table>
<thead>
<tr>
<th>Survey question</th>
<th>Number of women† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendance frequency</td>
<td></td>
</tr>
<tr>
<td>Number of times previously attended for a BPP</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5/49 (10.2%)</td>
</tr>
<tr>
<td>1–3</td>
<td>40/49 (81.6%)</td>
</tr>
<tr>
<td>4–7</td>
<td>3/49 (6.1%)</td>
</tr>
<tr>
<td>8–10</td>
<td>1/49 (2.0%)</td>
</tr>
<tr>
<td>Work and income disruption</td>
<td></td>
</tr>
<tr>
<td>Missed work because of BP monitoring</td>
<td>17/60 (28.3%)</td>
</tr>
<tr>
<td>Lost income as a result of missing work</td>
<td>8/59 (13.6%)</td>
</tr>
<tr>
<td>Mean (range) reported personal income lost</td>
<td>$230 ($50–400)</td>
</tr>
<tr>
<td>Partner/family member missed work</td>
<td>32/60 (53.3%)</td>
</tr>
<tr>
<td>Partner/family member lost income from missing work</td>
<td>21/60 (35%)</td>
</tr>
<tr>
<td>Mean (range) reported partner/family income lost</td>
<td>$206 ($50–600)</td>
</tr>
<tr>
<td>Shorter BPP would allow patient or family member to go back to work</td>
<td>32/56 (57.1%)</td>
</tr>
<tr>
<td>Family disruption</td>
<td></td>
</tr>
<tr>
<td>Young children at home to look after</td>
<td>28/60 (46.7%)</td>
</tr>
<tr>
<td>Paid for childcare so that could attend BPP</td>
<td>4/59 (6.8%)</td>
</tr>
<tr>
<td>Interference with other pregnancy care</td>
<td></td>
</tr>
<tr>
<td>Missed other appointments because of BPP</td>
<td>5/53 (9.4%)</td>
</tr>
<tr>
<td>Psychological impact</td>
<td></td>
</tr>
<tr>
<td>BPP is a stressful event</td>
<td>33/55 (60%)</td>
</tr>
<tr>
<td>Financial impact</td>
<td></td>
</tr>
<tr>
<td>Financial expenditure on parking/transport/refreshments to attend a BPP</td>
<td></td>
</tr>
<tr>
<td>$0</td>
<td>8/47 (18.6%)</td>
</tr>
<tr>
<td>$0.01–$20</td>
<td>16/47 (37.2%)</td>
</tr>
<tr>
<td>$20.01–$40</td>
<td>17/47 (36.2%)</td>
</tr>
<tr>
<td>$40.01–$60</td>
<td>6/47 (12.8%)</td>
</tr>
</tbody>
</table>

†The percentage is based on the number of women who answered that particular question, not the total number of women who partook in the questionnaire.
machine would have eliminated this effect but would have been difficult to arrange in a busy DAU.

A further strength of the study is that each woman acted as her own control over the two time periods and all women had nonsevere (<170/110) hypertension, realistically reflecting the type of patient population which typically undergoes a BPP in a DAU.

Finally, surveying patients about their experience with a BPP and their attitudes to a possible shortening of its duration is an area of patient care not commonly addressed in other studies.

Possible weaknesses of the study relate to factors which may have influenced the small increase in mean SBP seen over the longer time period. While not diminishing the overall equivalence of a one- and three-hour BPP according to the BHS criteria, the use of the automated Spacelabs device, performing the study over the time period of the morning BP surge and not proscribing caffeine/tobacco/ambulation may all have played a role in the slightly higher SBP in the three-hour cohort.

Conclusion

Our data demonstrate that a one-hour BPP obtains equivalent BP readings to a three-hour BPP. In addition, the shorter one-hour BPP has psychosocial and financial benefits for patients.

Acknowledgements

We would like to thank the DAU midwives for their support during the study and Karen Byth and Emma Gibbs for their assistance with the statistical analysis.

References

Caesarean section among immigrants with different obstetrical risks

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Abstract
Aim: To determine the variation in caesarean section rates among immigrant populations.
Background: Australia is one of the most multicultural in the world and is also among those with the highest caesarean section rates.
Design: Secondary data analysis.
Methods: Routinely collected data from a Local Health District between 2011 and 2015 were analysed. Women were categorized into regional groups based on country of birth. Obstetrical risk was classified using the Robson classification.
Results/Findings: In total 48,711 women gave birth, of whom 64.0% were born overseas; 13,966 had a caesarean section (28.7%). South and Central Asia women had a high number of caesarean sections (n = 4,139; 29.6% of all caesarean sections), a high overall adjusted caesarean section rate (31.4%; 95% CI, 30.5%–32.3%), and consistently high caesarean section rates among women with single cephalic term pregnancy without a previous caesarean section. High adjusted caesarean section rates were seen among South East Asia women with nulliparous, single cephalic, term pregnancy, and spontaneous labour. Demographic and clinical characteristics explained 83.5% of the variation in overall caesarean section rates between country of birth and 21.8% to 100% depending on Robson group.

Conclusions: Caesarean section rates varied by country of birth and within some Robson groups. The studied factors had various effects on the variation in caesarean section rates between country of birth and Robson groups.

KEYWORDS
caesarean section, country of birth, immigrant, Robson classification

SUMMARY STATEMENT
What is already known about this topic?
• Australia has a high caesarean section rate
• The caesarean section rate varies by country of birth and by Robson group.
• The extent of the variation in caesarean section rate between country of birth within each Robson group is unknown.

What this paper adds?
• The caesarean section rate varies by country of birth for all Robson groups combined and for Robson groups 1 to 4.
Women from South and Central Asia and South East Asia have a higher rate of caesarean section.

The studied factors explained most of the variation in overall caesarean section rates between country of birth (83.5%) and 21.8% to 100% depending on Robson group.

The implications of this paper:

- Future studies should explore the reasons behind the higher rates among some groups of women. Information including partners, extended family, time living in Australia, immigrant status, and feto-pelvic disproportion should be included whenever possible.
- Efforts to reduce the caesarean section rate such as health education through antenatal classes should focus on groups of women with high rate of caesarean section. Subsidized antenatal classes in suitable community languages might be useful.
- Health professionals should be aware of groups of women with higher risk of caesarean section.

1 | INTRODUCTION

Australia is one of the countries with the highest rates of caesarean section (CS) in the world, (33%) (AIHW, 2016). The rate of CS in private hospitals is much higher than in public hospitals (43% vs 30%) (Li, Zeki, Hilder, & Sullivan, 2013). A study undertaken in New South Wales (NSW) suggested that there is a wide variation in rates of CS among hospitals, ranging from 12% to 47% (Lee et al., 2013). A substantial proportion of the variation was not accounted for by demographic factors, medical conditions, pregnancy characteristics, or hospital type (public vs private). Differing hospital guidelines, clinician decision-making processes, and women’s preferences may contribute to the variation in rates of CS (McGrath & Ray-Barruel, 2009; Miller, Prosser, & Thompson, 2012; Moore, 2005; Robson, Carey, Mishra, & Dear, 2008).

With 28% of the Australian population born overseas (ABS, 2016b), Australia is also one of the most multicultural countries in the world. Beliefs, values, and traditions influence women’s attitudes and decisions about modes of delivery (Latifnejad, Zakerihamidi, & Merghati, 2015; Loke, Davies, & Li, 2015; Ugwu & de Kok, 2015). Women may prefer to have a CS for various reasons, such as fear of labour pain and perineal tearing (Loke et al., 2015), or because they consider CS to be a prestigious mode of birth (Latifnejad et al., 2015). Women may also refuse CS because of the socio-cultural norms about gender and religious ideologies (Ugwu & de Kok, 2015). As reported in a large meta-analysis of studies from developed countries, most groups of immigrants have different rates of CS compared with non-immigrants (Merry, Small, Blondel, & Gagnon, 2013). For Australia, immigrants from South Asia, Sub-Saharan African, and the Philippines have a higher rate of CS, and immigrants from East Asia have a similar rate to non-immigrant Australian women (Merry et al., 2013).

Despite the reported variation in the rate of CS for immigrants in Australia, the influence of beliefs, values, and traditions may vary between women with different obstetrical risks. For example, the influence should be minimal in cases of breech pregnancy because the safest option is to have a CS but should be greater in nulliparous, single-cephalic pregnancies, which are associated with minimal risk and the opportunity for elective CS for non-medical reasons mentioned above (Latifnejad et al., 2015; Loke et al., 2015).

The Robson classification for CS categorizes births into 10 groups based on parity, plurality, onset of labour, previous CS, foetal presentation, and gestational age (Robson, 2001) (Table 1). The Robson classification is well established and is recommended as the most appropriate method for obstetrical classification (WHO, 2015). In NSW, the rates of CS are highest among nulliparous women with a breech presentation (96.4%), but the highest proportion of CS is among women who have had a previous CS (36% of total CSs) (Lee et al., 2013). None of the studies on immigrants in Australia has used the Robson classification.

Western Sydney Local Health District (WSLHD) is a public health service responsible for nearly 1 million people residing in Western Sydney, of whom 43% are born overseas (EHA, 2016), a much higher proportion than the average of 28% for both NSW and Australia (ABS, 2016b). The top 3 countries of birth (COBs) of immigrants in Western Sydney are India, China, and the Philippines. By comparison, the top 3 COBs for immigrants in Australia are United Kingdom, New Zealand, and China (ABS, 2017). The WSLHD offers child birth and parenting classes targeting women from culturally and linguistically diverse backgrounds and women from low socioeconomic backgrounds (eg, teenagers, women receiving social welfare, and overseas students).

<table>
<thead>
<tr>
<th>Robson Group</th>
<th>Description</th>
<th>CS</th>
<th></th>
<th></th>
<th>Births</th>
<th></th>
<th></th>
<th>CS rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nulliparous, single cephalic, ≥ 37 weeks, spontaneous labour</td>
<td>1125</td>
<td>8.1</td>
<td>9566</td>
<td>19.6</td>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Nulliparous, single cephalic, ≥ 37 weeks, induced or CS before labour</td>
<td>3499</td>
<td>25.1</td>
<td>8435</td>
<td>17.3</td>
<td>41.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Multiparous (excluding previous CS), single cephalic, ≥ 37 weeks, spontaneous labour</td>
<td>341</td>
<td>2.4</td>
<td>13822</td>
<td>28.4</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Multiparous (excluding previous CS), single cephalic, ≥ 37 weeks, induced or CS before labour</td>
<td>1026</td>
<td>7.3</td>
<td>5876</td>
<td>12.1</td>
<td>17.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Previous CS, single cephalic, ≥ 37 weeks</td>
<td>5068</td>
<td>36.3</td>
<td>5918</td>
<td>12.1</td>
<td>85.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>All nulliparous breeches</td>
<td>663</td>
<td>4.7</td>
<td>816</td>
<td>1.7</td>
<td>81.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>All multiparous breeches (including previous CS)</td>
<td>460</td>
<td>3.3</td>
<td>635</td>
<td>1.3</td>
<td>72.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>All multiple pregnancies (including previous CS)</td>
<td>430</td>
<td>3.1</td>
<td>734</td>
<td>1.5</td>
<td>58.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>All abnormal lies (including previous CS)</td>
<td>258</td>
<td>1.8</td>
<td>276</td>
<td>0.6</td>
<td>93.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>All single cephalic, ≤ 36 weeks (including previous CS)</td>
<td>1096</td>
<td>7.8</td>
<td>2633</td>
<td>5.4</td>
<td>41.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1** Caesarean sections in WSLHD hospitals, by Robson 10-group classification, 2011–2015

Abbreviation: CS, Caesarean section.
Public hospitals in Australia provide care for public patients free of charge. Public hospitals also provide care for private patients with the costs claimed from private health insurance companies, and often with no out-of-pocket costs for patients. Approximately 10 000 women give birth each year in the 3 public hospitals of the WSLHD. Thirty per cent of them give birth by CS (NSW health, 2017). The hospitals are of different sizes and referral levels (1 large tertiary hospital, 1 medium, and 1 small) and are under the management of the WSLHD. Staff may rotate between hospitals. The hospitals have similar guidelines for not performing a CS at a woman’s request and, if a woman insists on having a CS, she is referred to counselling.

Information about the influence of COB on different obstetrical risks would be useful (Merry et al., 2013) for targeting resources and tailoring educational programs, such as free antenatal care classes, for groups of women who have high rates of CS. Results from this study would be relevant to other areas in Australia and in countries experiencing a similar pattern of immigration.

2 METHODS

2.1 Aim

Our aim was to investigate the variation in rates of CS by COB for each Robson group in the 3 public hospitals in the WSLHD (which we refer to as Hospital A, Hospital B, and Hospital C).

2.2 Design

Observational routinely collected health data.

2.3 Sample/participants

All mothers who gave birth in the 3 public hospitals of the Local Health District and their babies.

2.4 Data collection

Data were routinely recorded by the hospitals. Data collected between 2011 and 2015 were used in this study. Data included the women’s demographic characteristics (eg, age), comorbidities (eg, diabetes), reproductive history (eg, number of pregnancies), care during pregnancy and delivery (eg, as a private patient and if a private obstetrician was involved during antenatal care and/or labour), pregnancy and labour (eg, fetal presentation and onset of labour), and baby’s outcomes (eg, birth weight) (Table 2).

2.5 Ethical considerations

We used existing and de-identifiable data; therefore, the risk of breaching privacy and confidentiality for individual health care consumers was minimum. Ethics approval was obtained from the Local Health District.

2.6 Data analyses

Plural births were counted once, as a vaginal birth if all births were vaginal deliveries, or as a CS if one of the births was by CS (Lee et al., 2013). To categorize CS, we used the Robson 10-group classification, which is based on parity, plurality, onset of labour, previous CS, fetal presentation, and gestational age (Robson, 2001) (Table 1). This classification is recommended as the most appropriate (WHO, 2015).

Women were categorized into 12 regional groups, based on maternal COB using the list of countries from the Australian classification of countries (ABS, 2016a) (Table 2). However, for Australian-born women, Indigenous women have been reported to have disadvantage compared with non-Indigenous women (Trinh & Rubin, 2006) and therefore were categorized into different groups. We considered that North America (the United States and Canada), New Zealand, and Western Europe are all developed countries and have similar perspectives on childbirth. Therefore, these countries were grouped together. If a woman gave birth multiple times and the information on COB was only recorded for one of these births, this COB was used for the missing records. If the information was inconsistent, information on the last birth was used. The number of births and CSs, rates of CS, and contribution to the overall CSs were calculated for each Robson group and by COB.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Caesarean sections in WSLHD hospitals by country of birth, 2011–2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Births</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Non-indigenous Australian born</td>
<td>16 737</td>
</tr>
<tr>
<td>Indigenous</td>
<td>764</td>
</tr>
<tr>
<td>Oceania</td>
<td>1354</td>
</tr>
<tr>
<td>New Zealand, North America, Western Europe</td>
<td>2179</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>513</td>
</tr>
<tr>
<td>South and Central Asia</td>
<td>12 232</td>
</tr>
<tr>
<td>North East Asia</td>
<td>5212</td>
</tr>
<tr>
<td>South East Asia</td>
<td>3287</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>5026</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>1046</td>
</tr>
<tr>
<td>Latin America</td>
<td>361</td>
</tr>
<tr>
<td>Total</td>
<td>48 711</td>
</tr>
</tbody>
</table>

*P < 0.001. Due to missing values in some categories, data of 44 750 women were included in the modelling.
We used the Socio‐Economic Indexes for Areas (SEIFA index) of relative socio-economic disadvantage (ABS, 2013) to classify the women's socio-economic condition and conducted bivariate analyses between delivery mode (CS or not) and each factor. The proportions of women who had had a CS within each category of each factor were tabulated, and they were compared with each other using the Chi squared test.

We applied multi-level Poisson regression with a random intercept for COB to measure the group-specific adjusted deviation in the CS rate, while adjusting for other hospital, clinical, and demographic characteristics, where appropriate. Adjusted rates of CS were calculated by multiplying the adjusted incidence rate ratios obtained from the Poisson regression with the overall average rate. Proportional changes in CS rate variance among regional categories of birth were reported for multiple models with different sets of covariates to examine the contribution of demographic and pregnancy factors on CS variation. Models with the highest explained variation were chosen to derive COB-specific adjusted rates. Data were analysed in Stata, version 14 and R.

3 | RESULTS

Between 2011 and 2015, 48 886 mothers gave birth to 49 638 babies in the WSLHD hospitals. Information for 175 women (0.36%) was missing on either COB (n = 86) or obstetric risks (n = 90). These women were excluded from the analyses, leaving 48 711 women.

One-third of the women were born in Australia (34.4% of these women were non-Indigenous and 1.6% were Indigenous women). The remaining two-thirds were born outside Australia (64.0%). Women from South and Central Asia were the largest groups of immigrants giving birth (n = 12 232, 25.1%), followed by women from North East Asia (n = 5212, 10.7%) and women from North Africa and the Middle East (n = 5026, 10.3%) (Table 2). The most common COBs for migrants were India (15.0%), China (8.1%), Philippines (3.8%), Lebanon (3.5%), and New Zealand (2.8%).

3 | RESULTS

There was a significant difference in the proportion of Robson groups in each COB group. For example, Robson group 1 accounted for between 12.6% among women from Sub‐Sahara Africa and 27.8% among women from North East Asia (Figure 1).

Table 3 shows the characteristics of the group of women studied. Large proportions of women aged 25 to 29 years (33.3%) and 30 to 34 years (32.2%) had had previous pregnancies (58.1%). CS was more prevalent among the following groups:

- older women (e.g., the CS rate increased from 17.0% among teenagers to 43.2% among women 40 years or older)
- women living in areas with a higher SEIFA index
- women with diabetes, hypertension, or who had had a previous CS
- private or transferred patients
- women admitted to the 2 larger hospitals studied (Hospital A or Hospital C)
- women who had preterm babies with low birth weight and a low Apgar score at 1 minute.

The overall CS rate was 28.7% (n = 13 966) (Table 1). Women with a previous CS, single cephalic pregnancy at gestational age of 37 weeks or more (Robson group 5) had the highest number of CSs (n = 5,068; 36.3% of total CSs) and a very high CS rate (85.6%). Nulliparous women with a single cephalic pregnancy at gestational age of 37 weeks or more, or who had been induced or had a CS before labour began (Robson group 2), made up the second-largest group for CS (n = 3,499; 25.1% of total CSs) and had a relatively high CS rate (41.5%). Most women in this group had an induced labour (n = 7,820 [92.7%]), and only 615 women had CS before labour (7.3%).

Of the immigrants, women from South and Central Asia had the largest number of CSs (29.6% of total CSs) and a higher overall adjusted rate of CS (31.4%; 95% CI, 30.5%–32.3% vs the average of 28.7%; P < 0.001) (Table 2). These women also had consistently high adjusted rates of CS for Robson groups 1, 2, 3, and 4 (Figure 2). For...
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Births</th>
<th>Caesarean Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal demographics</td>
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<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 20</td>
<td>1211</td>
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</tr>
<tr>
<td>20–24</td>
<td>7286</td>
<td>15.0</td>
</tr>
<tr>
<td>25–29</td>
<td>16223</td>
<td>33.3</td>
</tr>
<tr>
<td>30–34</td>
<td>15670</td>
<td>32.2</td>
</tr>
<tr>
<td>35–39</td>
<td>6677</td>
<td>13.7</td>
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<tr>
<td>≥ 40</td>
<td>1644</td>
<td>3.4</td>
</tr>
<tr>
<td>SEIFA index of relative socio-economic disadvantage</td>
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<td></td>
</tr>
<tr>
<td>1st quintile (worst)</td>
<td>9697</td>
<td>19.9</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>9610</td>
<td>19.7</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>9939</td>
<td>20.4</td>
</tr>
<tr>
<td>4th quintile</td>
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<td>20.4</td>
</tr>
<tr>
<td>5th quintile (best)</td>
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<td>19.6</td>
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<td>Diabetes</td>
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<td></td>
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<tr>
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<tr>
<td>Yes</td>
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<td>12.2</td>
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<td>Hypertension</td>
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<tr>
<td>No</td>
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<td>94.7</td>
</tr>
<tr>
<td>Yes</td>
<td>2568</td>
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<tr>
<td>Smoking during pregnancy</td>
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<tr>
<td>No</td>
<td>44531</td>
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</tr>
<tr>
<td>Yes</td>
<td>4173</td>
<td>8.6</td>
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<tr>
<td>Pregnancy and delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive history</td>
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<td></td>
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<tr>
<td>Number of previous pregnancies</td>
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<td></td>
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<tr>
<td>0</td>
<td>20424</td>
<td>41.9</td>
</tr>
<tr>
<td>1 or more</td>
<td>28287</td>
<td>58.1</td>
</tr>
<tr>
<td>Number of previous CS</td>
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<td></td>
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<tr>
<td>0</td>
<td>41385</td>
<td>85.0</td>
</tr>
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<td>1 or more</td>
<td>7326</td>
<td>15.0</td>
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<td>Pregnancy and labour</td>
<td></td>
<td></td>
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<tr>
<td>Multifetal pregnancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47977</td>
<td>98.5</td>
</tr>
<tr>
<td>Yes</td>
<td>734</td>
<td>1.5</td>
</tr>
<tr>
<td>Fetal presentation</td>
<td></td>
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<tr>
<td>Cephalic</td>
<td>46878</td>
<td>96.2</td>
</tr>
<tr>
<td>Breech</td>
<td>1544</td>
<td>3.2</td>
</tr>
<tr>
<td>Face/brow/shoulder/transverse</td>
<td>288</td>
<td>0.6</td>
</tr>
<tr>
<td>Onset of labour</td>
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<td></td>
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<tr>
<td>Spontaneous</td>
<td>26996</td>
<td>55.4</td>
</tr>
<tr>
<td>Induced</td>
<td>14389</td>
<td>29.5</td>
</tr>
<tr>
<td>No labour</td>
<td>7326</td>
<td>15.0</td>
</tr>
<tr>
<td>Care during pregnancy and delivery</td>
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<td></td>
</tr>
<tr>
<td>Antenatal care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 13 weeks</td>
<td>23772</td>
<td>48.8</td>
</tr>
<tr>
<td>≥ 13 weeks</td>
<td>24758</td>
<td>50.8</td>
</tr>
</tbody>
</table>
example, the adjusted rate for Robson group 2 was 45.0% (95% CI, 42.6%–47.4%, vs the average of 41.5%; \( P < 0.001 \)).

In Robson group 1, women from South East Asia (predominantly from the Philippines, 48%) had an adjusted CS rate of 16.2% (95% CI, 14.2%–18.3%) compared with an overall average rate of 11.8% (\( P < 0.001 \)). Non-Indigenous Australian-born women contributed the most to the total number of CSs (32.7%) but had a lower adjusted CS rate than the mean (27.3%; 95% CI, 26.4%–28.1% vs 28.7%; \( P < 0.001 \)). Non-Indigenous Australian born women also had lower rates of CS in Robson group 4.

Women from North East Asia had lower adjusted CS rates for all Robson groups (25.8%; 95% CI, 24.2%–27.4% vs the average of 28.7%; \( P < 0.001 \)) and specifically for groups 1, 2, and 10. For example, their adjusted CS rate for Robson group 2 was 36.6% (95% CI, 32.6%–40.6% vs the average of 41.5%; \( P < 0.001 \)). Maternal characteristics plus pregnancy and delivery characteristics explained the highest proportion of variation in CS rate for the total sample (83.5%), Robson groups 1 (21.8%), and Robson group 2 (55.1%). For Robson group 3, maternal characteristics plus pregnancy, delivery characteristics, and baby’s health explained 37.8% of the variation. None of the included factors explained variation in CS rate within Robson group 4, but they fully explained the variation within Robson group 10. No variation (variance was close to zero) was seen within Robson groups 5 to 9.

4 | DISCUSSION

Most women in our study were born outside Australia (64.0%) compared with 35.5% for NSW (AIHW, 2016). The overall CS rate in our study (28.7%) was similar to that of other public hospitals in Australia (29.4%) (Li et al., 2013). The 2 groups with the largest number of CSs were women with a previous CS and a single cephalic pregnancy at term (Robson group 5) (\( n = 5068 \) or 36.3% of total CSs) and nulliparous women with a single cephalic pregnancy at term and an induced labour or CS before labour (Robson group 2) (\( n = 3499 \) or 25.1%). The CS rate in Robson group 2 (41.5%) should be reduced to avoid a very high chance of having a repeat CS in subsequent births (85.6% for Robson group 5). The small number of women who had a CS before labour in Robson group 2 (7.3%) reflected the policy of the WSLHD not to carry out CS based only on social reason or request.

Variation in the rates of CS existed between COB for all CSs and for Robson groups 1 to 4 and 10. However, a large proportion in the variation in overall CS rate among COB (83.5%) was explained by various factors, reflecting the heterogeneous population among each group of COB. Similarly, to results from the meta-analysis (Merry et al., 2013), women from South Asia had a higher adjusted overall rate of CS. In our study, they also had consistently higher adjusted rates for Robson groups 1 to 4 (nulliparous or multiparous, single cephalic, \( \geq 37 \) weeks with no previous CS, spontaneous, induced or CS before delivery).
Women from South and Central Asia are often skilled immigrants and are therefore likely to be educated and in employment (ABS, 2015). Higher education has been reported to be associated with an increase in the CS rate (Freitas, Sakae, & Jacomino, 2008) and time constraint may be a factor for women to prefer a scheduled CS. Less support from extended family or friends than non-immigrant women might also be a factor (Merten, Wyss, & Ackermann-Liebrich, 2007). Obesity has been reported to be more strongly associated with shoulder dystocia of the baby at birth in women from South and Central Asia than in Australian-born women, and weight management has been recommended for this group of women (Davies-Tuck, Mockler, Stewart, Knight, & Wallace, 2016).

Women from South East Asia, predominantly from the Philippines, had a higher adjusted CS rate for Robson group 1 (nulliparous, single cephalic, ≥ 37 weeks pregnancy and spontaneous labour) than average. Women from the Philippines have been reported to have the higher CS rate in Australia (Cassell, 1995) and in Norway (Vangen, Stray-Pedersen, Skondal, Magnus, & Stoltenberg, 2003). Interracial marriage between Filipino women and Australian men is common (ABS, 2006). It has been reported that 73% of Filipino women immigrated to Australia as a spouse or fiancée of an Australian man (Hugo, 1990). Interracial marriage could result in larger babies and cause fetopelvic disproportion (Vangen et al., 2003). For this Robson group 1, the studied factors only explained 21.8% of the variation, suggesting that factors such as fetopelvic disproportion could be important.

Non-Indigenous Australian-born women and women from North East Asia had lower overall rates of CS. Previous studies found no differences in rates of CS between the 2 groups (Merry et al., 2013). In this study, non-Indigenous Australian-born women also had lower rates of CS in Robson group 4. Social support might contribute to the lower rates of CS for these women. Women from North East Asia had lower rates of CS in Robson groups 1 and 2. Having fewer children, a healthier lifestyle and a lower BMI (von Katterfeld, Li, McNamara, & Langridge, 2011) might be protective factors for these women.

Very high rates of CS and/or a small sample size might be reasons for no variation between COB in Robson groups 5 to 9. Clinical indicators were the main reasons for CS in those groups.

4.1 | Strengths and limitations

To our knowledge, this is the first study that identifies COB within each Robson group with a higher rate of CS. This will allow better targeting of resources and tailoring of educational programs to reduce CS rates in each group.

Using data only from WSLHD public hospitals limited our sample size and might have limited the generalisability of our conclusions, compared with if we had used state-wide data and included private hospitals. However, using data from 1 health district minimizes the confounding effects of variations in hospital guidelines.
decision-making processes, which are factors that could account for substantial variation between hospitals (Lee et al., 2013; Schemman, Patterson, Nippita, Ford, & Roberts, 2015).

We did not collect data on COB of the babies’ fathers in our study. Inter-racial marriages in Australia are very common. Partners and members of the extended family, such as mothers or mothers-in-law, may play important roles in decisions about child birth. Until 2011, half of Australia’s migrants had been living here for 5 years or less, and one-quarter of migrants were refugees (ABS, 2016c). The time spent living in Australia and the woman’s migration status (e.g., if she was a refugee or a skilled migrant) may also have affected the rates of CS, but these data were not available for analysis.

5 | CONCLUSIONS

This was the first step in understanding the variation of CS rate by COB and by Robson group. We tried to explain the reasons behind the higher CS rates in some groups, using existing literature, but no previous studies have analysed CS rate by Robson group. Therefore, future studies should re-examine the reported factors in the context of obstetrical risks and explore factors beyond what have been identified. Such factors could include information about partner, extended family, time living in their adopted country, immigrant status, and feto-pelvic disproportion.

Until then, efforts to reduce CS rate, such as health education through antenatal classes, should target these groups of women. At the moment, the hospitals run regular antenatal classes in English and in Mandarin. Subsidized antenatal classes and in more languages might be useful in encouraging women to attend. Knowledge about pregnancy and childbirth would improve women’s self-care during pregnancy and encourage them to be more actively involved in the delivery process, which might reduce CS rate. Health professionals should be made aware of groups of women with higher risk of CS.

ACKNOWLEDGEMENT

The authors would like to thank the women whose information was used in the study and Ms. Olivia Wroth for her professional editing.

CONFLICT OF INTEREST

None declared.

AUTHORSHIP STATEMENT

All listed authors meet the authorship criteria by participating in the design of the study, data analyses, interpretation of results, and writing of the manuscript. All authors are in agreement with the content of the manuscript.

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How to cite this article: Trinh LTT, Assareh H, Achat H, Chua S, Guevarra V. Caesarean section among immigrants with different obstetrical risks. Int J Nurs Pract. 2018;24:e12638. https://doi.org/10.1111/ijn.12638
Caesarean section by country of birth in New South Wales, Australia

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\section*{Article Info}

\textbf{Article history:} Received 28 June 2018
Received in revised form 19 October 2018
Accepted 26 November 2018
Available online xxx

\textbf{Keywords:}
Caesarean section
Country of birth
Obstetric risk
Robson classification

\section*{Abstract}

\textbf{Objective:} To determine rates of caesarean section by country of birth and by obstetric risks.

\textbf{Methods:} We analysed the New South Wales Perinatal Data Collection data of women giving birth between January 2013 and December 2015. Obstetric risk was classified using the Robson’s 10-group classification. Multilevel logistic regression with a random intercept was used to measure the variation in caesarean section rate between immigrants from different countries and between regional immigrant groups.

\textbf{Results:} We analysed data from 283,256 women, of whom 90,750 had a caesarean section (32.0%). A total of 100,120 women were born overseas (35.3%), and 33,028 (33.0%) had a caesarean section. The caesarean section rate among women from South and Central Asia ranged from 32.6% for women from Pakistan to 47.3% for women from Bangladesh. For South East Asia, women from Cambodia had the lowest caesarean section rate (19.5%) and women from Indonesia had the highest rate (37.3%). The caesarean section rate for North Africa and the Middle East ranged from 28.0% for women from Syria to 50.1% for women from Iran. Robson groups that accounted for most of the caesarean sections were women who had previous caesarean section (36.5%); nulliparous women, induced or caesarean section before labour (26.2%); and nulliparous women, spontaneous labour (8.9%).

\textbf{Conclusions:} The caesarean section rate varied significantly between women from different countries of birth within the same region. Women from some countries of birth had the highest caesarean section rates in some Robson groups.

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Statement of significance

\textbf{Problem or issue}

Information on CS rate by COB is essential for a multicultural country with a high CS rate such as Australia, but is currently limited.

\textbf{What is already known}

Immigrants from some regions such as South and Central Asia, South East Asia and Sub-Saharan African have a higher CS rate than Australian-born women. However, the CS rate may vary between countries within the same region. Some studies have been conducted on CS rates among women from the Philippines, Vietnam and Somalia, but information on other COBs is not available.

\textbf{What this paper adds}

We analysed variation in CS rates for the most common 49 COBs in NSW, adjusted for a range of associated factors. Different CS rates between countries within the same regions of COB, and higher CS rates for some COBs in some obstetrical risk groups were highlighted and explained using available literature.

1. Introduction

Caesarean section (CS) rates in Australia are high and increasing.\textsuperscript{1} A woman’s country of birth (COB) is one of the factors associated with the CS rate, and the impact of the COB varies depending on the host country.\textsuperscript{2,3} Australia has a high proportion of immigrants (28%).\textsuperscript{4} In a recent study in some public hospitals, 64% of women who gave birth were born overseas.\textsuperscript{5} Therefore...
information on CS rate by COB is useful. Immigrants to Australia from South and Central Asia, South East Asia and Sub-Saharan African, and from non-English speaking countries have higher rates of CS than non-immigrants. Countries in the same region may have similar cultures and languages, but may also have different socioeconomic environments that contribute to the CS rate. A study of four south-east Asian countries found a great variation in CS rate between countries.\(^3\) A report on CS rate by UNICEF also show large differences between countries in the same region.\(^3\) For example, the CS rate in Iran was 46%, a much higher rate than the rate of 22% in Iraq. Therefore information by individual COB would be more useful than by region. Studies in Australia reported the CS rate among immigrants from the Philippines, Vietnam and Somalia.\(^2\) Compared to Australian born women, immigrants from the Philippines and nulliparous women from Somalia had higher CS rate, while immigrants from Vietnam and multiparous women from Somalia had similar CS rate. However, these studies were published at least a decade ago. Information on other COBs is not available. In addition, these studies reported CS rates by emergency or elective status and by women’s parity, instead of using the most appropriate classification,\(^2\) the Robson classification, which divides births into 10 groups based on obstetric history, onset of labour, fetal presentation, number of neonates, and gestational age (Table 1). The ten groups are mutually exclusive. Each woman can be assigned to only one of the groups based on the available characteristics that are routinely recorded.\(^6\)

In Australia, the Australian Institute of Health and Welfare has used the Robson classification for the first time in 2018 to analyze data of women who gave birth in 2015.\(^9\) However prior to this, the Robson classification has been used to report local CS rates.\(^3,10\) The groups that accounted for the majority of CSs are women at term with a singleton pregnancy and having had a previous CS (group 5), nulliparous with induction or pre-labour CS at term (group 2) and nulliparous women with spontaneous term births (group 1).\(^3,10\) We aimed to determine the CS rate by individual COB, by Robson group across New South Wales (NSW). Results will be useful for targeting strategies to reduce CS rates in groups with high CS rates.

2. Methods

We analysed the NSW Perinatal Data Collection data \(^11\) of women giving birth between January 2013 and December 2015. Data from all mothers and babies in NSW were routinely recorded in this dataset. Information included mothers’ demographic characteristics (e.g. age and maternal COB), maternal health (e.g. diabetes), reproductive history (e.g. number of pregnancies), care during pregnancy (e.g. antenatal care), labour and delivery (e.g. fetal presentation and onset of labour), hospital factors (e.g. obstetric hospital level of risk), and baby’s outcomes (e.g. Apgar score) (Table 2). Some of this information was used to divide women into 10 Robson groups\(^9\) (Table 1). To classify the women's socioeconomic status, the postcode of residence was matched with the postal area index of the Socio-Economic Indexes for Areas (SEIFA), index of relative socioeconomic disadvantage, 2011 census year.\(^12\) We calculated the proportions of women giving birth and undergoing CS in each category, and we used the chi squared test to determine the significant differences between categories.

To group COBs into regions, we used the geographical classification from the Australian Bureau of Statistics\(^13\) and further divided into smaller groups based on cultural similarities (Table 3). For example, countries in Eastern Europe are former socialist countries, and women from those countries might have similar perspectives on childbirth, and therefore were grouped together, and were separated from women who come from Western Europe. Similarly, Latin America is different to North America, so women from Latin America were separated from women whose COB was either Canada or the United States of America.

To study individual COBs, records of women from COBs with at least 350 women were included, which resulted in 48 countries and 96.4% of all women. We calculated the number of births and CSs, rates of CS and contribution to the overall CS rates for each Robson group (Table 1), region of COB (Table 3) and for each COB. We utilised multilevel logistic regression models to measure the variation in CS rate between immigrants from different countries and between regional immigrant groups. To account for differing risk factors between women within each Robson group, we set demographics (age), maternal (diabetes, hypertension and smoking status) and baby health (birth weight, Apgar score) characteristics as covariates in the models and derived adjusted results. For all Robson groups, we use all the above variables plus the Robson grouping. Variations between countries and regions were obtained from two separated models where countries and regions were defined as random intercepts, respectively. Countries were not nested in the regions in the models to avoid imposition of any clustering effect on the estimated variation for countries. Models at country and region levels were constructed for each Robson group. In addition, overall models in which Robson grouping was also added as a covariate were constructed to measure the overall variations across countries and regions.

We did not use SEIFA in adjusting the data analysis because we wanted to measure variation between COBs adjusted only for clinical aspects. Data were analysed in Stata, version 14 \(^14\) and R version 3.3.0.\(^15,16\) Approval for publication was obtained from the NSW Ministry of Health.

3. Results

In the three-year period (2013–2015), data from 286,452 women, who gave birth to 290,687 babies in NSW, were recorded.

<table>
<thead>
<tr>
<th>Robson group</th>
<th>Caesarean sections</th>
<th>Birth</th>
<th>Caesarean sections rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>1. Nulliparous, single cephalic, ≥37 weeks, spontaneous labour</td>
<td>8,096</td>
<td>8.9</td>
<td>56,622</td>
</tr>
<tr>
<td>2. Nulliparous, single cephalic, ≥37 weeks, induced or CS before labour</td>
<td>23,732</td>
<td>26.2</td>
<td>52,812</td>
</tr>
<tr>
<td>3. Multiparous (excluding previous CS), single cephalic, ≥37 weeks, spontaneous labour</td>
<td>1,565</td>
<td>1.7</td>
<td>68,488</td>
</tr>
<tr>
<td>4. Multiparous (excluding previous CS), single cephalic, ≥37 weeks, induced or CS before labour</td>
<td>6,216</td>
<td>6.8</td>
<td>37,934</td>
</tr>
<tr>
<td>5. Previous CS, single cephalic, ≥37 weeks</td>
<td>33,149</td>
<td>36.5</td>
<td>37,559</td>
</tr>
<tr>
<td>6. All nulliparous single breeches</td>
<td>4828</td>
<td>5.3</td>
<td>5,285</td>
</tr>
<tr>
<td>7. All multiparous single breeches (including previous CS)</td>
<td>3135</td>
<td>3.5</td>
<td>3,655</td>
</tr>
<tr>
<td>8. All multiple pregnancies (including previous CS)</td>
<td>2679</td>
<td>3.0</td>
<td>4,121</td>
</tr>
<tr>
<td>9. All single abnormal lies (including previous CS)</td>
<td>1308</td>
<td>1.4</td>
<td>1,484</td>
</tr>
<tr>
<td>10. All single cephalic, &lt;36 weeks (including previous CS)</td>
<td>6,042</td>
<td>6.7</td>
<td>15,296</td>
</tr>
<tr>
<td>Total</td>
<td>90,750</td>
<td>100</td>
<td>283,256</td>
</tr>
<tr>
<td>Characteristic</td>
<td>All births</td>
<td>Caesarean sections</td>
<td>P Value*</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>------------</td>
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<td>---------</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Maternal demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>7,815</td>
<td>2.8</td>
<td>1,399</td>
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<tr>
<td>20–24</td>
<td>34,907</td>
<td>12.3</td>
<td>7,665</td>
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<tr>
<td>25–29</td>
<td>76,645</td>
<td>27.1</td>
<td>21,006</td>
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<td>30–34</td>
<td>98,108</td>
<td>34.6</td>
<td>32,807</td>
</tr>
<tr>
<td>35–39</td>
<td>52,663</td>
<td>18.6</td>
<td>21,273</td>
</tr>
<tr>
<td>≥40</td>
<td>13,095</td>
<td>4.6</td>
<td>6,576</td>
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<td><strong>SEIFA index of relative socio-economic disadvantage</strong></td>
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<td></td>
</tr>
<tr>
<td>1st quintile (most disadvantaged)</td>
<td>57,424</td>
<td>20.4</td>
<td>16,167</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>55,311</td>
<td>19.7</td>
<td>16,745</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>56,871</td>
<td>20.2</td>
<td>18,243</td>
</tr>
<tr>
<td>4th quintile</td>
<td>56,536</td>
<td>20.1</td>
<td>18,930</td>
</tr>
<tr>
<td>5th quintile (least disadvantaged)</td>
<td>55,263</td>
<td>19.6</td>
<td>20,104</td>
</tr>
<tr>
<td>Maternal health</td>
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<tr>
<td><strong>Diabetes</strong></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>257,698</td>
<td>91.0</td>
<td>80,530</td>
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<tr>
<td>Yes</td>
<td>25,558</td>
<td>9.0</td>
<td>10,220</td>
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<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td>No</td>
<td>267,957</td>
<td>94.6</td>
<td>84,021</td>
</tr>
<tr>
<td>Yes</td>
<td>15,299</td>
<td>5.4</td>
<td>6,729</td>
</tr>
<tr>
<td><strong>Smoking during pregnancy</strong></td>
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</tr>
<tr>
<td>No</td>
<td>256,796</td>
<td>90.7</td>
<td>83,728</td>
</tr>
<tr>
<td>Yes</td>
<td>26,460</td>
<td>9.3</td>
<td>7022</td>
</tr>
<tr>
<td>Reproductive history</td>
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<tr>
<td><strong>Number of previous pregnancies</strong></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>124,451</td>
<td>43.9</td>
<td>41,129</td>
</tr>
<tr>
<td>1 or more</td>
<td>158,756</td>
<td>56.1</td>
<td>49,614</td>
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<tr>
<td><strong>Number of previous caesarean sections</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>234,845</td>
<td>83.9</td>
<td>52,227</td>
</tr>
<tr>
<td>1 or more</td>
<td>45,148</td>
<td>16.1</td>
<td>38,202</td>
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<td>Pregnancy and labour</td>
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<tr>
<td><strong>Multifetal pregnancies</strong></td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>279,135</td>
<td>98.5</td>
<td>88,071</td>
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<tr>
<td>Yes</td>
<td>4121</td>
<td>1.5</td>
<td>2,679</td>
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<td>Fetal presentation</td>
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<tr>
<td>Cephalic</td>
<td>272,016</td>
<td>96.0</td>
<td>80,728</td>
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<tr>
<td>Breech</td>
<td>9680</td>
<td>3.4</td>
<td>8,648</td>
</tr>
<tr>
<td><strong>Face/brow/shoulder/transverse</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1546</td>
<td>0.5</td>
<td>1,364</td>
<td>88.2</td>
</tr>
<tr>
<td>Onset of labour</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>144,104</td>
<td>50.9</td>
<td>17,171</td>
</tr>
<tr>
<td>Induced</td>
<td>84,322</td>
<td>29.8</td>
<td>18,752</td>
</tr>
<tr>
<td><strong>No labour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54,827</td>
<td>19.4</td>
<td>54,826</td>
<td>100.0</td>
</tr>
<tr>
<td>Care during pregnancy and delivery</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Antenatal care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤13 weeks</td>
<td>156,095</td>
<td>55.4</td>
<td>53,472</td>
</tr>
<tr>
<td>&gt;13 weeks</td>
<td>125,645</td>
<td>44.6</td>
<td>36,900</td>
</tr>
<tr>
<td><strong>Patient type</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>197,109</td>
<td>69.6</td>
<td>52,749</td>
</tr>
<tr>
<td>Private (in private or public hospital)</td>
<td>86,147</td>
<td>30.4</td>
<td>38,001</td>
</tr>
<tr>
<td><strong>Hospital type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public, obstetric level ≤3</td>
<td>24,654</td>
<td>8.7</td>
<td>6,190</td>
</tr>
<tr>
<td>Public, obstetric level 4</td>
<td>54,097</td>
<td>19.1</td>
<td>13,935</td>
</tr>
<tr>
<td>Public, obstetric level 5</td>
<td>55,526</td>
<td>19.6</td>
<td>15,836</td>
</tr>
<tr>
<td>Public, obstetric level 6</td>
<td>83,066</td>
<td>29.4</td>
<td>25,377</td>
</tr>
<tr>
<td>Private</td>
<td>65,634</td>
<td>23.2</td>
<td>29,212</td>
</tr>
<tr>
<td><strong>Referred from another hospital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>276,878</td>
<td>97.7</td>
<td>87,808</td>
</tr>
<tr>
<td>Yes</td>
<td>6378</td>
<td>2.3</td>
<td>2,942</td>
</tr>
<tr>
<td>Baby's health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term (&lt;37 weeks)</td>
<td>263,513</td>
<td>93.0</td>
<td>81,693</td>
</tr>
<tr>
<td>Preterm (&lt;37 weeks)</td>
<td>19,731</td>
<td>7.0</td>
<td>9,056</td>
</tr>
<tr>
<td>Baby's birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;2500 g)</td>
<td>16,086</td>
<td>5.7</td>
<td>7,425</td>
</tr>
<tr>
<td>Medium (2500–4000 g)</td>
<td>238,250</td>
<td>84.2</td>
<td>73,335</td>
</tr>
<tr>
<td>Large (&gt;4000 g)</td>
<td>28,730</td>
<td>10.1</td>
<td>9,967</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≥7)</td>
<td>258,957</td>
<td>92.2</td>
<td>82,144</td>
</tr>
</tbody>
</table>

*All values are significant at the 0.001 level.*
Of these women, 3,196 (1.1%) had missing data on either COB (2,362 [0.82%]) or obstetric risk (864 [0.30%]). We included data from 283,256 women in analyses.

Table 2 shows the characteristics of the women, the number and percentage of births and CS in each category and p values from Chi squared tests. Large proportions of women were aged 25–29 years (27.1%) or 30–34 years (34.6%), had previous pregnancy/ies (56.1%) and were public patients (69.6%). The overall CS rate was 32.0%. The CS rates increased from 17.9% among teenagers to 50.2% among women 40 year old or older (p < 0.001), and from 28.2% in areas with the lowest SEIFA index to 36.4% in areas with the highest SEIFA index (p < 0.001). Women who had diabetes had a higher CS rate (40.0%) than women who did not (31.2%, p < 0.001). The CS rate among women who had hypertension was higher (44.0%) than among women who did not (31.4%, p < 0.001). Private patients had a higher CS rate (44.1%) than public patients (26.8%, p < 0.001).

We assessed the women using the Robson classification. In Table 1 are number of women giving birth and proportion per total number for each Robson group. The number of CSs and rate are also presented. The group 5 women (previous CS, single cephalic pregnancy at gestational age of 37 weeks or more) had the highest number of CSs (33,149 [36.5% of total CSs]) and a very high CS rate (88.3%). The group 2 women (nulliparous women with a single cephalic pregnancy at gestational age of 37 weeks or more, induced or had a CS before labour began) was the second largest group for CSs (23,723 CS [26.2% of total CSs]) and had a relatively high CS rate (44.9%) (Table 1).

Table 3 presents the number of births and CSs by region of COB. Results of immigrant were presented separately to results of non-immigrants. One-third of the women were born outside Australia (100,120 [35.3%]). Among the immigrants, women from South and Central Asia were the largest group (20,310 [20.3%]). These women accounted for the largest proportion of CSs among immigrants (23.7%) and the highest overall rate of CS (38.5%). Another large group with a high overall rate of CS was women from South East Asia (15,965 [15.9% of all immigrants]). This group had a CS rate of 32.7%. Women from Sub-Saharan Africa and Latin America also had high CS rates (34.7% and 34.6%, respectively), although women from these regions accounted for small proportions (4.0% and 2.9%, respectively) of all migrants (Table 3).

We found variation between COBs as well as between regions. In Fig. 1 are odds ratio by COB grouped into region for each of the Robson groups as well as all births. The overall CS rates among women from South and Central Asian countries ranged from 32.6% (2,175 births; OR = 0.99; 95%CI = 0.87–1.11) for Pakistan to 47.3% (2,424 births; OR = 1.60; 95%CI = 1.51–1.70) for Bangladesh. Among South East Asian countries, women from Cambodia had a much lower CS rate (19.5%; 829 births; OR = 0.72; 95%CI = 0.36–1.07) than women from Indonesia (37.3%; 2378 births; OR = 1.30; 95%CI = 1.20–1.41). For North Africa and the Middle East, the CS rate was lower in Syria (28.0%; 500 births; OR = 0.80, 95%CI = 0.57–1.04) but was much higher in Iran (50.1%; 1088 births; OR = 1.55, 95%CI = 1.41–1.70).

Of the 33,028 CSs among immigrants, eight COBs with a high CS rate accounted for 10,102 CSs or 30.6%. The COBs from South and Central Asia responsible for 20.5% of CSs were India (4,191 CS; 12.7% of all CSs among immigrants); Bangladesh (1,147 CS; 3.5%); Nepal (817 CS; 2.5%); and Sri Lanka (589 CS; 1.8%). The COBs from South East Asia accounting for 7.8% of CSs were the Philippines (1686 CS; 5.1%) and Indonesia (887 CS; 2.7%). The COBs from the Middle East and North Africa accountable for 2.4% of all CSs were Iran (545 CS; 1.7%); and Sudan (240 CS; 0.7%).

COBs that had higher overall CS rates also had higher CS rates in several Robson groups. These were women from Bangladesh (high CS rates in groups 1, 2, 4, 5 and 10), Sri Lanka, Indonesia and the Philippines (groups 1, 2 and 3), India (groups 1, 2, 4, 8 and 9), Nepal (groups 1 and 2), Iran (groups 1, 2, 5 and 8), Fiji (group 2), Thailand and Sudan (group 3) and Egypt (group 5) (Fig. 1). The estimated variances of random intercepts from the models were presented in the Appendix.
4. Discussion

The overall CS rate of 28% was lower than the average of New South Wales of 30.9% because only public hospitals were included in this study. CS rates varied greatly between individual COBs within each region. The largest variations were observed for South and Central Asia, South East Asia, North Africa and the Middle East. There are maternity services for women who speak certain languages (e.g. Persian or Mandarin). These languages are often used by women from countries within the same region. For example, women from Iran, Afghanistan and other countries in the Middle East speak Persian but their CS rates may be different. The maternity services should further tailor their services to specific groups of COBs (e.g. Iran).

The different CS rates in the COBs and the circumstances of the women’s immigration might have contributed to the variation. Immigrants bring perceptions and practices of care during pregnancy and childbirth with them from their countries of origin, resulting in a similar CS rate. For example, immigrants from Pakistan and Bangladesh were often skilled immigrants and were often better off financially in their COB. The CS rate among women from Pakistan (32.6%) was similar to the rate for the wealthiest groups in Pakistan (34%). The rate for women from Bangladesh (47.3%) was slightly lower than the rate for the wealthiest group in Bangladesh (49.8%). The very high rate in Bangladesh could be explained by the availability and affordability of private health care. Similarly, the CS rate among women from Iran of 50.1%, was similar to the rate of 51% in Iran. The high CS rate in Iran is possibly due to the commercialisation of CS for non-medical reasons.

Women’s perceptions and practices could also be influenced by their new lifestyle and the health care system in Australia, resulting in a CS rate that is closer to the average in NSW. For example, The CS rate for Cambodian women was 19.5%, much higher than the highest CS rate of 3% in Cambodia but still lower than the average of NSW of 32.0%. Another example is CS rate among women from Samoa (25.5%), much higher than the highest CS rate in Samoa of 9%. Changes in immigrants’ perception and practices may be influenced by duration of stay in Australia for which data were not available in this study but should be an area for further research.

Of the 90,750 CSs, 36.5% belonged to Robson group 5 (having had a previous CS), 26.2% were from group 2 (nulliparous with induction or CS before labour) and 8.9% were from group 1 (Nulliparous, spontaneous labour). These groups accounted for 71.6% and were similar to results from other studies. Women from Bangladesh, Iran and Egypt had a high rate of CS in group 5 (previous CS), similar to the reported CS rate in their home country. Most women who had a previous CS in Iran (80.5%) preferred to have a repeat CS. The common practice of having a CS because of the previous CS may have affected attitudes and beliefs of women from these countries and may result in a high repeat CS rate. Antenatal education and counselling may be beneficial to change attitudes and beliefs among these women. Multiparous women are less likely to attend antenatal education, so special attention should be focused on these groups to improve access to antenatal education.

Women from Bangladesh, Sri Lanka, India, Nepal, the Philippines, Indonesia, Iran and Fiji had a high CS rate in Robson groups 1 and/or 2. Antenatal education for first-time mothers may be effective in improving maternal physical and mental health, mental preparation for childbirth, increasing use of pain relief during labour and reducing the CS rate. Barriers that prevent women from attending antenatal education are lack of awareness, time constraints, lack of transport, distance, cost and language barriers. These barriers are more profound among immigrants. Measures to improve access to antenatal education may reduce CS rates in first-time mothers from these COBs.

The COBs with high rates in these Robson groups also had a high overall CS rate and accounted for a large proportion of all
CSs. These were four from South and Central Asia (India, Bangladesh, Nepal and Sri Lanka, accounted for 20.4% of all CS among immigrants), two from South East Asia (the Philippines and Indonesia, accounted for 7.8%) and two from the Middle East and North Africa (Iran and Sudan, 2.4%). These eight COBs accounted for 10,102 CSs or 30.6% of all CSs among immigrants. Reducing CS rates among these COBs, especially the ones from South and Central Asia and South East Asia would significantly reduce the overall CS rate.

While antenatal education affects women’s perception and practice about CS, hospital policies, knowledge and attitude toward CS of clinicians who care for the women during pregnancy and childbirth may also play important roles on whether or not a CS is carried out.36 This is evidenced by a significant variation in CS rate between hospitals even after adjusting for women’s characteristics.10 Hospitals should have policies to discourage CS for non-clinical reasons, referring women to counselling and supporting women who want to have a vagina birth. Clinicians should be educated to commit to limiting CS whenever possible. This may be possible in public hospitals but more difficult in private hospitals due to the commercial benefits.

Strengths and limitations

Our study provides information on CS rates by individual COB and by obstetric risk in New South Wales, a multicultural state with a high CS rate. Our large sample size allowed robust statistical analysis and identification of statistically significant differences by region and by COB. We offer some explanations for the differences between COBs within a region as well as for groups with a very high rate of CSs. With the expansion of migrations and multicultural communities in developed and developing countries, our findings can be of interest and inform policies in other Australian states and similar countries.

However, due to a lack of data on other factors that might affect CS rates, such as duration of stay in Australia, status of immigration, COB of partners, and ethnicity for women who were born in Australia, we could only make assumptions using the existing literature. Data on individual levels would have further reinforced our findings and explanations. We do not have separate data on induced labour and CS before labour to separate groups 2 and 4 into 2a, 2b, 4a, 4b by induced labour and CS before labour. This division would be of benefit especially for group 2 in this study.

5. Conclusions

CS rates varied between and within groups of COBs. CS rates might reflect the CS rate in COBs, after being adjusted for the health system in Australia, and for a woman’s circumstances of immigration. Targeted interventions are required for groups of women from certain COBs with higher CS rates. Future studies should explore the reasons for the higher rates of CS among these immigrant groups.

Ethical statement

Approval for publication was obtained from the NSW Ministry of Health on the 22 June 2018. There is no approval number.

Authorship statement

All listed authors meet the authorship criteria by participating in the design of the study, data analyses, interpretation of results and writing of the manuscript. All authors are in agreement with the content of the manuscript.

Conflict of interest

None declared.

Acknowledgement

The authors would like to thank the women whose information was used in the study and Ms. Olivia Wroth for her professional editing.

Appendix A. Variances and associated 95% confidence intervals for estimated random intercepts obtained from multilevel models where random intercepts set as country of birth and region.

<table>
<thead>
<tr>
<th>Model</th>
<th>Country of birth as random intercept</th>
<th>Region as random intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Variance (95% CI)</td>
<td>Variance (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>0.049 (0.034–0.076)</td>
<td>0.033 (0.011–0.076)</td>
</tr>
<tr>
<td>Robson 1</td>
<td>0.055 (0.038–0.087)</td>
<td>0.036 (0.017–0.099)</td>
</tr>
<tr>
<td>Robson 2</td>
<td>0.054 (0.038–0.085)</td>
<td>0.033 (0.016–0.111)</td>
</tr>
<tr>
<td>Robson 3</td>
<td>0.145 (0.100–0.227)</td>
<td>0.063 (0.030–0.210)</td>
</tr>
<tr>
<td>Robson 4</td>
<td>0.036 (0.025–0.056)</td>
<td>0.026 (0.012–0.087)</td>
</tr>
<tr>
<td>Robson 5</td>
<td>0.108 (0.075–0.170)</td>
<td>0.027 (0.013–0.090)</td>
</tr>
<tr>
<td>Robson 6</td>
<td>0.000 (0.000–0.000)</td>
<td>0.000 (0.000–0.000)</td>
</tr>
<tr>
<td>Robson 7</td>
<td>0.023 (0.016–0.036)</td>
<td>0.027 (0.013–0.091)</td>
</tr>
<tr>
<td>Robson 8</td>
<td>0.144 (0.100–0.226)</td>
<td>0.020 (0.009–0.066)</td>
</tr>
<tr>
<td>Robson 9</td>
<td>0.307 (0.212–0.485)</td>
<td>0.156 (0.074–0.521)</td>
</tr>
<tr>
<td>Robson 10</td>
<td>0.077 (0.053–0.121)</td>
<td>0.033 (0.016–0.111)</td>
</tr>
</tbody>
</table>

Note: Variances were from models with demographic, maternal and baby health characteristics as covariates. For the model “All” Robson grouping was also added as a covariate. CSs were calculated using a two-tailed Chi-square distribution.

References


Can Ambu self-inflating bag and Neopuff infant resuscitator provide adequate and safe manual inflations for infants up to 10 kg weight?

Mark Tracy,1,2 Rajesh Maheshwari,1,3 Dharmesh Shah,1,3 Murray Hinder1,3

ABSTRACT
Background Manual resuscitation devices for infants and newborns must be able to provide adequate ventilation in a safe and consistent manner across a wide range of patient sizes (0.5–10 kg) and differing clinical states. There are little comparative data assessing biomechanical performance of common infant manual resuscitation devices across the manufacturers’ recommended operating weight ranges. We aimed to compare performance of the Ambu self-inflating bag (SIB) with the Neopuff T-piece resuscitator in three resuscitation models.

Methods Five experienced clinicians delivered targeted ventilation to three lung models differing in compliance, delivery pressures and inflation rates; Preterm (0.5 mL/cmH2O, 25/5 cmH2O, 60 per minute), Term (3 mL/cmH2O 30/5 cmH2O, 40 per minute) and Infant (9 mL/cmH2O, 35/5 cmH2O, 30 per minute). The Neopuff was examined with three gas inflow rates (5 litres per minute (LPM), 10 LPM and 15 LPM) and the Ambu with no gas inflow.

Results 3309 inflations were collected and analysed with analysis of variance for repeated measures. The Neopuff was unable to reach set peak inflation pressures and exhibited seriously elevated positive end expiratory pressure (PEEP) with all inflow gas rates (p<0.001) in this infant model. The Ambu SIB accurately delivered targeted pressures in all three models.

Conclusions The Ambu SIB was able to accurately deliver targeted pressures across all three models from preterm to infant. The Neopuff infant resuscitator was unable to deliver the targeted pressures in the infant model developing clinically significant levels of inadvertent PEEP which may pose risk during infant resuscitation.

INTRODUCTION
Resuscitation of newborns at birth in transition from the fetal state differs from resuscitation of infants and adults. The dramatic changes in pulmonary and cardiovascular systems at this time are highly interrelated with the elimination of fetal lung fluid,1, 2 initiation of respiration and establishment of a functional residual capacity (FRC), with concurrent, unique changes in the newborn circulation. The fetal circulation with parallel ‘loops’ of the ductus arteriosus, foramen ovale and placental respiration via the umbilical arterial/venous connections is coupled with low systemic and high pulmonary vascular resistance. The rapid and dramatic changes that occur following birth, dictate either a safe normal transition or pathological state which may require some level of assistance or full resuscitation. Surfactant deficiency, structural pulmonary immaturity together with possible disease states that can lead to preterm birth such as premature rupture of membranes, chorioamnionitis, placental disease and intrauterine growth restriction, can all affect the transition physiology and complicate both the need for resuscitation and the clinical response.

Bradycardia, asystole and apnoea require assistance with manual ventilation, and at birth, a crucial component is to support the establishment of a FRC and initiate effective alveolar ventilation.3 Provision of positive pressure ventilation (PPV) is the cornerstone of resuscitation and some form of manual ventilation device with mask or endotracheal tube is required. The devices used can be either flow independent such as self-inflating bags (SIBs) or flow dependent such as T-piece resuscitators (TPRs) or anaesthetic bag systems. Two international standards organisation (ISO) documents

What is already known on this topic?
▸ Flow dependent T-piece resuscitators (TPRs) have become popular devices for newborn resuscitation in the developed world for term and preterm infants.
▸ There is insufficient evidence currently to support the use of positive end expiratory pressure with positive pressure ventilation in neonatal resuscitations.
▸ There are little data to support the use of flow dependent TPRs for infant resuscitation in the term newborn to 10 kg weight range.

What this study adds?
▸ The flow independent Ambu self-inflating bag can deliver targeted pressures in lung models from preterm to 10 kg body weight.
▸ The Neopuff T-piece resuscitator (TPR) design imposes increased resistance to passive lung deflation.
▸ Neopuff TPRs used in infant resuscitation may not deliver required peak inspiratory pressure and develop significant unintended elevations in positive end expiratory pressure which may reduce the effectiveness of resuscitation.
They describe test conditions of set lung compliance and resistance to delivered tidal volume for infants and newborns less than 5 kg body mass and infants between 5 kg and 10 kg. Many brands of SIBs and TPRs are rated by the manufacturer for use in infancy/paediatrics up to 10 kg in body mass, thus crossing the two recommended weight ranges. There are little data on how these manual resuscitation systems perform biomechanically across this range of body mass (0.5–10 kg), disease states and starting cardiopulmonary states. The use of the TPR device for resuscitation at birth is widespread but there are limited data to support its use on the full term newborn (birth weight approx 3.5 kg) or infant (weight ≤10 kg). The Neopuff TPR (NTPR) device uses circuit flow occlusion to inflate the lung to a preset peak inspiratory pressure (PIP) and an adjustable flow resistance (figure 1) to provide preset positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) dependent on circuit gas in flow and delivery mode. Previous studies have focused on lower compliance (0.5–1.0 mL/cmH₂O) short time constant lung models indicative of the preterm lung.11-14 A recent UK newborn resuscitation practice survey indicates that TPRs are in widespread use during term newborn resuscitation.9 In New South Wales, Australia, where over 60% of all births occur in rural or non-tertiary units,13 the NTPR is in common use for term newborn resuscitation. The recent 2015 ILCOR guideline for paediatrics16 does not provide information on inflation pressures for use in infant resuscitation. Australia has a web based resuscitation programme for healthcare professionals called RESUS4KIDS that includes information on the use of the NTPR in infancy.17 Suggested starting ventilation settings from the RESUS4KIDS site for infants requiring resuscitation (eg, with bronchiolitis) are PIP of 20 cmH₂O PEEP 5 cmH₂O inflow of 15 litres per minute (LPM) and a rate of 20 inflations per minute (IPM).18 Studies of infants ventilated with severe bronchiolitis indicate the need for higher levels of pressure support with reported PIPs ranging from 26 cmH₂O to 40 cmH₂O with inflation rates of 20–30 bpm.19-21

We aimed to examine the biomechanical performance of one brand of SIB, the Ambu Spur II (Ambu A/S Ballerup, Denmark) with fitted Ambu manometer and PEEP valve and one brand of TPR the Neopuff (Fisher & Paykel, New Zealand) infant resuscitator both rated by the manufacturer as suitable for use in infants up to 10 kg body mass in three lung/resuscitation models. These models were: an extremely preterm newborn model (body mass equivalent 1 kg), a term newborn model (body mass equivalent 3 kg) and an infant model (body mass equivalent 10 kg). Each model incorporates appropriate test lung compliance, resistance and ventilation settings. The flow dependent NTPR was tested across the range of the manufacturer’s recommended gas inflow rates22 of 5 LPM, 10 LPM and 15 LPM. Outcome measures were the delivered respiratory mechanical data at the interface of the test lung. Our null hypothesis was that both systems would perform adequately and similarly, regardless of the type of device (SIB or NTPR) or gas inflow rates to the flow dependant device (NTPR).

METHODS

The preterm model consisted of a test lung with compliance of 0.5 mL/cmH₂O (Draeger, Lubeck, Germany) typical of preterm surfactant deficiency with targeted ventilation parameters of 60 IPM, PIP of 25 cmH₂O and PEEP of 5 cmH₂O. The term newborn model consisted of a test lung with compliance of 3 mL/cmH₂O (Smart Lung Infant, IMT Medical, Buchs, Switzerland) typical of an asphyxiated apnoeic infant with targeted ventilation parameters of 40 IPM, PIP 30 cmH₂O and PEEP of 5 cmH₂O. The infant model was based on a 10 kg 6–12-month-old child with severe bronchiolitis with test lung compliance of 9 mL/cmH₂O (Michigan Instruments USA) with targeted ventilation parameters of rate 30 IPM, PIP of 35 cmH₂O and PEEP of 5 cmH₂O. Test lung resistance was 50 cmH₂O/L/s for all three models. A single NTPR (part number: RD900AEU) and delivery circuit (part number RD 1300-10) with a measured compliance of 0.4 mL/cmH₂O, tubing flow resistance of 6 cmH₂O/L/s at 30 LPM and five single use Ambu SIB (SPUR II) fitted with disposable PEEP 20 valve (part number 199 102 001) and disposable manometer (part number 322 003) were used in this bench study. A Florian respiratory function monitor (RFM) (Accutronics, Medical Systems AG, Zug, Switzerland) was connected via the hot wire pneumotach and pressure sensor line sited between the device providing PPV and the test lung. The Florian monitor and ventilation was calibrated with an external syringe of known volume and pressure/liter via a ventilator calibration analyser (PF300, IMT Medical, Buchs, Switzerland) with pressure resolution of 0.1 cmH₂O with pressure accuracy of ±0.75%, and flow calibration with resolution of 0.05 L/min with accuracy of ±1.75%. The analogue signals output from the RFM were collected and digitised at 200 Hz with analysis software (Grove Medical, London, UK). The test lungs and monitoring system were pressurised to static pressure of 50 cmH₂O and given no fall in pressure over 120 s, the system was deemed leak-free.

Five experienced paediatricians who routinely used both devices in neonatal and infant settings, were asked to provide PPV for 2 minutes to each randomly sequenced lung model at the prescribed targeted ventilation parameters using SIB and NTPR (randomly set for 5 LPM, 10 LPM or 15 LPM gas inflow). The SIB PEEP valve was set to 5 cmH₂O using the attached manometer as per manufacturer’s insert instructions,20 and no gas inflow was provided to SIB. When using SIB, operators targeted the prescribed lung model PIP with the attached manometer. When using NTPR the required pressures (PIP and PEEP) for each lung model were set as per manufacturer’s instructions22 before each inflation run. The RFM pneumotach was re-zeroed and NTPR gas inflow were set and checked using the ventilator calibration analyser (IMT Medical) at the start of each randomised gas inflow change or lung change. Operator was blinded to RFM display and inflation rate was guided by audible metronome for each lung model inflation rate. The Spur II SIB was tested and

Figure 1 Cross-section diagram of Neopuff T-piece circuit. (Diagram supplied by Fisher and Paykel, Auckland New Zealand).
found to comply with ISO standard for operator powered resuscitators⁴ for body mass range of <5 kg and 5–10 kg. The NTPR was found to comply with ISO standards for low driven resuscitators⁵ for body mass range of <5 kg and 5–10 kg.

Data analysis
Analysis was conducted using Stata (V13 MP, Statacorp, College Station, Texas, USA). The first five inflations were discarded and inflations for the next 60 s were analysed with each sequence. A total of 3309 inflations were analysed; 2613 for NTPR and 696 for Ambu SIB. Measured parameters included the PIP, PEEP, tidal volume and inflation/deflation times. The total system deflation time constant was calculated from regression on F-V loop (s) by Grove analysis software for SIBs and for the NTPR across all gas inflow rates.

Analysis of variance (ANOVA) for repeated measures was used to determine differences in delivered ventilation between device type, lung model and inflow rates. Differences between means determined by ANOVA were reported with p values adjusted F test using Box’s conservative e. p Values of <0.05 were considered statistically significant. The ANOVA for repeated measures allows a valid statistical comparison between different rates, devices and lung compliance delivered by the same individual when the repeat measurements between individuals are not independent. Bonferroni corrections of estimates were made to adjust for multiple comparisons.

RESULTS
Preterm model
The measured mean PIPs were similar, close to targeted PIP of 25 cmH₂O and not significantly different across devices and flows. The measured mean PEEP were statistically different across device and flow with the highest mean PEEP of 6.1 cmH₂O at inflow of 5 LPM with the NTPR (table 1 and figure 2). The measured mean PEEP was 4.8 cmH₂O for the SIB. The measured mean inflation time was 0.30 s with SIB, and between 0.47 s and 0.48 s for NTPR p<0.001 (table 1). The delivered tidal volumes were similar across all groups ranging from 10.4 mL with NTPR at 5 LPM to 11.4 mL with NTPR at 15 LPM (table 1). The mean total system deflation time constant was significantly shorter with SIB (0.06 s) and was inversely related to the NTPR inflow rate ranging from 0.21 s to 0.10 s, p<0.001 (table 1).

Term model
Compared with the targeted PIP (30 cmH₂O), the measured mean PIPs were 30.0 cmH₂O with SIB, 21.6 cmH₂O for NTPR with inflow 5 LPM, 27.2 cmH₂O for NTPR with inflow 10 LPM and 28.6 cmH₂O for NTPR with inflow 15 LPM p<0.001. The measured mean PEEP was highest with the NTPR at 5 LPM with a mean of 6.4 cmH₂O p<0.001 and lowest with SIB at 5.0 cmH₂O (table 1 and figure 3). The inflation time was significantly shorter with the SIB 0.28 s compared with NTPR (0.52–0.54 s), p<0.001. The delivered mean tidal volumes ranged from 31.3 mL with NTPR with inflow of 5 LPM to 35.6 mL with NTPR with inflow of 15 LPM compared with 45.1 mL with SIB, p<0.001 (table 1). The mean total system deflation time constant was significantly shorter with SIB (0.10 s) and was inversely related to the NTPR inflow rate ranging from 0.44 s to 0.22 s, p<0.001 (table 1).

Infant model
Compared with the targeted PIP (35 cmH₂O), the measured mean PIPs were 35.3 cmH₂O with SIB, 18.0 cmH₂O for NTPR with inflow 5 LPM, 24.4 cmH₂O for NTPR with inflow 10 LPM and 28.2 cmH₂O for NTPR with inflow 15 LPM, p<0.001. The measured mean PEEP was 5.2 cmH₂O with SIB and for the NTPR PEEP was significantly elevated at all three gas inflows ranging from 9.8 cmH₂O to 10.8 cmH₂O, p<0.001 (table 1 and figure 4). The mean inflation time was significantly shorter with SIB at 0.33 s compared with NTPR (0.80–0.83 s, p<0.001). The delivered mean tidal volumes ranged from 56.6 mL with NTPR at inflow rate of 5 LPM to 148.4 mL at inflow rate of 15 LPM which compared with 88.2 mL with SIB, p<0.001 (table 1). The mean total system deflation time constant was significantly shorter with SIB (0.46 s) and was inversely related to the NTPR inflow rate ranging from 2.81 s to 1.55 s, p<0.001 (table 1).

DISCUSSION
This is the first study we are aware of, that examines the biomechanical performance of two common infant manual resuscitators across the manufacturers’ quoted body mass ranges. The Ambu Spur II was able to accurately deliver the targeted PIP and PEEP in all three models corresponding to body mass range of extremely preterm to 10 kg. The NTPR was not able to deliver the targeted PIP in the 10 kg infant model with performance inversely related to gas inflow rates (table 1 and figure 4). The NTPR in the infant model exhibited seriously elevated inadvertent PEEP levels with means similar across all three gas inflow rates (table 1). Tidal volumes were noted to be excessive with the preterm model assuming a 1 kg infant with mean volumes between 10.4 mL/kg and 11.4 mL/kg for both devices. Similarly in the term model, assuming a 3 kg infant, the mean TV ranged from 10.4 mL/kg with NTPR at 5 LPM to 18.5 mL/kg at 15 LPM compared with the Ambu SIB with a mean value of 15 mL/kg. In the 10 kg infant model, the mean tidal volumes ranged with the NTPR from 5.6 mL/kg at 5 LPM to 14.8 mL/kg at 15 LPM compared with 8.8 mL/kg with the Ambu SIB.
We speculate that the greater tidal volumes observed with NTPR at flow rates 10 LPM and 15 LPM in the term and infant models are related to the longer inspiratory times due to operators attempting to reach required PIP. The impact of excessive tidal volumes may be mitigated by mask leak however; this is clinically unmeasured and highly variable. Further, should the clinically unrecognised mask leak be ‘corrected’ by improved mask technique, or endotracheal intubation, the infant may be exposed to a potentially large change in delivered tidal volumes.

Limitations of our study are shared with other manikin and test lung studies of the ability to generalise results to actual human resuscitations. Further, our results cannot be used to comment on the performance of other brands of TPRs or SIBs.

The measured total system deflation time constant (table 1) incorporates both test lung and device imposed resistance and compliance to provide the Grove Spectra derived value. Three lung deflation time constants are required to allow 95% of the previous tidal volume to deflate passively.²³,²⁴ Device imposed expiratory resistance increases total respiratory system time constant that can result in incomplete emptying of the previous inflation volume, possibly inadvertent PEEP with the potential for gas trapping, and increase in lung volume. In an infant this can increase distal airway pressure in the alveoli resulting in decreased lung compliance, and pulmonary air leak.²⁵–²⁶ The mean total system deflation time with SIB in our infant model was 0.46 s which was less than the measured lung deflation time of 1.67 s at a delivery rate of 30 IMP. This explains the lack of any significant inadvertent PEEP observed. In the infant model using NTPR for all three gas inflow rates (5 LPM, 10 LPM and 15 LPM) with tidal volumes ranging from 31.3 mL/kg to 45.1 mL/kg with SIB, p<0.001 (table 1).

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Table 1  Measured respiratory parameters with differing resuscitation models, device type and Neopuff gas flow rates

<table>
<thead>
<tr>
<th>Model</th>
<th>PIP cmH2O Mean/SD/CV%</th>
<th>PEEP cmH2O Mean/SD/CV%</th>
<th>Tidal volume mL Mean/SD/CV%</th>
<th>Inflation rate/min Mean/SD/CV%</th>
<th>Inflation time (s) Mean/SD/CV%</th>
<th>Deflation time (s) Mean/SD/CV%</th>
<th>Total system deflation time constant (s) Mean/SD/CV%</th>
</tr>
</thead>
</table>
| Preterm model
| Ambu SIB    | 25.1, 1.86, 6.5         | 4.8*, 0.3, 5.8          | 11.0, 0.7, 6.5             | 62.0, 5.8, 9.2                | 0.30*, 0.08, 26.2             | 0.67*, 0.10, 14.5              | 0.06*, 0.01, 14.1               |
| Neopuff flow 5 | 25.4, 0.8, 0.3      | 6.1*, 0.4, 5.7          | 10.4*, 0.3, 3.0            | 60.1, 2.2, 3.7                | 0.47, 0.04, 9.3               | 0.53, 0.04, 8.3                | 0.21*, 0.01, 3.8                |
| Neopuff flow 10 | 25.3, 0.3, 1.1     | 5.3*, 0.2, 3.2          | 11.1, 0.3, 2.6             | 60.1, 1.9, 3.1                | 0.48, 0.06, 12.4              | 0.52, 0.06, 11.9               | 0.13*, 0.01, 3.3                |
| Neopuff flow 15 | 25.2, 0.1, 0.4    | 5.1*, 0.2, 2.0          | 11.4, 0.2, 1.7             | 60.1, 2.1, 3.5                | 0.48, 0.05, 11.4              | 0.52, 0.06, 10.9               | 0.10*, 0.01, 2.3                |
| Term model
| Ambu SIB    | 30.0*, 2.0, 6.5        | 5.0*, 0.5, 9.0          | 45.1*, 4.7, 10.5            | 40.0, 1.9, 4.8                | 0.28*, 0.06, 20.9             | 1.22*, 0.11, 9.3               | 0.10*, 0.01, 4.4                |
| Neopuff flow 5 | 21.6*, 4.0, 18.4     | 6.4*, 0.8, 12.0         | 31.3*, 7.6, 24.3            | 40.0, 2.0, 4.9                | 0.54, 0.12, 21.8              | 0.97, 0.15, 15.6               | 0.44*, 0.2, 5.2                |
| Neopuff flow 10 | 27.2*, 3.2, 12.0   | 5.4*, 0.3, 4.9          | 49.8*, 9.2, 18.4            | 40.1, 2.0, 4.9                | 0.52, 0.13, 24.2              | 0.98, 0.14, 13.9               | 0.28*, 0.02, 5.6                |
| Neopuff flow 15 | 28.6*, 0.7, 2.6     | 5.1, 0.1, 2.0           | 55.6*, 2.6, 4.7             | 39.4, 2.2, 5.2                | 0.56, 0.10, 17.7              | 0.97, 0.10, 10.6               | 0.22*, 0.01, 2.6                |
| Infant model
| Ambu SIB    | 35.3*, 1.9, 6.4        | 5.2*, 0.4, 7.1          | 82.2*, 16.7, 18.9           | 30.1, 2.2, 7.2                | 0.23*, 0.07, 22.7             | 1.67*, 0.15, 8.8               | 0.46*, 0.10, 13.7               |
| Neopuff flow 5 | 18.0*, 3.9, 21.7     | 10.8*, 2.7, 25.1        | 56.6*, 13.2, 23.3           | 30.2, 2.2, 7.4                | 0.83*, 0.19, 23.4             | 1.17, 0.21, 17.6               | 2.81*, 0.54, 19.1               |
| Neopuff flow 10 | 24.4*, 5.3, 21.6    | 10.7*, 2.2, 21.3        | 110.7*, 21.4, 19.3          | 30.1, 1.6, 5.3                | 0.81*, 0.16, 19.9             | 1.19, 0.16, 14.1               | 1.92*, 0.22, 0.12               |
| Neopuff flow 15 | 28.2*, 4.0, 14.0   | 9.8*, 1.7, 15.5         | 148.4*, 20.5, 13.8          | 30.1, 2.1, 7.0                | 0.80*, 0.17, 21.7             | 1.20, 0.23, 19.2               | 1.55*, 0.18, 11.1               |

Analysis of variance repeated measures.
*p<0.001.
NS pairwise difference Bonferroni adjustment.
PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; SIB, self-inflating bag.
15 LPM) total system deflation time constants (2.81 s, 1.92 s and 1.55 s) were greater than measured deflation times (1.17 s, 1.19 s and 1.20 s). This indicates insufficient lung deflation time resulting in the observed inadvertent PEEP (figure 5).

The results of our study indicating an inability of the NTPR to deliver PIP close to those set in the 10 kg infant model combined with the inadvertent PEEP observed suggest, effective resuscitation of infants with similar lung compliance could be inadequate. The compliance setting we chose for our term lung model may be considered conservative (3 mL/cmH$_2$O) with some human studies suggesting higher term infant values (4–5 mL/cmH$_2$O). This could alter performance of the NTPR at all gas inflow rates in term resuscitation with the development of clinically important inadvertent PEEP.

The provision of a set PEEP is determined in the NTPR by gas inflow rate and the dialled flow resistance of the adjusted PEEP setting (figure 1). The NTPR and the Ambu SIB with both manometer and PEEP valve would allow appropriate manual inflations for preterm infants given the data in this study and our previous work demonstrating adequate and consistent PEEP delivery with the Ambu SIB with PEEP valve. However, Finer et al reported eight occurrences out of 120 video studies of actual resuscitations of preterm newborns <1 kg using NTPR of seriously elevated PEEP levels above set values. The range of measured PEEP in these cases was 6.7 cmH$_2$O to 15.8 cmH$_2$O with set PEEP of 5 cmH$_2$O. Finer concluded ‘the NTPR has the potential to cause an inadvertent and potentially toxic increase of PEEP which might not be noticed by the operator’. Hinder et al recently showed in preterm and term lung models an associated rise in PEEP with rising lung compliance at different PIPs when using NTPR.

Disease states in newborns such as meconium aspiration, bronchopulmonary dysplasia and bronchiolitis or severe asthma in infants requiring mask ventilation may have significantly elevated FRCs or air trapping and so may respond adversely to the levels of inadvertent PEEP seen with the NTPR. The Ambu SIB with PEEP valve delivers consistent and accurate PEEP levels in the infant model approximating a 10 kg infant in our study without the risk of inadvertent PEEP.

The attraction of the TPR devices is their ability to deliver preset pressures, provide sustained inflations and deliver a continuous positive end expiratory pressure (CPAP) via mask in newborns and infants with serious respiratory distress who do not require positive pressure inflations. The NTPR is frequently used to stabilise breathing infants needing CPAP in New South Wales Australia. Given the results in our study, inadvertent PEEP may be a serious issue complicating the use of the NTPR used to provide CPAP in a spontaneously breathing infant.

CONCLUSION

The Ambu Spur II with fitted manometer and PEEP valve accurately delivered targeted PIP and PEEP across the three models corresponding to the manufacturer’s quoted body mass range. The NTPR accurately delivered targeted set PIP and PEEP in

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Figure 5  Recordings of infant model airway pressure waveforms for Ambu self-inflating bags (A) and Neopuff T-piece resuscitators at flow rates of 5 litres per minute (LPM), 10 LPM and 15 LPM (B–D).
the preterm model, in the term model with inflow rates of 5 LPM it could not deliver targeted PIP with some degree of inadvertent PEEP and in the infant model it could not deliver targeted set PIP with significant inadvertent PEEP at all inflow rates (5–15 LPM). The manufacturer should consider the value of inflow rates of 5 LPM and the upper range of body mass suitable for use with this device.

Acknowledgements The authors thank Ambu Australia for supply of self-inflating bags to examine in this study.

Contributors MT is primary researcher responsible for conceiving, designing, data collection, statistical analysis and writing manuscript. RM and DS contributed towards interpretation, manuscript construction and review. DS contributed to interpretation, manuscript construction and review. MT contributed by assisting in design, data collection, statistical analysis, manuscript writing and review.

Competing interests None declared.

Ethics approval This study was approved by the Western Sydney Local Health District Human Research and Ethics committee (SAC2014-5-6.3999).

Provenance and peer review Not commissioned; externally peer reviewed.

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Cardiovascular impact of intravenous caffeine in preterm infants

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ABSTRACT

Aim: To evaluate the acute effect of intravenous caffeine on heart rate and blood pressure variability in preterm infants.

Methods: We extracted and compared linear and nonlinear features of heart rate and blood pressure variability at two time points: prior to and in the two hours following a loading dose of 10 mg/kg caffeine base.

Results: We studied 31 preterm infants with arterial blood pressure data and 25 with electrocardiogram data, and compared extracted features prior to and following caffeine administration. We observed a reduction in both scaling exponents ($\alpha_1$, $\alpha_2$) of mean arterial pressure from detrended fluctuation analysis and an increase in the ratio of short- (SD1) and long-term (SD2) variability from Poincare analysis (SD1/SD2). Heart rate variability analyses showed a reduction in $\alpha_1$ (mean (SD) of 0.92 (0.21) to 0.86 (0.21), p < 0.01), consistent with increased vagal tone. Following caffeine, beat-to-beat pulse pressure variability (SD) also increased (2.1 (0.64) to 2.5 (0.65) mmHg, p < 0.01).

Conclusion: This study highlights potential elevation in autonomic nervous system responsiveness following caffeine administration reflected in both heart rate and blood pressure systems. The observed increase in pulse pressure variability may have implications for caffeine administration to infants with potentially impaired cerebral autoregulation.

INTRODUCTION

Caffeine therapy is prescribed predominantly to prevent and treat apnoea of prematurity in neonatal intensive care. In the short term, it reduces the frequency of apnoea, intermittent hypoxia and use of assisted ventilation (1,2). Part of the methylxanthine group, caffeine is a nonspecific inhibitor of adenosine receptors (A1 and A2a receptors) (3). However, there are conflicting reports on the effects of caffeine on cardiac function: some studies report increased cardiac output (4), while others report no significant changes (5,6) to left ventricular output. The Caffeine for Apnoea of Prematurity (CAP) trial was a large, randomised, placebo-controlled trial to evaluate the outcomes of caffeine therapy for apnoea of prematurity in very low birthweight infants over the short and long term (7,8). Caffeine improves neurocognitive outcomes at corrected 18–21 months and reduces incidence of cerebral palsy and risk of motor impairment (8). These differences did not persist at five years follow-up (9), although at 11 years, caffeine therapy was associated with a reduced risk of motor impairment (10).

Our group examined the effects of a 10 mg/kg loading dose of caffeine base on cerebral oxygenation and cerebral blood flow velocity in a group of 40 preterm neonates in 2010. We showed significant reductions in Doppler cerebral blood flow velocity and cerebral tissue oxygenation measured via near-infrared spectroscopy (6).

Previous work has examined the clinical outcomes of caffeine therapy (8,11), the impact of timing and dosage (12–14), as well as its acute effect on various physiological

Key Notes
- Caffeine administration increases beat-to-beat pulse pressure variability
- A standard loading dose of caffeine alters nonlinear dynamics of heart rate and blood pressure variability, increasing SD1/SD2 of mean arterial pressure and decreasing $\alpha_1$ of heart rate
- Caffeine likely increases autonomic nervous system responsiveness as shown by detrended fluctuation analysis and Poincare analysis

Abbreviations
- ABP, Arterial blood pressure; CAP, Caffeine for apnoea of prematurity; DFA, Detrended fluctuation analysis; ECG, Electrocardiogram; HRV, Heart rate variability; MAP, Mean arterial pressure; PI, Pulse interval; PP, Pulse pressure; SD, Standard deviation; SE, Standard error.

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variables (5,6,15). These effects are generally quantified using linear statistics such as mean and standard deviation (SD) which may not adequately capture the complex and nonlinear behaviour of physiological systems. Ulanovsky et al. (15) found no effect of 15–20 mg/kg loading dose of caffeine citrate on nonlinear dynamics of the heart rate of 21 preterm infants. This finding may well represent a type II error due to the small sample size.

Pharmacological studies (16) have contributed to the understanding of autonomic cardiac control on heart rate and blood pressure dynamics. In the context of heart rate variability (HRV), high frequency components (or short time windows) of heart rate are mainly modulated by parasympathetic activity. Both sympathetic and parasympathetic activity can be characterised using measures obtained from the Poincare plot (a plot of each data point against the consecutive point n + 1 in a time series) (17). These measures include variability in the direction perpendicular (SD1) and parallel (SD2) to the line of identity, reflecting short- and long-term variability, respectively. The ratio SD1/SD2 is thought to reflect sympathovagal balance (17). Detrended fluctuation analysis (DFA) is one method of nonlinear time series analysis developed to characterise fluctuations over a range of scales (18). This technique has been applied to characterising heart rhythm dynamics during development (19) and prior to impending intraventricular haemorrhage (20). Studies using selective autonomic blockade in adult human (16) subjects have helped to clarify the effect of sympathetic and parasympathetic activity on the scaling exponents from DFA.

In this study, we aimed to characterise the cardiovascular impact of a 10 mg/kg loading dose of caffeine base using both linear and nonlinear variability analysis, newly applied to our published data set (6). We hypothesise that caffeine administration would have acute effects on the autonomic nervous system and blood pressure control, which are evident from changes in DFA and Poincare measures of heart rate and blood pressure variability.

PATIENTS AND METHODS
Data collection
This study was approved by the Western Sydney Area Health Service Human Research and Ethics Committee (ethics number: 06/062) and informed parental consent was obtained in all cases. Physiological data from preterm infants (gestational age <34 weeks) requiring caffeine therapy were collected between August and December 2006. Eligibility criteria required that caffeine therapy was initiated for either weaning from mechanical ventilation, reducing extubation failure risk or treatment of apnoea of prematurity. Infants with significant congenital anomalies and high-grade peri-intraventricular haemorrhage at the time of study were excluded.

A loading dose of 10 mg/kg caffeine base was delivered intravenously to all enrolled infants over half an hour. Data collection commenced at least 20 minutes prior to caffeine administration, and concluded at least four hours following dose completion. Time series analysis focused on two time points (i) prior to dose administration and (ii) in the two hours following dose completion, during which plasma concentrations of caffeine is presumed to be greatest (21).

After single-point calibration to atmospheric pressure, intra-arterial blood pressure data were measured via an arterial line (umbilical or peripheral catheter) and collected using a bedside patient monitor (NCMS Philips Agilent System, Philips Healthcare, North Ryde, Australia). ECG data were acquired using the same patient monitor. ECG was not monitored for certain infants to preserve skin integrity.

Preprocessing
Signal preprocessing, feature extraction and subsequent analyses were undertaken in Python (Python Software Foundation, version 2.7 https://www.python.org/). The arterial blood pressure signal was down-sampled to 200 Hz. While DFA is generally robust against nonstationarities, it can be susceptible to longer term trends. Thus, we corrected for baseline drift characterised by a series of median filters (widths of 100, 300, 500 and 1000 ms) and the analysis techniques were then applied to the detrended signal. The ECG signal was similarly down-sampled to 200 Hz for computational efficiency and preprocessed using successive median filters of widths 200 and 600 ms to characterise the baseline wander (22).

Feature extraction
From the arterial blood pressure signal, we extracted the beat-to-beat mean arterial pressure, pulse pressure (systolic − diastolic) and the interval between successive systolic beats (pulse interval). From the ECG signal, we extracted the RR intervals following R-peak identification with Hilbert transform-based QRS detector algorithm (22). From each of these time series, the linear (mean, SD) and nonlinear (DFA: α1 and α2, Poincare: SD1, SD2 and SD1/SD2) features were extracted, as explained further below.

Detrended fluctuation analysis characterises the absence or presence of long-range correlations in a signal (18) and is well-suited to cope with nonstationarities (that is, constantly changing statistical properties), which are often present in physiological signals (23). DFA takes the cumulative sum of the mean-centred signal y, divides it into boxes of equal size n, detrends each box k then determines the root mean square fluctuation within the box (Equation 1). This process is repeated for varying box sizes n. The scaling exponent α is defined as gradient of the log–log relationship between box size n and corresponding root mean square fluctuation F(n).

$$F(n) = \left( \frac{1}{N} \sum_{k=1}^{N} \left| y(k) - y_{n}(k) \right|^2 \right)^{0.5}$$

A scaling exponent α = 0.5 is characteristic of a completely random series and an increasing α indicates
increasing long-range correlations. For DFA of the blood pressure time series, we partitioned the relationship into short ($\alpha_2$) and long-term ($\alpha_3$) scaling exponents, defined respectively as $2 \leq n \leq 30$ and $35 \leq n \leq 200$, consistent with previous work reported for blood pressure (24). For HRV, these were defined as $2 \leq n \leq 16$ and $32 \leq n \leq 200$, respectively.

Poincare analyses offer a means of visualising short and long-term variability, displaying each data point $n$ in a time series with respect to its neighbouring data point $n + 1$, for all points. These recurrence plots can be quantified in terms of SD1 (the SD in the direction perpendicular to the line of identity, a measure of short-term variability) and SD2 (the SD in the direction along it, a measure of long-term variability (17)), while the SD1/SD2 ratio reflects the balance between short- and long-term variability.

These features were extracted from a running 10-minute window of the respective time series, shifted in increments of 50 seconds. Quality criteria included (i) mean pulse rate of 40–250 beats per minute, (ii) a maximum of 10 seconds without detected peaks and (iii) a maximum loss of 20% for each time series following removal of outliers (>150% change from previous data point). For eligible windows, outlier removal affected <2.5% of all data points. Two additional criteria were applied to the arterial blood pressure signal: (iv) a maximum period of 10 seconds with sub-zero signal and (v) a maximum of 20% of the signal showing evidence of clipping (<0.05 mV change between subsequent systolic blood pressure points).

Statistical analysis was performed using R version 3.3.1 (R Core Team, 2012) and lme4 (Bates, Maechler & Bolker, 2012). We used a linear mixed-effects model to analyse the relationship between the extracted features and caffeine, adjusting for gestational age and birthweight Z-score calculated from Fenton growth charts (25) (fixed effects) and including intercepts for subjects as a random effect. Residual plots showed no curvature or pattern, with no obvious deviations from normality. Statistically significant variables (defined as $p < 0.05$) were confirmed with likelihood ratio tests of the full model against the model without the effect in question.

Sensitivity analyses
There were 11 subjects with arterial blood pressure data and six subjects with ECG data that had insufficient high-quality data at both time points (prior to and following caffeine administration). As a sensitivity analysis, we restricted the data set to the 20 and 19 subjects with complete arterial blood pressure and ECG data, respectively. We then determined the mean feature for each subject and compared pre- and postcaffeine values using a paired t-test or Wilcoxon test, depending on confirmed normality (Shapiro–Wilk test, $p > 0.05$).

RESULTS
Of the 40 infants enrolled in the previously published study (6), 31 had available arterial blood pressure data and 25 had ECG data (16 infants with both signals available). The characteristics of both subsets are summarised in Table 1. Mean (SD) length of data collected for all infants was 365 (176) minutes.

Table 2 summarises the mean and SD from all infants for features from linear statistical analysis, Poincare analysis and DFA. Figure 1 summarises the $\alpha_2$ and SD1/SD2 ratio changes across each of the four physiological time series. Linear mixed-model coefficients are summarised in Table S1. Following caffeine administration, mean arterial pressure $\alpha_2$ decreased significantly, while SD1/SD2 from Poincare analysis increased. An example of increased an increased SD1/SD2 ratio is shown in Figure S1. These changes were driven predominantly by an increased SD1, a marker of short-term variability. Mean arterial pressure $\alpha_1$ also exhibited a significant albeit mild decrease following caffeine.

Mean pulse pressure was not altered significantly following caffeine administration, though SD increased. We similarly observed an increase in SD1 and SD2 with their ratio not significantly altered. For HRV, $\alpha_1$ was lower at the postcaffeine time point. Figure S2 shows plots from DFA and Poincare analysis of a single analysis window of ECG data. Our cohort of preterm infants exhibited similar albeit slightly lower scaling exponents for HRV and blood pressure than those reported previously (15).

Following a sensitivity analysis, the direction of change of all variability parameters in this subset remained consistent with those reported in Table 2. Statistical significance also held for all parameters except for pulse pressure $\alpha_1$ (paired $t$-test $p = 0.063$).

Table 1 Cohort characteristics for preterm infants with arterial blood pressure data (ABP subset) and with electrocardiogram data (ECG subset)

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABP subset (n = 31)</th>
<th>ECG subset (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27.0 (23.6–33.3)</td>
<td>29.0 (24.3–33.3)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>934 (552–2100)</td>
<td>1265 (681–2100)</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>2.0 (0.1–7.8)</td>
<td>1.7 (0.1–7.8)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/14 (54.8%/45.2%)</td>
<td>15/10 (60%/40%)</td>
</tr>
<tr>
<td>Intubated</td>
<td>30 (96.8%)</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>CPAP</td>
<td>1 (3.2%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>No respiratory support</td>
<td>0 (0%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>RDS</td>
<td>28 (90.3%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Died</td>
<td>1 (3.2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are presented as median (range) or number (%). CPAP = Continuous positive airway pressure, RDS = Respiratory distress syndrome.

DISCUSSION
Caffeine is widely used in the neonatal intensive care unit as a respiratory stimulant to reduce the frequency of apnoea and to aid weaning from mechanical ventilation (1). It is thought to act as an adenosine antagonist at the A$_1$ and A$_2a$ receptors, stimulating the central respiratory centres and increasing chemoreceptor responsiveness to hypercapnia.
Loading of caffeine is generally commenced when the preterm infant is still invasively ventilated and requiring positive pressure ventilation, often from soon after delivery. Alterations in inspiratory and expiratory pressures with subsequent changes in mean airway pressure and blood gases impact significantly on intracranial pressure (27). The potential for additive negative impact with airway pressure gases impact significantly on intracranial pressure (27). The subsequent changes in mean airway pressure and blood pressure did not achieve statistical significance from likelihood ratio tests denoted by $p < 0.05$, $**p < 0.01$.

We compared both linear and nonlinear measures of heart rate and blood pressure variability at two time points; prior to a loading dose of caffeine and in the two hours following dose completion. Using linear mixed modelling, we found that the linear measures of variability (mean, SD) for mean arterial blood pressure and heart rate did not change significantly following caffeine (Table 2). While our findings are consistent with previous studies (5,15), it may be that the linear metrics do not adequately capture altered dynamics in heart rate and blood pressure control. The decrease in $\alpha_1$ of HRV following caffeine administration from a mean (SD) of 0.92 (0.21) to 0.86 (0.21) (linear mixed-effects coefficient $-0.06$, standard error 0.02, $p < 0.01$) suggests weaker long-range correlations, consistent with an increase in parasympathetic activity (16).

We observed a mild increase in variability (SD) of pulse pressure, which may be an important consideration in infants with impaired cerebrovascular autoregulation: discordance between systemic and cerebral blood flow may contribute to brain injury. Analysis of long-term outcomes from the CAP trial has nevertheless shown no adverse neurodevelopmental outcomes in infants receiving caffeine therapy rather than placebo (7,9,10).

The observed changes in heart rate and blood pressure dynamics may represent a range of influences and conditions. For example, the increase in vagal tone may simply represent a gradual relaxation of the subjects over the monitoring period or maturation of the autonomic nervous system, rather than the direct effect of caffeine. Nakamura et al. (19) reported correlations between postnatal age and neurodevelopmental outcomes in infants receiving caffeine. These findings suggest an enhanced reactivity of the autonomic nervous system (29) following a loading dose of caffeine in preterm infants, as characterised by increased vagally mediated heart rate and blood pressure variability.

Ulanovsky et al. (15) showed nonlinear HRV metrics were unchanged in a cohort of preterm infants following a loading dose of caffeine. They compared similar metrics from a 10-minute window extracted from each time point for each subject: prior to dose administration and in the one to two hours following completion. Comparisons showed no significant alterations in these parameters which may represent a type II error. Our subset of 31 infants with arterial blood pressure data had a median (range) gestational age of 27 (23.6–33.3) weeks (6), notably more preterm than the mean (SD) 30.3 (2.5) weeks gestation in the 21 infants reported by Ulanovsky et al. (15). This earlier study also compared a single window at each time point, which may not adequately account for natural variability within each subject.

To our knowledge, this is the first study to examine changes in nonlinear dynamics of blood pressure variability following caffeine administration in preterm infants. The decrease in mean arterial pressure $\alpha_1$ (1.12 (0.21) to 1.07 (0.16), linear mixed-effects coefficient $-0.06$, standard error 0.02, $p < 0.01$) suggests weaker long-range correlations, consistent with an increase in parasympathetic activity (16).

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0.02, p < 0.05) suggests an altered complexity that may also be associated with increased vagal tone. This finding was also reflected by Poincare analysis with an elevated SD1/SD2 ratio for mean arterial pressure (17,30). In adult subjects, vagal blockade by atropine has led to an increased short-term scaling exponent for the beat-to-beat blood pressure time series, while sympathetic inhibition by clonidine conversely reduced these exponents (16). It is also possible that the changes in the blood pressure scaling exponents were driven by those in heart rate: altered RR intervals influence the period of diastolic decay in the arterial pressure pulse via the Windkessel mechanism and may alter systolic blood pressure by shortening or lengthening the period of diastolic filling (16).

The altered heart rate dynamics in this cohort of infants were more clearly discerned using DFA than by Poincare analysis. The improved sensitivity of DFA over Poincare analysis for time rather than amplitude-based features also remained true of pulse interval which is often used as a proxy of heart rate, despite susceptibility to cardiorespiratory coupling. It is possible that DFA, which specifically quantifies correlations over time, may be more suited to temporal metrics such as pulse and heart rate intervals, whereas Poincare analysis, which quantifies variability, may better describe amplitude-based metrics such as mean arterial and pulse pressures.

One of the limitations of this study was the signal quality of the arterial blood pressure data, where artefacts and evidence of clipping may have influenced the extracted time series. We sought to mitigate this by applying quality control criteria and adopting maximal thresholds for abrupt variations in beat-to-beat values (quality criteria iv). Another limitation was that not all subjects had sufficiently high-quality data at both time points, although sensitivity analyses of the results with the restricted subset of data showed consistent results. We also used a linear mixed-effects model for the statistical analysis to mitigate the impact of missing values. As there was no control group of

![Figure 1](image-url)
infants not receiving caffeine therapy, there is also potential that other factors or postnatal development may have influenced the findings. This study was also limited by the sample size and the concurrent availability of ECG and arterial blood pressure data. The statistical analysis of HRV features was based on a different albeit overlapping subset of infants.

CONCLUSION
This study demonstrated that with a standard loading dose of caffeine, preterm infants showed enhanced autonomic nervous system responsiveness, reflected by indices of parasympathetic activity from both heart rate and blood pressure systems. Our findings improve our understanding of the mechanisms behind caffeine therapy. The use of advanced nonlinear analyses of heart rate and blood pressure variability used in this study may be applicable in other contexts of cardiovascular control. Our observation of increased pulse pressure variability may also hold implications for caffeine administration to infants with potentially impaired cerebral autoregulation.

FUNDING
The authors have no funding to report.

CONFLICT OF INTERESTS
The authors declare no conflict of interest.

References


SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Examples of SD1/SD2 from Poincare analysis of mean arterial pressure showing broadening of ellipse following caffeine administration in a single infant.

Figure S2 Examples of (a) detrended fluctuation analysis and (b) Poincare analysis of heart rate for a single analysis window.

Table S1 Summary of linear mixed model coefficients (standard error) and statistical significance for gestational age in weeks, birthweight Z-scores and caffeine (pre-caffeine = 0, post-caffeine = 1). Statistical significance is denoted by *p < 0.05, **p < 0.01.
Comparison of the effect of caseload midwifery program and standard midwifery-led care on primiparous birth outcomes: A retrospective cohort matching study

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A R T I C L E   I N F O

Article history:
Received 28 August 2017
Revised 17 September 2018
Accepted 16 October 2018

Keywords:
Cohort matching
Continuity of care
Midwife-led care
Midwifery
Normal birth
Caseload midwifery

A B S T R A C T

Background: The effectiveness of continuity of care during the perinatal period is well documented, but implementing continuity of care model to practice requires evaluation.

Aim: To evaluate the effect of a caseload midwifery program (CMP) on birth outcomes and rates of perinatal interventions at a metropolitan tertiary hospital in Australia, compared with standard midwifery-led care (SMC).

Methods: This was a retrospective, matched-cohort study. We extracted the data of 1000 nulliparous women from records of 19,001 women who gave birth at the hospital from 2011 to 2014. We used basic statistical tests to compare baseline demographic data, and logistic regression to calculate odds ratios, to evaluate maternal and neonatal outcomes.

Results: Adjusted regression analysis for the primary outcome showed that compared with women who received SMC, women who received care through CMP had an increased rate of normal vaginal birth (69% vs. 50%, OR = 1.79, 95% CI = 1.38–2.32). Assessment of secondary outcomes showed that the women in CMP group had decreased rates of instrumental birth (15% vs. 26%, OR = 0.48, 95% CI = 0.35–0.66), episiotomy (23% vs. 40%, OR = 0.43, 95% CI = 0.33–0.57), epidural analgesia (33% vs. 43%, OR = 0.64, 95% CI = 0.50–0.83) and amniotomy (35% vs. 50%, OR = 0.56, 95% CI = 0.43–0.72). The CMP group also had greater rates of water immersion (54% vs. 22%, OR = 4.18, 95% CI = 3.17–5.5), physiological 3rd stage (7% vs. 1%, OR = 11.71, 95% CI = 3.56–38.43) and 2nd degree tear (34% vs. 24%, OR = 1.60, 95% CI = 1.21–2.11). There were no significant differences between the two groups for rates of other secondary outcomes including Caesarean section, cervical ripening procedures, third- and fourth-degree tears, postpartum haemorrhage and neonatal outcomes.

Conclusion: CMP care is associated with increased rate of normal vaginal birth which supports wider implementation of the model. In addition, using routinely collected data and a cohort matching design can be an effective approach to evaluate maternal and neonatal outcomes.

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Introduction

Continuity of midwifery care

Midwifery-led continuity of care has been shown to improve perinatal outcomes for women and their newborns. Strong evidence shows that women who receive midwifery-led continuity of care have lower rates of preterm birth, instrumental vaginal birth and episiotomy when compared with women who receive all other...
models of maternity care (Sandall et al., 2016). According to a recent Cochrane review by Sandall et al. (2016) “midwife-led continuity of care confers important benefits and shows no adverse outcomes” (p 24). However, questions remain about the best models to organise and provide continuity of care (Sandall et al., 2016).

The available evidence presents heterogeneity models and study designs, limiting conclusions about what accounts for the observed difference in outcomes of continuity of midwifery-led care (Symon et al., 2016). The effectiveness of a model is influenced by differences in structures, personal attributes of midwives providing that model of care and institutional infrastructure that supports it (Allen et al., 2016; Hartz et al., 2011; Symon et al., 2016). Despite these, there is a general assumption that continuity of midwifery-led care models are underpinned by the philosophy of normality and this marks them as a key for improving maternity care outcomes (Renfrew et al., 2014; Sandall et al., 2009). The effort to increase access to continuity of midwifery-led care in the high-income countries is partly motivated by growing rate and cost of caesarean section and other childbirth interventions. Countries, such as New Zealand (Skinner and Fourre, 2010), Sweden (Waldenström et al., 2000) and the United Kingdom (Leap et al., 2010) have policies advocating continuity of care. World Health Organisation (WHO) also recommends that in settings with well-functioning midwifery programmes, midwife-led continuity of care models to support woman throughout the antenatal, intrapartum and postnatal continuum (World Health Organisation, 2016).

In Australia, the policy directives, such as Maternity — towards normal birth in NSW; include recommendations on promoting continuity of care as one of the leading strategies that aim to increase the vaginal birth rate and decrease the rate of caesarean section (Office of Kids and Families, 2010). Those directives prompted considerable efforts to establish programs providing continuity of midwifery-led care at a tertiary hospital in which this study was undertaken. The hospital was considered one of the pioneering centres for introducing Team Midwifery continuity of care model in early 1990’s (Kenny et al., 1994). However, despite its initial and well-documented success, the Team Midwifery Program ceased its operation by mid-2000 due to operational and staffing issues. Lessons learned from that experience were used when setting up a structure for the caseload midwifery program (CMP) that commenced its operation in May 2011.

Standard midwifery-led care versus caseload midwifery program

Costs of all maternity care provided by public hospitals for women who are Australian citizens or eligible permanent residents are covered in full by Medicare (Australian universal health-care scheme). At our hospital, almost 30% of those women, receive standard midwifery-led care (SMC). Those women meet criteria for low-risk pregnancy care described by the protocol of the Department of Women’s and Newborn Health at booking in. SMC is delivered by midwives who work shifts of 8–10 hours. There is no expectation that women receiving SMC see the same midwife more than once during their pregnancy, birth or postnatal care. Women who access SMC and develop pregnancy complication are usually transferred out of midwifery-led care, and are referred to medical staff who takes responsibility for coordinating perinatal care.

CMP is managed under the same funding structure as SMC, but, it works under different clinical structure. The CMP program began at our hospital with four full-time midwives working as partners in practice. The number of midwives working in the program was gradually increased to more than 12, and by October 2014, the CMP had provided care to more than 1000 women at the hospital (13.5% of all women who received care by midwives). The CMP midwives work in pairs or small groups and are on call to provide care for the caseload women throughout pregnancy, birth and up to two weeks postnatally. Thus, women receiving CMP care can expect one midwife to provide the majority, if not all, of their maternity care.

Although all women that qualify for midwifery care can opt for the CMP, access to the program is limited by both the number of midwives that practice CMP and the number of women under the care of each caseload midwife. Entry is for low risk women with an upper gestational limit of 32 weeks and as per the National Midwifery Guidelines for Consultation. Women with identified risks factors at booking in are referred to the Antenatal Clinic. For woman meeting the eligibility criteria and who chooses or is interested in CMP, the midwife will check the availability for the woman’s expected date of birth month. Where there is vacancy and entry to CMP, the midwife enters the woman’s details in the repository. The woman is, then, contacted to arrange ongoing appointments by one of the CMP midwives. Where there is no CMP vacancy for the woman’s expected date of birth month, suitable women may be offered a wait list option. The wait list is reviewed fortnightly at the caseload review and allocation meeting. Where there is no Caseload vacancy, the booking-in appointment detailed in the woman’s maternity booking letter from Women’s Health Clinic is kept and the woman is advised to attend her booking-in as scheduled. Each fortnight at the caseload review and allocation meeting, the Midwifery Unit Manager together with MCP midwives assign new referrals that have been received. This review ensures that there are reasonable workloads for individuals in the practice. Allocations and wait lists are maintained in the repository by the Midwifery Unit Manager or a representative and the primary midwife.

According to our hospital’s guideline on ‘Midwifery Caseload Practice’, each full-time caseload midwife is responsible for the care of 36 women per year, with a practice partnership for an additional 36 women per year. Part time midwives care for the appropriate percentage as per their part time equivalent.

In our hospital, the number of women under the care of CMP midwives has been decided based on low-risk entry and no-exit care model. From the commencement, efforts were made to establish effective pathway for consultation with medical staff and other health professionals to ensure safe care. So, when women in the CMP develop pregnancy complications and require a higher level of care, midwives consult an obstetrician champion and other health professionals to develop appropriate care plans, and women retain continuity of care from their CMP midwife. Caseload midwives and the Obstetric Champion meet together on a regular basis to ensure women receive care that is appropriate and leads to the best possible outcomes. Collaboration, communication and consensus decision making about care for women occurs at those meetings and midwives utilise the Australian College of Midwives (ACM) National Midwifery Guidelines for Consultation and Referral as the framework (Table 1). As a result, even when pregnancy complications arise, the CMP midwives remain lead clinicians coordinating and providing the care to women who require multidisciplinary involvement and increased level of surveillance.

Evaluation of outcomes

Implementation of the CMP necessitates a commitment from the organisation and clinicians working within the program. It also requires restructuring of the workforce and reallocation of resources. These changes may significantly affect the patient’s care and outcomes (Dawson et al., 2017). Routine evaluation of these changes and their impacts on patients’ outcomes can help inform further quality-improvements and broader implementation of the program at the hospital. This has been emphasised on in the study by Evan et al. (2000) indicating that “without routine effectiveness data we will fail to guarantee national standards of excellence or
ensure the public ‘confidence in the quality of the services they receive’ (p 254).

From the inception of the CMP program in our hospital, outcomes for women receiving care under the CMP have been monitored through internal audits as a routine part of our practice surveillance and improvement policy. Those audits report on perinatal outcomes Results have shown that the rate of vaginal birth for women accessing the CMP is over 80%, compared with 58% for women accessing all other types of maternity care at our hospital (Gidaszewski and Hook, 2013).

Although these findings seem reassuring, examining outcomes in such a way gives rise to biased conclusions and justifiably provokes criticism. The simple comparison of birth outcomes in routine hospital audits has questionable value as a true indication of the effectiveness of the CMP, because, the compared groups had potentially different baseline characteristics and risk profiles (Rosenbaum and Rubin, 1983; Song and Chung, 2010). To minimise the potential effects of those confounding variables, we conducted a cohort-matched study to identify comparison group similar characteristics to the CMP group. The primary outcome of our study was the spontaneous vaginal birth in the two groups between the women who received care from CMP and those who received SMC. The secondary outcomes were the rates of preterm birth, prelabour interventions, analgesia in labour, perineal trauma, labour complications and postpartum haemorrhage, length of labour as well as neonatal Apgar scores of less than seven at 5 minutes and number of neonates that experienced complications at birth (hypoglycaemia, hypothermia and respiratory distress).

Methods

Setting and design

This study was conducted at a metropolitan tertiary hospital in Sydney, Australia. The hospital is one of the country’s largest providers of maternity care with more than 5500 births per year. We used a retrospective, cohort-matched study design. This approach enables identification of comparison cohort of non-participants with similar variable characteristics as the treatment group when a large group of non-participants is available (Caliendo and Kopeinig, 2008). It also simulates randomisation and allows for a quasi-random assignment that can successfully mimic experimental design (Stuart, 2010). Cohort-matching reduces sample selection bias and minimises potential bias in assessing the effect of the intervention that can occur due to the differences in baseline characteristics of the comparison groups. It allows the use of routinely collected observational data to estimate the effect of interventions (Austin, 2011).

The study proposal was submitted and met the criteria for Quality Assurance project in accordance with NHMRC Guidelines. Ethics approval was obtained from Western Sydney Local Health District Human Research Ethics Committee in November 2015 (Ethics approval number: SAC2015/11/6.2).

Data and cohort selection

The study cohorts were identified from our electronic maternity database (ObstetriX) used to record perinatal information for all births at the hospital. Obstetrix is an obstetric information system based on the clinical dataset developed in Australia by the NSW Health Obstetrix Consortium. The database is routinely completed by midwives for every pregnancy and birth in most hospitals in NSW Local Health Districts.

For our study, the data from Obstetrix were collectively run as an archetype report and saved as a Microsoft Excel datasheet. We identified data for all women who gave birth during the period 1st May 2011 to 30th October 2014. These dates corresponded to the introduction of the CMP in 2011 and the CMP cohort reaching 1000 births in 2014. A total of 19,001 records of women who gave birth during the study period were identified. We extracted the following variables from our database: demographic information; obstetrical and gynaecological history; medical history; pregnancy, labour and birth outcomes; and the newborn’s characteristics and outcomes. Study cohorts were identified based on the model of midwifery care during pregnancy, as recorded at the time of entry to the birth unit. Missing and out of range data were checked against medical records before data were de-identified for matching and further analysis.

The final study cohort included only nulliparous women and combined the total population of nulliparous women who received care from the CMP (n = 500) and the comparison group that was selected by matching for parity, country of birth, age and body mass index (BMI) on a 1:1 basis (Fig. 1). These variables were matched for because of their known effects on labour outcomes. We selected only nulliparous women to minimise the effect of other confounding factors associated with multiparity. After matching, the study cohort totalled 1000 out of which 67% or 335 pairs were matched exactly on all parameters. We were able to close matched remaining 33% using predetermined criteria as follows: When there was not an exact match for a specific country of birth, a country with similar demographic and geographical characteristics was matched, for example, Pakistan was matched to Afghanistan or Cambodia was matched to Laos. Age

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Standard midwifery-led care versus caseload midwifery program.</th>
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</thead>
<tbody>
<tr>
<td>CMP</td>
<td>Costs of all maternity care are covered by Medicare (Australian universal healthcare scheme).</td>
</tr>
<tr>
<td></td>
<td>The CMP midwives work in pairs or small groups and are on call to provide care for the caseload women throughout pregnancy, birth and up to two weeks postnatal.</td>
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<td>Access to the program is limited by both the number of CMP midwives and the number of women under the care of each caseload midwife.</td>
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</tr>
<tr>
<td></td>
<td>Part time midwives care for the appropriate percentage as per their part time equivalent.</td>
</tr>
<tr>
<td></td>
<td>The CMP is based on a low-risk entry and no-exit care model.</td>
</tr>
<tr>
<td></td>
<td>If women in the CMP develop pregnancy complications and require a higher level of care, CMP midwives remain lead clinicians coordinating and providing the care to the women, while consulting an obstetrician champion and other health professionals to develop appropriate care plans.</td>
</tr>
<tr>
<td>SMC</td>
<td>Costs of all maternity care are covered by Medicare (Australian universal healthcare scheme).</td>
</tr>
<tr>
<td></td>
<td>Women who receive SMC meet criteria for low-risk pregnancy care at booking in.</td>
</tr>
<tr>
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<td>SMC is delivered by midwives who are rostered to work shifts of 8–10 hours.</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Women who access SMC and develop pregnancy complication are usually transferred out of midwifery-led care and are referred to medical staff who takes responsibility for coordinating perinatal care.</td>
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</table>

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</tr>
</tbody>
</table>
was matched to the closest age (±3 years) within age groups described in Table 1. BMI was matched to the closest match within the BMI categories: underweight, normal weight, overweight and obese (World Health Organisation, 2000). Data were cleaned and coded by a hospital-employed biostatistician and stored in a file on a password-protected computer drive accessible only to the research team.

Statistical analysis

We used simple statistical analysis tests to compare baseline demographic data. The chi-squared test was used if the variable was categorical and the Wald test was used for ordinal variables and non-parametric data. Continuous, parametric data were analysed using the Student t test. Comparisons were presented using frequencies and percentages, or means and 95% confidence intervals (CIs), or medians and interquartile ranges (IQRs), where appropriate. We calculated odds ratios (ORs) with corresponding 95% CIs, using adjusted logistic regression, to compare pregnancy outcomes. We defined statistical significance as P < 0.05. All statistical analyses were performed in SAS, version 9.3 (SAS Institute).

Results

Over 38% (n = 7226) of all women who gave birth at the hospital received midwifery-led care, including CMP and SMC, of whom 51% (n = 3683) were nulliparous (total population in our study). Out of all the nulliparous women, 13.6% (n = 500) received care from the CMP and the remaining received care from SMC. Comparison of the demographic characteristics between the study cohort (n = 1000, including 500 CMP and 500 matched SMC) and the total population of nulliparous women who received midwifery care (n = 3683) showed significant differences between the two cohorts in terms of country of birth and age distribution (Table 2).

The study cohort (n = 1,000) had a smaller proportion of non-Australian-born women (46% vs. 69%, P < 0.001) compared to the total population of nulliparous women receiving midwifery care (n = 3,683) (Table 2). The mean age of the study cohort was 28 years (ranged 17–40 years) compared to 27 years (range 14–45 years) in the total population (P < 0.001). The age distribution showed a higher percentage of women in the 25–35 age group (80% vs. 72%) in the study cohort compared with the total population, but no significant differences in other age groups were found between the study cohort and total population. The mean BMI was 23.5 (ranged 14–44) in the study cohort, compared with 23 (ranged 14–59) in the total population. (Table 2).

Comparison of CMP and SMC cohorts

Although no significant differences were found in baseline demographics between the CMP and SMC cohorts (Table 3), comparison of outcomes of interest showed some statistically significant differences between the two cohorts as follows.

- Primary outcome - mode of birth: The rate of normal vaginal birth (NVB) was higher for women receiving CMP care compared with those receiving SMC (69% vs. 50%, OR = 1.79, 95% CI = 1.38–2.32). The rate of instrumental birth was lower in the CMP cohort (15% vs 26%, OR = 0.48, 95% CI = 0.35–0.66). The differences in these outcomes between the two cohorts were statistically significant (P < 0.001), however, no statistically significant difference was found in the rate of caesarean section (16% vs. 19%, OR = 0.32, 95% CI = 0.61–1.17) (p > 0.05) (Table 4).

- Secondary outcomes: Compared with SMC cohort, the CMP cohort was significantly less likely to have epidural analgesia, amniotomy and episiotomy (p < 0.05) (Table 3). The women in CMP cohort were significantly more likely to experience a spontaneous rapture of membranes, use water immersion for pain management, have physiological third-stage labour management (Table 4) and have a shorter length of labour for the three labour stages (Table 4). No statistically significant differences were found between the two cohorts concerning the rate of other labour interventions and birth outcomes (Table 4).

Discussion

Despite baseline similarities, our findings showed that, compared to the SMC cohort, women who received care through the CMP had a greater chance of having a NVB and were more likely to use water immersion for pain management during labour. They were also less likely to have complications in labour, receive epidural analgesia, have an episiotomy or experience instrumental birth.

These findings are reassuring especially when we consider that unlike SMC cohort, the CMP cohort operated under no exit policy allowing the CMP midwives to continue providing care to women who developed pregnancy complication. Although, there was no statistically significant difference in the numbers of women diagnosed with gestational diabetes or hypertensive disorders between the two cohorts (Table 3), a review of files showed some differences between our study cohorts in the timing of the diagnosis and severity of their condition. Our findings are consistent with the unit’s protocols that mandate the transfer of pregnancy care from SMC to medically-led care when management of hypertension or gestational diabetes requires medication. On the other hand, no exit policy meant that CMP cohort included more women who had an earlier diagnosis of PHH treated with medication and also included women whose diabetes needed treatment with insulin. Despite the difference in number and acuity of maternal complications, there was no corresponding effect on neonatal outcomes.
Table 2
Comparison of demographic characteristics between the study cohort and total population of all nulliparous women accessing midwifery-led care at the hospital during the period 1 May 2011–30 October 2014.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study cohort (n = 1000)</th>
<th>Total population (n = 3683)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of birth, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>541 (54%)</td>
<td>1160 (31%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>459 (46%)</td>
<td>2523 (69%)</td>
<td></td>
</tr>
<tr>
<td>BMI at first antenatal visit, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 19</td>
<td>2 (0.2%)</td>
<td>23 (1%)</td>
<td></td>
</tr>
<tr>
<td>19–25</td>
<td>89 (9%)</td>
<td>429 (12%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 25–30</td>
<td>626 (63%)</td>
<td>2292 (62%)</td>
<td>0.016</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>216 (22%)</td>
<td>693 (19%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>67 (7%)</td>
<td>246 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (range)</td>
<td>23.5 (14–44)</td>
<td>23 (14–59)</td>
<td>0.030</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18</td>
<td>2 (0.2%)</td>
<td>31 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18–24</td>
<td>163 (16%)</td>
<td>844 (23%)</td>
<td></td>
</tr>
<tr>
<td>25–35</td>
<td>795 (80%)</td>
<td>2656 (72%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 35</td>
<td>40 (4%)</td>
<td>152 (4%)</td>
<td></td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>28 (17,40)</td>
<td>27 (14,45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI = body mass index.

Table 3
Baseline characteristics between matched study cohorts.

<table>
<thead>
<tr>
<th>CMP characteristic</th>
<th>CMP (n = 500)</th>
<th>SMC (n = 500)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of birth, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>272 (54.5%)</td>
<td>269 (54%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Other</td>
<td>228 (45.5%)</td>
<td>231 (46%)</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 21</td>
<td>16 (7%)</td>
<td>18 (8%)</td>
<td></td>
</tr>
<tr>
<td>21–24</td>
<td>16 (7%)</td>
<td>18 (8%)</td>
<td></td>
</tr>
<tr>
<td>BMI at first antenatal visit, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 19</td>
<td>2 (0.2%)</td>
<td>3 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>19–25</td>
<td>89 (9%)</td>
<td>93 (9%)</td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>23 (14–42)</td>
<td>23 (14–44)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks), mean (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 26</td>
<td>40 (23–42)</td>
<td>40 (20–42)</td>
<td>0.380</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>8 (2%)</td>
<td>13 (3%)</td>
<td>0.362</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>6 (1.2%)</td>
<td>3 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>33 (7%)</td>
<td>17 (3%)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

CMF: caseload midwifery practice; SMC: standard midwifery-led care.
* Complications at the end of pregnancy.

Table 4
Adjusted odds ratios and 95% confidence intervals of birth outcomes in women who received care through the CMP and SMC.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>CMP (n = 500)</th>
<th>SMC (n = 500)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vaginal birth</td>
<td>344 (69%)</td>
<td>276 (50%)</td>
<td>&lt;0.001</td>
<td>1.79 (1.38–2.32)</td>
</tr>
<tr>
<td>Instrumental vaginal birth</td>
<td>74 (15%)</td>
<td>132 (26%)</td>
<td>&lt;0.001</td>
<td>0.48 (0.35–0.66)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>82 (16%)</td>
<td>94 (19%)</td>
<td>0.319</td>
<td>0.85 (0.61–1.17)</td>
</tr>
<tr>
<td>Cervical ripening</td>
<td>38 (8%)</td>
<td>53 (11%)</td>
<td>0.099</td>
<td>0.69 (0.45–1.07)</td>
</tr>
<tr>
<td>Spontaneous rupture of membranes</td>
<td>338 (68%)</td>
<td>274 (55%)</td>
<td>&lt;0.001</td>
<td>1.72 (1.33–2.23)</td>
</tr>
<tr>
<td>Amniotomy</td>
<td>177 (35%)</td>
<td>248 (50%)</td>
<td>&lt;0.001</td>
<td>0.56 (0.43–0.72)</td>
</tr>
<tr>
<td>Systocinon in labour</td>
<td>256 (51%)</td>
<td>279 (56%)</td>
<td>0.145</td>
<td>0.83 (0.65–1.07)</td>
</tr>
<tr>
<td>Pyrexia in labour</td>
<td>13 (3%)</td>
<td>35 (7%)</td>
<td>0.089</td>
<td>1.85 (0.91–3.77)</td>
</tr>
<tr>
<td>Hypertension in labour</td>
<td>7 (1%)</td>
<td>16 (3%)</td>
<td>0.290</td>
<td>1.68 (0.65–4.36)</td>
</tr>
<tr>
<td>Epidural</td>
<td>164 (33%)</td>
<td>216 (43%)</td>
<td>0.001</td>
<td>0.64 (0.5–0.83)</td>
</tr>
<tr>
<td>Water immersion</td>
<td>269 (54%)</td>
<td>109 (22%)</td>
<td>&lt;0.001</td>
<td>4.18 (3.17–5.5)</td>
</tr>
<tr>
<td>Blood loss at delivery &gt; 500 mL</td>
<td>44 (9%)</td>
<td>51 (10%)</td>
<td>0.450</td>
<td>0.85 (0.56–1.30)</td>
</tr>
<tr>
<td>Physiological 3rd stage management</td>
<td>33 (7%)</td>
<td>3 (1%)</td>
<td>&lt;0.001</td>
<td>11.71 (3.56–38.43)</td>
</tr>
<tr>
<td>Epidistomy</td>
<td>113 (23%)</td>
<td>202 (40%)</td>
<td>&lt;0.001</td>
<td>0.43 (0.33–0.57)</td>
</tr>
<tr>
<td>2nd degree tear</td>
<td>169 (34%)</td>
<td>121 (24%)</td>
<td>0.001</td>
<td>1.60 (1.21–2.11)</td>
</tr>
<tr>
<td>3rd or 4th degree tear</td>
<td>21 (4%)</td>
<td>23 (5%)</td>
<td>0.758</td>
<td>0.91 (0.5–1.67)</td>
</tr>
<tr>
<td>All vaginal births, 2nd degree tear and episiotomy [n/N (%)]</td>
<td>272/418 (65%)</td>
<td>299 (74%)</td>
<td>0.008</td>
<td>0.67 (0.49–0.9)</td>
</tr>
<tr>
<td>SVB, 2nd degree tear and episiotomy [n/N (%)]</td>
<td>195/444 (53%)</td>
<td>172 (63%)</td>
<td>0.165</td>
<td>0.79 (0.57–1.1)</td>
</tr>
<tr>
<td>Birth weight &lt; 2.5 kg</td>
<td>12 (2%)</td>
<td>17 (3%)</td>
<td>0.346</td>
<td>0.70 (0.33–2.23)</td>
</tr>
<tr>
<td>Birth weight &gt; 4 kg</td>
<td>35 (7%)</td>
<td>26 (5%)</td>
<td>0.234</td>
<td>1.37 (0.81–2.32)</td>
</tr>
<tr>
<td>Apgar score &lt; 7 at 5 min</td>
<td>6 (13%)</td>
<td>8 (2%)</td>
<td>0.59</td>
<td>1.34 (0.46–3.89)</td>
</tr>
<tr>
<td>Neonatal complication at birth**</td>
<td>55 (11%)</td>
<td>65 (13%)</td>
<td>0.33</td>
<td>0.83 (0.56–1.21)</td>
</tr>
</tbody>
</table>

OR = odds ratio. CI = confidence interval. CMP = caseload midwifery program. SMC = standard midwifery-led care.
Values are given as Number (Percent).
** Includes hypoglycaemia, hypothermia and respiratory distress.
For example, the higher number of women with diabetes in the CMP group (32 vs. 17) did not translate into more neonatal complications at birth. In fact, there was a higher number of babies born to SMC cohort that had complications at birth (65 in SMC cohort vs. 55 in the CMP cohort). However, bigger sample size and more robust methodology are needed to make more detailed and conclusive determination about the differences highlighted by our study.

Our findings support previous studies from Australian (Tracy et al., 2014) and other countries, such as New Zealand (Grigg and Tracy, 2013) and the United Kingdom (Homer et al., 2017), as well as Cochrane reviews on the continuity of care and carer (Hodnett, 2001; Waldenström and Turnbull, 1998). These studies indicated that women receiving caseload care were more likely to have a NVB and were less likely to have epidural analgesia, episiotomy or other labour and birth interventions. In another study (McLachlan et al., 2012) conducted in an Australian tertiary hospital, 2,314 women (1610 nulliparous and 704 multiparous women) were randomised to either caseload midwifery care or standard hospital care. Results of their study showed higher rates of normal vaginal birth for nulliparous women who received caseload care. Although in contrast to our study, McLachlan et al. found no difference in the rates of instrumental birth between the groups.

Our results showed a significantly lower rate of instrumental birth for women who received CMP care. A potential explanation for this finding in our study could be the lower rate of epidural use and a higher rate of water immersion for labour pain relief in women receiving CMP care. Evidence to this claim is the report of previous research indicating that compared with non-pharmacological methods of pain management, epidural use in labour is significantly associated with higher rate of instrumental birth (Anim-Somuah et al., 2011).

Overall continuity of care as provided by a CMP at our hospital is associated with lower rates of labour intervention and increased rate of normal birth. Our study shows that women with similar characteristics, despite being cared for in the same setting and receiving care according to same protocols, had different outcomes. The reasons for this are most likely complex and beyond the scope of our study. What makes programs that provide the continuity of care special for many women and midwives is the possibility of a professional relationship that allows for a deeper connection and partnership between the midwives and women (Williams et al., 2010). This partnership is founded on equality and is made possible because of better communication, knowledge of each other, trust and closeness (Williams et al., 2010). These elements of care are difficult to assess or measure, but we suppose that they may help women and midwives optimise the birth experience and potentially explain some of the differences in perinatal outcomes.

Evidence-based care is subjected to ongoing, rigorous, systematic quality assurance monitoring and evaluation (Kitson et al., 1998). The effects of different treatments or interventions on patient outcomes are best shown by using randomised allocation and comparing the groups that have similar baseline characteristics. Although randomised controlled trials (RCTs) are widely accepted and considered the gold standard for studies of intervention, they require prospective design, economic resources and expertise that are not always available in a clinical setting with competing clinical and research priorities (Campbell et al., 2007; Ross et al., 1999).

However, our choice of retrospective methodology was not influenced by the limited resources available to us. We questioned ethics of randomisation under circumstances where we were employed to establish and provide this continuity of care service, developed because of the already existing evidence (Wong et al., 2015). Our study was carried out to show a ‘real life’ perspective on our practice using a more balanced approach to analyse data that is routinely collected and already used for monitoring of our service.

We chose the methodology that allowed us to use a quasi-random assignment and which can successfully mimic the experimental design of an RCT (Stuart, 2010). Cohort matching aims to minimise the effect of differences in baseline characteristics and to decrease or eliminate the effects of confounding factors between the comparison groups (Grootendorst et al., 2010). The study cohort was selected from the total population of women who already met criteria for low-risk pregnancy care at booking in and continued to receive midwifery care on entry to birth unit. Because of the size of our population, we had a large number of potential participants and possible matches. Well-matched samples minimise the influence of differences in those characteristics during the assessment of the effect of the intervention (Stuart, 2010). Similarly, in our study, the sample matching design helped us to reduce potential sample selection bias and allowed our study cohort to be very similar in terms of characteristics that are associated with different outcomes in our population.

Study limitations and strengths

One of the limitations of our study was our retrospective design, which necessitated the use of routinely collected data. We relied on information entered by clinical midwives into a database not purpose-built for our research. To ensure that correct information had been entered and to minimise the effect of missing out-of-range data or data that did not seem valid, we checked the sample against individual medical records and corrected or established them to be true, when possible.

Also, despite the large size of data, we were not always able to find an exact match for all women in the CMP group. We had to use our judgment when matching similar demographic data for the women’s country of birth, age and BMI. Nevertheless, to minimise potential sample bias, we used predetermined ranges to match our cohorts, and we were blinded to outcome values during the matching process.

Not including data on clinical complications at baseline might have been a potential confounding factor for the results and they need to be considered in any future research. However, since we compared the labour and birth outcomes of only low risk women, we expected that the two groups were similar in term of clinical risks at baseline, and as such we believe that this would have had minimal impacts on our results.

Furthermore, our results may not be generalised to the entire population of pregnant nulliparous women due to collecting data from one single site and retrospective design of the study which limited our ability to account for all potential confounding factors.

It is always very important to be cautious when interpreting results of observational studies. Although they can provide a valuable insight about the potential effect of intervention, any difference should only be interpreted as an association rather than a result of the intervention (Harris et al., 2006). Despite this, we believe that our chosen methodology provides reliable answers to our research question because our results are consistent with other research about caseload midwifery care (Forster et al., 2016; Tracy et al., 2014).

The strength of our study was the large number of women we were able to include; 1,000 over a period of four years from 2011 to 2014. Arguably, our large study cohort minimised the potential shortcomings of our study design and was effective in demonstrating differences in care outcomes between the two models of care provided to women with similar baseline characteristics and perinatal risk profiles.
Conclusion

Results of our study highlight the positive effect of CMP on the rate of normal vaginal birth. They also show that CMP can be associated with lower rates of some perinatal interventions and with similar neonatal outcomes to women receiving SMC at the hospital. Our findings can be used to support efforts for broader implementation of the model at the hospital, and add more evidence about the positive impact of continuity of midwifery care on care outcomes.

Conflict of interest

The authors have no conflict of interest.

Ethical approval

Ethic’s approval was obtained from Western Sydney Local Health District Human Research Ethics Committee in November 2015 (Ethics approval number: SAC2015/11/6.2).

Acknowledgements

The authors would like to acknowledge the in-kind support received from the Department of Women’s and Newborn Health at Westmead Hospital and editorial assistance from Olivia Wroth and Sarah Malov.

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[References text]


World Health Organisation. WHO recommendation on midwife-led contin-


implementation-strategies/who-recommendation-midwife-led-continuity-care-during-pregnancy

Complexity of gastroschisis predicts outcome: epidemiology and experience in an Australian tertiary centre

Sarah J. Melov1*, Irene Tsang2, Ralph Cohen2,4, Nadia Badawi3,4,5, Karen Walker3,4,5, Soundappan S. V. Soundappan2,4 and Thushari I. Alahakoon1,4

Abstract

Background: Gastroschisis is a congenital anomaly of the fetal abdominal wall, usually to the right side of umbilical insertion. It is often detected by routine antenatal ultrasound. Significant maternal and pediatric resources are utilised in the care of women and infants with gastroschisis. Increasing rates of gastroschisis worldwide have led institutions to review local data and investigate outcomes. A collaborative project was developed to review local epidemiology and investigate antenatal and neonatal factors influencing hospital length of stay (LOS) and total parental nutrition (TPN) in infants born with gastroschisis.

Methods: We performed a five-year review of infants born with gastroschisis (2011–2015) at a major Australian centre. Complex gastroschisis was defined as involvement of stenosis, atresia, ischemia, volvulus or perforation and closed or vanishing gastroschisis. We extracted data from files and databases at the two participating hospitals, a major maternal fetal medicine centre and the affiliated children’s hospital.

Results: There were 56 infants antenatally diagnosed with gastroschisis with no terminations, one stillbirth (2%) and one infant with ‘vanishing’ gastroschisis. The mean maternal age was 23.9 years (range, 15–39 years). The mean gestation at delivery was 36 weeks (range, 25–39 +3 weeks). Of the 55 neonates who received surgical management, 62% had primary closure. The median LOS was 33 (IQR, 23–45) days and the median duration of TPN was 26 (IQR, 17–36) days. Longer days on TPN (median 35 vs 16 days, \( P = 0.03 \)) was associated with antenatal finding of multiple dilated bowel loops. Postnatal diagnosis of complex gastroschisis was made in 16% of cases and was associated with both longer LOS (median 89 vs 30 days, \( P = 0.003 \)) and days on TPN (median 46 vs 21 days, \( P = 0.009 \)).

Conclusion: Complex gastroschisis was associated with greater days on TPN and LOS. We found no late-gestation stillbirths and a low overall rate of 1.8%, suggesting the risk for stillbirth associated with gastroschisis is lower than previously documented. This information may assist counselling families. Improved data collection worldwide may reveal causative factors and enable antenatal outcome predictors.

Keywords: Gastroschisis, Antenatal diagnosis, Outcome, Incidence, Stillbirth, Length of stay, Congenital anomaly

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Background

Gastroschisis is a congenital defect of the fetal abdominal wall, resulting in extrusion of abdominal contents. It is usually diagnosed in the antenatal period [1] and requires early neonatal surgical intervention. Extensive resources of maternal fetal medicine, neonatology and pediatric surgery are used in antenatal diagnosis, neonatal management and treatment of infants with gastroschisis. Published literature has documented a 14% termination rate with early diagnosis [1].

Rising rates of gastroschisis have been reported worldwide, with a well-recognized higher prevalence in younger women [2, 3]. From an incidence of 0.06–0.8 per 10,000 in the 1960s, [4–6] gastroschisis has become more prevalent over the last few decades to its current rates of 4.5–5.13 per 10,000 pregnancies [7–9]. Global variations in incidence have been reported, with 10.9 per 10,000 [10] in Greenland and 29.9 per 10,000 in Mexico [11]. Ethnic variations in incidence [9, 12] and evidence of regional or geospatial clustering have also been described [13, 14]. Controversy and conflicting reports have existed about the influence of terminations [15] and misdiagnosis or incomplete data capture [16] on reporting of the incidence of gastroschisis.

The reason for a higher prevalence of gastroschisis in the babies of a younger maternal age group is not clear. Studies investigating its association with factors such as maternal drug use, smoking, [7, 17] nutritional factors, paternal age, [6] maternal infection, [18] pesticide use [19] and other environmental agents [20] have not been conclusive, except that an association with smoking has been consistent [21].

Many studies of gastroschisis have focused on finding definitive antenatal predictors for adverse events, but no clear prognostic indicators have been found to assist with management or counselling of women and their families. A recent meta-analysis of 26 studies had inconclusive results, stating that only intra-abdominal bowel dilatation (IABD), stomach enlargement and polyhydramnios may be associated with more adverse outcomes [22].

Controversy exists regarding best practice for monitoring and delivering babies with gastroschisis. “Matting” a type of bowel injury characterized by varying degrees of thickened bowel wall, rigidity, adherent dilated bowel loops and discoloration is thought to be associated with poorer outcome [23]. It has been suggested that delivery at earlier gestation reduces bowel matting. However, the aetiology of matting is poorly understood and longer exposure to amniotic fluid has not been associated with increased bowel matting. Youssef [24] found a 3.6% decrease in severe matting with every extra week a fetus was in utero. Planned delivery prior to 36 weeks of completed gestation does not seem to confer any short- or long-term outcome advantages but may contribute to adverse outcomes [25, 26].

Westmead Hospital (WH) and The Children’s Hospital at Westmead (CHW) are affiliated tertiary referral centres, and one of only three facilities in New South Wales, Australia that provide a collaborative tertiary pediatric surgical service for pregnancies complicated by gastroschisis. The state of New South Wales (NSW) has mandatory reporting to the NSW Register of Congenital Conditions. Aggregate data on gastroschisis was provided by the NSW Centre for Epidemiology and Evidence, Ministry of Health data for the last ten-year period available (2004–2013) in the NSW Register of Congenital Conditions database. This data reveals Westmead Hospital cared for more gastroschisis cases than any other hospital in the state (n = 78, 35.5%).

The primary aim in our study at WH and CHW, was to determine predictors for hospital length of stay (LOS) and days on total parental nutrition (TPN). Our secondary objectives were to review epidemiology and uncover other predictors for infant outcome to discharge, generating important local data to inform service planning for the leading centres of care for gastroschisis in NSW, Australia.

Methods

We conducted a five-year retrospective review of all neonates antenatally diagnosed with gastroschisis and born at WH during the five-year period from January 2011 to December 2015. Patients were identified using existing databases at WH and CHW. Antenatal data were extracted from the WH obstetric and ultrasound database. Neonatal data were retrieved from the CHW Grace Centre for Newborn Intensive Care database and the surgical database. We reviewed individual patient notes for all cases.

Data recorded included maternal demographic data, antenatal risk factors, delivery details and postnatal management aspects including LOS, TPN, categorisation into complex or simple gastroschisis, primary or secondary closure and infection, with data collected until patient discharge. Complex gastroschisis was defined as additional intestinal morbidity at first postnatal surgical evaluation of any of the following: stenosis, atresia, ischemia, volvulus, perforation [27] and closed or vanishing gastroschisis. Bowel dilation in the fetus was defined as any dilation of the bowel greater than 8 mm [28]. Small for gestational age was defined as estimated fetal weight < 10th centile, with polyhydramnios and oligohydramnios defined by reference amniotic fluid index nomograms for gestation used in our ultrasound practice [29].

Time on TPN was the duration until full enteral feeding was achieved.

Antenatal care at our institution for women with a gastroschisis baby includes care with the high risk
maternal fetal medicine clinic, a named maternal fetal medicine specialist consultant and named caseload midwife from booking for continuity of care. Surveillance for gastroschisis includes ultrasound monitoring every 2 weeks from 28 weeks and a fetal cardiotocography (CTG) three times per week from 32 weeks.

**Statistical analyses**

We analysed the associations between the primary outcomes of LOS and time on TPN and the clinical or demographic factors of country of mother’s birth, insurance status, gestation at diagnosis, gestation at first maternal fetal medicine consultation, day and time of delivery, gestation at birth, fetal gender, mode of delivery, as well as if they had a surgical primary or delayed closure.

Statistical analysis was performed using SAS 9.4. Continuous variables are presented as median and interquartile range if skewed and mean (standard deviation) or range otherwise. Categorical variables were described by frequencies and percentages.

Associations between clinical and demographic factors and study outcomes were examined using chi-square tests, logistic regression, Spearman correlation and the Wilcoxon rank-sum test. There was no adjustment made for multiple statistical comparisons. All statistical tests were performed at a 2-sided level, where \( P < 0.05 \) is considered statistically significant.

**Results**

There were 56 babies with gastroschisis identified antenatally in the five-year period, born at WH. One fetal death at 25 weeks was reported with a localised stricture of an amniotic band at the fetal end of the umbilical cord and was excluded from outcome analysis. The only fetus with a concurrent anomaly had mild hydronephrosis and was included in outcome analysis.

There were 55 babies with gastroschisis in the five-year period that were analysed for neonatal outcome of LOS and days on TPN. One mother gave birth to two infants with gastroschisis over consecutive study years. Another mother gave birth to a second infant with gastroschisis in the year after the study period. No postnatal diagnosis of gastroschisis was made and there were no terminations of a pregnancy in the study period of a fetus diagnosed with gastroschisis.

Most patients identified were from outside the local hospital district, with 30% (\( n = 17 \)) from within the local tertiary referral hospital district area and three from New Caledonia. Of the 45 babies of known gestation at diagnosis, 60% (\( n = 27 \)) were diagnosed before or at 14 weeks, with 25 (56%) women diagnosed at their nuchal translucency screening ultrasound. The mean gestation at primary diagnosis was 15 weeks (range, 11–22 weeks).

The mean maternal age was 23.9 years (range, 15–39 years). Most women (64.3%) recorded a body mass index in the normal range (18.5 - \(< 25 \) kg/m\(^2\)) at first booking-in visit (Table 1). All patients had spontaneous conception and there were two twin pregnancies recorded (one dichorionic diamniotic pregnancy and one monochorionic diamniotic pregnancy). One patient disclosed recent cannabis use and one polysubstance use, with 27% of women reporting current cigarette smoking (Table 1). Genitourinary infections have been proposed to

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Westmead Hospital, 2011–2015, ( n/% )</th>
<th>All NSW, 2011–2015, mean % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 20 )</td>
<td>13 (23.2%)</td>
<td>2.9% (2.5–3.2%)</td>
</tr>
<tr>
<td>20–24</td>
<td>22 (39.3%)</td>
<td>12.6% (12.0–13.1%)</td>
</tr>
<tr>
<td>25–29</td>
<td>13 (23.2%)</td>
<td>27.2% (26.8–27.7%)</td>
</tr>
<tr>
<td>( \geq 30 )</td>
<td>8 (14.3%)</td>
<td>57.3% (56–58.7%)</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>7 (12.5%)</td>
<td>3.6% (3.1–4.0%)</td>
</tr>
<tr>
<td>Body mass index(^3)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>18.5 to &lt; 25</td>
<td>36 (64.3%)</td>
<td></td>
</tr>
<tr>
<td>25 to &lt; 30</td>
<td>14 (25%)</td>
<td></td>
</tr>
<tr>
<td>( \geq 30 )</td>
<td>4 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (26.8%)</td>
<td>9.9% (8.9–11.1%)</td>
</tr>
<tr>
<td>No</td>
<td>41 (73.2%)</td>
<td>90.1% (88.9–91.1%)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Asthma</td>
<td>19 (33.9%)</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>11 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>10 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>Genital herpes</td>
<td>3 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Recurrent UTI(^4)</td>
<td>10 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First birth</td>
<td>37 (66.1%)</td>
<td>43.9% (43.4–44.2%)</td>
</tr>
<tr>
<td>( \geq ) Second birth</td>
<td>19 (33.9%)</td>
<td>56.1% (55.8–56.6%)</td>
</tr>
<tr>
<td>Consanguineous</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>No</td>
<td>55 (98.2%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>41 (73.2%)</td>
<td>64.8% (63.3–66.4%)</td>
</tr>
<tr>
<td>Non-Australian</td>
<td>15 (26.8%)</td>
<td>35.2% (33.6–36.7%)</td>
</tr>
</tbody>
</table>

*Urinary Tract Infections*

\( N/A \) not available, NSW New South Wales, *Source: Centre for Epidemiology and Evidence; NSW Mothers and Babies 2015. Sydney, NSW Ministry of Health, 2016*
be associated with gastroschisis [30], in our study 17.9% (n = 10) of all women had a history of recurrent urinary infections. Table 1 reports other medical conditions that were disclosed by the 56 women with ≥10 frequency.

Thirteen percent of women (n = 7) identified as Aboriginal (Table 1) and none identified as Torres Strait Islander. Other nationalities represented in the cohort were New Caledonia (n = 3), New Zealand (n = 3), the Philippines (n = 2) and Lebanon (n = 2). There were no women born in an East Asian or South Asian country group (United Nations geoscheme) in our cohort, these are the two most common groups (Table 2) in our local area of the Western Sydney Local Health District (WSLHD). In New South Wales maternity databases only have country of birth and not ethnicity as a data collection point.

Of the 30 women who attended their nuchal translucency combined first trimester screening, 93% of results (n = 28) were recorded as low risk. None of the high risk results proved to have karyotype abnormalities. At the 18–22-week ultrasound, there were 28 reports of intra-abdominal dilated bowel loops, with 21% (n = 6) noting the presence of multiple dilated bowel loops on scan images at this gestation. There were 29 cases that reported to show fetal intra-abdominal dilated bowel loops, of these 55% (n = 16) documented multiple dilated bowel loops present on their ultrasound. Significant bowel dilation > 18 mm [31] was found in 35% (n = 19) and was not associated with greater days on TPN or LOS. Stomach enlargement was not documented as a significant finding in any of our antenatal ultrasounds.

Polyhydramnios was recognised in seven patients and oligohydramnios in four. Small for gestational age was predicted on ultrasound in 40% of fetuses (n = 22) after 25 weeks. An antenatal review by a pediatric surgeon was recorded in 66% of cases at a mean gestational age of 30 weeks (range, 14–38 weeks).

Table 3 details birth information. The mean gestation at delivery was 36 weeks (range, 25–39+3 weeks), with a 1:1.2 infant malefemale ratio. Most births (55.4%) occurred out of normal working hours (Table 4). The median LOS was 1.3 h (IQR, 1.1–2.2 h) in the Westmead neonatal intensive care unit for initial stabilisation prior to transfer via an enclosed walkway to the adjacent Children’s Hospital. A total of 62% of babies had primary closure of the defect (see Table 5 for a summary of surgical details). The median LOS was 33 days (IQR, 23–45 days) with the median duration of TPN 26 days (IQR, 17–36 days) (Table 5).

No independent factor had a significant impact on both LOS and duration of TPN except postnatal diagnosis of complex gastroschisis, however the finding at any gestation of multiple dilated bowel loops was associated with more days on TPN (P = 0.03) (Table 4). There were nine patients (16%) that had a postnatal diagnosis of complex gastroschisis, with an associated longer LOS and duration of TPN (Fig. 1, Table 5). The median LOS for simple gastroschisis (median 30 days, IQR, 23–39) was more than doubled for complex gastroschisis (median 89 days, IQR, 57–147). Similar differences were seen in duration of TPN, with a median 21 days for simple (IQR, 17–31) and 46 days (IQR, 34–187) for complex gastroschisis. Complex gastroschisis babies had the same median gestation at birth of

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Babies born with gastroschisis, WSLHD address, n = 17</th>
<th>All WSLHD births, n = 49,647</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroschisis</td>
<td>3.4 per 10,000</td>
<td>–</td>
</tr>
<tr>
<td>Australian-born mother</td>
<td>10 (58.8%)</td>
<td>17,782 (35.8%)</td>
</tr>
<tr>
<td>Non-Australian-born mother</td>
<td>7 (41.2%)</td>
<td>31,865 (64.2%)</td>
</tr>
<tr>
<td>*Southern Asia</td>
<td>0 (0.0%)</td>
<td>13,261 (26.7%)</td>
</tr>
<tr>
<td>East Asia</td>
<td>0 (0.0%)</td>
<td>5516 (11.1%)</td>
</tr>
</tbody>
</table>

*Most common non-Australian born group in WSLHD

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diagnosed with gastroschisis, n = 56</th>
<th>All NSW births, mean % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcome, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>55 (98.2%)</td>
<td>99.14% (99.1–99.2%)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1 (1.8%)</td>
<td>0.58% (0.5–0.6%)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0</td>
<td>0.22% (0.2–0.3%)</td>
</tr>
<tr>
<td>Weeks’ gestation at birth, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 31</td>
<td>2 (3.6%)</td>
<td>0.72% (0.7–0.8%)</td>
</tr>
<tr>
<td>32–36</td>
<td>34 (60.7%)</td>
<td>6.22% (6.0–6.4%)</td>
</tr>
<tr>
<td>37–41</td>
<td>20 (35.7%)</td>
<td>91.82% (91.7–91.9%)</td>
</tr>
<tr>
<td>Labour induced</td>
<td>23 (41.0%)</td>
<td>28.7% (26.6–30.5%)</td>
</tr>
</tbody>
</table>

*NSW New South Wales, N/A not available, *Source: Centre for Epidemiology and Evidence; NSW Mothers and Babies 2015. Sydney, NSW Ministry of Health, 2016

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36.3 weeks (range 33.3–38 weeks) as simple gastroschisis babies median value (range 30–39.3 weeks). The median birth weight was also comparable between complex gastroschisis (2430 g, range 1900–3090 g) and simple gastroschisis (2398 g, range 1300–3860 g).

One woman with an antenatal ultrasound diagnosis of gastroschisis gave birth to a baby with undiagnosed ‘vanishing’ gastroschisis. The baby required surgery for bowel obstruction, malrotation and jejunal atresia, and this complex infant had a lengthy hospital stay of 328 days. All babies with complex gastroschisis had Australian born mothers except the baby with vanishing gastroschisis whose mother was born in Lebanon. All live-born babies survived to discharge. Follow-up data were available for Australian babies (n = 52, 95%) until 1 month after discharge, with no deaths.

Table 4 Variable association with primary outcome LOS, time on any TPN

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n = 55</th>
<th>TPN Median days Rho (r)</th>
<th>P value</th>
<th>LOS Median days Rho (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of Birth†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>40 (73)</td>
<td>26</td>
<td>0.73</td>
<td>33</td>
<td>0.51</td>
</tr>
<tr>
<td>Other</td>
<td>15 (27)</td>
<td>22</td>
<td>–</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>Health insurance†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No private</td>
<td>46 (84)</td>
<td>27</td>
<td>0.87</td>
<td>34</td>
<td>0.29</td>
</tr>
<tr>
<td>Private</td>
<td>9 (16)</td>
<td>19</td>
<td>–</td>
<td>27</td>
<td>–</td>
</tr>
<tr>
<td>Gestation‡ at diagnosis n = 44</td>
<td>(80)</td>
<td>r = 0.15</td>
<td>0.32</td>
<td>r = 0.07</td>
<td>0.63</td>
</tr>
<tr>
<td>Gestation‡ at MFM review n = 46</td>
<td>(84)</td>
<td>r = 0.07</td>
<td>0.64</td>
<td>r = –0.01</td>
<td>0.94</td>
</tr>
<tr>
<td>Ultrasound‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal bowel dilation &gt; 18 mm</td>
<td>19 (35)</td>
<td>31</td>
<td>0.17</td>
<td>37</td>
<td>0.27</td>
</tr>
<tr>
<td>Fetal bowel dilation &lt; 18 mm</td>
<td>35 (65)</td>
<td>21</td>
<td>–</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>7 (13)</td>
<td>22</td>
<td>0.5</td>
<td>26</td>
<td>0.20</td>
</tr>
<tr>
<td>No polyhydramnios</td>
<td>47 (87)</td>
<td>28</td>
<td>–</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Multiple dilated bowel loops</td>
<td>16 (30)</td>
<td>35</td>
<td>0.03</td>
<td>38</td>
<td>0.06</td>
</tr>
<tr>
<td>No Multiple dilated loops</td>
<td>38 (70)</td>
<td>16</td>
<td>–</td>
<td>27</td>
<td>–</td>
</tr>
<tr>
<td>Bowel wall &gt; 3 mm</td>
<td>4 (7)</td>
<td>24</td>
<td>0.78</td>
<td>28</td>
<td>0.40</td>
</tr>
<tr>
<td>Bowel wall &lt; 3 mm</td>
<td>50 (93)</td>
<td>26</td>
<td>–</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td>Birth time/day ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mon-Fri 8 am-8 pm</td>
<td>24 (44)</td>
<td>29</td>
<td>0.44</td>
<td>37</td>
<td>0.18</td>
</tr>
<tr>
<td>Mon-Fri 8 pm-8 am</td>
<td>17 (31)</td>
<td>28</td>
<td>–</td>
<td>42</td>
<td>–</td>
</tr>
<tr>
<td>Sat-Sun 8 am-8 pm</td>
<td>6 (11)</td>
<td>24</td>
<td>–</td>
<td>31</td>
<td>–</td>
</tr>
<tr>
<td>Sat-Sun 8 pm-8 am</td>
<td>8 (15)</td>
<td>19</td>
<td>–</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>Gestation at birth‡ n = 55</td>
<td>(100)</td>
<td>r = –0.11</td>
<td>0.42</td>
<td>r = –0.15</td>
<td>0.27</td>
</tr>
<tr>
<td>Caesarean birth‡</td>
<td>30 (56)</td>
<td>27</td>
<td>0.90</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>24 (44)</td>
<td>23</td>
<td>–</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>Female gender‡</td>
<td>31 (56)</td>
<td>22</td>
<td>0.91</td>
<td>33</td>
<td>0.73</td>
</tr>
<tr>
<td>Male gender‡</td>
<td>24 (44)</td>
<td>27</td>
<td>–</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td>Birth weight‡ n = 55</td>
<td>(100)</td>
<td>r = –0.13</td>
<td>0.36</td>
<td>r = –0.17</td>
<td>0.21</td>
</tr>
<tr>
<td>Simple gastroschisis‡</td>
<td>46 (84)</td>
<td>21</td>
<td>0.009</td>
<td>30</td>
<td>0.003</td>
</tr>
<tr>
<td>Complex gastroschisis‡</td>
<td>9 (16)</td>
<td>46</td>
<td>–</td>
<td>89</td>
<td>–</td>
</tr>
<tr>
<td>Primary closure‡</td>
<td>34 (62)</td>
<td>23</td>
<td>0.60</td>
<td>30</td>
<td>0.19</td>
</tr>
<tr>
<td>Secondary Closure‡</td>
<td>21 (38)</td>
<td>28</td>
<td>–</td>
<td>37</td>
<td>–</td>
</tr>
</tbody>
</table>

P value is based as indicated: Spearman’s correlation coefficient= with Rho(r) reported in table
Wilcoxon rank-sum test † with median reported in table
Some missing data therefore total may not equal 55

LOS length of stay, TPN total parenteral nutrition, US Ultrasound, MFM Maternal Fetal Medicine
Stillbirth rates for gastroschisis have improved in high-resource countries from 50% in the 1960s [35] to more recent estimates in research and literature of 4.5–10% [3, 36]. Although there is evidence of an increased risk of intrauterine death [36] with increasing gestation for babies with gastroschisis, we report no late-gestation deaths in our study. Pregnancy surveillance and regular patient education are part of standard care, as is ongoing care from a caseload midwife, and pregnant women are encouraged to contact the hospital or midwife if they are concerned about reduced intrauterine fetal movement. Increased surveillance and patient education leading to earlier delivery of compromised fetuses may be a factor in our study’s absence of late-gestation stillbirths.

Two consistent associations reported with gastroschisis have been young maternal age and smoking; both factors were confirmed in our study. The overall smoking rate in the study group was 27%, which is more than twice the overall smoking rate of 10% in NSW during the same period. It is also an interesting observation in this cohort that in a 5 year period, none of the gastroschisis cases were the result of an assisted reproduction.

Ethnicity has been reported as affecting prevalence, with a higher rate of gastroschisis reported for babies of Caucasian women, and one study reporting a 263% increase in incidence among non-Hispanic black women from the period before 2005 compared to the period 2006–2012 [9]. Our study also revealed ethnicity as a possible factor influencing prevalence. Thirteen percent of our study cohort identified as Aboriginal, which is a higher proportion than that of the NSW population; Aboriginal and Torres Strait Islander women have been recorded as 2.9% of the total NSW female population [37]. In our cohort, non-Australian-born mothers accounted for 27% of babies with gastroschisis (Table 1), which is lower than the NSW average of 35%. For maternal addresses in the Western Sydney Local Health District (WSLHD) subgroup (n = 17), 41% of pregnancies with gastroschisis were non-Australian-born (Table 2), in contrast to the high proportion of the culturally and linguistically diverse population of the WSLHD, at over 60% [38]. Of particular note was that none of the pregnancies in this cohort had women born in South Asian countries while they account for 20.8% of all pregnant women delivering in the local health district [38].

Asthma was reported as a pre-existing condition for 34% of women in our study, higher than the 10.9% reported in the NSW female population [39] and may be an area for future investigation.

Increasing awareness of incidence-clustering of gastroschisis has led to calls for further investigation and improved data collection worldwide, to identify possible teratogenic causative agents [40]. The rising prevalence of gastroschisis has been discussed for over 20 years, but

### Table 5: Characteristics of neonatal gastroschisis, Westmead Hospital/CHW, 2011–2015, n = 55

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total LOS, both Hospital&lt;sup&gt;a&lt;/sup&gt;, days</td>
<td>55</td>
<td>33 (23–45)</td>
</tr>
<tr>
<td>LOS, Complex gastroschisis, days</td>
<td>9</td>
<td>89 (57–147)</td>
</tr>
<tr>
<td>LOS, Simple gastroschisis, days</td>
<td>46</td>
<td>30 (23–39)</td>
</tr>
<tr>
<td>Duration of TPN, days</td>
<td>55</td>
<td>26 (17–36)</td>
</tr>
<tr>
<td>TPN, Complex gastroschisis, days</td>
<td>9</td>
<td>46 (34–187)</td>
</tr>
<tr>
<td>PN, Simple gastroschisis, days</td>
<td>46</td>
<td>21 (17–31)</td>
</tr>
<tr>
<td>Duration of tube feeding, days</td>
<td>51</td>
<td>20 (13–32)</td>
</tr>
<tr>
<td>Duration of CVL, days</td>
<td>55</td>
<td>28 (18–43)</td>
</tr>
<tr>
<td>Age at primary surgery, hours</td>
<td>29</td>
<td>5 (5–7)</td>
</tr>
<tr>
<td>Surgical findings&lt;sup&gt;b&lt;/sup&gt; cases (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel perforation</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Bladder herniated</td>
<td>4 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Presence of peel</td>
<td>22 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Presence of matting</td>
<td>7 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Bowel ischemia</td>
<td>3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Intestinal atresia present</td>
<td>7 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Adhesions</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Primary repair surgery,</td>
<td>34 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Primary repair with skin</td>
<td>3/34 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Primary repair skin/muscle/fascia</td>
<td>28/34 (82.4)</td>
<td></td>
</tr>
<tr>
<td>Use of patch for closure</td>
<td>3/34 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Delayed closure surgery</td>
<td>21 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Delayed surgery final closure, Mean ± SD, days</td>
<td>5.5 ± 2.5, range, 1–11</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Westmead Hospital. Neonatal Intensive Care and Grace Centre for Newborn Intensive Care: The Children’s Hospital Westmead (CHW)

<sup>b</sup>Surgical finding: complications do not add up to 100% due to overlapping LOS length of stay, IQR interquartile range, TPN total parenteral nutrition, CVL central venous line

### Discussion

We found postnatal diagnosis of complex gastroschisis to be associated with longer LOS and days on TPN, compared to simple gastroschisis, although the median birth weights and gestation at birth were comparable in the two groups. Our study found the only antenatal factor associated with adverse neonatal outcome was multiple dilated bowel loops.

For delivery gestation, a range from 30 weeks to 39<sup>a</sup> was not associated with longer LOS or greater time on TPN, despite other studies identifying early gestation at birth to impact on outcome [32, 33]. Our findings suggest that concerns relating to short term neonatal outcomes associated with delivery at late preterm gestation may not be as relevant in decision making. Our results could be due to the small number of cases, but other larger studies have found a similar lack of predictive antenatal factors [25, 34].

[35] Westmead Hospital, Neonatal Intensive Care and Grace Centre for Newborn Intensive Care: The Children’s Hospital Westmead (CHW)

[36] Surgical finding: complications do not add up to 100% due to overlapping LOS length of stay, IQR interquartile range, TPN total parenteral nutrition, CVL central venous line
there has been no commitment to coordinated data collection including demographic information, environmental assessment, stillbirths, terminations, births and surgical outcomes in Australia. Our study, in a major hospital, was the result of coordination between two hospitals and three departments (maternal fetal medicine specialists at the adult hospital, the children’s hospital neonatal intensive care unit, and the surgical department), and involved piecing together various databases and physical examination of patient records. The Australian and New Zealand Neonatal Network are establishing a surgical network that will improve future surgical neonatal data capture for our region. Ongoing funding, support and commitment to a comprehensive national database of birth anomalies, including collection of data on environmental exposures, ethnicity, terminations and stillbirths, and clinical outcome at tertiary hospitals worldwide, will provide valuable information to inform research into the possible causative agents for the rising prevalence.

Limitations of our study include the retrospective study design, retrospective review of ultrasound data, and small patient numbers. Patient numbers in this study were inadequate to assess the antenatal sonographic predictors for simple versus complex gastroschisis. We suggest further prospective studies into antenatal predictors of complex gastroschisis. However, a strength of our study is that all patients diagnosed with gastroschisis in our region are reviewed by our maternal fetal medicine specialists for counselling, any termination data, including for those terminated at an early gestation, would be captured at our unit.

Conclusions about the causes of rising trends are impossible without robust data collection for all pregnancies, including for all terminations and stillbirths. Improvement in ultrasound techniques and routine early scanning allows for early diagnosis of gastroschisis. A recent study in The Netherlands found that 14% of pregnancies with babies who had isolated gastroschisis were terminated when they were diagnosed before 18 weeks’ gestation [1]. Analysis of five British data repositories from 1991 to 1999 [41] found that 13% of pregnancies with gastroschisis ended in termination. There is no clear reason for no terminations of pregnancies involving babies with gastroschisis in our study. Australia-wide data on reasons for termination and numbers of terminations are unavailable.

Fig. 1 The primary outcomes length of stay in hospital (LOS) and days on total parenteral nutrition (TPN) for the live-born babies with simple and complex gastroschisis. a: Results for LOS (median and interquartiles). b: Results for TPN (median and interquartiles). Both outcomes were noted to be more than doubled with complex gastroschisis. *Significant difference $P < 0.05$
and will continue to confound data on the prevalence of conditions until data are more accurately captured.

All infants born after 25 weeks’ gestation in our cohort survived to discharge in this five-year study period. Improved multidisciplinary care, antenatal surveillance and timely surgical and neonatal care contribute to the current optimal outcomes. Reducing LOS and morbidity is an ongoing objective.

**Conclusion**

We found excellent outcomes for late-gestation infants born with gastroschisis, reporting that all live-born infants survived to discharge. In contrast with many other studies, our cohort had no terminations in the study period. In an ethnically diverse population, our finding that there was an increased incidence of infants born with gastroschisis in Australian-born women compared to overseas born women requires more research.

We found no antenatal predictor for hospital LOS, inclusive of gestation at delivery and multiple bowel loop dilation to be associated with greater time on TPN. However complex gastroschisis diagnosed in the postnatal period is associated with greater days on TPN and LOS. This information should be used to counsel parents. The future challenge is to develop consistent specific antenatal ultrasound markers differentiating simple and complex gastroschisis. Better antenatal prediction can provide useful information for parents and families in planning the postnatal period, especially when patients are referred to a tertiary centre from geographically distant areas.

**Abbreviations**

CHW: The Children’s Hospital at Westmead; IABD: Intra-abdominal bowel dilatation; LOS: Length of stay; NSW: New South Wales; TPN: Total parental nutrition; WH: Westmead Hospital; WSLHD: Western Sydney Local Health District

**Acknowledgments**

Elizabeth Barnes for assistance with statistical analysis.

**Availability of data and materials**

The data from this study is available on reasonable request from the study authors upon approval of the Western Sydney Local Health District Ethics Committee.

**Authors’ contributions**

TIA conceived the study. TIA and SJM wrote the first draft of the manuscript. SJM, IT, RC, NB, KW and SS contributed to design, analysis and corrected draft and final approval of the manuscript. Data extraction was performed by SJM and IT.

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**Ethics approval and consent to participate**

The study was approved in 2016 by the Sydney Children’s Hospitals Network Human Research Ethics Committee (reference no 113) and Western Sydney Local Health District (reference no 4691).

**Competing interests**

The authors declare that they have no competing interests.

**Publisher’s Note**

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**References**


Guidelines

Conjoint Urological Society of Australia and New Zealand (USANZ) and Urogynaecological Society of Australasia (UGSA) Guidelines on the management of adult non-neurogenic overactive bladder

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Due to the myriad of treatment options available and the potential increase in the number of patients afflicted with overactive bladder (OAB) who will require treatment, the Female Urology Special Advisory Group (FUSAG) of the Urological Society of Australia and New Zealand (USANZ), in conjunction with the Urogynaecological Society of Australasia (UGSA), see the need to move forward and set up management guidelines for physicians who may encounter or have a special interest in the treatment of this condition. These guidelines, by utilising and recommending evidence-based data, will hopefully assist in the diagnosis, clinical assessment, and optimisation of treatment efficacy. They are divided into three sections: Diagnosis and Clinical Assessment, Conservative Management, and Surgical Management. These guidelines will also bring Australia and New Zealand in line with other regions of the world where guidelines have been established, such as the American Urological Association, European Association of Urology, International Consultation on Incontinence, and the National Institute for Health and Care Excellence guidelines of the UK.

Keywords
overactive bladder, guideline, urinary incontinence, urodynamics, bladder

Introduction

The definition of the overactive bladder syndrome (OAB) was refined by the ICS in 2008. It is characterised by urgency, with or without urgency urinary incontinence (UUI) and is often associated with frequency and nocturia, in the absence of pathological or metabolic factors that would explain these symptoms [1]. OAB presence suggests underlying detrusor overactivity (DO) but may be caused by other voiding or lower urinary tract dysfunction [1]. OAB can be classified as ‘OAB-dry’ when there is no UUI component in the symptomatology, or ‘OAB-wet’ when there is an UI component. OAB can be neurogenic in origin or non-neurogenic (idiopathic), and should not be confused with UI. Although OAB can occur at any age, these guidelines will focus on the adult population and mainly on non-neurogenic OAB but, where relevant, will also include recommendations for its neurogenic counterpart.

Epidemiology

OAB can affect people of all ages. Neurogenic OAB tends to be associated with suprasacral and suprapontine pathology; the more common of these include suprasacral spinal cord injury (SCI), multiple sclerosis and spina bifida disease. In the non-neurogenic group, several authors reported its prevalence as being approximately 16% in some European and American cohorts [2,3]. OAB is recognised as a common disorder affecting quality of life (QOL) worldwide. There is also a significant economic cost involved. In 2010 in Australia, the total financial cost of UI (excluding burden of disease) was estimated to be nearly $43 billion [4].
Clinical Relevance

Due to the potential increase in the number of patients afflicted with OAB who will require treatment, the Functional and Female Urology Special Advisory Group (FUSAG) of the USANZ, in conjunction with the Urogynaecological Society of Australasia (UGSA), see the need to move forward and establish management guidelines for physicians who may encounter or have a special interest in the treatment of this condition. These guidelines, by utilising and recommending evidence-based data, will hopefully assist in the diagnosis, clinical assessment, and optimisation of treatment efficacy. They will also bring Australia and New Zealand in line with other regions of the world where guidelines have been established, such as the AUA [5,6], European Association of Urology [7], International Consultation on Incontinence (ICI) [1], and the NICE guidelines of the UK [8].

The Panel

The guidelines committee consists of nine members (eight urologists and one urogynaecologist), all of whom have a specialist interest in OAB management. The committee is divided into three subcommittees each specialising in a particular area: Clinical Assessment and Diagnosis, Conservative Management, and Surgical Management. A thorough literature review of the last 10 years, up to the end of 2014, was undertaken by each subcommittee to formulate a series of management recommendations, based on the Oxford Level of Evidence scale (OCEBM) [9]. Recommendations for clinical areas which do not have a sufficient evidence base may be formed by expert opinion from a consensus of the committee members. The drafting of the guidelines is supported by the executive board of both USANZ and UGSA, with no industry involvement, and with the final draft presented to, and endorsed by, the board of directors of both societies prior to submission for publication. These guidelines are a direct result of ex gratis time and effort put in by individual committee members.

1. Diagnosis and Clinical Assessment

Although there is no formal evidence, it is well accepted that history and examination is a fundamental initial step in the evaluation of a patient with OAB [10].

1a: History

**Level of Evidence: 4**

**Grade of Recommendation: C**

OAB symptoms that may be elicited on history include the triad of urinary urgency with or without UUI, frequency and nocturia. Urgency with or without UUI must be present for the diagnosis of OAB [11] (Table 1).

A clear understanding of the LUTS must be established, including the rapidity of onset, duration and, in particular, the severity of the symptoms. This can be assessed by pad usage including pad weight, size, and number used, and number of UI episodes per day. A bladder diary is essential to further clarify this and is discussed in more detail later.

It is important while taking the history to include assessment of the fluid intake including the amount and type of fluids. Caffeine, present in coffee, tea, green tea and caffeinated soda can influence and exacerbate urinary urgency and frequency by various mechanisms including a direct effect within receptors of the bladder wall [12]. Artificial sweeteners present in diet drinks may influence OAB symptoms although this association is not conclusive [13]. Alcohol also plays a well-recognised role in exacerbation of symptoms.

Other urological problems may need management preceding, or concurrently, with management of the OAB. This applies to stress UI and outflow obstruction, both of which may present with mixed symptoms [14,15]. In this situation a referral to a specialist is suggested.

Neurogenic OAB can occur not only in common neurological diseases such as multiple sclerosis, Parkinson’s disease, post cerebrovascular accident and spinal cord pathology but also in systemic conditions such as diabetes. It should be managed by a specialist due to the potential complexity of the condition and possible need for advanced testing such as video urodynamics [16]. OAB symptoms may be the first presentation in some neurological conditions and therefore an important component of a thorough history is evaluating for presence, or absence, of non-urological symptoms that may be neurological in origin.

Obstructive sleep apnoea is a common cause of nocturia through the effect of increased brain natriuretic peptide [17]. In this case the patient’s presenting symptom may be nocturia and only by directed questioning, examination, and review of a bladder diary will the possibility of sleep apnoea be identified.

**Table 1 Symptoms/signs and conditions that require specialist referral**

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<tr>
<th>Symptoms</th>
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<td>Sterile pyuria</td>
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<td>Nocturnal Incontinence</td>
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<td>Life-long incontinence</td>
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<td>Significant obstructive symptoms</td>
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<td>Associated bowel symptoms/constipation</td>
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<th>Signs</th>
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<td>Neurological deficits</td>
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<td></td>
<td>Evidence of pelvic or prostatic malignancy</td>
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<th>Surgical history</th>
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Referral to sleep studies and use of continuous positive airways pressure may be useful in reducing the symptoms.

A thorough medical history is important both for establishing other causes for the OAB symptoms, and to ensure there is no contraindication or the potential for complications with the introduction of treatment for OAB. Conditions to consider include cardiac history, in particular a prolonged QT interval, uncontrolled hypertension, narrow angle glaucoma, functional gastrointestinal pathology, myasthenia gravis, and renal and liver impairment.

It is vitally important to pay special attention to the elderly afflicted with OAB. OAB is more common with ageing [18], and this population generally has a lower physiological reserve to deal with adverse effects of treatment, as well as the clinical investigations preceding it. Elderly individuals who are at higher risk, such as those with cognitive dysfunction, weakness, reduced mobility, constipation, and glaucoma, and patients on polypharmacy, especially anticoagulants and drugs with anticholinergic effects, should be identified during the clinical assessment phase.

It is important to review the medication list of all patients. Some medications, such as diuretics, may cause increased urinary frequency, and there is a growing number of medications that have additive anticholinergic effects or interact with OAB drugs, particularly the β3 agonists.

1b: Examination

**Level of Evidence: 4**

**Grade of Recommendation: C**

General examination of the patient is important for alerting the physician to other possible mechanisms contributing to the voiding symptoms and the potential for complications related to treatment. These include obesity, cognitive state, hand coordination, and gait disturbance. A focused abdominal and pelvic examination is essential; particularly look for an over-distended bladder, pelvic mass or pelvic tenderness.

In the male, examination of the external genitalia may assist in excluding obstructive pathology. Pay particular attention to the urethral meatus, which may be stenosed, and the prostate, which should be assessed by DRE.

In the female, a vaginal examination should be performed, with particular attention to the presence of atrophic vaginitis, assessment of pelvic floor muscle strength using the Oxford grading, the presence of stress leakage with cough and valsala, and the presence of pelvic organ prolapse (POP). Ideally, the latter two should be carried out in the upright position.

A neurological examination should be included if there is suspicion of an undiagnosed underlying neurological disorder. A focused S2–S4 examination including sensation, anal tone and bulbocavernous reflex may be useful.

1c: Investigations

**Level of Evidence: 4**

**Grade of Recommendation: C**

Initial investigations recommended include urine microscopy and culture to exclude infection, microscopic haematuria (in the absence of infection) or sterile pyuria. In the case of recurrent UTIs, microscopic haematuria or persistent sterile pyuria, consider referral to a specialist.

A bladder diary is useful in supporting the diagnosis of OAB, as well as for excluding polydipsia, nocturnal polyuria where nocturnal volume voided is >20–33% of 24 h volume, and compromised functional capacity with voids <250 mL. This should document the time, type and volume of fluid taken, urine volume voided, and leakage episodes.

Finally, a post-void residual urine volume (PVR) is important to exclude obstruction and incomplete emptying.

Three essential elements are necessary before the management pathway for OAB is followed: a negative urine test, a bladder diary consistent for OAB, and minimal PVR, in the patient with uncomplicated OAB symptoms, as elicited on history and examination.

Complicated cases, such as patients with neurological disease, presence of microscopic haematuria or who have failed conservative treatment options, may require specific tests which are generally performed at specialist level. These include renal ultrasound to check for upper tract damage, caused by the high pressures generated from the bladder, frequently seen in neurogenic overactivity. Cystoscopy is required when there is recurrent UTI, haematuria, or persistent pyuria, and for assessment of possible obstructive pathology. Cystoscopy should also be considered in the patient who is refractory to medical therapy, as patients with bladder tumours may present with urinary frequency even in the absence of microscopic haematuria. Urodynamic testing (possibly with imaging and electromyogram) is useful in those refractory to conservative medical therapy and essential in those with underlying neurological disease.

2. Conservative Management

2a. Lifestyle modifications and behavioural therapies

**Level of Evidence: 1b – 2**

**Grade of Recommendation: B**

Conservative management of OAB includes lifestyle modifications involving diet, fluid intake, and weight loss, and
behavioural and physical therapies such as bladder training (BT) and pelvic floor muscle training (PFMT).

**Lifestyle modifications**

Patients should be encouraged to make lifestyle modifications.

**Reduce caffeine intake** Caffeine effects include CNS stimulation and smooth muscle relaxation. Some studies have shown that reduction in caffeine intake resulted in improvement in OAB symptoms. One randomised controlled trial (RCT) found that caffeine reduction together with BT resulted in greater reductions in urgency and frequency compared to BT alone [19]. In another study, the relationship between a decrease in the amount of dietary caffeine consumed and fewer daytime episodes of involuntary urine loss approached significance [20].

**Modify high fluid intake** A higher fluid intake may result in increased urinary frequency, worsening OAB symptoms. One study showed a 25% reduction in fluid intake reduced frequency and urgency [21]. The baseline intake of fluids must be taken into account before deciding to modify intake. There was no evidence to suggest increasing fluid intake improves urinary symptoms.

**Lose weight** One well performed study showed that a weight loss of 8% over 6 months reduced UUI episodes by 42% compared to 26% in controls [22].

**Behavioural and physical therapies**

Behavioural therapies include BT and scheduled voiding, where carers initiate the decision to void. Different strategies may be used, as no single regimen has yet been proven ideal. As well as following a voiding pattern, the patient should be instructed on bladder function and fluid intake, including caffeine restriction, and bowel habits. Patients may be asked to void according to a fixed voiding schedule. Alternatively, patients may be encouraged to defer voiding until the urgency sensation settles. ‘Timed voiding’ is voiding initiated by the patient, while ‘prompted voiding’ is voiding initiated by the caregiver.

UI was improved, but not cured, by timed bladder voiding at intervals of between 2.5 and 4 h in two key RCTs, which compared BT with no intervention [23,24]. BT has been compared with other treatments for UI in a number of other RCTs. BT alone is as effective as oxybutynin, tolterodine and solifenacin in controlling UUI and nocturnal UI [25–29].

PFMT is usually used in conjunction with urge suppression techniques [23,24,30].

**Recommendations**

**Behavioural interventions are effective for improvement of UI in women.**

The effectiveness of BT diminishes after the treatment has ceased.

**2b. Medical therapy**

**Antimuscarinic Medications: Oxybutynin, Tolterodine, Solifenacin, Darifenacin**

**Level of Evidence: 1a**

**Grade of Recommendation: A**

Antimuscarinic agents have been shown to work synergistically with behavioural therapy and BT [31]. There are many well-conducted RCTs looking at individual antimuscarinics as well as four systematic reviews [32–35], with the latter showing rates for improvement or cure of UUI based on short-term treatment of up to 3 months. There was no significant difference in efficacy across these agents, even when looking at immediate release (IR) formulation vs extended release (ER), which indicates that ER and IR formulations of antimuscarinics can offer similar clinical efficacy in short-term cure and improvement rates. It was also clear in these studies that patients who have more bothersome symptoms are more likely to experience symptom improvement.

For adverse effects of antimuscarinics, dry mouth is the most prevalent. It is more common with oxybutynin IR than tolterodine IR, but less than for darifenacin, 15 mg daily [34,36]. Oxybutynin ER has higher rates of dry mouth than tolterodine ER. Transdermal (TD) oxybutynin is effective in reducing UI episodes and is associated with a lower rate of dry mouth (9.6% vs 68% for oxybutynin IR, a nine times difference). The TD formulation had an overall higher rate of withdrawal due to allergic skin reaction [34]. M3-selective blockers are generally associated with fewer antimuscarinic side-effects than their non-selective counterparts; solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER [34]. In general, discontinuation rates were similar for each treatment arm in comparative RCTs, irrespective of differences in the occurrence of dry mouth.

More than half of patients will discontinue antimuscarinic agents within the first 3 months because of failure in efficacy, bothersome side-effects, and the financial burden. Many of the currently available M3-antagonists are not listed on the Pharmaceutical Benefits Scheme in Australia and patients are not subsidised. If the antimuscarinics are effective but causing significant side-effects, the clinician should try to maintain the drug therapy while offering conservative and supportive treatment. This can include oral moisturisers for dry mouth, and laxatives, a diet adequate in fibre and regular physical activity for constipation.
Concomitant behavioural modification (BT, PFMT, electrical stimulation) and antimuscarinic therapy have been shown to improve outcome parameters such as frequency, voided volume, UI and symptom inconvenience [37,38]. Behavioural treatments have also been shown to be equally efficacious as antimuscarinics in reduction of OAB symptoms. Behavioural therapies may improve UI episodes by 50–80%, and reduction has been shown in both men and women [39]. Several studies have also shown that weight loss can assist in OAB symptom improvement [22].

Care should be exercised when prescribing antimuscarinic agents in the elderly population. The National Overactive Bladder Evaluation (NOBLE) study showed that older people (aged >65 years) were disproportionately affected; >30% have OAB compared with 16.5% of the overall population [3]. Urgency and UUI in the elderly may be due to lesions in the bladder or the CNS [40]. Diagnoses such as Parkinson’s disease, myasthenia gravis, dementia and Alzheimer’s disease are of particular importance in the elderly as medications used to control these conditions may potentiate or reduce the effects of anticholinergics. It is important to consult the patient’s treating neurologist if planning to use an antimuscarinic agent for OAB in this group. Oxybutynin IR may worsen cognitive function, with the ER formulation safer as it does not cause delirium in the short term. Solifenacin, tolterodine and darifenacin have not been demonstrated to impair cognitive function in the healthy elderly [41,42].

As the population ages, there will also be an increase in the proportion of women developing POP. Some patients with POP present with OAB symptoms, but there is poor correlation between the two. There is some data to show that repair of POP may improve OAB symptoms in up to 80% of patients, but there is also the risk that a small but significant percentage of patients (<20%) develop de novo OAB [43].

Recommendations  
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinics for UUI (<30 days).

The combination of BT with antimuscarinic drugs may result in greater improvement of UI.

Exercise caution when prescribing antimuscarinics in the elderly, especially those with a background of dementia, Alzheimer’s disease, and other neurological conditions.

**Tricyclic Antidepressants: Imipramine, Amitriptyline, Nortriptyline**

**Level of Evidence:** 4

**Grade of Recommendation:** C

There are no recent studies on the use of tricyclic antidepressants for OAB. Generally their use is reserved for patients who cannot tolerate antimuscarinic medication or in whom these medications are contraindicated. The recent availability of a β3 agonist, mirabegron, may see their use decrease further.

**Topical Oestrogens**

**Level of Evidence:** 1b

**Grade of Recommendation:** A

Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women. Besides improving vaginal atrophy, vaginal oestrogen therapy reduces UI and frequency and urgency in OAB [44].

**Recommendation**  Vaginal oestrogen therapy should be offered to postmenopausal women with UI, and vaginal atrophy.

**Desmopressin**

**Level of Evidence:** 1b

**Grade of Recommendation:** B

An RCT found that nasal desmopressin was an effective and safe treatment in women with daytime UI [45], and there are data to support use of desmopressin to reduce nocturia in both men and women [46–49]. However, there is no published evidence reporting desmopressin cure rates for UI and no evidence comparing it with other non-drug treatments for UI [7].

Two recent systematic reviews showed that desmopressin may significantly decrease nocturnal frequency, and increased time to first void during sleep, resulting in an extended duration of the first sleep period and improved sleep quality. Dosage with 25 μg was already sufficient in some patients to reduce nocturnal frequency. A dose of 100 μg provided just more than an hour of additional sleep before the first void compared with placebo. Higher doses provided no significant increase in benefit [50,51].

The use of desmopressin carries a risk of developing hypertension and hyponatraemia (12%). Elderly patients started on this drug should have their blood pressure and serum sodium checked regularly, beginning in the first few days after starting treatment [52].
polyuria on bladder diary, after other causes are excluded, in conjunction with appropriate monitoring of serum sodium and blood pressure. Lower dosages (<100 μg) are recommended on initiating the drug.

**Mirabegron**

**Level of Evidence: 1b**

**Grade of Recommendation: A**

Mirabegron is a novel β3 agonist which produces relaxation of the bladder smooth muscle. Animal and *in vitro* data indicate that mirabegron enhances the urine storage function by stimulating β3 adrenoceptors in the bladder [53].

Efficacy of mirabegron was evaluated in three 12-week RCTs and one pooled analysis [54–57]. Mirabegron at doses of 25, 50 and 100 mg resulted in significantly greater reduction in UI episodes and micturition frequency per 24 h than placebo, with no difference in the rate of adverse events. The dry rates on treatment averaged between 45 and 50% with placebo achieving rates of 35–40%. However, like antimuscarinic medications, the statistically significant difference is consistent only for improvement of UI, and not cure. A 100 mg dose has not been shown to confer additional benefit compared to 50 mg [54]. At doses of 50 and 100 mg, rates of dry mouth were lower compared to tolterodine 4 mg [58], and no different than placebo [54].

The comparative risk of QTc prolongation and raised intraocular pressure have been specifically addressed in RCTs [59,60], which showed no difference from placebo for doses up to 100 mg. In a randomised phase 3 trial, mirabegron was associated with an average rise in pulse rate of 2 beats per minute and 4% of participants withdrew due to adrenergic side-effects [61].

Mirabegron at doses of 50 and 100 mg once daily for 12 weeks in men with LUTS and BOO did not adversely affect voiding urodynamic parameters (maximum flow rate and detrusor pressure at maximum flow) compared to placebo [62]. A sub-group analysis of one of the pivotal phase 3 trials assessed the efficacy of mirabegron in treatment naïve patients and those who had received prior antimuscarinic therapy for OAB [63]. Similar improvements in frequency of daily UI episodes and micturitions were seen in all groups.

Mirabegron has also been studied in the elderly in a prospective sub-analysis of individual and pooled efficacy and tolerability data from three randomised, phase 3 trials, and of tolerability data from a 1-year safety trial. Age groups targeted were >65 and >75 years. The drug was well-tolerated in both age groups: hypertension and urinary infection were among the most common adverse effects over 12 weeks and 1 year [64].

**Recommendations** Mirabegron is effective for the improvement of UI.

The β-mediated cardiovascular side-effects appear to be clinically insignificant.

Mirabegron is effective and well-tolerated in the elderly aged >65 years.

Offer mirabegron to people with UI, but warn patients receiving mirabegron that the possible long-term side-effects remain uncertain.

3. **Surgical management**

Patients who are refractory to behavioural and medical therapy, and desire additional therapy, should be evaluated by an appropriate specialist with an interest in the management of UI. Third-line treatment should be considered in the event of failure of, or intolerance to, two or more pharmacological therapies.

In refractory cases the following treatments may be offered: intradetrusor botulinum toxin-A, sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS). In the event one or more of these fail, the remaining options include augmentation cystoplasty, urinary diversion or permanent catheterisation. Indwelling catheters (transurethral or suprapubic) are not recommended as a management strategy for OAB, except as a last resort in selected patients, because of the adverse risk/benefit balance.

All patients who require complex treatment for their condition require ongoing follow-up in a specialist environment.

3a: **Botulinum Toxin-A (Onabotulinumtoxin-A)**

**Level of Evidence: 1**

**Grade of Recommendation: A**

The use of botulinum toxin-A as third-line treatment for DO and OAB symptoms has become clinically widespread. There is now substantial, high quality, clinical data to support its use with over 1900 participants in randomised, double-blind, placebo-controlled trials [65–72].

Several of these were dose-ranging studies [66–69]; however, the three most recent trials used a uniform dose. In a UK multicentre trial involving 227 women, a 200 IU dose of botulinum toxin-A produced a significant reduction in urinary frequency, urgency and leakage episodes in the treatment group compared to placebo at 6 months after
injection [70]. Complete continence was also more common after botulinum toxin-A than placebo (31% vs 12%). In a study run across 72 sites in the USA and Canada, 492 patients were randomised to receive either 100 IU botulinum toxin-A or placebo [71]. At week 12, the treatment group showed a significantly greater reduction from baseline in UI episodes, frequency and nocturia. There were also large, clinically significant, improvements in QOL domains in the botulinum toxin-A group, and voided volumes increased significantly. Complete continence occurred in 22.9% of treated patients compared with 6.5% of the placebo group.

Another phase 3 multicentre trial using 100 IU dose in 489 patients reported similar results [72]. At week 12, significant sustained reductions in daily UI episodes, frequency, urgency and nocturia were seen in botulinum toxin-A group over placebo. This was associated with significantly greater improvement in QOL scores. A recent meta-analysis [73] determined that, compared with placebo, botulinum toxin-A significantly decreased the mean number of daily UI episodes and daytime frequency while maximum cystometric capacity (MCC) and mean voided volume significantly increased. A systematic review and statistical comparison of standardised mean outcomes [74] reported that botulinum toxin-A injections in patients with OAB resulted in reductions of 29% in daily frequency, 38% in daily urgency and 59% in daily UI episodes (MCC improved by 58% and maximum detrusor pressure reduced by 29%).

Systemic adverse events are generally infrequent, mild and self-limiting [75], with the most common being uncomplicated UTI and urinary retention. In all but one smaller randomised trial [66], rates of UTI were significantly higher in the botulinum toxin-A treated group than in the placebo group (range 15.5–48.1%; 2.2–3.9 times higher). Infection risk may be dose related; one study reported UTI in 48.1% of patients receiving 200 IU compared with 36.4% of the 100 IU group [67]. A systematic review calculated the risk of UTI at 21% vs 7% in the placebo patients [74].

The risk of elevated PVRs and the need for clean intermittent self-catheterisation (CISC) is dose dependent but also varies with the criteria used to define urinary retention. Some earlier studies used a residual of 100 mL as an indication for CISC, and rates as high as 43% were reported. Recent studies have used more liberal and clinically sensible definitions, requiring patients to commence CISC with residuals >350 mL or >200 mL if symptomatic [71,72]. They reported 6.9% and 6.1% of patients, respectively, were required to perform CISC. Another study, using 200 IU, reported 16% of botulinum toxin-A treated patients commenced CISC compared with 4% of the placebo group [70]. In a statistical comparison of high level studies, the overall risk of CISC was calculated to be 12% [74]; however, QOL outcomes do not appear to be adversely affected by the need to perform CISC [76].

There is no universal agreement on injection technique, and sites used include sub-urothelial or intra-detrusor, trigone-including and trigone-sparing [77]. The few studies to date have not shown significant differences in outcome with varied injection depth [78,79] and there appears to be no increased risk of ureteric reflux with trigonal injections [78,80,81].

There is also no reported uniformity on optimal dosage, especially for patients with neurogenic OAB where doses up to 400 IU have been used. For idiopathic OAB there is more consensus and a dose of 100 IU is generally considered to provide a good compromise between efficacy and the risk of urinary retention. However, the UK NICE guidelines suggest an initial dose of 200 IU for refractory OAB symptoms unless there is particular concern over voiding dysfunction [8]. In Australia, bladder wall injections of botulinum toxin-A are approved under the Pharmaceutical Benefits Scheme in dosages of 200 IU for neurogenic DO (spina bifida, multiple sclerosis and SCI only), and 100 IU for idiopathic OAB symptoms.

**Recommendation** Patients with OAB symptoms who have failed to respond to supervised bladder retraining with lifestyle modification and who are refractory to, or intolerant of, two or more pharmacological therapies, may be offered bladder wall injections of botulinum toxin-A. Patients must be thoroughly counselled plus be willing and able to perform CISC if necessary.

3b (i): Sacral Neuromodulation (SNM)

**Level of Evidence:** 1

**Grade of Recommendation:** A

SNM is the most widely clinically applied, and has the most long-term safety and efficacy data, of three neuromodulation techniques. Neuromodulation works to address an imbalance of facilitatory and excitatory control systems by direct or indirect action on afferent nerves, predominantly the third sacral nerve (SNM) but in some cases the pudendal or tibial nerve. This electrical stimulation inhibits bladder activity by stimulating large diameter somatic afferent fibres, which in turn evoke a central inhibition of the micturition reflex in the spinal cord or brain.

Since the first report [82], over 100 000 implants have been placed worldwide. The technique has evolved over time, with a tined lead approach replacing the older style peripheral nerve evaluation-implant. The newer technique shows better efficacy [83] and this should be recognised when analysing available studies.
There are three systematic reviews [84–86], five RCTs [83,87–90] and 12 uncontrolled studies [91–102]. Therapeutic success is defined as a >50% improvement in symptoms such as leakage episodes or frequency episodes [103]. A recent study comparing SNM and standard medical therapy (SMT) demonstrated that SNM (70 subjects, 51 implanted) was superior to SMT (77 subjects) at 6 months with a therapeutic success rate of 61% in the SNM group and 42% in the SMT group [83]. Rates of adverse events were comparable in the groups (SNM 30.5% and SMT 27.3%) and notably the 6 month post-implant surgical intervention rate was low at two of 51 subjects with a full system implant (3.9%).

A large retrospective study with a mean follow-up of 46.88 months showed similar results [104], with about 70% of both the wet, and dry with urgency/frequency, OAB groups achieving therapeutic success, and 20% and 33%, respectively, achieving cure. Complication rates show device-related re-intervention of 41%, although this was reduced to 15% in those with the newer tined lead. Most re-interventions occurred within 2 years of implantation [104]. When studied prospectively, with a 5 year follow up, 56% of patients with OAB-wet and 40% who were dry achieved therapeutic success [95]. A 14-year experience from a single centre showed even higher success rates (84.8%) for OAB-wet [105]. One study showed that patients with OAB-wet and no urodynamically confirmed idiopathic DO can still benefit from SNM [106].

There are emerging data on the programming techniques used, such as changing the pulse rate [107].

Patient satisfaction has been studied in both short- and long-term studies. In the SNM vs SMT RCT, greater improvement in baseline OAB QOL at 6 months was found in the SNM group [83], and 90% of 207 patients with a mean follow-up of 77 months reporting being satisfied with the treatment [108]. Additionally, benefits on female sexual function scores have also been noted [109].

The ROSETTA trial [110] is an open-label RCT comparing botulinum toxin-A 200 IU and SNM for management of refractory UUI. Enrolment commenced in early 2012 and the primary outcome, effectiveness of treatment 6 months after starting therapy, will be analysed in 2015. Using a decision analysis, one group [111] concluded both techniques were reasonable strategies. In a small case series, patients who had previous botulinum toxin-A treatment for their OAB and then received SNM had good results, even with discontinuation of the botulinum toxin-A due to dissatisfaction with the therapy [112].

The choice to undertake SNM for refractory OAB needs to be carefully discussed with the patient. Willingness to modify the programming, ongoing cognitive capability to do so and the possibility of undertaking repeat procedures in up to 30% of cases needs to be balanced against the potential symptomatic improvements in the refractory OAB group. Until more data are available, clinicians need to make decisions with their patients based on the relative merits and complications of each method as it is applied to the patient’s particular situation (Expert Opinion).

MRI, except of the brain, is contraindicated after implantation and, in the event of pregnancy, it is recommended to turn off the program. SNM appears to be safe in the presence of a cardiac pacemaker [113]. SNM implantation requires more technical training than the use of botulinum toxin-A by doctors. However, SNM is a fully reversible treatment, it does not result in an elevated PVR and those patients with bowel dysfunction may receive benefits to both their symptomatologies from the single treatment modality. The ICI now gives SNM for patients with faecal incontinence a grade B or C recommendation depending on the presence and magnitude of the sphincter defect [1].

The Medtronic InterStim Therapy (Medtronic, MN, USA), was approved by the TGA in 2006, and the smaller InterStim II was approved in 2007, for detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome.

**Recommendation** SNM should be considered for those patients with refractory OAB who are willing to undertake a minimally invasive surgical procedure and are motivated to work with programming techniques. It may have particular application in those patients who are unable to self-catherise or in whom there is co-existing faecal incontinence.

**3b (ii): PTNS**

**Level of Evidence: 2**

**Grade of Recommendation: C**

PTNS, which was developed in the 1960s in an animal model, utilises the tibial nerve, a mixed sensory and motor nerve, for neuromodulation. As described in the previous section, this stimulation evokes a central inhibition of the micturition pathway in the spinal cord or brain. Stimulation is delivered in an outpatient setting, usually with a protocol of weekly 30 min visits for 12 weeks followed by a monthly visit for 12 months.

Three RCTs compared PTNS to sham procedure [114,115 (SUMiT)] and tolterodine [116 (OrBIT)]. Long-term follow-up studies of responders were performed for the SUMiT [117] and OrBIT trials [118]. Most patients studied had moderate to severe symptoms with baseline UI ranging from 2.2 to 9.8 episodes per day. In the SUMiT trial, moderate to marked improvement in bladder symptoms was reported in 54.5% of the PTNS group vs 20.9% of the sham group after
Augmentation Cystoplasty (AC)

Level of evidence: 3 – Retrospective comparative studies only

Grade of recommendation: C

Since the advent of botulinum toxin-A and neuromodulation, the indication to perform an AC to manage DO is much more limited. In this operation, a detubularised bowel segment, most commonly ileum, is grafted into the bivalved bladder wall. AC aims to improve functional bladder capacity, disrupt involuntary detrusor contraction and increase bladder compliance. There is no difference between bivalving the bladder sagittally and coronally [121].

Most of the literature on the use of AC is in neurogenic bladder dysfunction rather than non-neurogenic, especially in the management of the drug-refractory suprasacral neurological lesion which classically causes DO, reduced bladder compliance and detrusor-sphincter dyssynergia. Although there are no RCT data comparing AC with other treatment modalities for patients with OAB-wet, there are case series and retrospective comparative studies with varying duration of follow-up to 2003, but nothing since [122–124]. High satisfaction rates and improvement in urodynamic parameters (functional capacity, storage pressures and VUR) were reported in 32 patients with SCI [125]. Good outcomes were also reported in the antimuscarinic-refractory multiple sclerosis patient [126].

A group from the UK commented that although the last 10 years has witnessed a reduction in the total number of bladder reconstructive procedures in their country, these are essentially safe and effective, with long-term clinical and functional follow-up being mandatory [127]. For the non-neurogenic OAB cases, the causes could be idiopathic, or secondary to previous partial cystectomy, ageing, and pelvic irradiation. There are no studies comparing success rates between neurogenic and non-neurogenic patients in AC, but generally speaking results for the latter seem to be poorer (58% improved) than the former (90% improved) [7]. There is a small risk of malignancy associated with AC [128]. At the present time, due to the wider availability and high efficacy of pharmacological treatment as well as the advent of botulinum toxin-A and possibly neuromodulation, with or without CISC, AC is rarely indicated.

Detrusor Myomectomy

Level of evidence: 3 Retrospective comparative studies only

Grade of recommendation: C

Detrusor myomectomy is a rarely performed operation whereby the part of the detrusor musculature is separated and removed from the underlying mucosa. This is most commonly performed on the bladder dome due to ease of access. A ‘pseudodiverticulum’ is then developed in the hope of increasing bladder functional capacity, reducing storage pressures and improving urodynamic parameters and overall QOL. It was initially described in children [129].

A non-randomised study comparing AC to detrusor myomectomy initially showed lower short-time complication rates [130] but further follow-up revealed significant fibrosis of the pseudodiverticulum, which later led to the demise of this technique. Complications may include spontaneous bladder rupture and sepsis. There is a paucity of data regarding detrusor myomectomy; while short-term results may support detrusor myomectomy over enterocystoplasty.
[130], studies with longer follow-up (about 6 years) reported poor urodynamic and clinical outcomes. Some authors suggest that this technique be discouraged in favour of enterocystoplasty [131].

Urinary Diversion

**Level of evidence: 5 (Expert opinion)**

**Grade of recommendation: C**

Permanent ileal or colonic urinary conduits are very rarely indicated for refractory OAB symptoms. This indication is not to be confused with that of a devastated outlet with very poor urethral or rhabdosphincter function, such as the patient with severe post-prostatectomy UI after salvage radiotherapy with recurrent bladder neck stenosis. There is currently no evidence on the use of urinary diversion in this refractory OAB population, especially in non-neurogenic patients [121].

Permanet Catheterisation and Need for Cystoscopic Surveillance

**Level of evidence: 5 (Expert opinion)**

**Grade of recommendation: C**

The use of a permanent catheter, either urethral or suprapubic, in the definitive management of OAB is not recommended. There are however specific patient populations whereby this option may be considered appropriate. The two more common situations would be: (i) in the frail elderly who is not physically fit or cognitively suitable to be managed with either pharmacological or surgical options; (ii) in neurologically impaired patients who are not able to tolerate medications or surgical options to maximise storage, and unable to self-catheterise or undergo urinary diversion to maximise drainage. Provided the upper urinary tract is protected, management with pads, collecting devices, or absorptive undergarments should be tried before insertion of permanent indwelling catheters due to the risk of catheter-associated infections, blockages, urethral erosion, stone formation, and dysplastic and neoplastic changes to the urothelium [5]. Suprapubic catheters are easier to manage than urethral catheters, which may also lead to urethral erosion.

Need for Cystoscopic Surveillance

**Level of evidence: 3 (Systematic review of level 3 studies)**

**Grade of recommendation: C**

Several retrospective reviews concluded regular cystoscopy should be performed in patients with permanent catheters [132,133]. One group recommend cystoscopy every 12–24 months to exclude squamous dysplasia and malignant change, starting 2 years after catheter placement [134], although others have proposed starting at 10 years [135]. In a study of bladder malignancies in the SCI population, 32 patients were identified with bladder cancer out of 1319 patients seen between 1983 and 2007 [136]. Of these, 47% were squamous cell cancer and 31% TCC and, where the method of detection was known, 42% were found on screening cystoscopy. Interestingly, >50% of the patients did not have an indwelling catheter, suggesting that the neurogenic bladder, and not the indwelling catheter, may be the risk factor for bladder cancer. Urologists should be vigilant in the long-term screening of all patients with SCI for bladder cancer and not just those with indwelling catheters.

**Recommendation AC, detrusor myomectomy, urinary diversion and permanent catheterisation are not recommended as a management strategy for OAB, except as a last resort in selected patients, because of the adverse risk/benefit balance.**

Long-term cystoscopic surveillance for bladder cancer in neurogenic bladder patients with permanent catheterisation may be of benefit.

All patients who require complex treatment for their condition require ongoing follow-up in a specialist environment.

Conclusion

These guidelines were formulated to assist in the diagnosis, clinical assessment, and optimisation of treatment efficacy in patients with OAB. They should not be taken as absolutes, but rather as strategies for best practice as undertaken in Australia. Physicians should always consider individual patients’ specific needs when considering treatment options. The guidelines are a living document. It is recognised that research is ongoing in this area and, as medical knowledge expands and technology advances, treatment recommendations may change. It is envisaged that these guidelines will be reviewed and updated, where necessary, at regular intervals (currently proposed at 2–3 years).

Acknowledgements

The authors would like to thank Anne Norgrove for her assistance with editing the draft.

Conflicts of Interest

Associate Professor Tse reports personal fees from American Medical Systems, personal fees from Allergan, personal fees from Astellas, outside the submitted work.

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Guidelines

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Abbreviations: BT, bladder training; CISC, clean intermittent self-catheterisation; DO, detrusor overactivity; ER, extended release; FUSAG, Female Urology Special Advisory Group; IR, immediate release; MCC, maximum cystometric capacity; OAB, overactive bladder; PFMT, pelvic floor muscle training; POP, pelvic organ prolapse; PVR, post-void residual urine volume; QOL, quality of life; RCT, randomised controlled trial; SCI, spinal cord injury; SMT, standard medical therapy; TD, transdermal; UGSA, Urogynaecological Society of Australasia; (U)UI, (urge) urinary incontinence.
Original Article

Consanguinity and associated perinatal outcomes, including stillbirth

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Background: Consanguinity defined as the sexual union between two related individuals has been previously an infrequent practice in Australia, but recently there has been migration from countries with widespread practice of consanguinity. There is limited and conflicting evidence in the literature that suggests consanguinity to be associated with adverse obstetric outcomes.

Aim: To assess the effect of consanguinity on perinatal outcomes.

Materials and Methods: A retrospective analysis of singleton births over a ten-year period at an Australian tertiary hospital. The data were extracted from the hospital obstetric database and analysed for an association between consanguinity and perinatal outcomes, including stillbirth. Main outcome measures were stillbirth, threatened premature labour, fetal congenital abnormality, perinatal mortality and neonatal outcomes.

Results: There were 46 399 singleton births recorded over the ten-year study period, and 44 004 had consanguinity data available. The overall consanguinity rate was 5.5% (n = 2565), which remained consistent over the study period at our institution. Consanguinity was associated with higher rate of threatened premature labour (5.6% vs 4.7%, P = 0.003), fetal congenital abnormality (4.2% vs 3.1%, P = 0.004), perinatal mortality (2.4% vs 1.0%, P < 0.001) and reduced risk of hypertension in pregnancy (5.3% vs 3.4%, P < 0.001). Consanguinity was an independent risk factor for stillbirth with a relative risk of 2.88 (P < 0.001, 95% CI 1.98, 4.18).

Conclusion: Women from consanguineous relationships are at higher risk of adverse perinatal outcomes, including stillbirth. Given the 5% prevalence of consanguinity in our obstetric population, these findings have significant implications for preconception counselling, obstetric care and health resource allocation.

Key words: consanguinity, genetic phenomena, inbreeding, pregnancy complications, stillbirth.

Introduction

Consanguinity, defined as the sexual union between two related individuals has been a relatively infrequent practice in Australia.1 A population-based prevalence study in Western Australia revealed the estimates to be less than 1% of all marriages over a six-year (1994–1999) study period.2 Due to emergent migrant populations from countries within West Asia, South-East Asia, Middle East and North Africa where consanguinity is deeply rooted in certain cultures, the prevalence within Australia is also changing.1,3

There continue to be gaps in understanding the relationship between consanguinity and adverse pregnancy outcomes. Although there is anecdotal evidence linking the two factors, current research is both limited and conflicting. Children of consanguineous unions have previously been studied to investigate the prevalence of autosomal recessive conditions.4 In the general population, the risk of abnormality or death in early childhood is about 2–2.5% for nonconsanguineous couples compared to 5% in consanguineous couples. This change in prevalence may be due to the emergence of recessive disorders amongst the offspring.4 Some studies suggest that consanguinity deleteriously affects pregnancy outcomes, including rates of miscarriage, stillbirth, congenital abnormalities, prematurity and low birthweight.5–11 Other studies have contradicted or not conclusively supported these findings.12,13

The role of consanguinity and its effect on perinatal outcomes is an important issue for primary healthcare professionals, obstetric and medical carers, especially in

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Received 3 February 2016; accepted 20 May 2016.

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changing populations such as the Western Sydney Area Health District where in 2011 43% of residents were born overseas compared to 27% at the state level.\textsuperscript{14} In a previous audit conducted at our hospital, the incidence of consanguinity within the obstetric population was estimated to be as high as 4%.\textsuperscript{15} The demographics of this obstetric population compared to the rest of the country are unique and as such ethnic and cultural specific multidisciplinary care needs to be provided in the community and within the hospital setting. An understanding of the implications of consanguinity on perinatal outcomes can lead to targeted counselling and antenatal care for this obstetric population.

Materials and Methods

A retrospective cohort study was conducted using data extracted from the hospital obstetric database. All singleton births ≥20 weeks gestation at Westmead Hospital (tertiary referral centre) over a ten-year period from 1 January 2004 to 31 December 2013 inclusive were included in the analysis. Multiple pregnancies were excluded due to the different risk factors and cause of adverse perinatal outcomes compared to singleton births. Approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee reference number 3755.

The primary aim of the study was to determine whether consanguinity was an independent risk factor for stillbirth. The secondary aims were to investigate the association of consanguinity and the risk of other adverse perinatal outcomes.

Information on consanguinity was self-reported by the mother during the first booking in visit to the hospital. Data pertaining to consanguinity were categorised into unrelated and related for the purpose of this study, as there was no objective definition used in our hospital. Socio-demographic characteristics considered as risk factors to adverse perinatal outcomes were extracted such as maternal age, body mass index (BMI), country of birth, parity, previous caesarean section, utilisation of assisted reproductive techniques, history of maternal medical conditions such as hypertension, diabetes, heart disease, mental illness and lastly history of substance abuse, including alcohol and smoking, was also collected.

Perinatal outcomes, including congenital abnormalities, neonatal death, stillbirth, threatened premature labour (TPL), antepartum haemorrhage, hypertension in pregnancy, gestational diabetes, pre-eclampsia, gender, low birthweight (LBW), low Apgars and admissions to neonatal intensive care unit (NICU), were recorded. TPL is defined as uterine contractions before 37 weeks gestation.

The study was adequately powered where a sample size of 39 000 was required to have an 80% power to detect a statistically significant increase in stillbirth rate in the consanguineous group compared to the nonconsanguineous group (a two-group chi-square test with a 0.05 significance level).

Cross-tabulation between consanguinity and the different covariates was performed in order to define the characteristics of the study population. The association between consanguinity and perinatal outcomes was also cross-tabulated. All cross-tabulations were assessed using a chi-squared or Fisher’s exact test, ignoring missing values, with a two-sided 5% significance level concluding statistical significance. Multivariate logistic regression analysis was used to determine the risk factors for stillbirth which is represented as odds ratios (OR) and 95% confidence intervals.

The regression analysis included socio-demographic variables that are a potential risk factor for stillbirth such as age (per year), BMI, country of birth, consanguinity, parity, previous endocrine disease, previous hypertension, previous heart disease, previous mental health problems, smoking, illicit drug use, alcohol use and \textit{in vitro} fertilisation (IVF) pregnancy. As there was a concern that fetal anomalies may be a confounding factor for the association, if any, between consanguinity and stillbirth, subgroup analysis of the association between stillbirth and consanguinity was performed with two subgroups: presence or absence of fetal anomaly.

The statistical software package SPSS version 21 (SPSS, Inc. Chicago, IL, USA) was used to analyse the data. No adjustment for multiple comparisons was performed.

Results

During the ten-year study period, a total of 46 399 singleton births took place at Westmead Hospital, a tertiary obstetric unit. Births where consanguinity data were missing (\( n = 2395 \)) were excluded from the study. Of the remaining 44 004 births, 2565 were to consanguineous couples.

Women in consanguineous unions were more likely to be younger, parous, have a higher BMI, born overseas, have had a previous caesarean section, have had previous gestational diabetes, whilst being less likely to have a history of illicit drug use, smoking or alcohol consumption. There was no statistical difference between previous mental health problems, pre-existing hypertension, heart disease and IVF (Table 1).

The overall consanguinity rate was 5.5% over the ten-year study period. The consanguinity rate in Australian-born women was 3.8% as compared to 7.1% in women born overseas (\( P < 0.001 \)). Women born in Australia accounted for 25% of the consanguineous unions during our study period (Fig. 1). The rate of consanguinity based on country of birth was quite variable and at times may have been a gross overestimate due to extremely small numbers of singleton births to women from some countries during the study period.

The effect of consanguinity on perinatal outcomes is described in Table 2. Consanguinity is associated with a statistically significant increase in TPL (5.6% vs 4.7%, \( P = 0.028 \)), fetal anomalies (4.2% vs 3.1%, \( P = 0.004 \)), perinatal mortality (2.4% vs 1.0%, \( P < 0.001 \)) and lower Apgar score at five minutes (1.4% vs 1.1%, \( P < 0.001 \)).
Although the rate of low birthweight (<2500 g) was higher in the consanguineous group, this was not statistically significant (8.7% vs 7.7%, \( P = 0.057 \)) and similarly a low Apgar score at one minute is also not statistically significant, although borderline (10.6% vs 9.4%, \( P = 0.061 \)). There were no statistically significant differences in the outcomes such as intrauterine growth restriction (IUGR), gender of fetus, neonatal intensive care unit (NICU) admission, antepartum haemorrhage or maternal diabetes.

Previous caesarean section despite being a risk factor for stillbirth was not included in the multivariate logistic regression as data were only available for 25% of the population (\( n = 11,041 \) cases). Multivariate regression analysis of 39,758 (86.1%) patients was performed, where all cases had information pertaining to all variables of interest (except for previous caesarean section). The statistically significant variables in the multivariate logistic regression analysis of singleton stillbirth compared to singleton live birth are outlined in Table 3. Increasing maternal age in years (OR 1.05, 95% CI 1.02, 1.07), previous hypertension (OR 2.48, 95% CI 1.30, 4.73) and previous pre-eclampsia (OR 1.61, 95% CI 1.1, 2.56) emerged as independent risk factors for stillbirth after controlling for potential confounders. Consanguinity (OR 2.88, 95% CI 1.98, 4.18) also remained as a significant

<table>
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<th>Variable</th>
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<th>Consanguineous (%)</th>
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BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; LSCS, lower section caesarean section.

**Table 1** Characteristics of the study population based on consanguinity, 2004–2013 (total \( n = 44,004 \))

**Figure 1** Consanguineous cohort by country of birth (COB). Total singleton births with consanguineous data: 44 004. Total consanguineous births: 2565.
independent predictor for singleton stillbirth compared to unrelated couples.

This increase in stillbirth associated with consanguinity was consistent in pregnancies with and without fetal anomalies ($P < 0.001$).

**Discussion**

This large multicultural study exploring the effect of consanguinity on stillbirth and other perinatal outcomes builds on two previous studies conducted in western Sydney.\(^{16,17}\) Our study found consanguinity to be an independent risk factor for stillbirth after controlling for other confounders in a population where one in 20 deliveries is to consanguineous couples. Consanguinity was also associated with an increase in other adverse perinatal outcomes. The previous western Sydney study uncovered 35.8% of Lebanese-born women were in a consanguineous relationship and experienced increased perinatal mortality.\(^{16}\) Overall, for consanguineous couples, the previous study found a history of perinatal or infant death was higher than in nonconsanguineous couples (8.3% vs 1.9%, $P < 0.001$).\(^{17}\)

The large number of patients with information available on multiple potential confounding variables was a strength of this study. There are several limitations; firstly, a number of cases had missing information pertaining to consanguinity and were thus excluded from analysis (5.2%). However, it is likely that this effect was only marginal as there is no evidence that the missing information followed any specific pattern related to the exposure or outcome. Due to the retrospective nature of this data, other variables of particular importance, including previous caesarean section, were also missing, which is a potential confounder for adverse perinatal outcomes.

**Table 2**

<table>
<thead>
<tr>
<th>Pregnancy outcomes</th>
<th>Subgroup</th>
<th>Nonconsanguineous (%</th>
<th>n</th>
<th>Consanguineous (%</th>
<th>n</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened preterm labour</td>
<td>Yes</td>
<td>1925 (4.7)</td>
<td>41,439</td>
<td>143 (5.6)</td>
<td>2,565</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>356 (0.9)</td>
<td>30 (1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal anomaly</td>
<td>No</td>
<td>39,457 (95.2)</td>
<td>2403 (93.7)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1276 (3.1)</td>
<td>105 (4.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>706 (1.7)</td>
<td>57 (2.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>No</td>
<td>38,854 (93.8)</td>
<td>2449 (95.4)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2190 (5.3)</td>
<td>85 (3.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>395 (1.0)</td>
<td>31 (1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal outcome</td>
<td>Live birth</td>
<td>41,017 (99.1)</td>
<td>2502 (97.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stillbirth</td>
<td>236 (0.6)</td>
<td>37 (1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neonatal death</td>
<td>155 (0.4)</td>
<td>25 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>31 (0.07)</td>
<td>1 (0.04)</td>
<td></td>
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<td></td>
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<tr>
<td>Gestational age</td>
<td>20–&lt;28</td>
<td>455 (1.1)</td>
<td>44 (1.7)</td>
<td>0.003</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>28–&lt;37</td>
<td>2944 (7.1)</td>
<td>183 (7.1)</td>
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<td></td>
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<tr>
<td></td>
<td>37–&lt;42</td>
<td>37,886 (91.4)</td>
<td>2319 (90.4)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>≥42</td>
<td>140 (0.3)</td>
<td>16 (0.6)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>14 (0.03)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar at 1 min</td>
<td>≥7</td>
<td>37,382 (90.6)</td>
<td>2281 (89.5)</td>
<td>0.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;7</td>
<td>3891 (9.4)</td>
<td>269 (10.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>166 (0.4)</td>
<td>15 (0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar at 5 min</td>
<td>≥7</td>
<td>40,380 (98)</td>
<td>2461 (95.9)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;7</td>
<td>838 (2.0)</td>
<td>87 (3.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>221 (0.5)</td>
<td>17 (0.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>≥2500 g</td>
<td>38,214 (92.3)</td>
<td>2338 (91.2)</td>
<td>0.057</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2500</td>
<td>3191 (7.7)</td>
<td>224 (8.7)</td>
<td></td>
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<tr>
<td></td>
<td>Missing data</td>
<td>34 (0.08)</td>
<td>3 (0.1)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.05</td>
<td>1.02 1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>2.88</td>
<td>1.98 4.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-existing hypertension vs nil</td>
<td>2.48</td>
<td>1.30 4.73</td>
<td>0.006</td>
</tr>
<tr>
<td>Previous pre-eclampsia vs nil</td>
<td>1.61</td>
<td>1.01 2.56</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Variables included in the initial multivariate analysis before backwards stepwise variable selection: age (per year), body mass index, country of birth, consanguinity, parity, previous endocrine disease, previous hypertension, previous heart disease, previous mental health problems, smoking, illicit drug use, alcohol use, in vitro fertilisation.

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Ethnicity was not recorded in the obstetric database, with country of birth the only relevant data available. Previous studies demonstrate ethnicity to be a risk factor for stillbirth, where country of birth alone is inadequate and is not reflective of ethnic status. A weakness in this study is the lack of an objective definition for consanguinity within our obstetric database.

Some pregnancies are terminated prior to 20 weeks, often when a significant anomaly is detected. These pregnancies are not part of the statistical analysis in this study and other larger studies such as the Bradford cohort. Further research inclusive of this early pregnancy data would be of value particularly in an environment of increasing utilisation of first trimester morphology and chromosomal screening using noninvasive pregnancy testing (NIPT) and thus earlier diagnoses of genetic anomalies.

Consanguinity, where two individuals who are related as second cousins or closer with the inbreeding coefficient (F) equal or higher than 0.0156, is the common definition used in clinical genetics. Inbreeding coefficient (F) is a measure of the proportion of genetic material that will be shared between individuals because they originate from a common ancestor. To report and compare consanguinity rates amongst different populations, the two parameters best used are the mean inbreeding coefficient and the rates of marriages between first cousins.

Prospective data collection of consanguineous pregnancies and implementing a standardised definition of consanguinity are essential for accurate data collection and analysis. Such a data registry with information pertaining to consanguinity exists in Norway, where analysis revealed the risk of recurrence of stillbirth and infant death is higher for the progeny of first-cousin parents compared to unrelated parents.

There have been other studies supporting our findings demonstrating consanguinity and an increase in risk of preterm labour, fetal anomalies and stillbirth. It is interesting to note that our results demonstrated consanguinity to be associated with a higher risk of stillbirth (OR 2.88, 95% CI 1.98, 4.18) than previous maternal history of hypertensive disorders, including pre-eclampsia where significant resources are directed. The predominantly Pakistani cohort in the English Bradford study revealed a doubling of risk of anomalies associated with consanguineous parents. Our results also demonstrated statistically significant increase in fetal anomalies in the consanguineous cohort (4.2% vs 3.1%). However, this result is difficult to interpret and may be an underestimate, given that pregnancy loss due to fetal anomaly less than 20 weeks gestation was not included. Several other research groups have demonstrated the increased risks of neonatal and postneonatal deaths for the progeny of consanguineous unions. Consanguinity and risk of hypertension complicating pregnancy have not been reflected as observed in a previous study conducted in Jordan.

Despite our study limitations, this study provides an insight into potential perinatal outcomes of consanguineous unions at our tertiary centre. There has been a consistent rate of consanguinity amongst a very heterogeneous group of pregnant women over the study period. The results of this study have significant public health implications for our hospital and local health district, as well as for health services in general. It has also highlighted the limitations existing in our database and difficulty in obtaining accurate data pertaining to consanguinity and ethnicity, which are relevant to our patient population.

In this multicultural obstetric population, approximately one in 20 women booked are from a consanguineous union; however, one in four of these women were born in Australia. These findings suggest that consanguinity is both common and likely practiced amongst second-generation ethnic minority groups living in Australia who maintain original cultural practices. This information is important in guiding counselling, obstetric care and resource allocation. Further analysis should take place once a standardised definition is used for consanguinity to ascertain the impact on perinatal outcomes for this group of individuals. Ethnicity should be incorporated into all obstetric data collection.

The aetiology into the cause of stillbirth for consanguineous unions should also be investigated to determine preventative strategies for perinatal mortality. Consanguinity should be included as a significant risk factor in future research into perinatal outcomes, including stillbirth.

Due to the changing demographics of women delivering at our unit, it is important to implement culturally appropriate obstetric policies. Identification of these patients is important to ensure preconception counselling is attended and appropriate referral to antenatal care and genetic counselling services. This is of importance and relevant given the higher incidence of autosomal recessive disorders and fetal anomalies as demonstrated in other units. A study in Western Australia investigating genetic counselling to consanguineous couples found that a higher number of sessions on average were required compared to nonconsanguineous couples, suggesting the need for a dedicated culturally appropriate service.

It is important to note that consanguineous relationship discussion can be contentious. In the United States, first-cousin marriages are prohibited in 25 states with restrictions in a further six states except nonreproducing couples. This is a current issue in the United States as Texas legislated against first-cousin marriages only in 2005.

In developed countries, there is the capacity to provide access to health education, including genetic counselling. However, a nonjudgmental approach that encourages disclosure and community acceptance is vital given our changing demographic profiles to ensure success of such interventions.

This was a single-centre study and as such these findings are representative of our demographically diverse obstetric population. These findings should be replicated in other centres and countries before we can extrapolate these findings.
Acknowledgements

We thank Dr. Karen Byth, senior biostatistician at the Western Sydney Local Health District Research & Education Network, and Westmead Women’s and Newborn statistician Emma Gibbs for their assistance with statistical analysis.

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Continuity of midwifery carer moderates the effects of prenatal maternal stress on postnatal maternal wellbeing: the Queensland flood study

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Received: 10 January 2017 / Accepted: 19 September 2017 / Published online: 27 September 2017
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Abstract Poor postnatal mental health is a major public health issue, and risk factors include experiencing adverse life events during pregnancy. We assessed whether midwifery group practice, compared to standard hospital care, would protect women from the negative impact of a sudden-onset flood on postnatal depression and anxiety. Women either received midwifery group practice care in pregnancy, in which they were allocated a primary midwife who provided continuity of care, or they received standard hospital care provided by various on-call and rostered medical staff. Women were pregnant when a sudden-onset flood severely affected Queensland, Australia, in January 2011. Women completed questionnaires on their flood-related hardship (objective stress), emotional reactions (subjective stress), and cognitive appraisal of the impact of the flood. Self-report assessments of the women’s depression and anxiety were obtained during pregnancy, at 6 weeks and 6 months postnatally. Controlling for all main effects, regression analyses at 6 weeks postpartum showed a significant interaction between maternity care type and objective flood-related hardship and subjective stress, such that depression scores increased with increasing objective and subjective stress with standard care, but not with midwifery group practice (continuity), indicating a buffering effect of continuity of midwifery carer. Similar results were found for anxiety scores at 6 weeks, but only with subjective stress. The benefits of midwifery continuity of carer in pregnancy extend beyond a more positive birth experience and better birthing and infant outcomes, to mitigating the effects of high levels of stress experienced by women in the context of a natural disaster on postnatal mental health.

Keywords Prenatal maternal stress · Postnatal depression · Anxiety · Midwifery group practice · Natural disaster · Continuity of carer

Introduction

A large literature documents poor postnatal maternal mental health as a serious public health issue with negative consequences for the woman, her family, and her child’s development (Glasheen et al. 2010; O’Hara and McCabe 2013; Saulnier and Brolin 2015; Stein et al. 2014). These ill effects are evident in pregnancy and extend well into the postnatal period and for years afterward (O’Hara and McCabe 2013; Stein et al. 2014). Between 12 and 15% of Australian women experience depression in the first 6 months postpartum, with a 9.3% 1-year period prevalence rate of major depression for postpartum women. The prevalence of diagnosed depression among mothers of children aged 24 months or less is thought to be around 20% (Australian Institute of Health Welfare 2012). Although anxiety in the perinatal period is common, for example, 13% prevalence in Australian women 6-months
postnatally (Yelland et al. 2010), with high comorbidity with depression (Austin et al. 2010), it has received less attention than postnatal depression (Howard et al. 2014). Between 4 and 20% of women are reported to experience an anxiety disorder in the postpartum period, highlighting a lack of consistency in definitions and reporting (Leach et al. 2015).

Risk factors for postpartum mental health disorders include history of psychiatric disorder, antenatal depression, poor social support or marital distress, young age, and lower socioeconomic status (Beck 2001; Grant et al. 2008; Milgrom et al. 2008). Acute or chronic stress in pregnancy is also highly predictive of perinatal mental health problems (Leach et al. 2015; Lee et al. 2007; O’Hara and Swain 1996; O’Hara et al. 1991). A small body of research has focused on the role of severe stress in pregnancy and postnatal mental health. This research shows that experiencing a natural disaster in pregnancy (e.g. hurricane (Xiong et al. 2008), flood (Brock et al. 2015), or war (Kleinhaus et al. 2013) predicts poor perinatal mental health, but perhaps not worse than in the general population (Harville et al. 2009). The stress caused by natural disasters can vary depending on the degree to which pregnant women are affected (objective hardship) as well as the intensity of the women’s emotional response (subjective stress) (Dancause et al. 2011; Hilmert et al. 2016). A systematic review reported that the severity of exposure to a disaster in pregnancy predicts negative mental health outcomes (Harville et al. 2010).

Social support from the partner during pregnancy has been found to protect against the negative effects of a severe stressor on women’s postnatal mental health: women who had infrequent support during pregnancy experienced greater objective stress and less reduction in depressive symptoms following a disaster, while frequent support weakened the association between stress and depression (Brock et al. 2014; Tees et al. 2010). Social support from midwives may provide similar protection. Women who receive continuity of midwifery carer during pregnancy, birth, and the postnatal period, where a small team of midwives work together in a midwifery group practice (MGP), report increased support when compared to women in standard care (SC) models (Forster et al. 2016). Although continuity of midwifery carer has been shown to significantly improve birth outcomes for women when compared to SC (Sandall et al. 2016), it is not known whether MGP is able to buffer the negative effects that prenatal maternal stress (PNMS) can have on maternal postnatal wellbeing.

The present study

In January 2011, Brisbane experienced a devastating sudden-onset flood that killed 24 people and adversely affected 200,000 residents, costing the State over $AU2 billion (van den Honert and McAneney 2011). We capitalised on this natural disaster to examine the potentially protective role of continuity of midwifery carer on women’s postnatal mental health outcomes. We hypothesised that MGP care, when compared to SC, would protect pregnant women from the impact of objective levels of flood exposure and subjective levels of maternal flood-related distress on depression and anxiety at 6 weeks and 6 months postpartum.

Methods

Study design and setting

The 2011 Queensland Flood Study (QF2011), a longitudinal cohort study (King et al. 2015), piggy-backed on an established, randomised control trial (RCT) examining the impact of caseload MGP care versus SC on birth outcomes: the M@NGO trial (Tracy et al. 2011, 2013). Recruitment commenced once ethical approval was received (April 4, 2011) and continued to 1 year post-flood (mid-January 2012) at a major tertiary hospital in South Brisbane, Australia. Women completed a survey at recruitment into the study, and follow-up surveys were administered at 12 months post-flood and at 6 weeks and 6 months postpartum. A more detailed description of the QF2011 protocol is presented in King et al. (2015), and the M@NGO trial protocol is published in Tracy et al. (2011).

Participants

Eligibility criteria included living in the vicinity of Brisbane and being pregnant with a singleton pregnancy at the peak of the Queensland flood in January 2011, being over 18 years of age, and able to speak fluent English (King et al. 2015). Women who were already enrolled in the ongoing M@NGO RCT of pregnancy care (Tracy et al. 2013) were invited to also enrol in the QF2011 study if they met eligibility criteria. New women recruited into M@NGO were also invited to participate in the QF2011 study, as well as women who did not meet M@NGO eligibility (e.g. < 24 weeks pregnant). Recruitment was primarily face-to-face at antenatal appointments by midwives and research assistants (RAs) with additional advertisements placed in local media and doctors’ offices. All women were pregnant during the flood, and those outside of the M@NGO trial were already allocated to a model of care prior to recruitment in the study (thus could not be randomised). A total of $N = 38$ were pregnant and $N = 88$ had already birthed when recruited into QF2011. There were two groups of participants: women enrolled in both M@NGO and QF2011 ($n = 80$) and women enrolled in QF2011 only ($n = 46$). Due to the nature of the intervention neither the women themselves nor the care providers were blind to the intervention. All...
women were contacted by RAs for maternal and infant follow-up surveys; the RAs were blinded to care group allocation.

Maternity care groups

M@NGO participants were randomly assigned to either MGP or SC care, whereas the QF2011-only women self-selected their care type, or were allocated into MGP if places were available. The care type each woman received most during her pregnancy was considered her ‘model of care’. Care providers are documented at every antenatal visit in the women’s records and were all verified by research midwives. In MGP, women were assigned to a primary caseload midwife that worked within a team of four full-time midwives who self-manage their schedules to respond to the needs of the women under their care. They provided continuity of care through the antenatal, intrapartum, and postpartum periods, and their MGP practice partners provided back-up care if the primary midwife was on leave or had worked more than 12 continuous hours. Not all women received care in labour from a known midwife however with the M@NGO trial finding that 87% of participants had their known midwife or her back up in the caseload arm compared to 14% in SC (Tracy et al. 2013). MGP midwives provided a home-visiting support service up to 6 weeks postpartum. In the SC model, women received shared care from a community-based general practitioner for antenatal care, and/or hospital midwives and/or hospital doctors through antenatal clinics, birth suites, and postnatal wards. Thus, SC group women could receive care from different rostered doctors or midwives at each hospital visit. Some SC women chose the option to be discharged home early from hospital (before 48 h for vaginal birth and 72 h for caesarean section), which entitled them to a home visit from a domiciliary midwife (although some women only received a phone call). If a woman required more than one visit, it may have been from different midwives, which can also happen in the caseload model when midwives need to take unexpected leave, have worked long shifts, and are on a fatigue break or leave the program. The key differences between the models is the continuity that enables relationships to develop between women and their midwives and the 24/7 phone contact to a known midwife that is enabled in the caseload model. All routinely collected data during the maternity period is entered into an electronic database with each woman having a unique identifier.

Instruments

Prenatal maternal stress

Objective stress exposure At recruitment and 12 months post-flood objective hardship was assessed with the Queensland Flood Objective Stress Scale (QFOSS), a questionnaire tailored specifically for the Queensland flood event. Four key dimensions of stress from previous disaster-related PNMS studies were assessed: threat, loss, scope, and change. Each dimension had scores ranging from 0 (no impact) to 50 (extreme impact) and were summed to provide a total objective stress score, (range = 0–200); higher scores indicated higher levels of objective hardship.

Subjective stress Three separate instruments were administered at recruitment to assess the women’s subjective distress from the floods. The 22-item Impact of Event Scale – Revised (IES-R; Weiss and Marmar 1997) assessed post-traumatic-like symptoms in response to the flood during the preceding 7 days. The 13-item Peritraumatic Distress Inventory (PDI; Brunet et al. 2001) assessed women’s recollection of emotional distress and panic-like reactions experienced during the flood. And the 10-item Peritraumatic Dissociation Experience Questionnaire (PDEQ; Marmar et al. 1997) assessed the severity of dissociative-like experiences during the flood. To minimise the number of predictor variables, the three subjective stress scores were combined into the COmposite Score for MOthers’ Subjective Stress (COSMOSS). This composite variable is standardised, so a positive COSMOSS score represents a level of subjective stress higher than the group mean. The COSMOSS was calculated using principal component analysis (PCA) on IES-R, PDI, and PDEQ total scores from the initial 230 participants who provided PNMS data at recruitment. The PCA-derived algorithm was COSMOSS = 0.36 × IESR + 0.40 × PDI + 0.39 × PDEQ. The PCA resulted in one factor explaining 76.27% of the overall subjective stress variance.

Cognitive appraisal At recruitment, the women’s cognitive appraisal of the overall impact of the flood was assessed with the question: ‘If you think about all of the consequences of the 2011 Queensland flood on you and your household, would you say the flood has been…?’ Women rated their appraisal on a 5-point Likert scale, from very negative (−2) to very positive (+2). Due to the narrow range of responses, and to determine the impact of a negative cognitive appraisal, this item was dichotomized into ‘Negative’ and ‘Neutral/Positive’.

Maternal well-being

At the antenatal hospital registration visit (at around 14 weeks), and 6 weeks and 6 months postnatally, women completed the 10-item Edinburgh Postnatal Depression Scale (EPDS; Cox et al. 1987) to assess women’s emotional distress over the previous 7 days. Consistent with guidelines, women who scored above 12 on the EPDS, or who indicated self-harm intentions, were contacted by study RAs and offered referral.
At 6 weeks and 6 months, postnatally women completed the state scale of the State Trait-Anxiety Inventory (SAI; Spielberger et al. 1983) to assess their current level of anxiety.

Socioeconomic status and other pregnancy life events

To characterise socioeconomic status (SES) based on residence, we obtained each participant’s Economic Indexes For Area (SEIFA) score, which indicates the socioeconomic characteristics of neighbourhoods in Australia ($M = 1000$; $SD = 100$); higher scores indicate that an area is relatively advantaged compared to lower scores. Other major life events experienced in pregnancy were assessed using a modified version of the Life Experiences Survey (LES; Sarason et al. 1987), which describes 26 categories of life events (e.g., divorce, illness). The total number of life events was used here.

Statistical methods

We examined whether type of maternity care (MGP vs. SC) interacted with flood-related PNMS to explain variance in postnatal depression and anxiety at 6 weeks and 6 months, controlling for socioeconomic status, other life events in pregnancy, and depression in pregnancy. The following variables were sequentially entered into the regression models: (1) SEIFA score; (2) the number of stressful events during pregnancy; (3) EPDS at hospital registration; (4) care type: SC ($= 0$) vs. MGP care ($= 1$); (5) objective stress; (6) subjective stress or cognitive appraisal; and (7) interaction term between model of maternity care and each PNMS variable. Given the moderate sample size, we assessed the effects of different PNMS variables one by one in each model, always with adjustment for objective stress. Thus, three models were constructed for each of the four outcomes (depression and anxiety, at 6 weeks and 6 months), each one testing the interaction between model of maternity care (MGP vs. SC) and the three PNMS variables (objective, subjective, cognitive).

To assess and compare the effects of the potential predictors, in addition to the effect estimates (point estimate, standard error, and 95% confidence interval) and their significance, we calculated the proportion of the variance in the outcome variable explained by each variable at its entry, over and above that already explained by other variables already in the model, as well as the coefficients for the final model. All analyses used two-tailed tests with a significance level of 0.05 and were performed using SAS version 9.3 (SAS Institute; Cary, NC).

Results

There were 196 women who had depression and anxiety data at 6 weeks and/or 6 months. Each analysis only included women with complete data for all variables in the equation. Women were missing data for stressful life events in pregnancy ($n = 37$) and depression scores at hospital registration ($n = 36$). The mean gestation for hospital registration EPDS screening was 14.52 weeks with interquartile range 12.29–15.57. At 6 weeks postpartum, the analyses included 48 women in MGP and 54 in SC, and at 6 months, there were 65 in MGP and 53 in SC. Women with recruitment questionnaires were invited to participate at all stages of data collection and were not excluded if they missed earlier data collection points which explains the higher number of participants at the later time point.

At 6 weeks postpartum, the average number of at-home visits from a midwife after the birth was 5.93 ($n = 43$; $SD = 2.24$, range $= 2–12$) for MGP women and 1.90 ($n = 49$; $SD = 1.29$, range $= 0–6$) for SC women, a significant group difference ($t = -10.38$, $p$ value < 0.0001).

Table 1 shows the descriptive statistics for women in MGP and SC care models; there were no statistically significant group differences.

Maternal depression Table 2 shows the results from the six multivariable hierarchical linear models for predicting postnatal depression 6 weeks and 6 months postpartum with interactions between care type and objective hardship (model 1), cognitive appraisal (model 2), or subjective stress (model 3).

In all six models, there was a significant main effect of depression at hospital registration (explaining 26% of unique variance at 6 weeks, and 16% at 6 months), such that greater EPDS scores in early pregnancy predicted greater postnatal depression scores at both time periods.

Objective hardship In model 1, controlling for all main effects, there was a significant interaction between maternity care type and objective hardship that explained an additional 3.3% of variance in 6-week depression scores. As illustrated in Fig. 1, although there was no effect of objective hardship from the flood on depression in the MGP group, for women in SC, the more severe the objective hardship the greater their postpartum depression. Although there were no group differences in depression at low levels of objective hardship, depression was significantly more severe in the SC when objective hardship was 22 or greater, or approximately one quarter of a SD above the mean. The final model explained 36.0% of the variance in 6-week depression scores. For 6-month depression, only stressful life events and pregnancy depression were significant predictors, with the final model explaining 26.4% of variance.

Cognitive appraisal Table 2, model 2, shows that the interaction between cognitive appraisal and maternity care type was non-significant. This model explained 35% of the variance in 6-week depression scores. At 6 months, significant
effects were found only for life events and pregnancy depression, with the final model explaining 28.6% of the variance.

**Subjective stress** As shown in Table 2, model 3 explained 42.3% of the variance in 6-week depression. There was a significant interaction between care type and subjective flood-related stress which explained an additional 4.7% of variance. As illustrated in Fig. 2, although in the SC group the greater the flood-related subjective stress, the greater the depression ($p < .05$), MGP care buffered the effects of disaster-related subjective stress on depression at 6 weeks. Although there was little difference in depression scores when flood-related subjective stress was low, when stress levels were greater than 0.095 (meaning 9.5% of one standard deviation above the mean), depression in the SC group was significantly greater than that in the MGP group. For depression at 6 months postpartum, there was a significant, positive main effect of subjective stress,
Table 2  Three multivariable linear models for predicting postnatal maternal depression score at 6 weeks and 6 months, for (1) objective hardship, (2) cognitive appraisal, and (3) subjective stress. Coefficients are for the final model.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Regression coefficient</th>
<th>Variance explained (%)</th>
<th>Regression coefficient</th>
<th>Variance explained (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point estimate</td>
<td>Standard error</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>Model 1 Socioeconomic status</td>
<td>0.01</td>
<td>0.01</td>
<td>[−0.01; 0.02]</td>
<td>0.212</td>
</tr>
<tr>
<td>Stressful life events in pregnancy</td>
<td>0.18</td>
<td>0.17</td>
<td>[−0.16; 0.52]</td>
<td>0.289</td>
</tr>
<tr>
<td>Pregnancy depression</td>
<td>0.57</td>
<td>0.10</td>
<td>[0.37; 0.77]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Care type: MGP = 1, SC = 0</td>
<td>0.80</td>
<td>1.14</td>
<td>[−1.47; 3.07]</td>
<td>0.485</td>
</tr>
<tr>
<td>Objective hardship</td>
<td>0.08</td>
<td>0.04</td>
<td>[0.01; 0.16]</td>
<td>0.021</td>
</tr>
<tr>
<td>Objective hardship X Care type</td>
<td>−0.11</td>
<td>0.05</td>
<td>[−0.21; −0.01]</td>
<td>0.031</td>
</tr>
<tr>
<td>Model 2 Socioeconomic status</td>
<td>0.01</td>
<td>0.01</td>
<td>[−0.01; 0.02]</td>
<td>0.205</td>
</tr>
<tr>
<td>Stressful life events in pregnancy</td>
<td>0.17</td>
<td>0.17</td>
<td>[−0.17; 0.51]</td>
<td>0.326</td>
</tr>
<tr>
<td>Pregnancy depression</td>
<td>0.52</td>
<td>0.11</td>
<td>[0.31; 0.74]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Care type: MGP = 1, SC = 0</td>
<td>−2.46</td>
<td>1.31</td>
<td>[−5.06; 0.14]</td>
<td>0.064</td>
</tr>
<tr>
<td>Objective hardship</td>
<td>0.01</td>
<td>0.03</td>
<td>[−0.06; 0.07]</td>
<td>0.816</td>
</tr>
<tr>
<td>Cognitive appraisal: neutral and positive vs. negative</td>
<td>2.25</td>
<td>1.23</td>
<td>[−4.68; 0.19]</td>
<td>0.07</td>
</tr>
<tr>
<td>Cognitive appraisal X Care type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3 Socioeconomic status</td>
<td>0.01</td>
<td>0.01</td>
<td>[−0.001; 0.02]</td>
<td>0.079</td>
</tr>
<tr>
<td>Stressful life events in pregnancy</td>
<td>0.10</td>
<td>0.16</td>
<td>[−0.22; 0.42]</td>
<td>0.542</td>
</tr>
<tr>
<td>Pregnancy depression</td>
<td>0.52</td>
<td>0.10</td>
<td>[0.33; 0.71]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Care type: MGP = 1, SC = 0</td>
<td>−1.22</td>
<td>0.71</td>
<td>[−2.63; 0.19]</td>
<td>0.089</td>
</tr>
<tr>
<td>Objective hardship</td>
<td>−0.02</td>
<td>0.03</td>
<td>[−0.08; 0.05]</td>
<td>0.594</td>
</tr>
<tr>
<td>Subjective stress</td>
<td>2.44</td>
<td>0.63</td>
<td>[1.19; 3.69]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Subjective stress X Care type</td>
<td>−2.19</td>
<td>0.77</td>
<td>[−3.72; −0.66]</td>
<td>0.006</td>
</tr>
</tbody>
</table>

a 95% confidence interval around the point estimate (unstandardized coefficient); significant if it does not cross 0

b The Variance explained column presents the amount of additional variance explained by each variable, as it was originally entered into the equation hierarchically.
such that higher stress was associated with more depressive symptoms, but no significant care type interaction after controlling for other variables. The final model explained 33.9% of the variance in depression at 6 months.

Maternal anxiety Table 3 shows the results from the six multivariable hierarchical linear models for the postnatal maternal anxiety scores at 6 weeks and 6 months. Similar to the postnatal depression results, there was a significant main effect of depression at hospital registration on anxiety levels, explaining approximately 33% of unique variance at 6 weeks, and approximately 18% at 6 months.

Objective hardship, subjective stress, and cognitive appraisal At 6 weeks postpartum, there was a significant buffering against subjective stress ($p = 0.048$). Specifically, MGP women’s anxiety scores were not affected by subjective stress, whereas SC women’s anxiety scores were significantly affected: the higher the subjective stress from the flood, the higher the anxiety scores at 6 weeks (shown in Fig. 3). Although the groups did not differ in anxiety when subjective stress was low, the SC group had significantly more severe symptoms than the MGP group when subjective stress was greater than 0.732 (0.73 of 1 SD). There were no significant main effect or interaction results involving maternal cognitive appraisal at 6 weeks. The objective hardship model explained a total of 42.6% of the variance in 6-week anxiety scores, the cognitive appraisal model explained 41.9%, and the subjective distress model explained 45.3%.

At 6 months postpartum, neither objective hardship, subjective stress, nor cognitive appraisal explained significant amounts of variance in anxiety. None of the interactions with care type were significant. The three models explained 30.4, 31.5, and 30.9% of the variance in 6-month anxiety scores, respectively, primarily as a function of significant effects of pregnancy depression and other life events in pregnancy.

It is noteworthy that among the several potential predictors included in the regression models other than flood variables and care type, EPDS at hospital registration was the only variable that significantly predicted postnatal depression and anxiety at both 6 weeks and 6 months. Over and above the variance already explained by other variables in the model, pregnancy depression explained approximately 26 and 16% of the variance of postnatal maternal depression at 6 weeks and 6 months, respectively. In postnatal maternal anxiety, pregnancy depression explained about 33 and 19% of the variance in the outcome assessed at 6 weeks and 6 months, respectively. Stressful life events predicted greater levels of both depression and anxiety at 6 months only, explaining 8–9% of the variance, in all but one of the models (Table 2 model 3: depression and subjective stress ($p = 0.07$)).

Discussion

As predicted and as shown in previous research, this study demonstrates that a higher EPDS score at hospital registration in pregnancy, and a greater number of stressful life events a woman has experienced, predict more severe postpartum anxiety and depression. In addition however, the 6-week postpartum depression and anxiety of women who had been in standard care was a function of the severity of the objective exposure to the flood and their level of subjective distress; on the other hand, the women in the MGP (continuity) group appeared to be protected to some degree from both the objective and subjective aspects of their flood experiences. For those women who had higher levels of objective or subjective stress, the SC model of midwifery care was associated with significantly more severe depression and anxiety scores at 6 weeks.
### Table 3  
Three multivariable linear models for predicting postnatal maternal anxiety score at 6 weeks and 6 months, for (1) objective hardship, (2) cognitive appraisal, and (3) subjective stress

<table>
<thead>
<tr>
<th>Predictors</th>
<th>6 weeks (48 MGP, 54 SC)</th>
<th>6 months (65 MGP, 53 SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>Variance explained (%)</td>
</tr>
<tr>
<td></td>
<td>Point estimate</td>
<td>Standard error</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Stressful life events in pregnancy</td>
<td>0.12</td>
<td>0.33</td>
</tr>
<tr>
<td>Pregnancy depression</td>
<td>1.32</td>
<td>0.20</td>
</tr>
<tr>
<td>Care type: MGP = 1, SC = 0</td>
<td>1.89</td>
<td>2.25</td>
</tr>
<tr>
<td>Objective hardship</td>
<td>0.23</td>
<td>0.07</td>
</tr>
<tr>
<td>Objective hardship X Care type</td>
<td>−0.18</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Stressful life events in pregnancy</td>
<td>0.08</td>
<td>0.34</td>
</tr>
<tr>
<td>Pregnancy depression</td>
<td>1.32</td>
<td>0.21</td>
</tr>
<tr>
<td>Care type: MGP = 1, SC = 0</td>
<td>−4.61</td>
<td>2.59</td>
</tr>
<tr>
<td>Objective hardship</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>Objective hardship X Care type</td>
<td>−1.78</td>
<td>2.43</td>
</tr>
<tr>
<td>Cognitive appraisal: neutral and positive vs. negative</td>
<td>4.81</td>
<td>3.13</td>
</tr>
<tr>
<td>Cognitive appraisal X Care type</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Stressful life events in pregnancy</td>
<td>−0.01</td>
<td>0.33</td>
</tr>
<tr>
<td>Pregnancy depression</td>
<td>1.25</td>
<td>0.20</td>
</tr>
<tr>
<td>Care type: MGP = 1, SC = 0</td>
<td>−1.50</td>
<td>1.44</td>
</tr>
<tr>
<td>Objective hardship</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Subjective stress</td>
<td>3.62</td>
<td>1.28</td>
</tr>
<tr>
<td>Subjective stress X Care type</td>
<td>−3.14</td>
<td>1.57</td>
</tr>
</tbody>
</table>

*a* 95% confidence interval around the point estimate (unstandardized coefficient); significant if it does not cross 0

b The Variance explained column presents the amount of additional variance explained by each variable, as it was originally entered into the equation hierarchically
Continuity of midwifery carer moderates the effects of prenatal maternal stress on postnatal maternal health outcomes of the MGP model of care to standard care found that not only was MGP care safe, but it cost significantly less (Tracy et al. 2013).

Our findings are similar to those from a perinatal support program called Healthy Start, which buffered pregnant women’s wellbeing in the post-Hurricane Katrina disaster recovery period (Giarratano et al. 2015). While these findings were limited to young, poor, and less-educated mothers who had been severely impacted by the hurricane, they reported similar birth outcomes to the less at-risk population accessing standard care, suggesting a positive influence of the broader, personalised support that included home visits, case management, health education, assistance with social support, and other services. Similarly, the Nurse-Family partnership (NFP) studies, with low SES first-time mothers, showed that in-home visits from a nominated nurse home visitor during pregnancy and postpartum had beneficial effects on postnatal maternal life course with fewer subsequent pregnancies, greater participation in the workforce, and less reliance on social welfare (Olds 2013). Like the MGP program, the NFP has a high component of relational continuity between the woman and her care provider (nurse in NFP), which is likely to be a key component of positive maternal outcomes in both programs.

The continuity of care provided by the MGP model provides more personalised care than the SC model, with 24/7 phone access to a known midwife from booking in antenatally up until discharge from the program, group sessions for women aimed at increasing maternal and infant health literacy, peer support, and individualised case management through pregnancy, and birth and the early postpartum period. One key factor thought to be impacting outcomes is the therapeutic relationship that develops between the woman and her primary midwife (Sandall et al. 2016) that results in increased advocacy, empathic care (Walsh and Devane 2012), and engagement in health services (Allen et al. 2016). Recipients of MGP care report a more positive birth experience, with more control in labour and less anxiety than women in standard care (McLachlan et al. 2016). The flexibility of the model allows a more personalised and flexible approach both motivating and enabling midwives to go above and beyond what they are able to do in SC where the absence of continuity of carer and lack of time can see midwives focussing on the biomedical aspects of care while ignoring the psycho-social-emotional dimensions (Allen et al. 2017). In Australia, as a result of the M@NGO trial, the MGP model is being expanded to women who have identified risks or vulnerabilities in pregnancy with MGP teams being established and modified for Aboriginal and Torres Strait Islander women (Kildea et al. 2016, 2017), young women (Allen et al. 2016), and women from a refugee background. Whether the results seen following this sudden-onset stressor will translate to a vulnerable population with significant life stressors in pregnancy is currently being investigated in at least one study (Kildea et al.
The benefits of MGP were present to 6 weeks postpartum, which is the length time for which women can receive care under this program. However, the benefits did not extend to 6 months, particularly for levels of depression, at which time women were no longer receiving MGP care, suggesting the benefits may be limited to current care status only. However, it must be noted that the MGP model was not designed to counteract the long-term effects of traumatic events such as flooding which these women experienced during their pregnancy.

The role of the GP, Child and Family Health Nurse (CFHN), and other health providers who may offer support or specialised care is largely unexplored in this study and merit further research. Other Australian work has shown the transition from maternity care to child and family health services is less than ideal particularly regarding communication and handover of information (Homer et al. 2009). The GP will often have an ongoing relationship with a woman and her family while she receives pregnancy care from additional providers, while CFHNs are available from birth to 5 years. Given these are universal services in Australia with a broad reach, increasing support and strengthening communication between standard hospital care providers, GPs and CFHNs, particularly for women at risk, may provide opportunities for increased relation-based support and involvement when a natural disaster has occurred. Improved transfer of care from MGP to GPs and CFHNs at the 6-week handover may also assist to buffer the impact of the stress for longer periods. At the 6-month time point, the factors that continued to be associated with high levels of depression and anxiety were the number of non-flood life events in pregnancy and antenatal EPDS scores, which underlies the importance of screening and referral to specialised services, for example psychologists and perinatal mental health specialists. Potentially extending MGP or other support services further into the postpartum period for selected women might also produce more enduring, longer-term benefits for maternal mental health.

Both the objective severity of the hardship endured by the women from the flood and their emotional reactions (subjective stress) were predictive of postnatal depression at 6 weeks and 6 months even when controlling for depression in pregnancy; interestingly, whether the women considered that the effects of the flood were positive, neutral, or negative (cognitive appraisal) appeared to have no effect on postnatal anxiety or depression. However, depression scores during pregnancy were consistently the most predictive variable of postnatal mental health at 6 weeks (which explained 26–33% of the variance) and at 6 months (16–18% of variance). As has been previously documented (Ward et al. 2016), the number of stressful life events in pregnancy, other than the disaster, was predictive of postnatal mental wellbeing.

Women’s postnatal wellbeing has particularly important consequences for child development: children of women who experience postnatal depression or anxiety show increased rates of poor physical health, attachment disorders, and developmental psychopathology (Glasheen et al. 2010; Goodman and Gotlib 1999; Stein et al. 2014). Similar negative developmental outcomes are also associated with PNMS, with research showing that exposure to life-event stressors or natural disasters predict poorer birth outcomes, developmental delays, and behavioural problems (Talge et al. 2007). Therefore, the current finding that continuity of care protects women who are pregnant during a disaster by buffering her early postnatal mental wellbeing may also contribute additional indirect benefits to her child’s development.

The current study has several limitations. First, the women enrolled in the M@NGO trial were randomly assigned to MGP or SC and may have differed from the QF2011 women who self-selected their care type, or were allocated by the hospital staff, depending on spaces available in the MGP or other models. Indeed, we were unable to test this model in the randomised group due to uneven distribution between the groups. Allocation to model of care occurred prior to enrolment in the QF2011 study thus women were unable to be randomised, and self-selection into the model may have introduced a bias that was not detectable. No significant differences between the groups were found in the study variables; however, there may have been some (unidentified) reason that women differed between groups, or for women selecting a particular model of care in the QF2011 subsample. The flood status would not have been known at the time of allocation to care model; thus, women would not have not been directed towards this model of care due to presumed vulnerability by the allocation midwife. Additionally, we were unable to examine differences in partner and family support, which would have been valuable. Second, the final sample size was relatively small (N = 126) having been reduced due to missing data from 34 women, a common problem in longitudinal research. Nevertheless, there was sufficient power to detect significant group differences and interactions. Third, the sample of women was relatively homogenous, primarily Caucasian Australians of middle to upper socioeconomic status, therefore, potentially reducing the generalisability of the findings to the wider community. However, it is possible that the effects of a sudden-onset stressor like a natural disaster would more acutely affect other vulnerable populations who may not have the resources available to the current sample.

In summary, this is the first study to show that model of maternity care, MGP, mitigates the effects of higher levels of stress experienced by women up to 6 weeks postnatal in the context of a natural disaster. The longer-term impact of MGP care is not known; however, it may have indirect benefits for child development, which is closely linked with both PNMS and maternal postnatal wellbeing. Randomised trials have found that MGP care is a protective model of midwifery care, not only for women with no identified risk factors in...
Continuity of midwifery carer moderates the effects of prenatal maternal stress on postnatal maternal...
COUNSELLING IN FOETAL MEDICINE: A CASE OF CHORIANGIOCARCINOMA

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Background: Chorioangiomas are the most common placental tumours with a prevalence of approximately 1%, among placentas that have undergone histological examination (1). Chorioangiomas are often small, undetected and of little clinical significance. However, large chorioangiomas (>4 cm), while less common, are more likely to be diagnosed perinatally and are associated with a range of adverse perinatal outcomes as well as a significantly increased foetal mortality rate of 30–40% (2).

Method: We describe a case of a large chorioangioma and discuss the ultrasound features, and antenatal counselling in this clinical situation.

Results: A 37-year-old multiparous was referred at 30 + 5 weeks’ gestation with the antenatal diagnosis of a chorioangioma (6.9cmx4.9cmx3cm). The patient was managed expectantly with regular antenatal care, ultrasound assessment, and CTG monitoring. The parents were counselled regarding the risks of polyhydramnios, pre-eclampsia, preterm delivery, feto-maternal haemorrhage, fetal growth restriction, congestive cardiac failure, fetal anaemia, hydrops, and fetal death. This condition and the plan for the pregnancy was discussed in detail.

Conclusion: Given the high risk of poor perinatal outcomes associated with chorioangioma; extensive antenatal counselling, surveillance, appropriate treatment, and timely delivery are recommended to prevent potential complications and mortality, regard-less of the presence of complications at the time of diagnosis.

References:

Cytoreductive surgery for ovarian cancer: quality assessment

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Surgery is the cornerstone of treatment of ovarian cancer. Given the importance of achieving no or minimal macroscopic residual disease at primary surgery, performing an assessment of the quality of ovarian cancer surgery is crucial. Assessing the quality of care and surgical outcome allows us to establish baseline information, set standards of care and clear priorities, enable benchmarking against peers, and sustain quality improvement. We know that suboptimal care exists and variation in outcomes results. One way to monitor variation in outcomes is through a clinical quality registry (CQR). A CQR collects a defined minimum dataset to measure performance of an individual or center against a range of clinical quality indicators and provides risk-adjusted, benchmarked data to participating institutions. CQR’s are an excellent quality assurance measure as they capture all cases (an opt out system). They permit detection and analysis of unwarranted variations in care. This can provide indications of a systems or process problem, thereby motivating health care providers to improve services and care. Several groups have either developed quality indicators for advanced ovarian cancer surgery (The Scottish Cancer Taskforce and the European Society of Gynecological Oncology) or are in the process of doing so (Australian Society of Gynaecological Oncologists). Indicators should be evidence-based and determined by extensive discussion with experts and stakeholders to ensure appropriateness and buy-in. The Scottish Cancer Taskforce and European Society of Gynecological Oncology have set targets for their quality performance measures, which should provide a quantitative framework for improving care in the surgical management of ovarian cancer.

Key words: quality, clinical indicators, ovarian cancer, surgery

Introduction

Ovarian cancer is the most lethal of all gynecological cancers because most of these tumors have late stage presentation. The 5-year survival for advanced ovarian cancer in developed countries is ~25%. The cornerstone of treatment of most patients is surgery and chemotherapy.

Surgical cytoreduction of ovarian cancer was first described by Meigs [1], in his textbook, ‘Tumors of the Female Pelvic Organs’. Although it took many years for the use of cytoreductive surgery to become routine, the concept of surgical cytoresection as an aid to adjuvant treatment, which initially was radiation therapy, was the fundamental basis of this strategy. Support for aggressive surgical cytoreduction gained momentum with the publication of Griffith’s seminal paper [2]. Two publications by Hoskins et al. [3, 4], based on Gynaecologic Oncology Group (GOG) protocols, further supported the role of aggressive surgical cytoreduction and confirmed the inverse relationship between the amount of residual disease at primary surgery and optimal survival outcomes. Analysis of high-volume centers confirmed the importance of optimal tumor resection [5–8]. Aided by the concurrent development and routine use of cisplatin and paclitaxel chemotherapy, the concept of aggressive surgical cytoreduction followed by cytotoxic chemotherapy has become the standard of care for ovarian cancer.

Rationale for cytoreduction

While the biological rationale behind the benefit of surgical cytoreduction remains unclear, the presumption is that surgical
The adequate assessment of quality of care depends on a reliable definition of ‘quality care’. Maurer and mortality are often used as markers for quality of care, but they are crude, nonspecific measures rather than precise tools. Ultimately, quality of care is a value judgment, reflecting the attitudes and goals of the local health care system and society at large [14]. Definition of quality care may vary from one jurisdiction to another.

The quality of ovarian cancer surgery in each location may be judged by how many cases are carried out (is volume important?), how extensive the surgery is (is more always better?) how well the surgery is carried out (complications, survival, outcomes) and how accessible the service is (is it dependent on ethnicity, geography, sociodemographics, financial resources?). The concept of minimum standards, i.e. benchmarking, as opposed to centers of excellence, becomes important when access is an issue.

**Clinical quality registries**

It is accepted that ovarian cancer outcomes can be improved in many ways. Examples include: ensuring that surgery is carried out by suitably trained gynecological oncologists, ensuring correct diagnosis, optimizing chemotherapy, encouraging access to clinical trials, optimizing supportive care and engaging in risk reduction strategies. Nevertheless, suboptimal care exists and variation in outcomes results [15–18].

One way to monitor variation in outcomes is through a clinical quality registry (CQR). A CQR collects a defined minimum dataset to measure performance of an individual or center against a range of clinical quality indicators (CQIs) and provides risk-adjusted, benchmarked data to participating institutions [19]. This information allows health service providers to improve their systems and processes, with the expectation of improved patient care and outcomes. CQR’s are an excellent quality assurance (QA) measure as they capture all cases (an opt out system). They permit detection and analysis of unwarranted variations in care. This can provide indications of a systems or process problem, thereby motivating health care providers to improve services and care.

In Australia, clinical quality registers exist for several cancers, including prostate, lung, myeloma, and lymphoma. Documented improvements in quality of care have been reported with the prostate cancer registry, which demonstrated an improvement in timeliness of treatment, reductions in the percentage of patients with positive margins and a reduction in unnecessary surgery for men with low-risk disease [20].

Some jurisdictions have initiated the process of implementing quality assurance programs for ovarian cancer surgery. In 2013 (and updated in 2016), the Scottish Cancer Taskforce published its ovarian cancer quality performance indicators (QPI’s), which were developed after extensive consultation with stakeholders (http://www.healthcareimprovementscotland.org/our_work/cancer_care_ improvement/cancer_qpis/quality_performance_indicators.aspx; 30 May 2017, date last accessed). Initially, nine QPI’s were developed and targets set. Each cancer network in Scotland is required to report performance against QPI targets on an annual basis.

In 2016, the European Society of Gynecological Oncology (ESGO) published its quality indicators for advanced ovarian cancer surgery [21]. The Society recommended that these quality indicators be incorporated into institutional or governmental quality assurance programs in European countries. It was suggested that they might serve as a basis for certification of recognized gynecological oncology centers.

Very few jurisdictions have established clinical quality registries capable of benchmarking ovarian cancer care and ovarian cancer surgical outcomes. Clinical registries can function as a
Quality of care can be assessed and optimized by using structural, process and outcome quality indicators [22]. Outcome indicators are defined as states of health or events that follow care and that may be affected by it. They are not always direct measures of safety and quality of health care delivery because of the influence of patient factors. Examples include 30-day post-surgical mortality (clinical outcome) or percentage of patients returning to work within 6 weeks of surgery (patient reported outcome). Process indicators refer to what providers do and how well they do it, as defined by reference to best practice. They are usually more sensitive to differences in quality than outcome indicators and can be easier to measure. An example would be the percentage of patients who had a histologically confirmed diagnosis before starting neoadjuvant chemotherapy. Structural indicators refer to resources, e.g. adequacy of facilities and equipment, qualifications of staff or access to specific technologies. These are simple to collect but harder to directly relate to patient outcomes.

In establishing performance indicators, it is essential that targets are SMART; i.e. specific, measurable, achievable, relevant and timely [23]. Indicators should be evidence-based and determined by extensive discussion with experts and stakeholders to ensure appropriateness and participation.

The Scottish and European QPI’s, and the proposed Australian QPI’s (Table 1), were determined using similar methods, i.e. review of available literature and evidence, and consultation with and consensus from stakeholders (http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx; 30 May 2017, date last accessed) [21, 24]. The Scottish Taskforce and ESGO have set target levels. The QPI’s which are similar in all groups, are the rate of complete cytoreduction for advanced disease and multidisciplinary team (MDT) review. The Scottish group and ESGO mandate an appropriate pre-operative work-up and minimum requirements for pathology reporting. The Scottish group and the Australian pilot mandate reporting of postoperative complications, rate of optimal debulking with interval debulking, adequate surgery for early stage disease, pathological diagnosis before treatment with neoadjuvant chemotherapy, and proportion of patients receiving platinum-based chemotherapy. The Scottish group added documentation of risk of malignancy index for stage 1 disease as their tenth QPI. ESGO mandates recording the annual number of cytoreductive surgeries carried out per center and per surgeon/year, whether surgery was carried out by a gynecological oncologist, participation in clinical trials, availability of appropriate perioperative facilities and minimum requirements for an operative report.

Currently, QPI’s exist for patients at the time of initial diagnosis and treatment. None have yet been proposed for surgical management of recurrent disease. Despite the essential role of cytoreductive surgery in the primary setting, the surgical management of recurrent disease remains a subject of debate due to the lack of high quality evidence of benefit. Nevertheless, it is important to define reliable factors that predict complete tumor resection during secondary surgery for the patients with recurrent disease to facilitate selection of candidates who are most likely to benefit from this approach. This would then allow for development of suitable QPI’s for this group of patients as well.

The DESKTOP II trial demonstrated the utility of the AGO score in defining which patients are likely to achieve complete cytoreduction [25]. The DESKTOP III trial, recently reported in abstract form, showed a benefit in PFS when the score was used to select patients suitable for secondary cytoreduction [26]. The score could potentially form part of the minimal dataset for the DESKTOP II trial. The DESKTOP II trial demonstrated the utility of the AGO score in defining which patients are likely to achieve complete cytoreduction [25]. The DESKTOP III trial, recently reported in abstract form, showed a benefit in PFS when the score was used to select patients suitable for secondary cytoreduction [26].

### Table 1. Quality performance indicators across various jurisdictions

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<tr>
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<tr>
<td>MDT review</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Minimum requirements for op report</td>
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<td>✓</td>
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</tr>
</tbody>
</table>

*www.healthcareimprovementscotland.org

ESGO, European Society of Gynecological Oncology; MDT, multidisciplinary team.
quality assessment of the indication and performance of secondary cytoreductive surgery.

**Summary**

Quality assessment protocols for cytoreductive operations for ovarian cancer are an essential aspect of optimizing the benefits of the operation and mitigating risks.

- Assessment of quality of care and surgical outcome allows us to establish baseline information, set standards of care and clear priorities, enable benchmarking against peers, and inform quality improvement.
- Outcomes can be monitored by using a CQR, which collects a defined minimum dataset to measure performance of an individual or center against a range of QPIs and provides risk-adjusted, benchmarked data to participating institutions.
- A CQR collects a defined minimum dataset to measure performance of an individual or center against a range of QPIs and provides risk-adjusted, benchmarked data to participating institutions.
- A CQR permits detection and analysis of unwarranted variations in care, and can provide indicators of a systems or process problem, thereby motivating health care providers to improve services and care.
- Quality of care can be assessed and optimized by using structural, process and outcome quality indicators.
- Structural indicators refer to resources, e.g. adequacy of facilities and equipment, qualifications of staff or access to specific technologies.
- Process indicators refer to what providers do and how well they do it, as defined by reference to best practice.
- Outcome indicators are defined as states of health or events that follow care and that may be affected by it.
- Indicators should be evidence-based and determined by extensive discussion with experts and stakeholders to ensure appropriateness and participation.

**Acknowledgement**

The authors acknowledge the assistance of A/Prof. Robert Rome and Prof. John Zalcberg.

**Funding**

The publication of this supplement and the symposium on which it is based have been supported through partnership between the Spanish Ovarian Cancer Research Group (GEICO) and the European Society for Medical Oncology (ESMO).

**Disclosure**

The authors have declared no conflicts of interest.

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Dangerous Pressurization and Inappropriate Alarms during Water Occlusion of the Expiratory Circuit of Commonly Used Infant Ventilators

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Abstract

Background
Non-invasive continuous positive airways pressure is commonly a primary respiratory therapy delivered via multi-purpose ventilators in premature newborns. Expiratory limb occlusion due to water accumulation or ‘rainout’ from gas humidification is a frequent issue. A case of expiratory limb occlusion due to rainout causing unexpected and excessive repetitive airway pressurisation in a Draeger VN500 prompted a systematic bench test examination of currently available ventilators.

Objective
To assess neonatal ventilator response to partial or complete expiratory limb occlusion when set to non-invasive continuous positive airway pressure mode.

Design
Seven commercially available neonatal ventilators connected to a test lung using a standard infant humidifier circuit with partial and/or complete expiratory limb occlusion were examined in a bench test study. Each ventilator was set to deliver 6 cmH2O in non-invasive mode and respiratory mechanics data for 75%, 80% and 100% occlusion were collected.

Results
Several ventilators responded inappropriately with complete occlusion by cyclical pressurisation/depressurisation to peak pressures of between 19-4 and 64-6 cm H2O at rates varying between 2 to 77 inflations per minute. Tidal volumes varied between 10-1 and 24-3mL. Alarm responses varied from ‘specific’ (tube occluded) to ‘ambiguous’ (Safety valve open). Carefusion Avea responded by continuing to provide the set distending pressure and
displaying an appropriate alarm message. Draeger Babylog 8000 did not alarm with partial occlusions and incorrectly displayed airways pressure at 6.1 cmH2O compared to the measured values of 13 cmH2O.

Conclusions
This study found a potential for significant adverse ventilator response due to complete or near complete expiratory limb occlusion in CPAP mode.

Introduction
A recent adverse ventilator event occurred in our unit with a stable extremely preterm infant managed on 6 cmH2O nasal continuous positive pressure (nCPAP) delivered via a Draeger VN500 (Lübeck, Germany). This male infant was born at 28 weeks gestation with a birth weight of 1000 grams. After a brief period of intubation for Respiratory Distress Syndrome and treatment with surfactant (Curosurf, Chiesi Farmaceutici, S.p.A., Parma—Italy), he was extubated successfully to nCPAP. Sudden deterioration in the patient condition was observed with desaturation and bradycardia. The ventilator pressure waveform indicated cyclical pressurisation to a peak of 40 cmH2O falling to zero at a rate of approximately 77 inflations per minute and alarm message indicating high/low pressures. Patient was immediately taken off the ventilator circuit and provided with manual mask ventilation using a t-piece resuscitator. The infant recovered quickly and the ventilator circuit was subsequently discovered to have complete expiratory limb occlusion with water due to rainout in the opaque circuit. Given the high pressures observed, we regarded this “near miss” event as potentially life threatening. The VN500 in question and another 4 similar VN500 ventilators were tested to determine no faults in standard function yet all responded to complete expiratory limb occlusion in the same manner of cyclical pressurisation/depressurisation.

In searching the literature we were surprised to find a detailed case report published over thirty years ago by Hall[1] et al (1983) describing a similar complication of prolonged excessive airway pressure during circuit occlusion where the infant died. Following this event, Hall[1] et al bench tested 8 continuous flow, pressure-limited infant ventilators available at that time, examining response to complete expiratory limb occlusion. This study also assessed the specifications and design of the inspiratory pressure regulating valve of these ventilators. Hall[1] found in this study, the majority of infant ventilators tested exposed the patient to excessive and inadvertent airway pressures well over the set values on the ventilator during the occlusion.

Given the potential seriousness of this problem we planned to systematically test a range of neonatal ventilators commercially available and currently in use internationally. The aim of this study was to examine ventilator alarm response and pressure/flow changes when states of partial or complete expiratory limb occlusion were induced in a bench test setting for a range of neonatal ventilators set in non-invasive CPAP mode.

Background
The manufacture and software control of neonatal ventilators has increased markedly in the last decade. Many of the latest generation of neonatal ventilators are multifunction devices that offer both invasive (patient circuit to endotracheal tube) and non-invasive mechanical ventilation (patient circuit to nasal prongs or mask). The gas flow delivered to the patient circuit has
changed from constant flow to a proportional or demand flow in some brands and modes. This is common in adult ventilators but relatively new in the neonatal designs. Managing complex patient—ventilator interactions such as volume targeting and breath termination as well as monitoring alterations in delivered ventilation is becoming more complex[2] and demands a considerable level of clinical expertise.[3,4]

Mechanical ventilation in the neonatal intensive care unit environment has additional complexity due to widespread use of closed incubators used for thermoregulation. Exposure to expiratory limb tube kinking can occur with soft tube CPAP delivery hardware (midline delivery manifolds) and incubator doors. Water build up (rainout) in ventilator circuits due to the humidification process is common and the smaller diameter of neonatal circuits thus poses greater risk of partial or total occlusion. The amount of rainout and the time it takes to accumulate will vary depending on many factors (ventilator circuit type and design, incubator temperature,[5] nursery temperature,[6] circuit orientation (particularly the diameter of any downward facing loops in the expiratory limb tubing) and ventilator delivered tidal volume [7]). Ventilators are designed to cope with a wide range of potential error states including ‘rainout’ in ventilator circuits. The potential for partial or even total expiratory limb occlusion is significant, therefore heated patient circuits and evaporative expiratory systems are designed to minimize this problem. Due to the range of patient size, gestation and postnatal age, the location of the patient circuit temperature probe either in or outside a closed incubator is critical to prevent excessive circuit rainout. [5,8,9]

The paper by Hall[1] et al published over thirty years ago reported a serious systematic design fault in neonatal ventilator systems available at that time. We aimed to bench test the currently available neonatal ventilators using similar methods to those used by Hall[1] et al to determine if the previously identified design faults still exist in current ventilators. We also wished to determine if current international standards[10] were appropriate for ventilator delivered non-invasive CPAP.

**Materials and Method**

**Sample**

Seven commercially available neonatal ventilators were tested.

- VN500 (Draeger, Lubeck Germany)
- Fabian (Acoutronic, Hirzel Switzerland),
- SLE 5000 (SLE Ltd, South Croydon United Kingdom),
- Babylog 8000 (Draeger, Lubeck Germany).
- Avea (Carefusion, San Diego USA),
- Leoni (Heinen + Lowenstein, Bad Kissingen Germany)
- Sophie (Stephan Medizintechnik, Gakenbach Germany).

A Fisher & Paykel RT265 infant humidifier circuit was used on each ventilator except the Sophie ventilator which has a dedicated airway circuit and humidification system of different circuit diameter. (Thus the Sophie ventilator was only tested at 100% occlusion with operator adjusted over pressure valve manually set to its maximum value of 70cmH2O to simulate worst case).

**Bench Test**

Partial flow restrictors were manufactured using two precision drill bits with diameters of 2.783mm (#33 US number drill bit) and 2.260mm (#43 US number drill bit) and mounted inside airway adaptors. These restrictors represent occlusion values of 75-54% and 80-14% of the measured internal expiratory limb circuit diameter. Internal diameter of expiratory limb
tubing was measured at 11.38mm (+/-0.01mm). For 100% occlusion an airway adaptor containing a short section (length 80mm internal diameter 11.5mm) of exposed silicone tubing was used. Tubing was clamped with large artery forceps to achieve 100% occlusion, this was also tested against water insertion (approx. 20ml H2O) into expiratory circuit with tight (10cm across) downward facing circuit loop, with the same results. The humidifier base was not powdered on. Humidifier canister was installed on the base and filled with water to the prescribed level. The patient circuit was connected to a test lung with known compliance of 0.5 mL/cm H2O (Draeger, Lubeck, Germany). The entire system was pressure checked and found to be leak free. All manufacturer recommended pre use checks and calibrations were carried out prior to selecting CPAP treatment mode set to deliver 6 cmH2O of patient airway pressure for each ventilator tested. If circuit flow needed to be set manually in CPAP mode it was set to 8 litres per minute (LPM).

Airway pressures and flows delivered to a neonatal test lung were measured at the patient ‘y’ connector by the pneumotach and pressure transducer (Florian respiratory monitor). Data for each occlusion value was collected separately for 2 minutes using data acquisition software (Spectra, Grove Medical) at a sampling frequency of 200Hz.

Ventilator alarm response and ventilator displayed mean airway pressure for each occlusion value was also recorded. Respiratory monitor volume calibration was performed with a syringe of known volume and pressure with a traceable reference electronic manometer (IMT Medical Model PF3000).

Draeger Australia was contacted following our initial Australian Therapeutic Goods (TGA) alert (Report No: 27809) with the observed VN500 occlusion behaviour with software version SO2.30. In response Draeger provided software (sw) revisions SO2.31 and SO2.41 with altered alarm message for the situation described. This software change also allows the user to adjust the maximum flow limit in non-invasive CPAP mode from a minimum of 6LPM to 30LPM (the default at system/ventilator initiation). The bench testing for VN500 was performed on original sw version SO2.30 with a maximum flow rate of 36LPM and sw version SO2.41 at user adjusted maximum flow rates of 10, 20 and 30 LPM.

This study was approved by the Western Sydney Local Health District Human Ethics and Scientific committee, approval number SAC2013/8/6-2 (3793).

Results

Table 1 details the measured test lung respiratory data and ventilator response (MAP and alarm messages) by brand at each level of graded expiratory limb occlusion. Table 2 details changes between VN500 software versions SO2.30 and SO2.41.

Alarm Response

There was a wide variation in alarm response from no alarm state or message at expiratory limb occlusions of 75% to 80% occluded to ventilator systems showing an alarm message indicating a tube occlusion or obstruction. A “hose kinked” message was displayed with a 100% occlusion on the Babylog 8000, a “circuit occlusion” message occurred with a 100% occlusion with the Carefusion Avea and a “High pressure/Tube occlusion” message occurred with the Acutronics Fabian at 100% tube occlusion. The Draeger VN500 sw SO2.41 gave alarm message of airway pressure “low” at 75% and 80% occlusion even though the mean airway pressure was not low (6.4 to 6.8 cmH2O at 75% occlusion and 7.2 to 7.4 cm H2O at 80% occlusion) (Table 1).
Pressure Response

There was also a wide variation in ventilator responses to levels of occlusion from either continuing to provide continuous distending airway pressure at the set pressure with 75%, 80% and 100% expiratory limb occlusion; to states where the ventilator cyclically pressurized then dumped in a manner similar to time cycled pressure ventilation (Fig 1) delivering large tidal volumes (range 9-7mL to 24-3mL) (Table 1). The rate of these cycles varied from slow (2–7 pressurizations per minute) to rates of 11 to 77 in the case of the two versions of the VN500 software (Table 2 and Fig 2). One system (the Heinen + Lowerstein Leoni plus ventilator) cycled from pressurization and dumping at all levels of partial and complete expiratory limb occlusion. The Draeger Babylog 8000 with software version 5.01 was noteworthy in not displaying the correct patient MAP with a measured patient value of 13cmH₂O compared to the ventilator displayed, 6-1 cmH₂O at 80% expiratory limb occlusion with no alarm. The peak
airway pressure varied from 17.9 cmH₂O to 64.6 cmH₂O regardless of the CPAP being set to 6 cmH₂O. Auto PEEP was not noted on any brand below 70% occlusion.

### Discussion

This study found that amongst the range of ventilators tested the delivery of non-invasive CPAP therapy during partial or total expiratory limb occlusion had the potential to expose the neonatal lung to pressures and volumes that are clinically unacceptable and dangerous.

The study is potentially limited by the fact that our bench test setup is not designed to simulate the clinical scenario where the infant may have been protected by mask leak where high pressures were delivered. Our bench test is designed as a ‘no leak’ system to examine the worst case scenario should the infant have no or minimal mouth leak as might occur with a chin strap and good nasal nares seal to prongs. [11,12] Our results may not be generalizable to other brands of mechanical ventilator or software revisions not tested.

Ventilators are designed with an inspiratory pressure regulator (IPR) in the expiratory limb exhalation block. This allows the regulation of pressures delivered to the patient at safe and repeatable levels selected by the clinician. Thirty two years ago Hall et al showed that partial or total occlusion between the patient ‘y’ and the exhalation block can alter or mitigate the IPR ability to function correctly. [1]

Carefusion Avea ventilator was the only ventilator tested, that behaved in a manner most clinicians’ would regard as appropriate. That is, to alarm with a message that would immediately suggest the appropriate corrective action and to continue to provide the set CPAP level, even with 100% occlusion.

<table>
<thead>
<tr>
<th>Software Ver No</th>
<th>Flow limit LPM</th>
<th>Occlusion %</th>
<th>Resp Rate/min</th>
<th>VTi mL</th>
<th>Insp sec</th>
<th>Exp sec</th>
<th>Peak cmH₂O</th>
<th>PEEP/CPAP cmH₂O</th>
<th>MAP cmH₂O</th>
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<td>75</td>
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<td></td>
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doi:10.1371/journal.pone.0154034.t002
Although rainout is minimised in the Fisher & Paykel RT265 circuit due to its unique design with an evaporative material (Evaqua™), it is not completely eliminated in the expiratory limb. Visualization of rainout content in the expiratory limb is difficult due to its opaque design. Product literature recommends six hourly inspection and removal of rainout if needed.[13]

There are two common situations where we have clinically seen patient events with excessive expiratory limb rainout causing complete occlusion with the Fisher & Paykel RT265 circuit.

The first was with accidental disconnection of expiratory limb heater during patient equipment movement. There is no alarm to indicate this with the Fisher & Paykel MR850 and can be undetected. In other types of humidifier circuits (particularly non Evaqua™ bubble nasal
CPAP) without heated expiratory limbs, accumulation of expiratory limb rainout and delivered pressure may be increased.[14] The second situation is placing the Fisher & Paykel RT265 circuit temperature probe inside a closed incubator with high set temperature.[5,8,9] In this situation with an incubator temperature of greater than 34°C the Fisher & Paykel humidifier drives excessive vapourised water producing rainout. The manufacturer recommends the use of an extension tube to site the circuit temperature probe outside the incubator.

The software alteration by Draeger (reflected in software revisions SO2-31 and SO2-41) in response allows the user to adjust the pre-set (and maximum) inflow rate of 30 LPM to a minimum of 6 LPM in the non-invasive CPAP delivery mode. The impact in our bench test only showed some improvement at 100% expiratory limb occlusion with the cyclical pressurization/airway pressure dumping rate dropped from 76 to 13 per minute (but with a distending inspiratory time increase from 0-3 to 5-2 seconds), the pressurization tidal volume decreased slightly from 21.9 mL to 21 mL and the peak pressurization pressure decreased from 47.9 cmH₂O to 35.5 cmH₂O. At 75% and 80% expiratory limb occlusions, the VN500 with sw SO2-41 gave ambiguous airway pressure message “airway pressure low” message after 50 seconds (75% occlusion at 10 and 20 LPM) and 10 seconds (80% occlusion at 30 LPM) with displayed and measured airways pressures not lower than set values. This poses the risk of the user reacting to the alarm message by increasing the set pressure value inappropriately. In recent years there has been growing trends to not intubate preterm infants and use non-invasive respiratory therapies as first line. Morley et al showed that with early non-invasive nasal CPAP compared to invasive ventilation therapy, fewer infants received oxygen at 28 days and they had fewer days of ventilation but with an increase in incidence of pneumothorax (9.1% CPAP, 3.1% Intubated).[15] In this report the type of delivery device was not noted. Makhoul et al reported increased risks of pneumothorax using nCPAP via Aldadin-1 device (Electromedical Equipment, Brighton, England).[16] In preterm animal models as few as 6 excessive inflation pressures initiate severe lung injury.[17] There is potential for lung damage with inadvertent sustained distending pressures and repetitive cycling during neonatal CPAP with partial or total expiratory limb occlusion as a contributing factor.[18] Interaction between ventilator software, mechanics and delivered patient therapy is complex.

The current international safety standards designed to guide manufacturers in minimum safety standards is outdated and does not provide sufficient patient protection particularly in view of newer sophisticated functions and the wide distribution of patient weight in neonatal patients (500gm–6kg). The ISO standards 10651-1-2004 entitled “Lung ventilators for medical use part 1: Requirements.”[10] simply states “the maximum limited pressure at the patient connection port which may occur during the intended use or under single fault condition shall not exceed 120% of the maximum adjustable pressure”. This guidance does not provide satisfactory limits; nor does it distinguish between invasive intubated ventilator support (via endotracheal tube); or non-invasive naso-pharyngeal pressure support.

**Conclusion**

Our results are concerning given that the majority of ventilators tested responded to partial or complete expiratory limb occlusion in potentially hazardous ways. We found that there is a potential to expose the neonatal lung to pressures and volumes that would be clinically unacceptable. Currently, the ISO standards do not guide manufacturers to prevent this potential event. One ventilator tested behaved in an appropriate manner which would suggest it is currently within scope for all manufacturers to implement in future neonatal ventilator design. Of greater concern is the apparent lack of improvement in safety of ventilator inspiratory pressure
regulator design over the past thirty years since this problem was first brought to light by Hall et al in 1983.

Supporting Information
S1 Dataset. (XLS)

Acknowledgments
We thank Prof Sally Tracy, Dr Jan Klimek and Dr Melissa Luig for their helpful comments and suggestions. We also acknowledge and thank the ventilator manufactures for loan devices to examine.

Author Contributions
Conceived and designed the experiments: MH AP MT. Performed the experiments: MH AP. Analyzed the data: MT MH. Contributed reagents/materials/analysis tools: MH AP. Wrote the paper: MH MT.

References


Distribution of monocyte subsets and polarization in preeclampsia and intrauterine fetal growth restriction

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Abstract

Aim: Monocytes are likely to play a significant role in the pathogenesis of preeclampsia (PE) and intrauterine fetal growth restriction (IUGR), given their role in homeostasis and tissue repair. Our aim was to study the gestational changes in monocytes in normal pregnancy and to determine whether monocyte subsets and phenotype are altered in pregnancy complications, such as PE and IUGR.

Methods: A prospective cross-sectional case–control study was conducted. Pregnant women between 24 and 40 weeks of gestation (n = 54) were recruited and classified into four clinical groups of normal pregnancy, PE, IUGR and PE + IUGR. The maternal monocyte subsets classical, intermediate and nonclassical were compared for each clinical group. Monocyte polarization towards M1 (inflammatory) and M2 (repair) phenotypes was assessed by surface expression of CD86 and CD163 ratio, using flow cytometry.

Results: The classical monocytes were reduced and intermediate monocyte elevated compared to normal pregnancy in PE, IUGR and PE + IUGR in gestations <37 weeks and IUGR in 26–40 weeks. CD163 expression was increased and CD86/CD163 ratio decreased in IUGR compared to normal pregnancy for all subsets. Non-classical monocyte counts and CD163 expression increased with advancing gestation in normal pregnancy.

Conclusion: These results show for the first time, a shift towards increased intermediate maternal monocyte subtype in IUGR and in preterm PE as well as skewing of maternal peripheral monocytes (all subsets) towards M2 phenotype in pregnancies complicated by IUGR.

Key words: flow cytometry, intrauterine fetal growth restriction, M1/M2, monocyte subsets, monocytes, preeclampsia.

Introduction

Pregnancy is associated with a major adaptation of the maternal immune system to accommodate the semi-allogeneic fetus.¹,² Indeed, it has been proposed that pregnancy results in an activation of maternal monocytes and granulocytes suggesting an upregulation of the innate immune system.³

The study of immune cells in the placental bed has shown that while T cells and dendritic cells are present, uterine natural killer cells and macrophages are the most prominent in first and second trimester. The latter is known to decrease in the third trimester. Macrophages play a role in angiogenesis, trophoblast invasion, spiral artery remodeling, inflammation as well as resolution of inflammation.⁴ The decidual macrophages mainly show an M2 phenotype.⁵ While macrophages can arise from progenitors of yolk sac, in the decidua they appear to be mainly derived from blood monocytes.⁶

Received: March 31 2018.
Accepted: July 4 2018.
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It is now well established that monocytes are activated in pregnancy (Fass 2016). Most of the studies on monocytes in pregnancy have been in third trimester with only one study documenting phenotypical activation of monocytes across the gestation. The mechanism of monocyte activation and maturation in pregnancy has not been elucidated, although the placenta is likely to play an important role. Peripheral monocytes circulating through the placenta may come into contact with syncytiotrophoblast. Circulating factors released from the placenta such as cytokines, anti-angiogenic factors, microparticles, exosomes may also activate monocytes.

Pregnancy complications, such as preeclampsia and intrauterine fetal growth restriction (IUGR) are likely to result in further alterations to the immune system. A recent review summarized the current knowledge on maternal monocytes in preeclampsia and concluded that monocytes play a role in normal pregnancy and preeclampsia. An increase in peripheral blood monocytes and an altered activation status of these monocytes in preeclampsia as compared to healthy pregnancy has been suggested. However, monocytes are heterogeneous, and the role of the different populations in pregnancy is less clear. Monocytes are classified into three subsets on the basis of the expression of CD14 and CD16: classical (CD14+CD16−), intermediate (CD14++CD16+) and nonclassical (CD14+CD16++). Though there is a developmental relationship between these cells, changing from classical to intermediate to nonclassical, specific functions are considered the domain of specific subsets, in particular, the transitional intermediate population is considered inflammatory. It is, however, a minor population, making up only about 5% of monocytes. Classical monocytes are the major subset comprising approximately 85% of total monocytes.

A study into the characterization of monocyte subsets in preeclampsia found that the percentage of combined nonclassical/intermediate monocytes is higher during pregnancy in humans and in rats as compared to nonpregnant controls and even higher in preeclampsia. Monocyte subsets in isolated intrauterine fetal growth restriction are still to be explored. In addition to the distribution of subsets, the monocyte–macrophage system has also been shown to exist in two phenotypic variations: classical/pro-inflammatory (M1) and alternative/anti-inflammatory (M2). These functional phenotypes are thought to be influenced by physiological conditions of the body such as pregnancy, as well as pathological conditions involving allergy, inflammation, cancer and tissue repair such as in atherosclerosis. Monocyte–macrophage polarization and any imbalance are also thought to play an important role in diabetes and cardiovascular risk associated with pre-diabetes.

Monocytes from preeclamptic women have been found to express significantly higher levels of the M1 markers TLR4 and CD64, while the expression of the M2 markers CD163 and CD206 were significantly lower compared with normal term pregnant women. It was concluded that monocytes from women with PE showing M1 polarization are classically activated and produce higher levels of pro-inflammatory cytokines. The systemic inflammatory environment in preeclampsia may be responsible for this M1 skewing. Whether monocytes also adopt an inflammatory M1 phenotype in IUGR is not known, nor whether this differs for the different subsets in PE or IUGR. Therefore, here we characterized monocytes in pregnancy complications preeclampsia and IUGR, addressing changes in both monocyte subsets and polarization. We also assessed their characteristics by increasing gestation in normal pregnancy to evaluate gestation-related changes.

Methods

Study population
A prospective cross-sectional case–control study was conducted. Pregnant women between 24 and 40 weeks of gestation, as defined by first trimester ultrasound (n = 54), delivering at Westmead Hospital, Sydney Australia, during the period 2013–2014 were recruited and classified into four clinical groups of normal pregnancy, PE, IUGR and PE + IUGR. This study was conducted with the approval of the Western Sydney Local Health District Human Research Ethics Committee. Written consent was obtained from all participants in the study. The normal pregnancy controls were gestationally matched to the study groups. For each sample from a pathological pregnancy at gestational age between 26 and 40 weeks, at least two maternal venous samples from normal pregnancies were collected as controls in two-week gestational age groups 26–27, 28–29, 30–31, 32–33, 34–35, 36–37 and 38–40 weeks. All the term normal pregnancy samples were collected from elective caesarean deliveries at or after 37 weeks.

All patients classified as PE in this study satisfied the International Society for the Study of © 2018 Japan Society of Obstetrics and Gynecology
Monocytes in pregnancy complications

Hypertension in Pregnancy 2014 criteria for pre-eclampsia. IUGR was defined as birth weight less than 10th centile with elevated umbilical artery Doppler systolic/diastolic ratio or resistance index >95th centile for gestation. All patients with PE, PE + IUGR or IUGR underwent antenatal ultrasound examination after 24 weeks of gestation and within 7 days of delivery. Ultrasound assessments were performed using General Electric (GE) Voluson E8 ultrasound equipment. Patients with pre-existing hypertension, renal disease, pre-existing diabetes, gestational diabetes, multiple pregnancies, known chromosomal abnormalities and infectious causes of intrauterine fetal growth restriction were excluded from the study.

Flow cytometry
Maternal venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes, within 7 days prior to labor or caesarean delivery to exclude any immunological changes associated with the delivery process. Before cell staining for flow cytometry, an aliquot (500 μL) of the blood samples was used to establish total blood leukocyte numbers. Leukocytes were counted using a microcell counter (model Sysmex X1-1800c). Whole blood sample flow cytometry staining was performed to assess monocyte subset markers CD14 (BD 560349 V450), CD16 (Ab 140477) for gating and expression of polarization markers: CD86 and CD163 (BD 555658 PE and BD 556018 PE). Incubation with cell surface antibodies was followed by Optilyse C for lysing red blood cells and fixation. A three-color protocol was used for data acquisition using a flow cytometer FACS CantoII. Data analysis involved the identification of the three main monocyte populations classical CD14++CD16−, intermediate CD14++CD16+ and nonclassical CD14+CD16++ across the different clinical groups. The gating technique used in this study (Figs 1–2) for monocyte subsets paralleled those previously published. Forward and side scatter as well as surface expression of CD14 and CD16 were used to identify the monocyte populations with representative monocyte subset distributions. The proportion of monocytes in each subset was recorded.

Markers of monocyte polarization
Monocyte surface expression of CD86 as an M1 marker and CD163 as an M2 marker were investigated. The degree of expression of CD86 and CD163 was determined using a positive data set for each antibody, identified by using a matched concentration of the recommended isotype control for fluorochrome color (BD555749 Mouse IgG1 kappa) and volume and overlaying its image on the histogram (Figures S1, S2, Supporting Information). The median fluorescence intensity (MFI) was calculated for each marker in each clinical group. Median fluorescence intensity ratio of CD86/CD163 was evaluated as an indicator of the degree of monocyte M1:M2 polarization to an inflammatory versus healing phenotype and correlated with the clinical groups and monocyte subsets.

Statistical analysis
The statistical software packages SPSS for windows Version 21 and SPLUS version 8 were used. Analysis of variance for multiple comparisons was used to assess the association between tested variables. Kruskal Wallis nonparametric analysis of variance was used to test for homogeneity across the four clinical groups for each of the variables percentage of monocytes, percentage of monocyte subsets and median fluorescence intensity of CD86 and CD163. Where heterogeneity was identified, post hoc Mann–Whitney tests were used for pairwise comparisons between normal pregnancy and each of the clinical groups as well as between each of the pathological groups. The samples were then analyzed separately for all gestations, preterm <37 weeks, term >37 weeks as well as for combined intermediate and nonclassical CD16+ inflammatory monocytes.

Spearman nonparametric correlations were used for assessment of differential distribution of monocyte subtypes and inflammatory markers with increasing gestation in third trimester of pregnancy as tested in 24 normal pregnancies. All demographic values are presented as mean ± standard deviation (SD) of the mean. All results are presented as median ± interquartile centiles or as percentages. Two-tailed tests with a 5% significance level were used throughout.

Results
Clinical characteristics of the study population
Results are presented for 54 maternal samples from four clinical groups as listed below, ranging from 26 to 40 weeks of gestation. Maternal and fetal demographic data and clinical characteristics of the study population are shown in Table 1. There were no statistically significant differences noted between the pathological groups in gestational age at sample collection. Gestational age and weight at delivery were lower in study groups compared to controls (Table 1).

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Maternal circulatory blood monocyte subsets

The results for monocyte subsets as a percentage of total monocytes (Table S1) are presented for gestations 26–40 weeks (Fig. 3a), 26–36 weeks and 6 days preterm (Fig. 3b) and 37–40 weeks term (Fig. 3c). For all the study pregnancies ranging from 26 to 40 weeks, the percentage of classical monocytes was lower in the IUGR group compared to normal pregnancy (54.7% vs 72.4%, $P = 0.015$). The percentage of intermediate monocytes was increased in the IUGR group as compared to normal pregnancy (38.7% vs 22.5%, $P = 0.032$). There were no significant differences between the groups in the percentage of

Maternal leukocyte and monocyte counts in normal and pathological pregnancies

No differences were observed in the maternal peripheral leukocyte count and the total monocyte percentage by flow cytometry between normal pregnancy, PE, IUGR and PE + IUGR (Table S1).

There were more primiparous patients in the pathological groups compared to normal control. In the normal pregnancy cohort, the monocyte percentages in primiparous were not significantly different to the multiparas.
nonclassical monocytes. The subset analysis for pre-term pregnancies <37 weeks demonstrated significantly reduced classical monocytes in all three pathological groups: PE ($P = 0.042$), IUGR ($P = 0.003$) and PE + IUGR ($P = 0.021$) and increased intermediate monocytes in IUGR ($P = 0.003$) and PE + IUGR ($P = 0.03$). There were no differences demonstrable in the subset distribution for any clinical groups >37 weeks and between pathological groups.

The subset distribution into classical and combined intermediate and nonclassical inflammatory CD16+ monocytes was also analyzed separately. The results showed an elevated percentage of inflammatory subsets when compared to normal pregnancy in IUGR.

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(P = 0.015) for all gestations (Fig. 4a) and in all pathological groups PE (P = 0.042), IUGR (P = 0.003) and PE + IUGR (P = 0.021) for preterm gestations <37 weeks (Fig. 4b). There were no differences between clinical groups in inflammatory subsets in pregnancies >37 weeks (Fig. 4c).

**Monocyte polarization by clinical groups and subsets**

Monocyte surface expression of CD86 and CD163 and their ratio CD86/CD163 are presented in Table 2 and Figure 5. There was no demonstrable difference between the clinical groups in the MFI and percentage of total monocytes expressing CD86, with 98–99% of monocytes in each clinical group showing CD86 as a surface marker. The analysis of the MFI of monocyte CD86 expression according to monocyte subset showed a statistically significant decrease in intermediate monocyte CD86 expression in PE compared to normal pregnancy as well as an increase in nonclassical monocyte CD86 expression in PE + IUGR compared to normal pregnancy (Table 2).

Significantly more monocytes in the IUGR and PE + IUGR were noted to express CD163 (Table 2). The MFI of CD163 was also increased in IUGR and PE + IUGR compared to normal pregnancy, to varying degrees across the monocyte subsets. The total monocyte CD86/CD163 ratio was decreased in IUGR (Fig. 5). This difference was seen consistently across all the monocyte subsets, but more so in the intermediate monocyte subset. The inflammatory subsets intermediate and nonclassical monocytes also showed a lower CD86/CD163 ratio in IUGR + PE compared to PE only.

**Correlations between gestational age and distribution of monocyte subtypes and inflammatory markers in the third trimester of normal pregnancy**

There was a statistically significant correlation towards an increased percentage of nonclassical monocytes (P = 0.044) and increased monocyte expression of CD163 (P = 0.034) with gestation in normal pregnancy. No differences were noted in classical and intermediate monocyte percentages (Fig. 6, Table S2).

The ratio of CD86/CD163 MFI as a marker of M1/M2 polarization within the maternal circulation was relatively stable across gestations 26–40 weeks in normal pregnancy, with no demonstrable gestation related variations (Figure S3, Table S2).

**Discussion**

The current knowledge on human monocyte heterogeneity and their functional implications in pregnancy is incomplete. Though pro-inflammatory monocyte function and changes in subset distribution in preeclampsia have been described in a handful of studies, monocyte subset phenotypes and functional changes in isolated IUGR have not been reported.

The differential distributions of monocyte subsets in the maternal peripheral blood in normal pregnancies, PE, IUGR and PE + IUGR were investigated. This is the first study to examine monocyte subsets in normal pregnancy, PE, IUGR and PE + IUGR.
concurrently. We have shown a shift towards increased intermediate maternal monocyte subset in IUGR and PE + IUGR, increase in total inflammatory subsets (intermediate and nonclassical) in PE and IUGR, particularly in preterm gestations as well as skewing of maternal peripheral monocytes (all subsets) towards an M2-like phenotype in pregnancies complicated by IUGR.

Most studies on monocyte subsets have focused on the combined nonclassical/intermediate inflammatory monocytes. The present study used the recommended classification of monocytes into classical, intermediate and nonclassical subsets[13] as well as looking at the previously described combined inflammatory subsets. To test whether monocyte skewing towards an M1 or M2 phenotypes occurs in PE and IUGR, the study

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Figure 3 Graphical representation of the composite of monocyte subsets classical, intermediate and nonclassical across the four clinical groups. (a) All study samples gestation from 26 to 40 weeks. (b) Separate analysis presented for gestational age <37 weeks. (c) Samples >37 weeks at the time of sample collection. The sample numbers for 26–36 and 37–40 weeks are given in Table 1. There were no samples available for PE + IUGR >37 weeks *Significantly different from normal pregnancy, \( P < 0.05. \)
examined the expression of CD86 (M1 marker) and CD163 (M2 marker) on peripheral whole blood monocytes of the mother.

The study did not demonstrate a difference in the total white cell count or the percentage of monocytes with increased gestation in third trimester or across clinical groups. Previously published studies have shown an elevated percentage of leukocytes and monocytes in healthy pregnant women as compared to nonpregnant women and an even further elevation in preeclamptic women compared to normal pregnancy.17 The results in this study are, however, consistent with other published studies showing a stable proportion of monocytes throughout gestation.3 The variation in results may be due to most of the samples being in third trimester rather than across trimesters, smaller patient numbers and other factors associated with the pregnant state, which are not clinically evident such as subclinical infection. Screening for subclinical infection in the mother was not carried out as part of the study. As no differences were observed in the maternal peripheral leukocyte count or the total monocyte percentage between clinical groups, it would be reasonable to assume that a significant infection was unlikely to have contributed to any variation in monocyte

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distribution. There is no published literature on parity and their effects on maternal monocytes. While we could not demonstrate an effect of parity on the monocyte percentages in the normal pregnancy cohort, the effect on the difference in parity between normal and pathological groups is uncertain.

Comparison of monocyte subset distribution between clinical groups showed a statistically significant increase in intermediate monocytes and a decrease in classical monocytes in IUGR pregnancies across all gestational ages and also associated PE in preterm pregnancies <37 weeks. The percentage of nonclassical monocytes was not noted to be significantly different between the pathological groups. This is the first description of monocyte subsets by gestation in preeclampsia and IUGR. The fact that there were significant subset changes in the pathological groups compared to normal preterm gestations suggest that the monocyte population is different in PE and IUGR. The similarity of subset distribution between normal and pathological groups at term parallels that of angiogenic factors in these conditions and is consistent with the hypothesis that the maternal pathological changes in PE and IUGR may be an acceleration of the gestational-related physiological changes that occur in normal pregnancy with advanced and term gestation.

These findings are similar to those of Melgert et al. who showed that the percentage of combined

| Table 2 Maternal monocyte expression of CD86 and CD163 as markers of monocyte polarization |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
|                                             | Normal PE only | IUGR only | PE + IUGR |
| Percentage of monocytes expressing CD86    | 99.1 (98.9, 99.4) | 99.0 (98.7, 99.3) | 99.3 (98.2, 99.5) | 98.8 (98.6, 99.4) |
| Total monocytes CD86 MFI                   | 2432.5 (2069.5, 3269.5) | 2231.0 (2019.0, 2387.0) | 3153.5 (1891.0, 3812.0) | 2568.0 (1778.0, 2987.0) |
| Classical monocytes CD86 MFI               | 2628.0 (2315.0, 3309.0) | 2364.0 (2143.0, 2585.0) | 3338.0 (2096.0, 3916.0) | 2778.0 (1973.0, 3086.0) |
| Intermediate monocytes CD86 MFI            | 3470.0 (2822.5, 4743.5) | 2722.0* (2449.0, 3754.0) | 3759.5 (2640.5, 4588.5) | 3157.0 (2629.0, 3606.0) |
| Nonclassical monocytes CD86 MFI            | 5350.5 (4411.0, 6250.5) | 5073.0 (3959.0, 5904.0) | 5353.5 (2159.0, 6492.0) | 3828.0* (1737.0, 4882.0) |
| Percentage of monocytes expressing CD163   | 63.5 (56.1, 70.2) | 65.6 (62.1, 73.3) | 78.0* (65.0, 84.7) | 77.1* (64.2, 96.5) |
| Total monocytes CD163 MFI                  | 310.0 (225.5, 370.0) | 377.0 (247.0, 453.0) | 506.0 (241.5, 686.0) | 866.0* (452.0, 2717.0) |
| Classical monocytes CD163 MFI              | 427.0 (343.5, 521.0) | 447.0 (322.0, 564.0) | 662.0* (420.5, 770.0) | 679.0**,*** (579.0, 3056.0) |
| Intermediate monocytes CD163 MFI           | 480.5 (371.8641.3) | 438* (365564) | 633* (325807) | 781**,*** (463, 3231) |
| Nonclassical monocytes CD163 MFI           | 21.5 (3.0, 58.0) | 0 * (0, 0) | 50.5**,*** (0, 123.5) | 220.0**,*** (63.0, 282.0) |
| Total monocytes: CD86 MFI/CD163 MFI        | 3.41 (3.14, 3.86) | 3.05 (2.92, 3.20) | 3.69 (3.18, 4.10) | 1.80**,*** (0.96, 3.15) |
| Classical monocytes: CD86 MFI/CD163 MFI    | 4.44 (4.12, 5.66) | 4.09 (3.23, 4.63) | 4.44 (3.79, 4.83) | 2.49**,*** (0.95, 3.75) |
| Intermediate monocytes: CD86 MFI/CD163 MFI | 5.13 (4.12, 6.64) | 4.93 (3.29, 5.01) | 4.80 (4.14, 5.90) | 2.62**,*** (1.00, 3.78) |
| Nonclassical monocytes: CD86 MFI/CD163 MFI | 20.43 (16.70, 24.28) | 17.74 (15.58, 22.71) | 15.16* (9.64, 20.29) | 12.57**,*** (3.70, 15.52) |

Results are presented as median ± interquartile range for each continuous variable. P < 0.05. IUGR, intrauterine fetal growth restriction; MFI, mean fluorescence intensity; PE, preeclampsia; *Significantly different from normal pregnancy; **Significantly different from PE. ***Significantly different from IUGR.
atherosclerosis and fibrotic plaque development where these monocytes are thought to contribute to both inflammation and fibrosis. The intermediate monocytes may also play a similar inflammatory and fibrotic role in IUGR where villous thrombosis, loss of vascularity and fibrosis of infarcted areas play a significant role in the pathology of the placenta. The modulation of monocyte subset recruitment into tissues and their subsequent differentiation have been suggested as potential approaches for therapeutic interventions in human liver fibrosis. Parallel interventions in IUGR may be a therapeutic approach to

nonclassical/intermediate monocytes is higher during pregnancy in humans and in rats as compared to non-pregnant controls, being even higher in preeclampsia. A shift towards higher numbers of combined nonclassical/intermediate monocytes, in particular an increase in the intermediate subset has been associated with several inflammatory diseases including sepsis, rheumatoid arthritis, HIV infection, atherosclerosis, atopic dermatitis and asthma. An expansion of circulatory CD16+ monocytes (intermediate + nonclassical) has been demonstrated in chronic liver disease and fibrosis as well as

Figure 5 CD86/CD163 expression by clinical group and monocyte subset. *Significantly different from normal pregnancy, \( P < 0.05 \).
reduce the inflammation and damage to placental tissue in pregnancies complicated by IUGR.

We have also investigated gestational age-dependent variation in monocyte subsets. While there was a trend towards increased intermediate monocyte percentage with higher gestation, statistical significance was not achieved. The significant increase in nonclassical monocyte population percentage with gestation is a new finding described in this study and may reflect increasing injury and repair in the later term placenta. This finding is consistent with a study using an adenosine triphosphate (ATP) infusion to create a rat model of preeclampsia where the authors demonstrated that the percentage of nonclassical monocytes in pregnant rats increased even further with ATP infusion. This change was not seen in non-pregnant rats. They suggested that nonclassical monocytes are specifically altered in pregnancy and may play a role in the pathophysiology of preeclampsia. The current study also investigated the skewing of maternal monocytes towards an M1 or M2-like phenotype in normal pregnancy, preeclampsia and intrauterine fetal growth restriction. We demonstrated an increased number of monocytes expressing CD163 as well as an augmentation in the CD163 MFI with increasing gestational age in normal pregnancy. This increase in CD163 may represent a response to increasing maturational changes, damage and repair in the term placenta. This study is the first description of increased M2 polarization (as reflected by a decreased CD86/CD163 ratio) in IUGR and PE + IUGR. The findings are consistent with other studies of organ damage demonstrating the presence of predominantly M2 monocytes in severely burnt patients and may reflect the presence of tissue damage and an overactive repair response. The M2 skewing is also consistent with the Th-2 immune adaptation of pregnancy.

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Figure 6 Correlation between gestational age and monocytes for clinical groups normal pregnancy. (a) Monocytes as a percentage of total white cells. (b) Classical monocyte percentage. (c) Intermediate monocyte percentage. (d) Nonclassical monocyte percentage. \( r \), Spearman coefficient, \( P \), statistically significant change with gestation.
may also promote excessive tissue remodeling and fibrosis.\textsuperscript{36} The stable CD86/CD163 ratio with increased gestation in normal pregnancy is consistent with the observation that both CD86 and CD163 expression increased with gestation. This may represent a CD163/M2 response to an increasing M1 inflammatory change in normal pregnancy.

Recently, it has been suggested that classical monocytes preferentially differentiate into M1 macrophages in the decidua while nonclassical types differentiate into the M2 macrophages which are the more prominent type in the placenta.\textsuperscript{37} Further studies are therefore needed to evaluate the role of the different monocyte subsets in populating the macrophages in the placental bed.

Anti-inflammatory M2 but not pro-inflammatory M1 macrophages promote angiogenesis \textit{in vivo}.\textsuperscript{38} FGF signaling for M2a- and PiGF signaling for M2c-induced angiogenesis have been proposed as possible mechanisms. The increased in M2 profile in IUGR may represent a monocyte response to loss of vascularization in IUGR and a rebuilding effort. Further studies into the M1/M2 phenotypes of monocytes and macrophages in pregnancy complications of preeclampsia and IUGR may help to elucidate the mechanisms underlying the placental changes associated with these conditions and also possibly the difference between preeclampsia and IUGR.

Differences in the pathogenesis of early onset and late onset preeclampsia may have influenced the results of this clinical group.\textsuperscript{39} The study included mainly early onset preeclampsia although the patient numbers were inadequate to assess any differences between early and late onset preeclampsia. The monocyte functions in early versus late preeclampsia/IUGR may be worthwhile in investigating the differences in pathogenesis of the two conditions. It is now well established that maternal preeclampsia is associated with a long-term increased cardiovascular risk.\textsuperscript{40,41} The skewing of circulating monocytes towards inflammatory or healing phenotypes may play a determining role in the monocyte/macrophage function and predisposition to preeclampsia in pregnancy and long-term cardiovascular risk. Further studies into the monocyte/macrophage function may help to elucidate the known cardiovascular risk associated with preeclampsia in pregnancy.

Human monocytes are currently defined and classified by the extent of their cell surface expression of CD14 and CD16, with associated differences in function and phenotype related to the intensity of expression of these markers. With increasing interest in the function and behavior of monocytes, it is important to have an understanding of how differing strategies of analysis can affect results and how different protocols and population backgrounds can affect this highly morphogenic cell type.\textsuperscript{42} It is important to take into consideration that blood monocytes consist of a continuous population of cells, within which the dominant phenotype may vary depending on the background of the study population.

The possible development of placental disease with advancing gestation also leads to the possibility that a normal preterm pregnancy may result in a significant pregnancy complication later in gestation. Our study was strengthened by the use of umbilical artery Doppler to define growth restriction of placental origin. The variability in normal pregnancy and the difficulty in determining the disease status of the placenta by external clinical parameters led to variability in allocation of patient groups. These factors lead to difficulties in performing and interpreting research into monocytes in pregnancy and its complications. Smaller patient numbers and the variability in gestational ages within the clinical groups may have contributed to these results and further studies on larger patient groups are recommended to confirm any described trends in monocyte subset distribution.

It is possible that circulating monocyte CD163 expression may be useful as a biomarker for significant placental damage and need for repair. Correlation studies with CD163 expression and clinical outcomes such as IUGR, hypoxic damage, low Apgar score and stillbirth may be worthwhile to assess this as a biomarker.

Acknowledgments

This work was supported by Ella Macknight Research Scholarship, Royal Australian and New Zealand College of Obstetrics and Gynecology (RANZCOG) Research Foundation. We would like to acknowledge Karen Byth, senior medical statistician for statistical analysis of data.

Disclosure

The authors declare no conflict of interests.
Author contributions

T. I. A. and V. W. L. conceived and designed the study. T. I. A. carried out the experiments and drafted the manuscript. H. M., H. W. and N. F. participated in designing the study, optimization steps. X. M. W. performed the flow cytometry analysis. All authors critically revised the draft and approved the final manuscript.

References


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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:
Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial

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**IMPORTANCE** Standard treatment for endometrial cancer involves removal of the uterus, tubes, ovaries, and lymph nodes. Few randomized trials have compared disease-free survival outcomes for surgical approaches.

**OBJECTIVE** To investigate whether total laparoscopic hysterectomy (TLH) is equivalent to total abdominal hysterectomy (TAH) in women with treatment-naive endometrial cancer.

**DESIGN, SETTING, AND PARTICIPANTS** The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial was a multinational, randomized equivalence trial conducted between October 7, 2005, and June 30, 2010, in which 27 surgeons from 20 tertiary gynecological cancer centers in Australia, New Zealand, and Hong Kong randomized 760 women with stage I endometrioid endometrial cancer to either TLH or TAH. Follow-up ended on March 3, 2016.

**INTERVENTIONS** Patients were randomly assigned to undergo TAH (n = 353) or TLH (n = 407).

**MAIN OUTCOMES AND MEASURES** The primary outcome was disease-free survival, which was measured as the interval between surgery and the date of first recurrence, including disease progression or the development of a new primary cancer or death assessed at 4.5 years after randomization. The prespecified equivalence margin was 7% or less. Secondary outcomes included recurrence of endometrial cancer and overall survival.

**RESULTS** Patients were followed up for a median of 4.5 years. Of 760 patients who were randomized (mean age, 63 years), 679 (89%) completed the trial. At 4.5 years of follow-up, disease-free survival was 81.3% in the TAH group and 81.6% in the TLH group. The disease-free survival rate difference was 0.3% (favoring TLH; 95% CI, −5.5% to 6.1%; \( P = .007 \)), meeting criteria for equivalence. There was no statistically significant between-group difference in recurrence of endometrial cancer (28/353 in TAH group [7.9%] vs 33/407 in TLH group [8.1%]; risk difference, 0.2% [95% CI, −3.7% to 4.0%]; \( P = .93 \)) or in overall survival (24/353 in TAH group [6.8%] vs 30/407 in TLH group [7.4%]; risk difference, 0.6% [95% CI, −3.0% to 4.2%]; \( P = .76 \)).

**CONCLUSIONS AND RELEVANCE** Among women with stage I endometrial cancer, the use of total abdominal hysterectomy compared with total laparoscopic hysterectomy resulted in equivalent disease-free survival at 4.5 years and no difference in overall survival. These findings support the use of laparoscopic hysterectomy for women with stage I endometrial cancer.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00096408; Australian New Zealand Clinical Trials Registry: CRN12606000261516


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Endometrial cancer is the most common gynecological cancer in developed countries. Obese or nulliparous women, and those with Lynch syndrome have a particularly high risk for the disease. Endometrial cancer is usually treated surgically by removing the uterus and performing a bilateral salpingo-oophorectomy. It is not known how beneficial surgical staging is for early-stage disease, although postoperative treatment is tailored to histopathological risk factors and disease stage.

Laparoscopic hysterectomy is associated with less morbidity and results in better recovery than open operations, but it is not known if the operation results in equivalent survival outcomes. Laparoscopic hysterectomy could also pose greater risks of complications in obese patients, have a higher risk of intraoperative injuries, or result in post-site metastases. Three large randomized trials suggested that total laparoscopic hysterectomy may be equally safe as total abdominal hysterectomy and may have short-term advantages, including less pain, better quality of life, decreased risk of surgical adverse events, and economic savings.

These short-term advantages have supported the global trend to adopt laparoscopic hysterectomy despite little data to confirm its efficacy in regard to disease-free and overall survival. A meta-analysis included only 3 small trials (each had <160 participants) and 1 large trial (N = 2616) formally evaluating survival end points. The included trials were heterogeneous with respect to their laparoscopic hysterectomy technique; just 2 of the trials focused on patients with stage I endometrial cancer, and only 1 of the trials used total laparoscopic hysterectomy, whereas the other 3 trials allowed laparoscopic-assisted vaginal hysterectomy.

The primary hypothesis of the present trial was that total laparoscopic hysterectomy is associated with equivalent disease-free survival compared with the standard treatment of total abdominal hysterectomy for women with apparent stage I endometrial cancer.

**Methods**

**Study Design and Procedures**

The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial was a multinational, phase 3, randomized equivalence trial. Women with apparent stage I endometrial cancer were randomized to undergo total abdominal hysterectomy (with or without lymphadenectomy) or total laparoscopic hysterectomy (with or without lymphadenectomy). Patients were recruited between October 7, 2005, and June 30, 2010, while receiving treatment at 1 of 20 participating tertiary gynecological cancer centers in Australia, New Zealand, and Hong Kong.

Recruiting centers were eligible to participate after site-specific ethics approval was obtained. The centers differed greatly in size and commonly recruited between 0 and 10 patients per month. Ethics approval was obtained from each hospital’s human research and ethics committees. Written informed consent was obtained from patients prior to randomization.

The trial protocol and statistical analysis plan appear in Supplement 1. The design and methods of the LACE trial were described in 2006. The rationale for an equivalence trial was described in detail. In brief, the trial enrolled patients with histologically confirmed endometrioid adenocarcinoma of the endometrium with any grade from the International Federation of Gynecology and Obstetrics (FIGO) staging system and without evidence of extrauterine disease determined by imaging (computed tomography or magnetic resonance imaging of the abdomen and pelvis and chest radiograph or chest computed tomography). Women were ineligible if they had a histological cell type other than endometrioid on curettage, clinically advanced disease (stages II-IV using FIGO 2009 criteria or bulky lymph nodes on imaging), or uterine size greater than 10 weeks’ gestation.

Patient-related assessments were collected prior to surgery, at week 1, and at months 1, 3, and 6 after surgery. Patients were followed up at 12 months, and then annually for survival outcomes. Patients without events were censored on March 3, 2016, or on the date of last contact for those lost to follow-up. Investigators verified the surgery performed and the histopathological diagnosis, and collected patient baseline eligibility documents. The presence of recurrent disease was histologically confirmed whenever feasible.

There were 2 phases of the study design. The first phase focused on quality of life. In the event that the study would not be able to proceed to the clinical end point of disease-free survival, an allocation ratio of 2 patients to total laparoscopic hysterectomy and 1 patient to total abdominal hysterectomy for the first 150 patients was used to gain information on the quality-of-life effects of the intervention. Thereafter, to evaluate clinical outcomes in the second phase, a ratio of 1:0.76 was used to rebalance the treatment allocation using mixed-permuted block sizes of 3 and 6 via computer-generated random-number sequences. However, this did not prove to be practical and the allocation ratio was changed to 1:1. Randomization was performed centrally (School of Population Health, University of Queensland) to ensure allocation concealment.
Due to the 2:1 allocation for the first 150 patients, it was expected that about 55 more patients would be allocated to total laparoscopic hysterectomy vs total abdominal hysterectomy by the end of the trial. Randomization was stratified by treatment center, grade of differentiation, and history of cancer (during the second phase only). Blinding of treatment allocation was impractical in this setting (details about allocation and stratification appear in Supplement 1).

The surgical procedures and their steps have been described in detail. Prior to surgery, all patients had to have a complete physical examination, imaging (as described above), an electrocardiogram, and routine blood tests (clinical chemistry and hematology). For total laparoscopic hysterectomy, an anatomically curved silicone tube with a proximal airtight cap (McCartney Tube, OR Company), which prevents loss of pneumoperitoneum, was used that enables instrument access and facilitates the safe removal of specimens transvaginally. Total abdominal hysterectomy was performed through a vertical midline or lower transverse incision.

Surgeons were required to perform pelvic (with or without para-aortic) lymph-node dissection as part of the treatment in both groups. Lymph-node dissections were performed unless (1) the patient was morbidly obese, (2) the patient had grade 1 (well differentiated) or grade 2 (moderately differentiated) without myometrial invasion or had a depth of invasion of less than the inner half of the myometrium based on the frozen section, (3) the patient was medically unfit for lymph-node dissection, or (4) institutional guidelines advised against the lymphadenectomy. Morcellation was not allowed.

Histopathological findings were used to determine the need for adjuvant treatment according to local institutional clinical practice guidelines, and typically were discussed in multidisciplinary meetings. The delivery and management of radiation therapy or chemotherapy was performed according to local institutional clinical practice guidelines. Data on dosimetry or chemotherapy dosing were recorded.

All adverse events encountered during the clinical study were documented. The intensity of adverse events was graded using version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events. The incidence and risk factors for adverse events were previously reported.

For quality assurance, a rigorous accreditation process was followed as previously described. Surgeons were required to (1) be certified gynecological oncologists proficient in total abdominal hysterectomy or under the direct supervision of a certified gynecological oncologist in theater; (2) provide evidence of a minimal number of 20 supervised and documented total laparoscopic hysterectomies performed while serving as the main surgeon; and (3) have submitted an unedited video of a total laparoscopic hysterectomy for assessment by the trial credential committee. In addition, prospective surgeons had to perform a live total laparoscopic hysterectomy for treatment of endometrial cancer evaluated by 1 of the accredited surgeons from the LACE trial.

In addition to the above requirements, surgeons had to be (1) able to secure uterine vessels at the level of the uterus laparoscopically; (2) able to perform a laparoscopic retroperitoneal node dissection (pelvic); and (3) able to suture the vaginal vault laparoscopically. These surgical steps were checked during the accreditation process for every trial surgeon. Given that all participating surgeons were certified gynecological oncologists and there are variations in how these tasks can be achieved, no further standardization of surgical technique was attempted.

Patients were seen for follow-up every 3 months after surgery for the first 2 years and then every 6 months until they reached postsurgical year 5. Clinical assessments including gynecological examinations were performed at each visit. Routine medical imaging of asymptomatic women was not performed. However, medical imaging was performed to evaluate patients with symptoms that are consistent with disease recurrence.

Imaging was performed if there was a patient complaint or clinical finding to justify it. Clinical assessment and radiological workup with or without histological confirmation of disease recurrence proved the presence of recurrent disease. As per protocol, the presence of disease recurrence had to be proven by biopsy results whenever possible. However, clinical findings were relied on in exceptional circumstances where it would not have been ethically justifiable to take a biopsy, and if clinical, radiological, and tumor marker evidence was overwhelming.

The independent data and safety monitoring committee included 2 gynecological oncologists who were not otherwise involved in this trial, a medical oncologist, and a biostatistician. The committee met biannually and monitored patient safety and toxic effects data, serious adverse events, and mortality.

Outcomes
The primary outcome was disease-free survival, which was measured as the interval between surgery and the date of first recurrence, including disease progression or the development of a new primary cancer or death. Patients who were disease-free at the end of the study were censored at their last follow-up visit. Patients developing new primary tumors during the course of the study would be moved to a different risk profile compared with those not developing a new primary tumor. Because this was a pragmatic study, disease-free survival included the development of new primary disease to account for this risk. Similarly, death (from any cause) also was considered an event.

The reported prespecified secondary outcomes included disease recurrence, patterns of recurrence, and overall survival. The previously reported prespecified secondary outcomes were morbidity, pain, analgesic use, quality of life, and cost-effectiveness. Quality of life was assessed using the Functional Assessment of Cancer Therapy General Questionnaire. The proportion of women who showed an improvement of at least 10% or greater from baseline to 4 weeks after surgery was assessed; 55 of 179 women (31%) in the total laparoscopic hysterectomy group and 17 of 121 women (14%) in the total abdominal hysterectomy group achieved this threshold (between-group difference, 13.0% [95% CI, 7.7%-28.9%]; P < .001). Smaller quality-of-life benefits

Laparoscopic vs Abdominal Hysterectomy for Stage I Endometrial Cancer

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for total laparoscopic hysterectomy persisted into the late recovery phase 3 to 6 months after surgery. Although intraoperative adverse events were similar between the 2 groups, postoperative adverse events were less frequent in patients after total laparoscopic hysterectomy compared with those who received total abdominal hysterectomy. Costs were lower for total laparoscopic hysterectomy. 

Statistical Analysis
The statistical design and sample size calculations were based on a 4.5-year disease-free survival rate of 90% in the total abdominal hysterectomy group, and a 7% equivalence margin at 4.5 years. This corresponded to a disease-free survival rate of 83% and was deemed to be sufficiently small to declare total laparoscopic hysterectomy to be equivalent to total abdominal hysterectomy. A sample size of 755 patients was deemed sufficient to declare total laparoscopic hysterectomy equivalent to total abdominal hysterectomy with 90% power and a prespecified equivalence margin of 7% or less based on 5 years of patient accrual and 4.5 years of follow-up. An equivalence margin of 7% or less was determined to be clinically acceptable, as established for this and other disease sites. Evaluating the effect of postoperative radiotherapy on overall survival in endometrial cancer, used a 10% difference at 5 years and the LAP2 trial used a 5.3% difference in disease-free survival at 3 years.

Equivalence would be declared if both the lower and upper bounds of the 95% CI for the differences in the disease-free survival rates between surgical groups at 4.5 years after randomization were not greater than 7%. A P value of less than .05 rejects the null hypothesis and confirms equivalence.

All statistical analyses were conducted according to the intention-to-treat principle. Additional exploratory analyses were performed by exclusion of patients who did not receive the allocated surgery and by the surgery received. Treatment comparisons of continuous data were performed using t tests and using χ2 tests for categorical variables. Disease-free survival rates at 4.5 years were estimated using the Kaplan-Meier method. The hazard ratios (HRs) for disease-free and overall survival in the bivariate and multivariable models were obtained using proportional hazards models.

Exploratory multivariable analyses for disease-free and overall survival were performed with adjustment for prespecified prognostic factors including treatment type, age, body mass index (calculated as weight in kilograms divided by height in meters squared), FIGO surgical stage, grade of differentiation, lymph node involvement, history of malignancy, and Eastern Cooperative Oncology Group performance status score. Subgroup analyses were performed according to stratification variables and other prespecified clinically relevant groups, with tests for interaction by logistic regression in which the outcome was disease-free survival at 4.5 years (yes vs no).

All analyses were performed at the .05 level of significance (2-sided) and conducted using SAS version 9.3 (SAS Institute Inc) and STATA version 14.1 (StataCorp). No statistical adjustments to the analyses were made for multiple testing or to account for missing data. 

Results

Study Population and Assigned Treatment
Of 760 patients who were randomized (353 to total abdominal hysterectomy and 407 to total laparoscopic hysterectomy), 679 (89%) completed the trial (Figure 1). A total of 27 surgeons were accredited and enrolled their patients into the trial. The median follow-up time was 4.5 years. The 2 groups were well balanced across stratification and other baseline factors (Table 1). Medical comorbidities were equally distributed across both surgical groups. There were no statistically significant between-group differences in the types of tumor, with the majority being endometrioid adenocarcinomas (97%). There were no significant between-group differences in FIGO surgical staging, histological grade, number of metastatic lymph nodes, or adjuvant treatment (Table 2).

Of patients randomized to total laparoscopic hysterectomy, 27 (7%) did not receive the assigned surgical procedure, 24 (6%) were converted from laparoscopy to laparotomy (15 for anatomical reasons [ie, related to the incision to remove the uterus, uterus too large, vagina too narrow], 7 due to complications, and 2 for technical reasons). In the remaining 3 patients that did not undergo a total laparoscopic hysterectomy, 2 withdrew prior to surgery and 1 had her surgery abandoned due to clinically advanced disease with vaginal involvement that was unrecognized until the day of surgery (Figure 1).

Similarly, 5 patients (2%) randomized to total abdominal hysterectomy received total laparoscopic hysterectomy due to refusal of total abdominal hysterectomy and 2 patients withdrew prior to surgery. There were 81 patients (11%) lost to follow-up by 4.5 years; baseline characteristics did not differ in these patients compared with those who completed follow-up (eTable 1 in Supplement 2). For the primary analysis, all patients were included in their randomized treatment group.

Disease-Free Survival
In the intention-to-treat analysis of the primary outcome, 60 patients (17.0%) who had been assigned to total abdominal hysterectomy and 70 patients (17.2%) who had been assigned to total laparoscopic hysterectomy experienced an event by 4.5 years after randomization. Based on the Kaplan-Meier estimates, the probability of disease-free survival at 4.5 years was 81.3% in the total abdominal hysterectomy group and 81.6% in the total laparoscopic hysterectomy group (disease-free survival difference, 0.3% [95% CI, −5.5% to 6.1%], favoring total laparoscopic hysterectomy). Both the lower and upper boundary of the 2-sided 95% CI excluded the prespecified equivalence margin of 7% or less (P = .007), supporting the conclusion that total laparoscopic hysterectomy is equivalent to total abdominal hysterectomy.

Supporting per-protocol analyses revealed the probability of not having a disease-free survival event as 81.4% (346 patients) in the total abdominal hysterectomy group vs 83.0% (381 patients) in the total laparoscopic hysterectomy group at 4.5 years (providing a difference of 1.6% [95% CI, −4.3% to 7.5%] in favor of total laparoscopic hysterectomy).
In analyzing patients according to the surgery they received, the disease-free survival rates were 80.0% in the total abdominal hysterectomy group vs 82.9% in the total laparoscopic hysterectomy group (providing a difference of 2.9% [95% CI, −2.9% to 8.7%]).

Secondary Outcomes
In the intention-to-treat analysis, there was no statistically significant between-group difference in disease-free survival (HR, 1.03 [95% CI, 0.73 to 1.44]; P = .87) (Figure 2A), or in the primary site of recurrence, with 12 patients (3%) in the total abdominal hysterectomy group and 14 patients (3%) in the total laparoscopic hysterectomy group experiencing a cancer relapse at the vaginal vault, and 2% or less of patients experiencing a relapse in the pelvis, in the abdomen, at distant organs, or at multiple sites in both groups (Table 3). A post hoc sensitivity analysis of disease-free survival excluding the new primary cancers and deaths found a difference of −0.02% (95% CI, −4.22% to 4.18%) from Kaplan-Meier estimates (eFigure 1 in Supplement 2).

There were 2 patients with port-site metastases in the total laparoscopic hysterectomy group and both patients presented with multiple peritoneal metastases including those located at the port sites. Similarly, 2 patients in the total abdominal hysterectomy group developed recurrences at the site of the abdominal wound. One of these patients presented with multiple metastases affecting the liver and lung, and another patient had an isolated recurrence at the vertical midline scar.

In total, 24 patients (6.8%) in the total abdominal hysterectomy group and 30 patients (7.4%) in the total laparoscopic hysterectomy group died, with an estimated 4.5-year overall survival rate (based on Kaplan-Meier estimates) of 92.4% vs 92.0%, respectively (survival difference, −0.34% [95% CI, −4.4% to 3.7%]). There was no significant between-group difference in overall survival (HR, 1.08 [95% CI, 0.63 to 1.85]; P = .78) (Figure 2B). The cause of death was balanced across the treatment groups with the majority of deaths (56%) due to endometrial cancer (Table 3). Prognostic factors associated with disease-free survival and overall survival appear in eTable 2 in Supplement 2 and include history of malignancy, increasing age, and higher surgical and differentiation stage, but not randomized treatment.

Prognostic Factors for Disease-Free Survival
Exploratory analyses for differences in the rates of disease-free survival between the prespecified prognostic subgroups...
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Hysterectomy</th>
<th>Laparoscopic Hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abdominal (n = 353)</td>
<td>Laparoscopic (n = 407)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.1 (10.6)</td>
<td>63.3 (10.0)</td>
</tr>
<tr>
<td>Age group, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>197 (55.8)</td>
<td>232 (57.0)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>156 (44.1)</td>
<td>175 (43.0)</td>
</tr>
<tr>
<td>Body mass index, median (range)</td>
<td>32.7 (19.1–63.2)</td>
<td>33.1 (18.8–63.3)</td>
</tr>
<tr>
<td>Body mass index group, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>118 (33.0)</td>
<td>145 (36.0)</td>
</tr>
<tr>
<td>≥30</td>
<td>222 (62.9)</td>
<td>244 (60.0)</td>
</tr>
<tr>
<td>FIGO differentiation grade determined by dilation and curette, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Well differentiated)</td>
<td>223 (63.2)</td>
<td>259 (63.6)</td>
</tr>
<tr>
<td>2 (Moderately differentiated)</td>
<td>107 (30.3)</td>
<td>120 (29.5)</td>
</tr>
<tr>
<td>3 (Poorly or undifferentiated)</td>
<td>23 (6.5)</td>
<td>28 (6.9)</td>
</tr>
<tr>
<td>Any malignancy prior to the index malignancy, No./total (%)</td>
<td>20/303 (6.6)</td>
<td>28/306 (9.2)</td>
</tr>
<tr>
<td>Charlson comorbidity index, median (range)</td>
<td>3 (0–8)</td>
<td>3 (0–10)</td>
</tr>
<tr>
<td>Charlson comorbidity index group, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>158 (44.7)</td>
<td>172 (42.3)</td>
</tr>
<tr>
<td>≥3</td>
<td>195 (55.2)</td>
<td>231 (56.8)</td>
</tr>
<tr>
<td>Medication use, No. (%)</td>
<td>271 (76.8)</td>
<td>334 (82.1)</td>
</tr>
<tr>
<td>ECOG performance status score, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>303 (85.8)</td>
<td>352 (86.5)</td>
</tr>
<tr>
<td>1</td>
<td>50 (14.2)</td>
<td>55 (13.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

*Calculated as weight in kilograms divided by height in meters squared.

Change in denominators for this variable are due to phase 1 and phase 2 stratification scheme differences.

Higher scores indicate greater burden.

Ongoing without an end date (indicator of comorbidity burden).

Range is 0 (perfect health) to 5 (death).

A significant interaction (P = .04) for body mass index (<30 vs ≥30) was found, in which patients with a lower body mass index had higher rates of disease-free survival in the total abdominal hysterectomy group (86.6%) vs the total laparoscopic hysterectomy group (77.4%), whereas the total laparoscopic hysterectomy group had higher disease-free survival rates at 4.5 years for patients with a body mass index of 30 or greater (78.9% vs 84.4%, respectively). There were no statistically significant between-group differences in any of the other subgroup categories, including age (<65 years vs ≥65 years), FIGO stage (1 vs ≥1), Eastern Cooperative Oncology Group performance status score (0 vs 1), Charlson comorbidity index (<3 vs ≥3), or history of malignancy (yes vs no).

A multivariable analysis using proportional hazard regression of disease-free survival adjusting for prespecified prognostic factors did not materially change the treatment effect (eTable 2 in Supplement 2). The unadjusted HR was 1.03 (95% CI, 0.73–1.44; P = .87) and the adjusted HR was 1.00 (95% CI, 0.67–1.50; P = .98).

Discussion

In this clinical trial of 760 women with stage I endometrial cancer, disease-free survival at 4.5 years was 81.6% with total laparoscopic hysterectomy vs 81.3% with total abdominal hysterectomy (between-group difference, 0.3% [95% CI, −5.5% to 6.1%), meeting the criteria for equivalence. Although a limited number of clinical trials have attempted to address the performance and safety of these 2 surgical approaches, the current trial represents, to our knowledge, the first multicenter, international trial in which all surgeons were tasked to perform the total hysterectomy laparoscopically. Surgeons were assessed to ensure that they had sufficient technical competence to participate in this trial. Their proficiency in performing the operations was manifested by a low conversion rate and a high-disease-free survival rate.

The overall incidence of postoperative wound metastases was low (0.0047%); there was no between-group difference in frequency. The outcomes for the 2 groups were consistent irrespective of the analytic approach. Outcomes were similar for survival rates and HRs in both the intention-to-treat and as-treated analyses for disease-free and overall survival without endometrial cancer–specific recurrence and the 4.5-year time point was sufficiently long to capture any separation in the survival curves.

The apparent disease-free survival benefit of total laparoscopic hysterectomy in women with a BMI of 30 or greater is counterintuitive; however, because the 95% CIs for estimates in the individual subgroups overlap, this finding may be a statistical artifact. Laparoscopic surgery has benefits for patients with regard to quality of life, recovery after surgery, hospital stay, and adverse events. Given its better short-term outcomes, updated meta-analyses should now be conducted to determine whether total laparoscopic hysterectomy should become the standard approach for patients with stage I endometrial cancer.
Published reports from previous trials evaluating the differences in outcomes between open and laparoscopic hysterectomy have been summarized in a recent Cochrane meta-analysis.14 Until now, the only randomized evidence assessing long-term survival outcomes from a sufficiently powered and multicenter trial was the US Gynecologic Oncology Group’s LAP2 trial (GOG 222).25 The LAP2 trial recruited a total of 2616 women and did not meet the criteria for noninferiority based on a HR boundary of 1.4,25 potentially due to the smaller than expected recurrence rate. The results of this previous trial suggested that laparoscopic hysterectomy was not as good as the open operation in terms of recurrent disease. In that trial, laparoscopic hysterectomy had an estimated 3-year recurrence rate of 11.4% compared with 10.2% for open hysterectomy.

There are some important differences between the trial reported herein and the LAP2 trial. The LAP2 trial enrolled patients with all types of cancer histology, whereas the present trial enrolled patients with endometrioid cell type on preoperative uterine curetting. All patients enrolled into LAP2 had a retroperitoneal node dissection, including para-aortic nodes. The high conversion rate from laparoscopy to laparotomy (25.8% in LAP2 vs only 6% in this trial) can be explained by the requirement of aortic node dissection in LAP2.26

Table 2. Surgery and Adjuvant Treatment Characteristics

<table>
<thead>
<tr>
<th>Total Hysterectomy</th>
<th>Abdominal (n = 353)</th>
<th>Laparoscopic (n = 407)</th>
<th>Risk Difference (Laparoscopic Group Minus Abdominal Group), % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical and pathological characteristics, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to surgery from randomization, d</td>
<td>7 (0 to 74)</td>
<td>7 (0 to 62)</td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>Duration of operation, min</td>
<td>105 (35 to 249)</td>
<td>130 (50 to 300)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemoglobin level (change from baseline to 1 wk after surgery), g/dL</td>
<td>−19 (−111 to 31)</td>
<td>−17 (−55 to 15)</td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Pelvic or aortic lymph node dissection, No. (%)</td>
<td>206 (58.4)</td>
<td>161 (39.6)</td>
<td>−18.8 (−25.8 to −11.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>International Federation of Gynecology and Obstetrics surgical stage, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA (tumor limited to the endometrium)</td>
<td>237 (67.1)</td>
<td>286 (70.3)</td>
<td>3.1 (−3.5 to 9.7)</td>
<td></td>
</tr>
<tr>
<td>IB (invasion to &lt;half of the myometrium)</td>
<td>44 (12.5)</td>
<td>55 (13.5)</td>
<td>1.0 (−3.7 to 5.8)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>45 (12.7)</td>
<td>32 (7.9)</td>
<td>−4.9 (−9.2 to −0.5)</td>
<td></td>
</tr>
<tr>
<td>IIA (tumor invades the serosa of the corpus uteri, adnexa, or positive cytological findings)</td>
<td>4 (1.1)</td>
<td>11 (2.7)</td>
<td>1.6 (−0.4 to 3.5)</td>
<td></td>
</tr>
<tr>
<td>IIB (vaginal metastases)</td>
<td>1 (0.3)</td>
<td>4 (1.0)</td>
<td>0.7 (−0.4 to 1.8)</td>
<td>27</td>
</tr>
<tr>
<td>IIIC1</td>
<td>12 (3.4)</td>
<td>11 (2.7)</td>
<td>−0.7 (−3.2 to 1.7)</td>
<td></td>
</tr>
<tr>
<td>IIIC2</td>
<td>3 (0.8)</td>
<td>1 (0.2)</td>
<td>−0.6 (−1.7 to 0.5)</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>1 (0.3)</td>
<td>0</td>
<td>−0.3 (−0.8 to 0.3)</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>3 (0.8)</td>
<td>3 (0.7)</td>
<td>−0.1 (−1.4 to 1.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (0.8)</td>
<td>4 (1.0)</td>
<td>0.1 (−1.2 to 1.5)</td>
<td></td>
</tr>
<tr>
<td>Cell type, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>340 (96.3)</td>
<td>395 (97.1)</td>
<td>0.7 (−1.8 to 3.3)</td>
<td>.59</td>
</tr>
<tr>
<td>Clear cell</td>
<td>7 (2.0)</td>
<td>4 (1.0)</td>
<td>−1.0 (−2.7 to 0.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5 (1.4)</td>
<td>1 (0.2)</td>
<td>−1.2 (−2.5 to 0.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Mixed epithelial</td>
<td>3 (0.8)</td>
<td>0</td>
<td>−0.8 (−1.8 to 0.1)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1 (0.3)</td>
<td>2 (0.5)</td>
<td>0.2 (−0.7 to 1.0)</td>
<td>.80</td>
</tr>
<tr>
<td>Serous</td>
<td>12 (3.4)</td>
<td>7 (1.7)</td>
<td>−1.7 (−4.0 to 0.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Mucinous</td>
<td>2 (0.6)</td>
<td>7 (1.7)</td>
<td>1.1 (−0.3 to 2.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Small cell</td>
<td>0</td>
<td>2 (0.5)</td>
<td>0.5 (−0.2 to 1.2)</td>
<td></td>
</tr>
<tr>
<td>International Federation of Gynecology and Obstetrics differentiation grade, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Well differentiated)</td>
<td>185 (52.4)</td>
<td>231 (56.8)</td>
<td>4.3 (−2.7 to 11.4)</td>
<td>.27</td>
</tr>
<tr>
<td>2 (Moderately differentiated)</td>
<td>124 (35.1)</td>
<td>129 (31.7)</td>
<td>−3.5 (−10.2 to 3.3)</td>
<td></td>
</tr>
<tr>
<td>3 (Poorly or undifferentiated)</td>
<td>40 (11.3)</td>
<td>43 (10.6)</td>
<td>−0.8 (−5.2 to 3.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (1.1)</td>
<td>4 (1.0)</td>
<td>−0.2 (−1.6 to 1.3)</td>
<td></td>
</tr>
<tr>
<td>No. of lymph nodes examined, median (range)</td>
<td>10 (5 to 28)</td>
<td>11 (7 to 15)</td>
<td></td>
<td>.88</td>
</tr>
<tr>
<td>No. of metastatic lymph nodes, median (range)</td>
<td>0 (0 to 1)</td>
<td>0 (0 to 2)</td>
<td></td>
<td>.84</td>
</tr>
<tr>
<td>Adjuvant treatment, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>7 (2.0)</td>
<td>8 (2.0)</td>
<td>−0.01 (−2.0 to 2.0)</td>
<td>.99</td>
</tr>
<tr>
<td>Radiation treatment only</td>
<td>66 (18.7)</td>
<td>61 (15.0)</td>
<td>−3.7 (−9.1 to 1.6)</td>
<td>.17</td>
</tr>
<tr>
<td>Both chemotherapy and radiation treatment</td>
<td>19 (5.4)</td>
<td>22 (5.4)</td>
<td>0.02 (−3.2 to 3.2)</td>
<td>.99</td>
</tr>
</tbody>
</table>
In contrast, only half of all patients enrolled in the current trial received a retroperitoneal node dissection, and patients who received total laparoscopic hysterectomy were less likely to have a node dissection. This reflects the existing, wide variation in opinions about the need for comprehensive surgical staging and lymphadenectomy.\(^2\)

### Table 3. Survival Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Total Hysterectomy</th>
<th>Risk Difference (Laparoscopic Group Minus Abdominal Group), % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free survival (Kaplan-Meier estimates) at 4.5 y, %</td>
<td>81.3</td>
<td>81.6</td>
<td>0.3 (-5.5 to 6.1)</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer recurrence, new primary cancer, or death, No. (%)</td>
<td>60 (17.0)</td>
<td>70 (17.2)</td>
<td>0.2 (-5.1 to 5.6)</td>
</tr>
<tr>
<td>Endometrial cancer recurrence, No. (%)(^b)</td>
<td>28 (7.9)</td>
<td>33 (8.1)</td>
<td>0.2 (-3.7 to 4.0)</td>
</tr>
<tr>
<td><strong>Primary site of relapse, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal vault</td>
<td>12 (3.4)</td>
<td>14 (3.4)</td>
<td>0.04 (-2.5 to 2.6)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>4 (1.1)</td>
<td>2 (0.5)</td>
<td>-0.6 (-1.9 to 0.7)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>6 (1.7)</td>
<td>6 (1.5)</td>
<td>-0.2 (-2.0 to 1.6)</td>
</tr>
<tr>
<td>Distant organs</td>
<td>4 (1.1)</td>
<td>5 (1.2)</td>
<td>0.1 (-1.4 to 1.6)</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>2 (0.6)</td>
<td>6 (1.5)</td>
<td>0.9 (-0.5 to 2.3)</td>
</tr>
<tr>
<td>Any new primary cancer, No. (%)</td>
<td>27 (7.6)</td>
<td>37 (9.1)</td>
<td>1.4 (-2.5 to 5.4)</td>
</tr>
<tr>
<td>Breast</td>
<td>10 (37.0)</td>
<td>7 (18.9)</td>
<td>-18.1 (-40.3 to 4.0)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>5 (18.5)</td>
<td>3 (8.1)</td>
<td>-10.4 (-27.5 to 6.7)</td>
</tr>
<tr>
<td>Skin</td>
<td>9 (33.3)</td>
<td>19 (51.4)</td>
<td>18.0 (-6.0 to 42.0)</td>
</tr>
<tr>
<td>Hematological</td>
<td>1 (3.7)</td>
<td>4 (10.8)</td>
<td>7.1 (-5.2 to 19.4)</td>
</tr>
<tr>
<td>Lung</td>
<td>1 (3.7)</td>
<td>3 (8.1)</td>
<td>4.4 (-6.9 to 15.7)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0</td>
<td>1 (2.7)</td>
<td>2.7 (-2.5 to 7.9)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1 (3.7)</td>
<td>0</td>
<td>-3.7 (-10.8 to 3.4)</td>
</tr>
<tr>
<td>Deaths by cause, No. (%)(^c)</td>
<td>24 (6.8)</td>
<td>30 (7.4)</td>
<td>0.6 (-3.0 to 4.2)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14 (58.3)</td>
<td>16 (33.3)</td>
<td>-5.0 (-31.6 to 22.0)</td>
</tr>
<tr>
<td>Unrelated morbidity</td>
<td>2 (8.3)</td>
<td>5 (16.7)</td>
<td>8.3 (-9.0 to 25.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (33.3)</td>
<td>9 (30.0)</td>
<td>-3.3 (-28.3 to 21.7)</td>
</tr>
</tbody>
</table>

\(^{a}\) Rejects the null hypothesis and confirms equivalence.  
\(^{b}\) Any event that occurred between randomization and 4.5 years after randomization. Recurrence excludes deaths and new primary cancers.  
\(^{c}\) Any event that occurred between randomization and March 3, 2016.
Previously reported adverse event results of this trial confirmed results from the LAP2 trial and the results from other studies summarized in the Cochrane review. Intraoperative surgical complications were comparable between patients assigned to total abdominal hysterectomy and total laparoscopic hysterectomy in the 3 large trials conducted worldwide to date. In regard to postoperative surgical adverse events, the Dutch trial recorded similar postoperative surgical complications in the abdominal and the laparoscopic groups, whereas laparoscopic hysterectomy led to fewer postoperative surgical complications in LAP2 and in the present trial. Quality-of-life outcomes favored total laparoscopic hysterectomy over total abdominal hysterectomy in all 3 of these trials.

The present analyses showed that patients with endometrial cancer treated by total laparoscopic hysterectomy had equivalent survival outcomes up to 4.5 years after surgery. Other investigators reported that long-term survival outcomes are also promising for patients who undergo total laparoscopic hysterectomy.

Limitations

The limitations of this trial include that the blinding of patients and surgeons was not possible; however, lack of blinding is unlikely to affect the disease-free or overall survival outcomes reported herein, which were collected independently from the treating surgeons by dedicated clinical trial staff. Furthermore, randomization was performed prior to the patient being scheduled for surgery due to the different setup required for the surgical procedures.

Due to funding constraints, the trial followed a pragmatic 2-phase design, first focusing on quality of life, and then on disease-free and overall survival once the recruitment of a sufficiently large number of patients was supported by the funders of this trial. In this trial, performance of pelvic and aortic reperitoneal node dissection was left to the discretion of the surgeons, resulting in inconsistent application of this component of the operation in the study.

Conclusions

Among women with stage I endometrial cancer, the use of total abdominal hysterectomy compared with total laparoscopic hysterectomy resulted in equivalent disease-free survival at 4.5 years and no difference in overall survival. These findings support the use of laparoscopic hysterectomy for women with stage I endometrial cancer.
REFERENCES
Endorphins, oxytocin, sexuality and romantic relationships: An understudied area

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Author contributions: Khajehei M and Behroozpour E contributed to literature search, summarising the findings, preparing the manuscript draft and approving the final draft.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Received: June 22, 2018
Peer-review started: June 22, 2018
First decision: September 3, 2018
Revised: September 10, 2018
Accepted: October 12, 2018

Abstract

Endorphins are the body’s natural opioids that are created and released by the central nervous system, hypothalamus and pituitary gland. Endorphins have a reputation for pain reduction, enhancing excitement or satisfaction, boosting confidence, enabling control of emotions and generating feelings of euphoria, and are involved in the natural reward cycle. There is also evidence in the literature suggesting the role of endorphins in sexuality (including sexual function and sexual behaviours), as they may regulate the release of sex hormones, prolactin and growth hormone, which are involved in sexual function and love. Endogenous oxytocin is another intrinsic hormone whose role in inducing labour contractions, the delivery of the baby and stimulating lactation has been well studied. However, the potential impact of endorphins and oxytocin on sexuality and romantic relationships is not well understood. This article reviews the research on endorphins and endogenous oxytocin and how they relate to human sexuality and romantic relationships. Some animal studies report the effect of endorphin and oxytocin on sex hormones and mating behaviours, but these findings have not been supported by research into human behaviour, indicating many gaps in knowledge relating to the association between these hormones and human sexuality.

Key words: Romantic relationship; Sexual behaviour; Sexual function; Endorphins; Oxytocin; Sexuality

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Core tip: Less is known about the association between endogenous opioids and sexual function and behaviors in

Endorphins, oxytocin, sexuality and romantic relationships: An understudied area

INTRODUCTION

Endorphins are the body’s natural opioids, or endogenous opioids, that are created and released by the central nervous system (CNS), hypothalamus and pituitary gland. Endorphins have a reputation for pain reduction, enhancing excitement or satisfaction, boosting confidence, enabling control of emotions and generating feelings of euphoria, and are involved in the natural reward cycle. The release of endorphins in the human body is triggered by a variety of factors, including massage and bodywork[1], exercise[2], active performance of music[3], consumption of certain foods such as dark chocolate[4], environmental factors such as ultraviolet light[5], and childbirth[6]. There is also evidence in the literature suggesting the role of endorphins in sexuality. It is suggested that endorphins regulate the release of other hormones, such as sex hormones, prolactin and growth hormone, which are involved in sexual function and love[7,8].

Endogenous oxytocin is another intrinsic hormone whose receptors were first discovered in 1984 because of their role in inducing labor contractions, the delivery of the baby and stimulating lactation. Endogenous oxytocin is primarily synthesised in the hypothalamus and is then stored in the posterior pituitary gland, from where it is released into the bloodstream[9]. The release of endogenous oxytocin can be provoked by a variety of stimuli including sexual and reproductive stimuli (copulation, genital and breast stimulation, birth, olfactory stimuli, and sucking)[10] and non-sexual stimuli (i.e., grooming, massage and contact with offspring)[11].

The roles of endorphins and oxytocin are well researched and understood in some areas of health, but their potential impacts on sexuality and romantic relationships are only beginning to be understood. The purpose of this editorial is to review current understanding of endorphins and endogenous oxytocin and how they relate to human sexuality (including sexual function and sexual behaviours, for the purpose of this review).

EFFECT OF BETA-ENDORPHIN ON SEXUALITY AND ROMANTIC RELATIONSHIPS

Human studies

The association between beta-endorphin and sexuality and romantic relationships is mutual, with endogenous sex steroids affecting the neurobiology of sexual function by directly influencing receptors at the nuclear and membrane level or by indirectly affecting the neurotransmitters of neuropeptides (endogenous oxytocin and endorphins)[12]. For this reason, it has been suggested that endorphins may be involved in the regulation of sexual function in humans.

It has been suggested that a mild increase in the beta-endorphin level creates a sense of wellbeing, and that a greater increase may lead to analgesia and euphoria. A variety of behavioral experiences can activate the release of beta-endorphin. For example, exercise stimulates secretion of corticotropin-releasing hormone, resulting in an increase in ACTH and endorphins that may enhance an individual’s sexuality[13]. In addition to aerobic exercise, discontinuation of tobacco use and illicit drug use and reduced alcohol consumption improve tissue oxygenation, promote metabolism, reduce body mass index and stimulate endorphin release that may, in turn, boost sexual response[14].

An increase of endorphin levels during sexual activity in humans is presumed to contribute to attachment and bonding between partners, similar to that of a mother and her newborn[8]. However, contradictory reports in the literature question the association between sexuality and endorphin levels. For example, in a small study on 10 healthy women, sexual arousal and orgasm resulted in a sharp increase in cardiovascular parameters and plasma catecholamine concentrations along with an increase in the concentration of plasma prolactin, but no changes were seen in the plasma concentrations of beta-endorphin[15]. A similar neuroendocrine response pattern to sexual arousal and orgasm in men was reported in an earlier study by Krüger et al[16]. Although they showed a transient increase in heart rate and blood pressure as well as noradrenaline and prolactin plasma levels, no changes were seen in the plasma beta-endorphin and other endocrine variables.

Less is known about the association between endogenous opioids and sexual function and behaviors in humans, but it is known that exogenous opiates negatively affect the sexuality of male and female who misuse opiate drugs and contribute to their reduced sexual desire, impaired sexual arousal, decreased genital response, delayed or blocked ejaculation, orgasm dysfunction and infertility[17-19]. Opiate drugs negatively affect sexual function through reducing the levels of sex hormones, and their effect on the endocrine system begins immediately after they are taken[18]. Although little is known about the exact mechanism of sexual
Animal studies may have both excitatory and inhibitory effects on sexual function. Findings of animal studies suggest that opioid peptides, have both inhibitory and excitatory effects, in men and women while using opiate drugs, regular use suppresses the testosterone level in men regardless of the type of opioid being ingested. Testosterone levels in women are not affected by opiate drugs. This sex difference suggests that opiate drugs may have differential mechanisms for endocrine disruption in men and women, and this should be taken into consideration when treating sexual problems in people who are opiate-dependent. Since there may be different endocrine targets to aim for in non-opioid-dependent men and women while trying to treat their sexual dysfunction using pharmaceutical drugs, any future drug development for sexual dysfunction needs to consider these differences.

The negative effects of opiate drugs on male sexual function are reversible after opiate withdrawal or administration of opiate antagonists. The positive effects of opiate antagonists are increased luteinizing hormone (LH) pulsatility, raised serum testosterone levels, increased in vitro sperm motility after administration of naloxone, recurrent spontaneous penile erections, frequent orgasms and more intense sexual arousal and orgasm in healthy adult men who were not addicted to opiate, after administration of naltrexone. However, these findings are not supported by animal research, indicating a lack of substantial influence of acute or chronic naloxone administration on different sexual activities of isolated and group-housed male rats. Details of other animal research are discussed in the next section.

The limited research in humans, especially in women, has created inconsistent but, in some cases, interesting results. For example, in the study by Goldstein and Hansteen, a single male subject was recruited and the researchers prematurely concluded that there is no evidence of the involvement of endorphins in male sexual arousal. Other research by Gillman and Lichtigfeld found that administration of a 2 mg dose of naloxone on two separate occasions enhanced orgasm and pleasure in women, while a single 2 mg dose of naloxone inhibited arousal and orgasm for up to 10 min, suggesting that the relationship of naloxone to orgasm is dose-dependent and potentially parabolic. This is consistent with the notion that endogenous opiates, such as beta-endorphin, have both inhibitory and excitatory effects, but the explanation for the dose-response effect remains obscure.

Animal studies
Findings of animal studies suggest that opioid peptides may have both excitatory and inhibitory effects on sexual

performance and behaviours. When opioid peptides are released in response to stress, they impose their inhibitory effects by acting in the medial preoptic area and the paraventricular nucleus that, in turn, impairs sexual performance. According to animal studies, it is suggested that endorphins regulate the release of other hormones, such as sex hormones, prolactin and growth hormone, that are involved in sexual function and attachment. It has also been suggested that this may be relevant to the low level of sexual desire in people with symptoms of depression.

Preliminary studies have investigated the mechanisms of inhibition of sexual behavior by opioids. Myers and Baum showed that naloxone, the opiate receptor antagonist, has a facilitatory effect on masculine sexual performance in rats, resulting in the release of gonadotropin releasing hormone (GnRH). A later study indicated that infusion of opioid antagonists into the mesencephalic central gray matter increases neuronal GnRH output that in turn enhances the likelihood of lordosis behavior in estrogen-primed female rats. Other studies have shown that acute treatment with opioid antagonists augmented GnRH secretion followed by raised levels of serum LH and testosterone.

In a study by Csaba et al., administration of a single dose of endorphin to neonatal rats showed that sexual activity permanently decreased in females after five months and their tendency to refuse the male increased. Female rats showed a permanent increase in the density of uterine estrogen receptors, and male rats showed a decline in the serotonin level in the brain. Although little is known about the interaction of endorphin and other hormones or neurotransmitters in relation to human sexuality, results of the study by Csaba et al. suggest that there is a role for hormone imprinting at birth and that endorphin treatment influences sexual hormone production, which can affect sexual behaviors in later life.

During labor, the level of endorphin in the mother's blood increases and is dependent on the intensity of pain and the duration of labor. Therefore, it is presumed that neonatal endorphin imprinting affects later-life events such as sexual activity and aggression, because of the association between brain serotonin levels and aggressive behaviors. However, this hypothesis is based solely on data from rodent models, and its generalizability to other species, including primates (e.g., humans) is currently unclear.

The opioid peptides impose their excitatory effects by acting in the ventral tegmental area, increasing the activity of the mesolimbic dopaminergic system and promoting sexual arousal and motivation. There appears to be no research investigating the role of beta-endorphin in human sexuality, making it impossible to determine whether this is a general effect of all opioid peptides or if it is specific for other peptides such as enkephalin, as reported in the literature.

Research in animal models has found that beta-
endorphin affects brain activity and maintains a sense of balance and wellbeing by allowing the animals to perform feeding and drinking activities as well as social grooming\(^{43}\). A systematic review of animal studies\(^{44}\) has also suggested that beta-endorphin plays its main role in the appetitive and precopulatory phase of sexual behavior, in preparation for copulatory activities. Further, there is a relationship between beta-endorphin and sex hormones.

**EFFECT OF OXYTOCIN ON SEXUALITY AND ROMANTIC RELATIONSHIPS**

*Human studies*

Oxytocin is known as the "hormone of love". Endogenous oxytocin arouses feelings of pleasure, peace and security when in the company of a partner\(^{45}\). The release of endogenous oxytocin from the pituitary gland into the bloodstream is triggered by sexual stimuli such as hugging, touching, and genital and nipple stimulation in both genders, and its plasma level is correlated with the levels of arousal and lubrication, reaching a peak during orgasm\(^ {46}\). The release of endogenous oxytocin decreases fearfulness and works as an anxiolytic agent, diminishing the level of anxiety through inhibiting fear responses in the amygdala, which contains substantial numbers of oxytocin receptors\(^ {47}\). The release of endogenous oxytocin from the brain during intimate touching or sexual activity with a partner has been suggested to have a vital role in sexual monogamy in men and women\(^ {48}\).

Ecstasy [(3,4-methylenedioxyxymethamphetamine (MDMA)] is a recreational psychoactive drug and is often called the "love pill". Research has shown that ecstasy stimulates endogenous oxytocin activity via activation of serotonin 5-HT1A receptors resulting in an increase in feelings of love, empathy and connection to others\(^ {49}\).

A rise in endogenous oxytocin results in an increase of plasma endorphins, natural pain-killers that can diminish pain in women who suffer dyspareunia, due to anxiety or a lack of trust in their partner during the first stages of their relationship\(^ {50}\). Despite these, research has suggested that endogenous oxytocin may not be high before the commencement of sexual activity and it may not be the main trigger of sexual drive and desire preceding the initiation of sexual activity. According to this, the level of endogenous oxytocin increases after the woman receives appropriate stimulation and starts enjoying the sexual activity\(^ {51}\). This claim is supported by data from self-report studies indicating that some women may enjoy sexual activity and reach orgasm when sexual stimulation and intercourse occur\(^ {52}\), although they may not be the initiator of the sexual activity\(^ {53,54}\).

Higher plasma concentrations of oxytocin have been shown in people who have fallen in love as well as during the transition to parenthood. A magnetic resonance imaging study of 10 women and 7 men (mean age 21.4 years) has shown that brain areas involved in the formation of romantic attachment are rich in oxytocin receptors\(^ {55}\). The same brain regions are activated in new parents with great parental-infant attachment and new lovers in prolonged romantic relationships\(^ {56}\). These reports suggest that parent-child attachments and romantic bonds may share some fundamental mechanisms mediated by the oxytocinergic system, though it is not evident in the literature.

Postpartum loss of sexual desire, arousal and orgasm have been reported across many studies and have been shown to remain as long as one year\(^ {53}\) to many years after childbirth\(^ {57}\). Research suggests that changes in sexual function in postpartum women may not be only because of physical changes during the transition to motherhood, but may also be due to psychological and neuroendocrine alterations during and after childbirth. Neuroimaging assessments of seven mothers have shown changes in the prefrontal-limbic system during the transition to motherhood, including the amygdala, which is responsible for the expression of oxytocin receptors, suggesting that the amygdala may be less responsive to sexual images and stimuli in postpartum women\(^ {58}\). Another suggested alteration is that the brain may not release the expected amounts of endogenous oxytocin during sexual activity in postpartum women, and this may result in decreased self-reported feelings of sexual desire in these women\(^ {59}\).

A modest body of evidence suggests that any factor that can interfere with the release of endogenous oxytocin can cause sexual dysfunction in postpartum women. Among the various factors contributing to sexual problems in postpartum women\(^ {60-62}\) is the use of intravenous synthetic oxytocin during labour and birth. This factor is not subject to the standard mechanisms regulating endogenous oxytocin and affects the normal behaviors of the amygdala\(^ {63,64}\). Considering the low levels of endogenous oxytocin in women experiencing sexual problems, and the different mechanisms of action of intranasal and intravenous synthetic oxytocin, researchers have attempted to address the sexual problems of women by using an intranasal spray of synthetic oxytocin which was supposed to deliver lower doses of synthetic oxytocin to the body compared with intravenous synthetic oxytocin administered during labour. A case report by Anderson-Hunt and Dennerstein\(^ {65}\) showed copious vaginal transudate and a subsequent intense sexual desire two hours after the use of intranasal spray of synthetic oxytocin to facilitate breastfeeding. However, findings of their report may not be generalised to the entire population as they studied only one woman for a short period of time. Another study showed that intranasal administration of synthetic oxytocin improved attachment-related behaviors, such as eye gazing\(^ {66}\), interpersonal trust, compassion and positive communication\(^ {67}\).

The use of intranasal synthetic oxytocin in men has been shown to result in a remarkable increase in their
endogenous oxytocin levels together with increased secretion of catecholamines when they were engaged in sexual activity in a laboratory setting\(^6\). Nevertheless, no further evidence in the literature supports the use of synthetic oxytocin for female sexual dysfunction.

As mentioned earlier, there are mixed reports regarding the impact of oxytocin on romantic relationships. Some studies have indicated links between plasma oxytocin and positive communication, affiliation, emotional support and love\(^{69,70}\), but others have shown associations between elevated peripheral oxytocin and post-conflict anxiety and decreased levels of forgiveness in romantic couples\(^{45,71}\). These results, however, should be interpreted with caution due to controversy about the reliability of plasma oxytocin levels as a peripheral proxy for central concentrations.

**Animal studies**

A comprehensive review of animal studies on the effect of neuropeptides on the regulation of the brain, social cognitive processing and associated social behaviors has suggested a link between the oxytocinergic system and dopamine which promotes sexual behaviors such as pair bonding and sexual arousal\(^72\). This association may also contribute to an expectancy of future reward and the sexual arousal reward that are naturally expected later, as shown in rodents\(^73\).

When synthetic oxytocin is administered intranasally, it proceeds through the fluid-filled perineural channels created by the cells ensheathing the olfactory receptor neurons. It then travels through the cribiform plate in the skull and reaches the CNS\(^74\). In their study on primates, Chang et al\(^75\) showed increased levels of endogenous oxytocin in cerebrospinal fluid (CSF) after synthetic oxytocin spray inhalation, supporting the likelihood of central effects of synthetic oxytocin.

Unlike intranasal oxytocin, when intravenous synthetic oxytocin is administered, the blood–brain barrier inhibits it from reaching the brain and it therefore does not function as the “hormone of love”\(^76\). Other animal studies have reported that synthetic oxytocin may reach the brain, but it may act differently from the endogenous oxytocin and have different effects on the body\(^76,77\). They have shown that there is not always a correlation between peripheral and cerebral levels of oxytocin, suggesting that the two systems may be controlled independently and that intravenous synthetic oxytocin does not essentially raise oxytocin levels within the brain. Research on male prairie voles has shown inhibitory effects of synthetic oxytocin on pulsatile secretion of endogenous oxytocin that may last year\(^78\).

**CONCLUSION**

There is a lack of up-to-date data on the mechanism of action of endorphins and their role in regulating human sexuality. Some animal studies report the effect of beta-endorphin on GnRH, LH and testosterone, but these findings have not been supported by human research.

A thorough review of the literature has identified inconclusive reports and many gaps in knowledge of the association between endogenous oxytocin and sexuality. Further to this, there is no strong evidence supporting the positive effects of synthetic oxytocin on human sexual function and relationships. Although research in humans suggests a central role of these hormones in sexuality, the most reliable findings to date involve peripheral activation, mainly based on animal research.

The importance of physiological changes during sexual activity and how they can affect human relationships, and the gaps in the literature on the topic, highlight the need for high-quality research to extend our understanding of the hormonal physiology of sexual function and the role of endorphins and oxytocin in human sexuality. To fill the gap, further future studies are required to investigate the role of these hormones in human sexuality and their mechanism of action in men and women.

The inter-relationship between these two endogenous hormones and human sexuality is still unclear and no previous research has explored this association. Further future research is required to apply a methodological triangulation of qualitative and quantitative methods for analysing determinants of various aspects of human sexuality considering the role of endorphins and endogenous oxytocin. While the qualitative analysis may focus on behavioural sex differences, the quantitative analysis concentrates on how the two endogenous hormones influence human sexuality and sexual behaviours.

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endorphins, oxytocin and sexuality

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WJOG | www.wjgnet.com October 22, 2018 | Volume 7 | Issue 2 |
Objectives: We sought to summarize the evidence for interventions aiming at enhanced recovery after surgery (ERAS) in ovarian cancer through a systematic review.

Methods: We searched MEDLINE, EMBASE, and The Cochrane Library for studies testing ERAS interventions in patients undergoing surgery for ovarian cancer. Study selection and data extraction were done independently by 2 reviewers with disagreements resolved by discussion with a senior, third reviewer.

Results: We identified 25 studies including 1648 participants with ovarian cancer. Nine observational studies addressed ERAS protocols. Four of them were prospective, and 3 included historical controls. The other 16 studies reported single interventions, for example, early feeding, omission of pelvic drains, early orogastric tube removal, Doppler-guided fluid management, and patient-controlled epidural analgesia. Early feeding protocols were tested in 7 of the 12 randomized trials. Early feeding appeared to be safe and was associated with significantly faster recovery of bowel function.

Conclusions: Few studies have specifically studied ERAS interventions in ovarian cancer. All studies on protocols including multiple interventions were susceptible to bias. Early feeding is the intervention that is best supported by randomized trials. Application of evidence for ERAS derived from nonovarian cancer is challenged by the differences not only in the scope of surgery but also in ovarian cancer patients’ comorbidities. Postoperative morbidity is particularly high in these patients because of their poor nutritional status, perioperative fluids shifts, and long operating times. These patients may also show excessive response to surgical stress. Innovative, randomized trials are needed to reliably determine the feasibility, safety, and effectiveness of specific ERAS interventions in ovarian cancer.

Key Words: Enhanced recovery, Fast-track, Ovarian cancer, Perioperative care, Systematic review

Received November 26, 2016, and in revised form January 13, 2017.
Accepted for publication January 18, 2017.

(Int J Gynecol Cancer 2017;27: 1274–1282)
Traditional surgical paradigms have been challenged by the development of strategies intended to reduce postoperative morbidity, hasten recovery, and reduce the length of hospital stay. Surgery provokes a physical stress response with multiorgan dysfunction. Interventions aiming at stress reduction and preservation of the patient's organ function during a surgical procedure would potentially facilitate early recovery. These multimodal interventions are referred to as “enhanced recovery after surgery” (ERAS) or “fast track” protocols and include procedures ranging from preoperative counselling, avoidance of bowel preparation, shortening of preoperative fasting, tailored anesthesia and analgesia, avoidance of drains, early postoperative feeding, and mobilization. In the mid-1990s, these principles were incorporated into elective colonic surgery but have since been embraced by other surgical disciplines. In colonic surgery, several meta-analyses have concluded that the implementation of bundled ERAS programs in patients undergoing colonic surgery reduces complications and length of stay, but they have also highlighted the potential source of bias by insufficient blinding of outcome assessments and the heterogeneity of available protocols. The contribution of individual interventions to outcome improvement could not be assessed, and the evidence for individual interventions in these ERAS protocols is highly variable. As opposed to the previously published reviews of ERAS programs in gynecologic oncology, we think that the evidence needs to be specifically assessed in ovarian cancer patients for the following reasons. First, ovarian cancer patients are in many ways distinctly different not only from other gynecologic cancer patients but also from other surgical patients. At the time of diagnosis, they often have advanced-stage disease with a high symptom burden including abdominal distension, dyspnea, nausea, impairment of gastrointestinal function, cachexia, and malnutrition. Second, they are traditionally not eligible for minimally invasive techniques, and operative procedures often include multivisceral resections with high postoperative morbidity. And third, these patients may ultimately derive the greatest benefit from a clinical pathway facilitating postoperative recovery.

This systematic review aimed to identify interventions for enhancing recovery after surgery for ovarian cancer that have sufficient supporting evidence to warrant incorporation into guidelines or sufficient promise to warrant further evaluation in clinical trials.

METHODS

We searched MEDLINE, EMBASE, and The Cochrane Library from 1946 to April 2016 for studies of ERAS protocols and of individual ERAS interventions in patients undergoing laparotomy for ovarian cancer, irrespective of their design (http://links.lww.com/IGC/A467). Studies of ERAS protocols were defined by the inclusion of more than 1 intervention in a clinical pathway. We excluded reports in languages other than English, studies that did not report the number of participants with ovarian cancer, or those focusing solely on either venous thromboembolism prophylaxis or preoperative antibiotics.

FIGURE 1. PRISMA flowchart.
Two review authors (K.L. and P.-S.K.) selected studies by first screening titles and abstracts and then obtaining and independently reviewing full-text articles to assess their eligibility. Disagreements were resolved by discussion and consultation with a third author (A.B.). References and reviews were searched for further studies. Information on study methods, participants, surgical procedures, details of the ERAS interventions, and outcomes was extracted independently by K.L. and P.-S.K. Authors of 9 articles on ERAS protocols were contacted to obtain further information about their studies, and 4 responded.

Susceptibility to bias in individual studies was assessed with the Cochrane “risk of bias” assessment tool.\(^\text{15}\) We anticipated that heterogeneity of methods and outcomes would preclude quantitative pooling and analysis, and we therefore planned the review from the outset as a narrative synthesis.

**RESULTS**

**Description of Studies**

Figure 1 summarizes the selection process for studies. Electronic searches identified 4462 articles across the 3 databases. Fifteen additional studies were identified through cross referencing. We retrieved 115 full-text articles, and 25 studies met our inclusion criteria (Fig. 1).

**Characteristics of Studies Included**

The included studies were published between 1996 and 2014 and comprised 4838 participants, 1648 of whom had ovarian cancer (Table 1). We identified 12 randomized controlled trials (RCTs), which investigated individual interventions and not ERAS protocols. Risk-of-bias assessment in the included RCTs is summarized in Table 2. The remaining 13 studies had observational designs: 6 were prospective,\(^{28-34}\) and 2 included outcomes compared with a contemporaneous control group.\(^{32,33}\)

The ERAS protocols were evaluated in 9 observational studies but no randomized trials.\(^{28-30,34-39}\) Although the studies included patients undergoing surgery by laparotomy, procedures ranged from benign abdominal hysterectomies\(^{29}\) to complex cytoreductive surgeries.\(^{36,39}\) The number of patients undergoing bowel surgery was reported in 2 studies.\(^{34,39}\) The number and type of individual ERAS interventions varied across the protocols in these studies (Table 3), but all included more than 4 interventions. The heterogeneity of early feeding interventions in these ERAS protocols is illustrated in Table 4. The level of adherence to the ERAS protocol was reported in 4 studies.\(^{29,30,36,39}\)

Outcomes were compared with historical controls in 3 studies,\(^{29,30,34}\) with conflicting results. These studies reported significantly shorter length of stay in the ERAS group, but the magnitude of the average difference varied substantially from an average of 0.3 to 3 days. Rates of severe complications and

<table>
<thead>
<tr>
<th>TABLE 1. Description of included studies</th>
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<tr>
<td><strong>Domain</strong></td>
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<tr>
<td>ERAS protocols</td>
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<tr>
<td>Early feeding</td>
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<td>Pelvic drains</td>
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<td>Orogastric tube</td>
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<td>Fluid management</td>
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<tr>
<td>Analgesia (PCEA)</td>
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<tr>
<td></td>
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<tr>
<td>Chewing gum</td>
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</tbody>
</table>

*Numbers include only studies that specified the number of patients with bowel resection.
TABLE 2. Assessment of bias in the RCTs included

<table>
<thead>
<tr>
<th>Blinding of Outcome Assessment</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Random Participant and Personnel</th>
<th>Incomplete Outcome Data</th>
<th>Selective Reporting</th>
<th>Outcome Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
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<tr>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
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<tr>
<td>Unclear risk</td>
<td>Unclear risk</td>
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<td>Unclear risk</td>
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</tbody>
</table>

Early feeding interventions were evaluated in 7 randomized trials including 947 participants (441 with ovarian cancer) and 1 observational study. Surgery ranged from radical hysterectomy with retroperitoneal lymphadenectomy to cytoreductive surgery with upper abdominal surgery and bowel resection. Patients undergoing bowel resection were excluded in 3 studies. Details of the early feeding intervention varied substantially between studies. Regular diet on day 1 was investigated by 3 RCTs and compared with nil by mouth until presence of bowel sounds or flatus in 2 trials, and clear fluids on day 1 followed by diet as tolerated in 1 trial.

Early feeding was associated with significantly faster recovery of bowel function with shorter times to flatus and to tolerance of regular diet. Significantly shorter length of stay in hospital was reported in 4 trials, with average differences ranging from 0.2 to 1.7 days. Two studies reported significantly more nausea after early feeding (43.5% vs 24.3% [P = 0.006] and 56.7% vs 23.3% [P = 0.008], respectively).

Studies Evaluating Individual Components of ERAS

Early Feeding

Early feeding interventions were evaluated in 7 randomized trials including 947 participants (441 with ovarian cancer) and 1 observational study. Surgery ranged from radical hysterectomy with retroperitoneal lymphadenectomy to cytoreductive surgery with upper abdominal surgery and bowel resection. Patients undergoing bowel resection were excluded in 3 studies. Details of the early feeding intervention varied substantially between studies. Regular diet on day 1 was investigated by 3 RCTs and compared with nil by mouth until presence of bowel sounds or flatus in 2 trials, and clear fluids on day 1 followed by diet as tolerated in 1 trial.

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Perioperative Fluid Management

We identified no study that assessed fluid management in general in patients undergoing surgery for ovarian cancer. Specific intraoperative fluid management interventions such as esophageal Doppler monitoring (ODM) to guide fluid management in gynecologic oncology were investigated in 2 studies, 1 RCT and 1 prospective observational study. The RCT of 102 participants comparing ODM versus fluid management at the anesthetist’s discretion reported no differences in the length of hospital stay, total volume of intraoperative fluid, postoperative complications, or time to recovery of gastrointestinal function. Fluid management in the ODM group followed an algorithm that defined the administration of fluid boluses based on Doppler-estimated stroke volume. In the other study, variations in anesthetic practice were associated with distinct differences in fluid management (ODM vs standard hemodynamic monitoring). When ODM was used, fluid boluses were given based on the Doppler estimations of stroke volume, descending aortic corrected flow time, and cardiac output. This study reported that ODM patients had a better postoperative recovery (odds ratio, 2.83; 95% confidence interval, 1.20–6.68; P = 0.02) and fitness for discharge prior to or on day 5 (odds ratio, 2.81; 95% confidence interval, 1.01–7.78; P = 0.05). There were no differences in postoperative complications.

Postoperative Analgesia

Patient-controlled thoracic epidural analgesia (PCEA) and patient-controlled intravenous analgesia after gynecologic cancer surgery were compared in 2 studies (1 RCT and 1 prospective cohort study) with conflicting efficacy results. The RCT including 135 participants found lower pain scores at rest on the first postoperative day and less pain when...
coughing in the first 3 postoperative days, but significantly more pruritus and urinary retention in this group with PCEA. The other study showed no significant differences in pain scores between the groups, but 24% of patients with PCEA needed additional intravenous analgesia. Neither study found differences in nausea, vomiting, postoperative ileus, or time to discharge.

Avoidance of Drains and Nasogastric Decompression

The early removal of an orogastric tube versus leaving a nasogastric tube until return of bowel function was studied in 1 RCT including 109 participants. After early tube removal, patients had significantly shorter time to return of bowel function and less subjective complaints, but there were no differences in time to tolerating normal diet and length of hospital stay.

The omission of pelvic drains after abdominal surgery was evaluated in 1 RCT and 1 retrospective study. The RCT compared clinical outcome in 137 participants after lymphadenectomy followed by either no retroperitoneal drains versus low-pressure drains. Patients with drains had more postoperative complications (43% vs 22%,  = 0.01), particularly symptomatic lymphocysts, and the median length of hospital stay was 4 days longer ( < 0.0001). However, these patients were not discharged until after drain removal.

A retrospective study of 43 ovarian cancer patients with anastomotic leak after primary large bowel anastomosis reported that only 11% had no drain after the initial surgery. However, the observational design of this small study does not allow reliable conclusions on benefits of drains in detecting anastomotic leak or in reducing mortality.

Postoperative Chewing Gum

The effect of chewing gum after surgery on postoperative gastrointestinal function was studied in an RCT of 152 gynecologic cancer patients. Patients with extensive upper abdominal or bowel surgery were excluded. The intervention group chewed sugar-free gum for at least 30 minutes 3 times a day, starting on the first postoperative day and continued until the return of bowel function (not further specified). Controls received no additional treatment. Gum chewing was associated with significantly reduced times to first flatus (34 ± 11.5 vs 43.6 ± 14.0 hours,  < 0.001), first bowel motion (49.6 ± 18.7 vs 62.5 ± 21.5 hours,  < 0.001), tolerance of diet (4.0 ± 0.8 vs 5.0 ± 0.9 days,  < 0.001), and length of hospital stay (median, 5.9 vs 7.0 days;  < 0.001). Patients were treated in a standardized, rather conservative, clinical pathway including the removal of a nasogastric tube on day 1 and commencement of a semiliquid diet upon passing of flatus.

DISCUSSION

We identified no RCTs of ERAS protocols in patients with ovarian cancer. The observational studies of ERAS protocols were heterogeneous in their design, composition of interventions, specific interventions, patient selection, and surgical procedures. Randomized trials of individual ERAS

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative Education and Counselling</th>
<th>No Routine Oral Bowel Preparation</th>
<th>Preoperative Fasting for Fluids &lt;6 h</th>
<th>Oral Carbohydrate Loading</th>
<th>Avoidance of Long-acting Sedative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter et al 37</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wijk et al 29</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>de Groot et al 30</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Kalogera et al 36</td>
<td>X</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sidhu et al 28</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cascales Campos et al 35</td>
<td>X</td>
<td>Yes</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Chase et al 38</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Gerardi et al 39</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Marx et al 34</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
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\(\checkmark\), Specified in study protocol; X, not specified in protocol or not included in ERAS protocol.

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of Early Feeding</th>
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<tbody>
<tr>
<td>Carter et al 37</td>
<td>Day 1 light diet, day 2 normal diet</td>
</tr>
<tr>
<td>Wijk et al 29</td>
<td>Normal diet 2 h postsurgery</td>
</tr>
<tr>
<td>de Groot et al 30</td>
<td>Day 0 fluids, day 1 normal diet</td>
</tr>
<tr>
<td>Kalogera et al 36</td>
<td>Low residual diet 4 h postsurgery</td>
</tr>
<tr>
<td>Sidhu et al 28</td>
<td>Day 0 free fluids, day 1 light diet</td>
</tr>
<tr>
<td>Cascales Campos et al 35</td>
<td>Oral diet day 1</td>
</tr>
<tr>
<td>Chase et al 38</td>
<td>Day 1 clear fluids, advance as tolerated</td>
</tr>
<tr>
<td>Gerardi et al 39</td>
<td>Diet advancement to clear fluids prior to first flatus</td>
</tr>
<tr>
<td>Marx et al 34</td>
<td>Oral diet 4 h postsurgery</td>
</tr>
</tbody>
</table>
components were also heterogeneous and of moderate size, but provided support for the safety and efficacy of early postoperative feeding.

**Applicability of Evidence**

We searched specifically for studies including ovarian cancer patients, but unlike the recent Cochrane review on perioperative feeding interventions,\(^{31}\) we did not presuppose a required proportion of patients with ovarian cancer to be included. The applicability of our findings is therefore limited by the fact that only 34% of the study participants had ovarian, fallopian tube, or peritoneal cancer. Furthermore, the scope of surgery, if described, encompassed a wide range of procedures. Only a minority of studies included patients undergoing extensive cytoreductive surgery with multivisceral resections. These patients are in particular at high risk of postoperative morbidity because of their poor nutritional status, perioperative fluids shifts, and extended operating times. Also, these patients may show excessive response to surgical stress with metabolic catabolism and systemic inflammatory response syndrome. Even though we collected information on the number of ovarian cancer patients undergoing bowel resection, this information is obviously only a poor surrogate for the complexity of the surgery. This limits the generalizability of our findings to patients with advanced-stage ovarian cancer. The applicability of studies testing individual interventions is limited by differences in preoperative and postoperative care. Their efficacy is less certain within standardized clinical protocols.

**Quality of the Evidence**

We found limited high-quality evidence for the efficacy of ERAS protocols or specific ERAS interventions, despite a comprehensive search strategy and inclusive eligibility criteria to identify pertinent studies. Publication bias and, to a lesser extent, the exclusion of studies in languages other than English may have biased our findings toward results favoring ERAS interventions.

The collected data on ERAS within gynecologic oncology need to be acknowledged, but studies of ERAS protocols including women with ovarian cancer were highly susceptible to selection bias and confounding because of their observational designs.

None of the studies of ERAS protocols included a contemporaneous control group, and they were all single-site studies. The available studies of ERAS protocols involve bundles of interventions that varied between individual studies. The fact that these heterogeneous bundles have shown to be beneficial in observational studies does not allow reliable inferences about efficacy or safety. Compliance within ERAS protocols has been insufficiently investigated but has been reported to be crucial for the success of the program.\(^{32}\)

Studies of individual ERAS interventions included 12 RCTs with an average sample size of 132 participants (range, 51–254 participants). The moderate sample size of the individual trials (all but 2 trials included <200 participants) and the inconsistent definition and adequate reporting of a primary end point increased the risk of overstating the efficacy of the interventions. The included RCTs were prone to performance and detection bias. Given the nature of the interventions, it was impossible to blind participants and/or study investigators to the interventions. Clinical outcomes were also mostly assessed by a clinician not blinded to the patient allocation. We identified 2 prospective studies on individual interventions with contemporaneous controls,\(^{32,33}\) but allocation bias on behalf of the anesthetic team may have influenced the results.

**Comparison With Previous Reviews and Implications for Practice and Research**

Three previous systematic reviews have assessed the current evidence for ERAS in gynecologic oncology,\(^{10-12}\) 2 of them providing a detailed search strategy and information on study selection.\(^{11,12}\) One included studies on patients with both malignant and benign conditions.\(^{11}\) The review concurred with ours that the available evidence on ERAS in
gynecologic oncology is based on a range of nonrandomized studies at high risk of bias. Our review adds to these reports by assessing evidence about individual ERAS interventions, including RCTs on interventions relevant to ovarian cancer patients. Recently, the Enhanced Recovery After Surgery Society has published guidelines for the perioperative management of patients with gynecologic cancer. These guidelines acknowledge the heterogeneity in the level of evidence for specific interventions. For many interventions, the level of evidence was graded as moderate or low, indicating the need for more research to assess their impact on outcome improvement. However, while not taking resource utilization into account, the recommendations also considered the balance between desirable and undesirable effects. Thus, low-quality data could be sufficient to strongly recommend an intervention when no harm was to be expected. Furthermore, recommendations were based on findings from other surgical disciplines where there were no sufficient data in gynecologic oncology. The most robust evidence is available for early feeding interventions, even though the majority of studies were conducted at a time when the concept of a multimodal approach to improve perioperative care was still in its infancy. This was confirmed by a Cochrane review showing that early feeding after major gynecologic surgery hastens recovery of bowel function without increasing gastrointestinal morbidity. The role of early feeding in ovarian cancer patients with the potential of gastric paresis after extensive upper gastrointestinal surgery is less well studied, but one may be able to extrapolate from findings in surgical patients undergoing upper gastrointestinal procedures where early feeding seems to be safe and associated with shorter length of stay. Even though the definition varied, early feeding was the only ERAS component that was included in all ERAS protocols. Mechanical bowel preparation and the routine use of abdominal drains have not been shown to be beneficial in colorectal surgery. Uncertainty remains regarding the role of bowel preparation in surgical procedures that involve anastomoses below the peritoneal verge and the role of drains in patients at high risk of postoperative fluid collections (ie, after full peritonectomy). Published ERAS protocols in patients undergoing peritonectomy procedures and hyperthermic intraperitoneal chemotherapy still use intra-abdominal drains postoperatively, and less than half of the reviewed ERAS protocols here have specifically avoided the use of drains in their pathway. The variable uptake of the omission of these procedures may be due to ongoing uncertainty about the applicability of evidence from either nonovarian cancer surgery or less complex surgeries in gynecologic malignancies or strong beliefs in traditional surgical paradigms.

Reduced fasting times and the administration of carbohydrate loading have been part of some of the published ERAS protocols included in this review. Particularly, the additional benefit of carbohydrate loading in the context of reduced fasting times is uncertain. Postoperative interventions to enhance recovery of gut function such as gum chewing have promising preliminary data, but their efficacy in a contemporary clinical pathway and well-designed trials still needs to be determined.

Perioperative fluid management impacts on cardiac and pulmonary function, tissue perfusion and oxygenation, wound healing, and postoperative ileus and renal function. Optimizing fluid management is important for enhancing recovery after surgery. However, the optimal fluid management, hemodynamic parameters, and monitoring strategies to guide fluid management in ovarian cancer patients remain unknown. Studies on esophageal Doppler ultrasound, an invasive technique requiring specific expertise, have been inconclusive in these patients where fluid management is further complicated by extensive fluid shifts during and after surgery because of low albumin levels, ascites, and the risk of postoperative fluid collections. Fluid management in the RCT also in the control arm was restrictive compared with previous trials on ODM, and the potential benefits may have been further negated by the rather conservative perioperative management in the trial.

Multimodal analgesia should aim to minimize opioid administration to avoid impairment of bowel function, but the optimal analgesic regimen may also be dependent on the clinical setting (eg, availability and experience with epidural anesthesia administration) and the management of adverse effects (eg, avoidance of fluid loading in the management of epidural anesthesia-induced hypotension).

Thromboembolic and antibiotic prophylaxis are certainly important in women undergoing surgery for advanced-stage ovarian cancer and may be considered standard of care. However, these 2 topics were considered beyond the scope of this review.

CONCLUSIONS

There is limited high-quality evidence about individual interventions designed to enhance recovery after surgery for ovarian cancer and no high-quality evidence about protocols including multiple such interventions. The available data on heterogeneous bundles of interventions do not obviate the need to determine whether the interventions work, either as a package or individually. Because length of stay may not be the most important parameter when delivering quality care to patients, clinically more relevant outcome measures, which also include patient-reported outcomes, should be assessed.

Some components of ERAS are already standard of care, and innovative prospective clinical research studies, including RCTs of specific interventions depending on what is already standard of care at specific sites, are needed to determine the benefits and costs of ERAS interventions in advanced-stage ovarian cancer surgery before untested interventions become entrenched as standard of care. This is especially important because many ERAS interventions are resource intense, and adherence may be impaired by the complexity of the pathway.

REFERENCES


Enhanced Recovery After Surgery for Suspected Ovarian Malignancy
A Survey of Perioperative Practice Among Gynecologic Oncologists in Australia and New Zealand to Inform a Clinical Trial

Kristina Lindemann, MD, PhD,*Þþ Peey-Sei Kok, MD,*† Martin Stockler, MD, PhD,*† Peter Sykes, MD,¶ and Alison Brand, MD, PhD†‡**

Objectives: The objective of this survey was to review the current standard of perioperative care of patients with suspected advanced ovarian cancer in Australia and New Zealand in order to determine the level of equipoise for specific interventions.

Methods: In May 2016, a web-based questionnaire (SurveyMonkey Inc, Palo Alto, CA) was sent to all gynecologic oncologists in Australia and New Zealand (n = 56). Descriptive statistics were used.

Results: Response rate was 75%. Prevention of hypothermia, extended thromboembolic prophylaxis, antibiotic prophylaxis, and the avoidance of the routine use of drains were standard of care. Bowel preparation was given by 10% routinely and by 35% when bowel resection was planned. Fasting times for fluids of six hours or more were common (55%). Only 26% had shortened fasting times of two hours. Twelve percent used carbohydrate loading. The majority of patients started a light diet within the first postoperative day and advanced diet subsequently as tolerated. Six respondents (15%) used thoracic epidural, whereas the majority (73%) administered an opioid-based intravenous patient-controlled analgesia as the predominant postoperative analgesia, mainly as part of a multimodal pain management. The majority of respondents expressed an interest in a trial concept of individual ERAS interventions.

Conclusions: Only a minority of ERAS interventions can be considered standard of care in ovarian cancer surgery. The existing level of equipoise among gynecologic oncologists in Australia and New Zealand, and their interest in a trial concept of individual ERAS interventions allows further assessment of the feasibility and efficacy of interventions in a randomized controlled trial.

Key Words: ERAS, Fast-track, Ovarian cancer, Perioperative care, Survey

Received October 16, 2016, and in revised form January 20, 2017. Accepted for publication February 20, 2017. (Int J Gynecol Cancer 2017;27: 1046–1050)
Recently, traditional surgical paradigms have been challenged by the development of clinical pathways aiming at reducing morbidity, speeding recovery, and ultimately at shortening hospital stays.1 These enhanced recovery after surgery (ERAS) principles have been developed in colorectal surgery but have since been adopted by other disciplines. The Enhanced Recovery After Surgery Society was formed to define a standardized approach to “multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery.” Recently, guidelines for the care of gynecologic cancer patients have been released,2,3 but in the absence of randomized controlled trials of ERAS principles in gynecologic cancer,4 evidence has mainly been derived from observational studies, which often include a broad range of interventions and surgical procedures. Surgeries in these studies ranged from minimally invasive procedures for benign conditions to cytoreductive surgery for ovarian cancer. Despite the lack high-quality evidence, perioperative care has evolved, and many interventions aiming at enhanced recovery have been implemented in daily practice. Yet, one survey in gynecologic oncology and several in other disciplines have revealed a variable degree of uptake underlining the piecemeal implementation of ERAS principles.5–11

The objective of this survey was to review the current standard of perioperative care of patients with suspected advanced ovarian cancer in Australia and New Zealand in order to determine the level of equipoise for specific interventions. We also assessed the general interest in a trial concept on individual interventions of an enhanced recovery pathway.

MATERIALS AND METHODS

In May 2016, a web-based questionnaire using the survey tool SurveyMonkey (SurveyMonkey Inc, Palo Alto, CA) was sent to all currently practicing gynecologic oncologists listed in the ANZGOG (Australia New Zealand Gynaecological Oncology Group) and ASGO (Australian Society of Gynaecologic Oncologists) databases. The survey was also distributed at the Annual Scientific Meeting of ASGO held in May 2016, and respondents could fill out the survey on site. Two subsequent reminders were sent until an insignificant increase in response rate was achieved. The survey was developed using validated research techniques of surveying physicians.12 The survey inquired about specific components of perioperative practice, and the respondents were asked to provide this information regarding their current clinical care for patients with suspected ovarian cancer treated in the public sector. The questions in the first part of the survey were constructed using the ERAS guidelines for gynecology2,7 as a framework to delineate components of perioperative practice. In the second section of the questionnaire, participants were asked about their interest in a trial concept evaluating individual interventions of an ERAS pathway. We specifically asked to rate the interest in a given intervention on a scale of 1 to 4 (where 1 = not interesting and 4 = very interesting) and inquired about the willingness and ability to randomize patients to these interventions.

Statistical Analysis

Descriptive analyses were used. Percentages were calculated with the number of respondents who answered the question as denominator. The STATA statistical package, version 12.0 (Stata Corp LP, College Station, TX), was used for the data analyses.

RESULTS

Study Population

Of 56 invited gynecologic oncologists, 42 (75%) responded. Respondents treated a median of 25 patients per year with suspected advanced ovarian cancer (range, 0–120) in the public sector. The vast majority (95%) reported they performed bowel surgery in 30% of the patients or fewer. Despite the fact that only a third of the respondents followed a written ERAS protocol, 81% of the respondents provided ERAS-specific counseling to their patients prior to surgery (55%) (Fig. 1a).

Preoperative Interventions

Bowel preparation was administered by 36% of respondents when a bowel resection was planned. Only 10% administered it routinely. Most of those who administered bowel preparation used oral bowel preparation alone or with an enema. Fasting times for fluids of six hours or more were common (55%). Only 26% had shortened fasting times of two hours prior to induction of anesthesia (Fig. 1b).

Carbohydrate loading was infrequently used (12%) and was administered on the day of surgery in all cases (Fig. 1c).

A combination of cephalosporin and metronidazole was commonly used as antibiotic prophylaxis (71%) and

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FIGURE 1. a–d, Preoperative ERAS components.
administered at 60 minutes or less before skin incision (52%) or at induction of anesthesia (14%). The remaining surgeons started the antibiotics at skin incision. Prolonged antibiotic prophylaxis was mainly considered in patients with operative times of three hours or more.

Only a minority respondents administered premedications (17%) (Fig. 1d) with either benzodiazepines or pregabalin/gabapentin (alone or in combination with nonsteroidal anti-inflammatory drugs or paracetamol).

**Perioperative and Postoperative Interventions**

All respondents used thromboembolic prophylaxis with either perioperative pneumatic compression devices and/or compression stockings. Thromboembolic prophylaxis was extended for at least four weeks by 62%. However, 14% of the respondents administered it only until discharge.

The majority (98%) prevented intraoperative hypothermia using an active warming device. A third of the respondents reported commencing the device in the anaesthetic bay (32%), as opposed to in the operating theater.

Prophylaxis of postoperative nausea and vomiting (PONV) was given by 81% of the respondents, and 62% used at least two drugs in the management of PONV (Fig. 2a). Various combinations of dopamine and serotonin antagonists, antihistamines, and/or corticosteroids were administered. The vast majority did not follow a written protocol for fluid management (90%). An overview of the reported fluid as well as anaesthetic regimen is provided in Figures 2b and c.

Pelvic drains were not routinely used. However, 14% used a pelvic drain in conjunction with any bowel resection; another 14% used it only after a low rectal anastomosis.

Even though the commencement of a light diet was highly variable (Fig. 2d), the majority (76%) started within the first postoperative day and advanced diet subsequently as tolerated. Only 2% routinely offered a normal diet to the patient on day 0.

There was significant heterogeneity in the type of postoperative analgesia used, including intravenous patient-controlled (IV PCA), locoregional (thoracic and lumbar epidural analgesia, single-shot spinal with intrathecal morphine), and local analgesia (eg, local wound infiltration, transversus abdominis plane block). Six respondents (15%) used thoracic epidural (EDA), whereas the majority (73%) administered an opioid-based IV PCA as an adjunct to local or locoregional analgesia, such as transversus abdominis plane block, single-shot spinal with intrathecal morphine, or wound infiltration. A multimodal approach to postoperative analgesia, defined as the administration of at least two types of analgesics, was the standard for the majority (98%) including either oral or IV opioids in 83%. Other combinations included paracetamol, nonsteroidal anti-inflammatory drugs, and/or pregabalin/gabapentin.

Prophylaxis of postoperative ileus was routinely administered by 17%, either with laxatives or postoperative gum chewing (in combination or alone). Almost half of the respondents reported that they followed a written protocol for postoperative mobilization (43%), as opposed to general encouragement of postoperative mobilization, but the specifics of these protocols varied widely.

**Interest in Potential Trial Concept on ERAS Components**

Eighty-eight percent of the respondents completed this part of the survey. In particular, interventions aiming at shortening of fasting times, carbohydrate loading, and enhanced postoperative bowel function were rated as at least somewhat or very interesting by 73% to 95% of the respondents. Eighty percent to 97% expressed their willingness to randomize patients in a trial concept of these individual ERAS interventions. Despite the general interest in interventions relating to anaesthetic and fluid management of ovarian cancer patients, only 69% and 57%, respectively, were willing or able to randomize to such interventions.

**DISCUSSION**

This survey assessed patterns of current perioperative care in patients undergoing surgery for ovarian cancer in Australia and New Zealand. Even though only a minority of surgeons followed a written ERAS protocol, patients were counseled specifically for ERAS principles acknowledging the impact of patients’ commitment to the program. Certain aspects of a clinical pathway of enhanced recovery such as the prevention of hypothermia, thromboembolic and antibiotic prophylaxis, and the avoidance of the routine use of
drains have widely been implemented in current practice. However, there was significant heterogeneity in preoperative fasting and postoperative feeding routines, postoperative pain and fluid management, and prophylaxis of nausea and vomiting.

The ERAS principles were initially developed in colorectal surgery, and several surveys have assessed patterns of care among colorectal surgeons outside clinical trials.\textsuperscript{8,10,13} Despite some regional differences, bowel preparation was widely used in 2003.\textsuperscript{8} More recent guidelines have adopted the recommendation to omit routine bowel preparation in colonic surgery.\textsuperscript{14} Still, a randomized study on an ERAS protocol in patients undergoing colorectal resection left it to the attending surgeon to determine whether bowel preparation was necessary and reported its omission in only 25% of the patients in both arms.\textsuperscript{15} Bowel preparation can be considered standard of care in Germany,\textsuperscript{11} whereas a Dutch single-center study reported that bowel preparation was avoided in 90% of gynecologic oncological procedures.\textsuperscript{16} In Australia and New Zealand, 55% of gynecologic oncologists have completely abandoned this procedure regardless of a planned bowel resection.

Preoperative fasting of three hours and preoperative carbohydrate loading have been reported in 61% of colorectal surgery patients, even outside clinical trials.\textsuperscript{9} This is in contrast with patterns of care reported in vascular surgery,\textsuperscript{5} gynecology,\textsuperscript{11} and in this survey, where the majority used fasting times exceeding six hours and rarely administered carbohydrate loading. The most recent ERAS guidelines advocate for a regular diet within the first 24 hours.\textsuperscript{3} However, even after the implementation of an ERAS protocol, only 58% of gynecologic oncology patients were reported to be given a normal diet on day 1.\textsuperscript{16} The majority of patients in Australia and New Zealand were offered a light diet in the first 24 hours after surgery, but only 2% of the surgeons routinely offered a normal diet on the day of their surgery. Thoracic EDA has emerged as the standard locoregional analgesia in colorectal surgery and has been reported to be used in 93% of the procedures.\textsuperscript{8} Centers in the Netherlands and Germany routinely administered an EDA for patients undergoing gynecologic oncology procedures.\textsuperscript{11,16} In Australia and New Zealand, IV PCA was most commonly used for patients undergoing surgery for ovarian cancer, but in all cases as part of a multimodal analgesic management. Only 15% used thoracic EDA as the predominant analgesia. The more frequent use of IV PCA in this survey may reflect the concern of fluid overload to compensate EDA-associated hypotension and prolonged urinary catheter use in patients with EDA. There have also been concerns about the necessity for additional PCA in cases with inadequate pain relief.\textsuperscript{17} Evidence in colorectal surgery suggests that perioperative fluid overload delays the return of gastrointestinal function and prolongs hospital stay,\textsuperscript{18} whereas fluid restriction aiming at maintenance of weight may reduce cardiopulmonary and wound complications.\textsuperscript{19} The heterogeneity in perioperative fluid management reported here suggests that the optimal regimen in surgery for ovarian cancer has not yet been determined. The detailed evaluation of goal-directed fluid therapy was beyond the scope of this survey, and the hemodynamic parameters and monitoring strategies that were utilized to guide goal-directed fluid management were not assessed.

The strengths of this survey include its response rate of 75% and the assessment of all components of perioperative care. Analysis of the results was done anonymously and did not allow for the quantification of differences between nonresponders and responders. Response bias was minimized by giving respondents enough time to complete the survey and by giving them the option to reopen and complete the survey in case they needed to obtain information from other staff members (eg, anesthetists). Response bias may still have influenced the results because respondents may have answered questions in a way that overestimates the adherence to ERAS principles.

This survey also aimed to determine the level of equipoise among gynecologic oncologists to test individual interventions and to assess the potential interest in this trial concept. The differing level of heterogeneity of specific interventions may help to guide the trial design. Extended thromboembolic prophylaxis and antibiotic prophylaxis, the prevention of hypothermia, and the avoidance of drains can be considered standard of care. National guidelines have facilitated the implementation of antibiotic prophylaxis in clinical practice. There is also growing evidence supporting the prolonged use of thromboembolic prophylaxis after cancer surgery.\textsuperscript{20} Early feeding practices have been adopted widely, but the optimal feeding protocol still needs to be determined. Multimodal postoperative analgesia is routinely used, but the best combination of analgesics and the role of preemptive analgesia in opioid-sparing pain management is less well defined. This applies also to the prophylaxis of PONV where the optimal combination of antiemetic drugs is still uncertain. Even though reduced fasting times seem promising, the optimal duration of fasting is unclear, as well as the role of preoperative carbohydrate loading. The existing level of equipoise warrants further assessment of the feasibility and efficacy of these interventions in a randomized controlled trial. The heterogeneity of fluid management underlines the uncertainty regarding the optimal care in ovarian cancer. Further research on how to monitor fluid management intraoperatively is needed. Trials in enhanced recovery are certainly challenged not only by the heterogeneity in current practice but also by the necessity in multidisciplinary collaboration, especially in interventions involving anaesthetic management. This is confirmed by the finding that surgeons would be more willing and able to randomize to interventions without such interface.

The piecemeal uptake of ERAS principles has been reported in several disciplines.\textsuperscript{7,9,11} Reasons for the variable implementation may include difficulties in multidisciplinary collaboration and in adherence to a clinical protocol outside a clinical trial, as well as lack of financial resources. Furthermore, surgeons may be uncertain about the generalizability of evidence on ERAS derived from other surgical disciplines because of the larger scope of surgery and comorbidities in patients with advanced ovarian cancer. Most importantly, procedure-specific evidence on ERAS interventions must be established. This survey confirms the high interest in testing ERAS principles in a randomized
controlled design. We also demonstrated the appropriate level of equipoise for specific interventions among gynecologic oncologists in Australia and New Zealand to design such a trial concept.

ACKNOWLEDGMENTS

The authors thank Prof Hayne Dickon (Department of Surgery, Fiona Stanley Hospital, The University of Western Australia) and Elisa Poviano (Department of Surgical Sciences, University of Turin and Obstetrics and Gynecology Unit, Martini Hospital, Turin, Italy) for their support in designing the survey. They also acknowledge the help of Sarah Hope (Australia New Zealand Gynaecological Oncology Group, Assoc Prof Jim Nicklin (Director of Gynaecological Oncology, The Wesley Hospital, Brisbane, Australia), and Ken Jaaback (Department of Gynaecological Oncology, John Hunter Hospital, Newcastle, Australia) in the administration of the survey.

REFERENCES

Evaluating Maternity Units: a prospective cohort study of freestanding midwife-led primary maternity units in New Zealand—clinical outcomes

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ABSTRACT

Objective To compare maternal and neonatal birth outcomes and morbidities associated with the intention to give birth in a freestanding primary level midwife-led maternity unit (PMU) or tertiary level obstetric-led maternity hospital (TMH) in Canterbury, Aotearoa/New Zealand.

Design Prospective cohort study.

Participants 407 women who intended to give birth in a PMU and 285 women who intended to give birth at the TMH in 2010–2011. All of the women planning a TMH birth were 'low risk', and 29 of the PMU cohort had identified risk factors.

Primary outcomes Mode of birth, Apgar score of less than 7 at 5 min and neonatal unit admission. Secondary outcomes: labour onset, analgesia, blood loss, third stage of labour management, perineal trauma, non-pharmacological pain relief, neonatal resuscitation, breastfeeding, gestational age at birth, birth weight, severe morbidity and mortality.

Results Women who planned a PMU birth were significantly more likely to have a spontaneous vaginal birth (77.9% vs 62.3%, adjusted OR (AOR) 1.61, 95% CI 1.08 to 2.39), and significantly less likely to have an instrumental assisted vaginal birth (10.3% vs 20.4%, AOR 0.59, 95% CI 0.37 to 0.93). The emergency and elective caesarean section rates were not significantly different (emergency: PMU 11.6% vs TMH 17.5%, AOR 0.88, 95% CI 0.55 to 1.40; elective: PMU 0.7% vs TMH 2.1%, AOR 0.34, 95% CI 0.08 to 1.41). There were no significant differences between the cohorts in rates of 5 min Apgar score of <7 (2.0% vs 2.1%, AOR 0.82, 95% CI 0.27 to 2.52) and neonatal unit admission (5.9% vs 4.9%, AOR 1.44, 95% CI 0.70 to 2.96). Planning to give birth in a primary unit was associated with similar or reduced odds of intrapartum interventions and similar odds of all measured neonatal well-being indicators.

Conclusions The results of this study support freestanding midwife-led primary-level maternity units as physically safe places for well women to plan to give birth, with these women having higher rates of spontaneous vaginal births and lower rates of interventions and their associated morbidities than those who planned a tertiary hospital birth, with no differences in neonatal outcomes.

INTRODUCTION

In Aotearoa/New Zealand, birthplace options include 18 secondary-level and 6 tertiary-level obstetric-led maternity hospitals (TMHs), which have midwifery and specialist obstetric, anaesthetic and paediatric services onsite; 54 freestanding primary level midwife-led maternity units (PMUs) offering birthing facilities, which have midwifery services onsite and funded home birth.1 In 2014, 87.6% of births occurred in a secondary or tertiary hospital, 9.1% in a freestanding PMU and 3.4% were home births.2 This study examined outcomes for women who planned to give birth in the
The contemporary international research into the comparative clinical outcomes for PMUs and obstetric-led hospitals (TMH/OU) include prospective cohort studies, retrospective studies and population-based cohort studies. All but three of these studies report the same pattern of similar or improved neonatal outcomes and reduced ‘interventions’ (such as labour augmentation, instrumental assisted birth, episiotomy and emergency caesarean section) and their associated maternal morbidity for women planning a PMU birth, when compared with women of similar well-being (risk status) planning a TMH birth. The three discrepant studies, which report worse neonatal outcomes for PMU babies than those born in an OU, are population-based studies from the USA. The lack of integration of midwifery and midwife-led maternity units (birth centres) in the American maternity system arguably limits the applicability of these, and other research from the USA, to the neonatal unit. Secondary outcomes were onset of labour, analgesia, blood loss, management of third stage of labour, perineal trauma, non-pharmacological pain relief, neonatal resuscitation, breastfeeding, gestational age at birth, birth weight, severe morbidity and mortality.

METHODS
Sample and recruitment
The study was set in the Christchurch area, in Canterbury. There is a TMH and four PMUs in the area. Two of the PMUs are located semi-rrurally outside the city boundaries (19.6 and 35.4 km from the TMH), and the two urban units are situated on hospital sites but operate independently as freestanding primary maternity units (3.8 and 10.8 km from the TMH). Women who develop complications are transferred to the TMH. The TMH has a neonatal unit (NNU) which includes a tertiary level neonatal intensive care unit and lower level special care nursery.

All of the women invited to join the study had a midwife as their Lead Maternity Caregiver (LMC), who provided continuity of care from booking until 6 weeks post partum. The clients of 95% of local midwives were invited. The midwives were either members of the New Zealand College of Midwives’ owned Midwifery Provider Organisation (MMPO)—90% of local midwives—or they had agreed to complete the forms required (17 midwives). Only 5% of local midwives, who were not members of the MMPO, did not agree to complete the forms required. All eligible women booked to give birth in any one of the four PMUs were invited to participate. Women who booked to the tertiary hospital were invited, if they were well (at ‘low risk’ of pregnancy complications) based on information on the hospital booking form. An a priori decision was made to invite all women booked to give birth in any one of the PMUs to participate, regardless of the presence of risk factors. For the purposes of this study, women with ‘risk factors’ were defined as those with any level two or three referral criteria as defined in the New Zealand Maternity Referral Guidelines. For example, women who had had a previous caesarean section or were expecting twins were ineligible. Eligible women were invited to participate via a postal invitation to join the study, with a phone follow-up to those who did not respond. After 6 months of recruitment, ethics approval was sought and granted to change the study protocol and extend the follow-up calls from only PMU booked to both PMU-booked and TMH-booked eligible women, when it became evident that they were an effective recruitment tool. The recruitment rates for each group then became similar for the two cohorts. Women were able to join the study any time after hospital booking and before labour.

Recruitment began in March 2010, was suspended for 1 month after a major earthquake in September 2010 and stopped prematurely after a subsequent severe earthquake in February 2011. Following the September earthquake, two PMUs were closed for a week and
services resumed within 2 weeks. After the February earthquake, the city’s busiest PMU closed and was subsequently demolished, and another was closed for 7 weeks. The semi-rural PMUs remained open. The TMH was also affected through damage to its water supply and drainage systems but remained open. Participants gave birth between March 2010 and August 2011, with 39% giving birth before the first earthquake, 41% between the two major quakes and 20% after the February earthquake. Figure 1 details the study recruitment, inclusions and exclusions details.

**Data collection**

The clinical outcome data for 88% of participants were collected from data submitted by midwives to the MMPO. Participants’ midwives also completed the ‘Midwives...
Transfer Form’ to collect some data not captured by the MMPO database. The remaining 12% of data were provided by 17 midwives, who were not members of the MMPO, on customised study forms. Data collected (including that from the 6-week postpartum survey) were manually checked for completeness and accuracy, with incomplete or inconsistent records followed-up with the MMPO database staff, the participants’ midwives or hospital records.

Data analysis

Women’s outcomes were analysed by stated intention to give birth either in a PMU or TMH at the time of study entry. Measures of categorical data were analysed with $\chi^2$ tests and continuous data were analysed using t-test. Fisher’s exact test was used with cell size <5 (need for neonatal resuscitation variable). Independent variables known from prior studies to be associated with the outcome of interest were examined. Those variables found to be associated in the univariate analysis with p<0.05 were then examined in multivariate models. ORs with 95% CIs were calculated for the primary and secondary outcomes. Multivariate logistic regression was used for dichotomous outcomes to adjust for relevant confounders. Likelihood ratio tests were used to assess the contribution of each independent variable nested in the full model. Adjustments for all outcomes are outlined below the tables. Multivariate regression models were restricted to subjects with no missing values. No inferential statistics were carried out on severe maternal/neonatal morbidity and mortality outcomes due to the rarity of events and small numbers involved.

RESULTS

Participants

A total of 702 women joined the study based on their intended birthplace. Overall approximately 30% of those invited joined the study; this included women who were followed-up by telephone. Figure 1 details the study’s recruitment, inclusions and exclusions. The cohort allocation was based on the intended birthplace the women identified on their study consent form. Among the 10 women excluded from the TMH cohort analysis due to their risk status, which was subsequently identified from the database, were two women having twins, three women with BMI >40 and three women with a ‘neurological disorder’ (eg, epilepsy). Among the 29 women included in the PMU cohort identified as having ‘risk factors’ were 15 women with body mass indices (BMIs) of 35–42, 2 with a ‘neurological disorder’, 7 with ‘thyroid disease’ and 2 with previous caesarean (and subsequent vaginal birth). While women who have had caesareans previously are not recommended for primary unit birth in New Zealand, these two women had their PMU booking accepted. Consequently, 29 PMU women with known risk factors, and no TMH women with known risk factors or complications which made them unable to book at a PMU, were included in the analysis. There was no loss to follow-up.

Approximately half (46.9%) of the women who intended to give birth in a PMU did so, with most plan changes occurring antenatally or in labour prior to admission. Only 12.6% of those admitted to a PMU in labour were transferred to the TMH, a further 4.7% transferred between birth and 48 hours (four women, five babies), giving a total postadmission transfer rate of 17.3%. Details of the rates, reasons timing, urgency and outcomes of transfers have been reported previously. 18

Table 1 shows the demographic differences between the groups. There were some significant differences between the two cohorts. The women who planned to give birth in a PMU were younger, heavier, more likely to have given birth before, to be Māori and to live rurally, than the women who planned to give birth in the TMH. There were no differences in the groups’ smoking or relationship status. Additionally, data on the participants’ income and education levels were sought in the survey (82% response rate) as they are not collected by the database. The TMH respondents had significantly higher incomes than those planning a PMU birth, with no significant differences in the education levels identified.

The study’s primary maternal outcome measures, analysed by intended birthplace on study entry, are illustrated in table 2. After adjusting for confounding factors (maternal age, smoking status, parity, term, augmentation, induction, excludes elective caesarean section), women from the PMU cohort were significantly more likely to have a spontaneous vaginal birth (77.9% vs 62.3%, AOR 1.61, 95% CI 1.08 to 2.39) and less likely to have an instrumental-assisted (ventouse or forceps) vaginal birth (10.3% vs 20.4%, AOR 0.59, 95% CI 0.37 to 0.93). The caesarean section rate—elective (0.7% PMU vs 2.1% TMH) or emergency (11.6 PMU vs 17.5% TMH)—was not significantly different between the cohorts.

Table 2 describes secondary maternal outcomes, showing the numbers, percentages and ORs by planned place of birth. The PMU cohort was significantly more likely than women from the TMH cohort to have spontaneous labour onset (66.8% PMU vs 49.1% TMH), meconium liquor (18.7% PMU vs 12.6% TMH), no analgesia (42.4% PMU vs 25.0% TMH) or use non-pharmacological pain relief (75.0% PMU vs 65.2% TMH) and have physiological management of the third stage of labour (41.8% PMU vs 19.3% TMH). Women from the PMU cohort were significantly less likely to have labour augmentation (17.2% PMU vs 28.2% TMH) or an episiotomy (7.8% vs 19.7% TMH), compared with women from the TMH cohort. The cohorts had similar rates of induction, postpartum haemorrhage, other perineal trauma (table 2) and length of labour (data not shown).

The primary neonatal outcome measures are detailed in table 3. There were no significant differences between the cohorts in rates of 5 min Apgar score of less than 7 (incidence rate of 2.0% PMU and 2.1% TMH AOR 0.82,
Table 1  Participants’ demographics by planned birthplace

<table>
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<th>Characteristics</th>
<th>Primary (PMU) (n=407)</th>
<th>Tertiary (TMH) (n=285)</th>
<th>p Value (\chi^2) (&lt;0.05)</th>
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<td>67 (23.6)</td>
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<td>30–34 years</td>
<td>142 (34.9)</td>
<td>120 (42.3)</td>
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<td>&lt;0.0001</td>
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<td>Proportion of nulliparous women</td>
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<td>30 (7.4%)</td>
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<tr>
<td>Smoker</td>
<td>31 (7.6%)</td>
<td>15 (5.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City or semirural</td>
<td>308 (75.7%)</td>
<td>248 (87.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rural or remote rural</td>
<td>99 (25.3%)</td>
<td>37 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>Has a partner</td>
<td>377 (92.4%)</td>
<td>260 (91.6%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>233 (58.7%)</td>
<td>196 (69.3%)</td>
<td></td>
</tr>
<tr>
<td>25–35</td>
<td>149 (37.5%)</td>
<td>79 (27.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;35</td>
<td>15 (3.8%)</td>
<td>8 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Income*</td>
<td>(n=326), no (%)</td>
<td>(n=226), no (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;NZ$25 000 per annum before tax</td>
<td>20 (6.1%)</td>
<td>14 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>$25 000 to $50 000</td>
<td>95 (29.1%)</td>
<td>34 (15.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>$50 000 to $75 000</td>
<td>99 (30.4%)</td>
<td>70 (31.0%)</td>
<td></td>
</tr>
<tr>
<td>&gt;NZ$75 000</td>
<td>112 (34.4%)</td>
<td>108 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>Education*</td>
<td>(n=331), no (%)</td>
<td>(n=230), no (%)</td>
<td></td>
</tr>
<tr>
<td>No postschool completed</td>
<td>67 (20.2%)</td>
<td>36 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>Apprenticeship, certificate</td>
<td>55 (16.6%)</td>
<td>32 (13.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diploma</td>
<td>56 (16.9%)</td>
<td>41 (17.8%)</td>
<td></td>
</tr>
<tr>
<td>Degree</td>
<td>153 (46.2%)</td>
<td>121 (52.6%)</td>
<td></td>
</tr>
</tbody>
</table>

*Different denominator—survey response data, not full study cohorts (82%).
BMI, body mass index; NS, not significant;

95% CI 0.27 to 2.52) and admission to the neonatal unit (5.9% vs 4.9% AOR 1.44, 95% CI 0.70 to 2.96). There were also no significant differences in the secondary neonatal outcomes, as detailed in table 3.

**DISCUSSION**
This study found that women planning a freestanding PMU birth when compared with women of similar well-being (risk status) planning a TMH birth had more favourable clinical outcomes.

Studies such as this observational prospective cohort study have both limitations and strengths. The limitations include the small study size which prevented strongly powered statistical analysis of clinical outcomes and not knowing the ‘risk status on admission in labour’ of participants. The major disruptive earthquakes which occurred during the study period were a serious ‘confounder’, resulting in the premature end of recruitment; and major damage to the city and its infrastructure, including power, water, roads and hospitals. This caused generalised community stress and
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary (n=407)</th>
<th>Tertiary (n=285)</th>
<th>Unadjusted OR (95% CI)</th>
<th>p Value (&lt;0.05)</th>
<th>Adjusted OR (95% CI)</th>
<th>p Value (&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal</td>
<td>318 (77.9%)</td>
<td>177 (62.3%)</td>
<td>2.14 (1.53 to 2.99)</td>
<td>&lt;0.0001</td>
<td>1.61 (1.08 to 2.39)*</td>
<td>0.02**</td>
</tr>
<tr>
<td>Instrumental assisted vaginal</td>
<td>42 (10.3%)</td>
<td>58 (20.4%)</td>
<td>0.45 (0.29 to 0.69)</td>
<td>&lt;0.0001</td>
<td>0.59 (0.37 to 0.93)*</td>
<td>0.02</td>
</tr>
<tr>
<td>Emergency caesarean</td>
<td>47 (11.6%)</td>
<td>50 (17.5%)</td>
<td>0.61 (0.40 to 0.94)</td>
<td>0.026</td>
<td>0.88 (0.55 to 1.40)*</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Labour onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>272 (66.8%)</td>
<td>140 (49.1%)</td>
<td>2.09 (1.53 to 2.85)</td>
<td>&lt;0.0001</td>
<td>1.94 (1.40 to 2.67)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction</td>
<td>59 (14.5%)</td>
<td>55 (19.3%)</td>
<td>0.71 (0.47 to 1.06)</td>
<td>NS</td>
<td>0.77 (0.50 to 1.16)†</td>
<td>NS</td>
</tr>
<tr>
<td>Elective caesarean</td>
<td>3 (0.7%)</td>
<td>6 (2.1%)</td>
<td>0.34 (0.09 to 1.38)</td>
<td>NS</td>
<td>0.34 (0.08 to 1.41)†</td>
<td>NS</td>
</tr>
<tr>
<td>Augmentation</td>
<td>70 (17.2%)</td>
<td>80 (28.2%)</td>
<td>0.53 (0.37 to 0.76)</td>
<td>0.001</td>
<td>0.54 (0.37 to 0.79)†</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Meconium liquor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76 (18.7)</td>
<td>36 (12.6%)</td>
<td>0.63 (0.41 to 0.97)</td>
<td>&lt;0.05</td>
<td>0.54 (0.35 to 0.85)‡</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Non-pharmacological pain relief</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural/spinal</td>
<td>85 (20.9%)</td>
<td>107 (37.5%)</td>
<td>0.44 (0.31 to 0.62)</td>
<td>&lt;0.0001</td>
<td>0.57 (0.38 to 0.85)§</td>
<td>0.006</td>
</tr>
<tr>
<td>Intramuscular/intravenous narcotic</td>
<td>18 (4.4%)</td>
<td>23 (8.1%)</td>
<td>0.52 (0.28 to 0.99)</td>
<td>NS</td>
<td>0.58 (0.30 to 1.11)§</td>
<td>NS</td>
</tr>
<tr>
<td>No analgesia</td>
<td>173 (42.4%)</td>
<td>71 (25.0%)</td>
<td>2.20 (1.58 to 3.08)</td>
<td>&lt;0.0001</td>
<td>2.04 (1.40 to 2.96)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NO</strong></td>
<td>128 (31.4%)</td>
<td>81 (28.5%)</td>
<td>1.15 (0.82 to 1.60)</td>
<td>NS</td>
<td>0.91 (0.64 to 1.29)§</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Postpartum haemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500 ml</td>
<td>311 (76.4%)</td>
<td>215 (75.4%)</td>
<td>1.05 (0.74 to 1.50)</td>
<td>NS</td>
<td>0.80 (0.54 to 1.18)*</td>
<td>NS</td>
</tr>
<tr>
<td>500–999 ml</td>
<td>71 (17.4%)</td>
<td>57 (20.1%)</td>
<td>0.84 (0.57 to 1.24)</td>
<td>NS</td>
<td>1.07 (0.70 to 1.61)*</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;1000 ml</td>
<td>24 (5.9%)</td>
<td>13 (4.6%)</td>
<td>1.30 (0.65 to 2.60)</td>
<td>NS</td>
<td>1.74 (0.85 to 3.59)*</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Management of third stage of labour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td>170 (41.8%)</td>
<td>55 (19.3%)</td>
<td>3.0 (2.11 to 4.27)</td>
<td>&lt;0.0001</td>
<td>2.43 (1.63 to 3.60)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active</td>
<td>237 (58.2%)</td>
<td>230 (80.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perineal trauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/gaze</td>
<td>62 (15.2%)</td>
<td>54 (19.0%)</td>
<td>0.77 (0.51 to 1.15)</td>
<td>NS</td>
<td>1.05 (0.68 to 1.64)¶</td>
<td>NS</td>
</tr>
<tr>
<td>First/second/labial/vaginal</td>
<td>200 (49.0%)</td>
<td>119 (41.9%)</td>
<td>1.35 (0.99 to 1.83)</td>
<td>NS</td>
<td>1.20 (0.88 to 1.66)¶</td>
<td>NS</td>
</tr>
<tr>
<td>Third/fourth</td>
<td>9 (2.2%)</td>
<td>5 (1.8%)</td>
<td>1.26 (0.42 to 3.80)</td>
<td>NS</td>
<td>1.43 (0.46 to 4.42)¶</td>
<td>NS</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>32 (7.8%)</td>
<td>56 (19.7%)</td>
<td>0.35 (0.22 to 0.55)</td>
<td>&lt;0.0001</td>
<td>0.42 (0.26 to 0.69)¶</td>
<td>0.001</td>
</tr>
<tr>
<td>Extended to third/fourth</td>
<td>4 (1.0%)</td>
<td>4 (1.41%)</td>
<td>0.69 (0.17 to 2.79)</td>
<td>NS</td>
<td>0.61 (0.13 to 2.85)¶</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, smoking status, parity, term, augmentation, induction.
†Adjusted for maternal age, smoking status, parity, term.
‡Adjusted for maternal age, smoking status, parity, term, augmentation, excludes elective CS.
§Adjusted for maternal age, smoking status, parity, term, augmentation, induction, excludes elective CS.
¶Adjusted for maternal age, smoking status, parity, term, excludes elective CS.
**Statistically significant p values and outcomes are presented in bold.
NS, not significant.
Table 3  Neonatal clinical outcomes by planned place of birth

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary (n=407)</th>
<th>Tertiary (n=285)</th>
<th>Unadjusted OR (95% CI)</th>
<th>p Value (&lt;0.05)</th>
<th>Adjusted OR (95% CI)</th>
<th>p Value (&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>8 (2.0%)</td>
<td>6 (2.1%)</td>
<td>0.93 (0.32 to 2.72)</td>
<td>0.90</td>
<td>0.82 (0.27 to 2.52)</td>
<td>0.72</td>
</tr>
<tr>
<td>Need for resuscitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>345 (84.8%)</td>
<td>234 (82.1%)</td>
<td>NS†</td>
<td></td>
<td>0.97 (0.63 to 1.50)</td>
<td>NS†</td>
</tr>
<tr>
<td>Suction</td>
<td>11 (2.7%)</td>
<td>9 (3.2%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>15 (3.7%)</td>
<td>17 (6.0%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPP (mask)</td>
<td>33 (8.1%)</td>
<td>25 (8.8%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPP (endotracheal tube)</td>
<td>3 (0.7%)</td>
<td>0</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to NNU</td>
<td>24 (5.9%)</td>
<td>14 (4.9%)</td>
<td>1.21 (0.61 to 2.37)</td>
<td>NS</td>
<td>1.44 (0.70 to 2.96)</td>
<td>NS</td>
</tr>
<tr>
<td>Perinatal outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUD§ or stillbirth¶</td>
<td>2 (0.5%)</td>
<td>0 (0.0%)</td>
<td>††</td>
<td>NS</td>
<td></td>
<td>††</td>
</tr>
<tr>
<td>Neonatal death**</td>
<td>1 (0.26%)</td>
<td>0 (0.0%)</td>
<td>††</td>
<td>NS</td>
<td></td>
<td>††</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>7 (1.7%)</td>
<td>6 (2.1%)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2500–4500</td>
<td>386 (95.1%)</td>
<td>268 (94.7%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4500</td>
<td>13 (3.2%)</td>
<td>11 (3.5%)</td>
<td>NS‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (completed weeks)</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37</td>
<td>13 (3.2%)</td>
<td>11 (6.6%)</td>
<td>NS††</td>
<td>NS</td>
<td></td>
<td>NS††</td>
</tr>
<tr>
<td>37–41</td>
<td>379 (93.1%)</td>
<td>264 (92.6%)</td>
<td>NS††</td>
<td>NS</td>
<td></td>
<td>NS††</td>
</tr>
<tr>
<td>42–43</td>
<td>15 (3.7%)</td>
<td>10 (0.2)</td>
<td>NS††</td>
<td>NS</td>
<td></td>
<td>NS††</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth</td>
<td>383 (96.7%)</td>
<td>271 (97.8%)</td>
<td>0.60 (0.24 to 1.74)</td>
<td>NS</td>
<td>0.73 (0.26 to 2.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Exclusive at 48 hours</td>
<td>355 (89.2%)</td>
<td>240 (85.4%)</td>
<td>1.41 (0.89 to 2.23)</td>
<td>NS</td>
<td>1.35 (0.84 to 2.20)</td>
<td>NS</td>
</tr>
<tr>
<td>Exclusive or fully at 6 weeks</td>
<td>328 (80.6%)</td>
<td>224 (78.6%)</td>
<td>1.13 (0.78 to 1.64)</td>
<td>NS</td>
<td>1.14 (0.76 to 1.70)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, smoking status, parity, augmentation, induction, term.
†Fisher’s exact test for listed proportions of modes of resuscitation.
‡Refers to a dichotomous outcome of ‘resuscitation or not’ adjusted for maternal age, smoking status, parity, augmentation, induction, term.
§Antenatal IUD identified at 38 weeks during routine antenatal visit, baby slightly small for gestational age (SGA), no cause found, no pregnancy complications, well woman.
¶Stillbirth antepartum haemorrhage (APH)/placental abruption at 34 weeks; transfer to TMH and obstetric supervised care at 20 weeks with pregnancy induced hyertension (PIH) ×3 a/n admissions.
**Neonatal death at 3 weeks of age, late onset group B streptococcus (GBS) infection.
††Numbers too small. Multivariate model cannot converge.
IPP, inspiratory positive pressure; IUD, intrauterine death; NNU, neonatal unit (includes neonatal intensive care or special care nursery);

trauma and had a major confounding effect on birthplace choice (with 28% of antenatal changes in planned birthplace due to earthquakes). It is not possible to quantify the quakes’ impact on individual participants or identify if one cohort was more adversely affected that the other.

Another limitation is that the study sample is not representative of the childbearing women in New Zealand. The proportion of women under the age of 25 who joined the study is considerably lower than in the population of women from the region who gave birth at the time (11.9% as compared with 21.5% of women giving birth were under 25 in the study and the Canterbury region, respectively). Māori women were also less likely to take part in the study—5.2% of the participants and 12.5% of women birthing in Canterbury in 2010 were Māori. Self selection bias is also present in both groups, as all of the women chose their preferred birthplace, leaving open the possibility of psychological or motivational differences between the groups. Selecting a prospective comparative reference cohort from the referral hospital goes some way in addressing the selection bias.

Differences in the beliefs and values of the women in the PMU and TMH cohorts in this study have been identified and discussed in previous publications. In common with prior research, we found that ‘safety’ was the paramount consideration in women’s birthplace decision-making, although the two groups had different perceptions of the concept. Accessing the specialist services/facilities (if needed) was the most important
factor for women planning a TMH birth. In contrast, the PMU group identified several factors, including ‘closeness to home’, ‘ease of access’, the ‘atmosphere’ of the unit and avoidance of unnecessary intervention’ as important. This study found women who planned a PMU birth expressed confidence in the birth process, their ability to give birth, the maternity system (for specialist referral or transfer) and/or the primary unit itself. In contrast, women who planned a TMH birth did not express confidence in these things, although almost all study participants expressed confidence in their midwife.

The influence of the personal philosophy of midwives who choose to provide women particular birthplace options were beyond the scope of this study. In this context, LMC midwives work autonomously and independently of the birth facilities and choose their practice context, which arguably means they are not providing labour and birth care in a place in which they do not feel confident and competent. This does not mean that their practice is not influenced by the organisational context of the respective facilities, as has been demonstrated in previous New Zealand research. The focus of the current research was the women and not the 135 midwives providing their care, the majority of whom provide care in both PMU and TMH facilities and a few of whom offer only one or other option to women. The women also chose their own midwife, knowing the options she offered prior to booking with that midwife, with a few changing midwives during pregnancy, if they found the midwife’s beliefs and values in conflict with their own. As reported previously, a relatively small proportion of study participants identified their decision was influenced by the recommendation of their midwife (PMU 4.35%, TMH 6.24%) via the 6-week postpartum survey (82% response rate). Additionally, women indicated the extent to which their midwife influenced their birthplace decision on a Likert scale, with significantly more women in the TMH cohort indicating that their midwife had no influence on their decision (39% vs 23% for PMU cohort). Similar proportions of each cohort identified their midwives as having ‘a lot’ of influence (26% and 25%).

It is unclear the extent to which the different beliefs and values held by midwives and/or women influence the clinical outcomes in respective birth environments. Research to date has also identified other variables, including the design of a ‘birth space’ and the institutional control exerted. It is difficult to control for these influences, both independently and collectively, and therefore identify the extent of their impact.

The study’s strengths include its context of New Zealand’s unique system of maternity care, where women receive continuity of care from a midwife, even in the event of specialist consultation and regardless of the place of birth. (Most other studies of PMUs and TMHS are confounded by having to also compare, and not be able to control for, different models of care. Data were collected prospectively and comprehensively on all aspects of antenatal, labour and postnatal transfers for women planning a primary unit birth in a contemporary western context, where all the women in the study received continuity of care.

Some of the clinical outcomes that were found to be different between primary and tertiary cohorts in other studies were not significantly different here. For example, all other comparable studies have reported higher rates of caesarean section for TMH groups compared with PMU groups, whereas this study found no difference in caesarean section rates—elective or emergency. The other New Zealand research had the highest caesarean section rate differential reported to date (relative risk 4.62). This difference may be due to the small size of the current study or by differences in the timing of the identification of the cohorts. The retrospective Davis et al (2011) study is the only one to identify the cohorts by intended birthplace in labour, whereas the cohorts in each of the other studies were established antenatally (on hospital booking or study entry). Our prospective study found 107 (26.3%) of the total PMU cohort of 407 women changed plans to give birth at the tertiary hospital prior to labour. The risk status of women at the start of labour cannot be identified for this or the other New Zealand research.

This study, along with the Danish study found no significant differences in the neonatal outcomes measured. In contrast, the large Birthplace in England study, the Australian EMU study and the previous New Zealand study all reported higher rates of neonatal unit admission for tertiary than primary cohorts. What is consistent in these studies is that those who plan to give birth in a freestanding PMU have been shown to have similar or better neonatal outcomes, and none which are worse than the women (of similar risk status) who plan to give birth in a hospital. This study is no exception, further underlying the beneficial results of primary maternity unit care with a higher proportion of Māori women and rural dwelling women (table 1).

The international evidence published to date is that well women who plan to give birth in a TMH are more likely to suffer physical harm in the form of peripartum morbidity, such as episiotomy and caesarean section, than those who plan to give birth in a freestanding PMU. This morbidity is not resulting in better outcomes for their babies, as the evidence to date, including this study, reports the clinical outcomes for babies from the two groups as either comparable or better for the PMU cohorts. The notion that the ‘interventions’ undertaken at the tertiary hospital on well women are either protecting the wellbeing of women or ‘saving babies’ is not supported by the evidence published in comparable contexts. Given the complexity of birth, it is difficult to identify causal factors for the increased rate of ‘interventions’ and their associated morbidities in tertiary when compared with primary facilities. Arguably, it is not possible to undertake a comprehensive and sufficiently powered study to establish the relative physical safety of
freestanding maternity units and tertiary hospitals for well women at ‘low risk’ of complications. Birthplace research is difficult and complex, with several potential biases and confounding factors. The commonly held anecdotal association of hospitalisation and reduced mortality and morbidity rates has never been supported by evidence. Despite this, the supposition of ‘safety’ of hospital birth for all women remains, arguably as a result of the power of obstetrics and its hold on ‘authoritative knowledge’. Hospital has become the cultural ‘gold standard’ by default. While it is possible that rare and severe incidents might happen at a PMU, which might have been prevented or mitigated if the woman was at a TMH, it is also possible that as many iatrogenic or nosocomial rare and severe incidents happen at a TMH. Childbearing women and their families are concerned that their ‘safety’ is optimised and harm minimised; maternity care providers, healthcare funders and planners share these concerns. This study, and other recent research, has found planning to give birth at a PMU for well (‘low risk’) women is ‘safer’ for women and at least as safe for their babies, if safety is defined as ‘the reduction of risk of unnecessary harm to an acceptable minimum’. Even using the narrow outcome measure of physical ‘safety’ or well-being, the existing evidence does not support hospitals as safer places for well women to give birth, in the context of professional skilled caregivers, effective referral and transfer systems and access to specialist facilities and services for those in need of them.

This study provides clinicians and maternity policy-makers and planners with evidence which supports the safety of freestanding PMUs and their role in a modern integrated maternity system. It illustrates the efficacy of referral and booking guidelines and midwives’ use of them in practice. It provides evidence of the effective systems of collaborative multidisciplinary consultation and transfer between facilities, including emergency and non-emergency transport. Generalisation of these findings should be undertaken with caution, as it is unclear if the model of maternity care, with continuity of midwifery care for all participants, has impacted on the outcomes.

Future research, including a larger national prospective cohort study in Aotearoa/New Zealand, would provide stronger evidence of comparative birthplace clinical outcomes between primary and tertiary level facilities in this context. The inclusion of all participants’ risk status on admission in labour and the details of antenatal and predelivery labour birthplace plan changes and labour transfers would strengthen the findings. Further research into other potentially influential variables such as the beliefs and values of women and caregivers, birth space design and institutional control would also be valuable in helping to identify the causes of different outcomes for well women giving birth in different context.

CONCLUSION

This research adds to the growing international body of research on freestanding PMUs. It adds to the worldwide body of research confirming primary units as physically, socially and emotionally/psychologically safe places for well women to plan to give birth, in contexts of maternity systems with integrated midwifery care and primary level maternity units or birth centres. The task now is to disseminate this research, combined with the international primary maternity unit birthplace literature, to childbearing women, maternity care providers and healthcare policy-makers and planners. This research is unique as it is the first birthplace prospective cohort study undertaken in Aotearoa/New Zealand, the only country in the world to have continuity of care as a core tenet in its maternity system. As such, it is important for all those with an interest in all aspects of the safety of birth.

Acknowledgements We thank the women who took part in the study, despite the earthquakes. We also thank the midwives who participated and supported the project, all those who assisted from the MMPO and the participating hospitals and maternity units in Christchurch.

Contributors CP: principal author; led the New Zealand arm of the study, including its design, recruitment, data collection, cleaning, analysis and interpretation; preparation and modification of the manuscript and carried out all practical aspects of the publication process. SKT: conceived of the study, led its design and coordination; involved in data analysis and interpretation and critical manuscript revision. MT: involved in the design of the study, led data analysis and interpretation; critical manuscript revision and approved the final manuscript. RD: involved in the design and conduct of the study, data interpretation, critical manuscript revision and approved the final manuscript. MC: involved in the design and conduct of the study, critical manuscript revision and approved the final manuscript.

Funding This study was supported by the National Health and Medical Research Council of Australia (Project Grant number: 571901). All rights reserved. No commercial use is permitted unless otherwise expressly granted.

Competing interests None declared.

Ethics approval New Zealand Upper South B Regional Ethics Committee (URB/09/12/063), 08/02/10. Northern Sydney Health Human Research Ethics Committee (HREC/09/HNE/78); University of Technology Sydney Human Research Ethics Committee; University of Sydney Human Research Ethics Committee (SSA/09/HNE/79); Hunter New England Human Research Ethics Committee (09/03/18/5.06).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No further unpublished data from the study are available.

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REFERENCES


Excisional treatment in women with cervical adenocarcinoma in situ (AIS): a prospective randomised controlled non-inferiority trial to compare AIS persistence/recurrence after loop electrosurgical excision procedure with cold knife cone biopsy: protocol for a pilot study

Paul A Cohen, Alison Brand, Peter Sykes, David C H Wrede, Orla McNally, Lois Eva, Archana Rao, Michael Campion, Martin Stockler, Aime Powell, Jim Codde, Max K Bulsara, Lyndal Anderson, Yee Leung, Louise Farrell, Pennie Stoyles

ABSTRACT

Introduction Adenocarcinoma in situ (AIS) of the uterine cervix is the precursor to invasive endocervical adenocarcinoma. An excisional biopsy such as a cold knife cone biopsy (CKC) should be performed to exclude invasive adenocarcinoma. Loop electrosurgical excision procedure (LEEP) is an alternative modality to CKC but is controversial in AIS. There is a perception that there is a greater likelihood of incomplete excision of AIS with LEEP because the depth of excised tissue tends to be smaller and the tissue margins may show thermal artefact which can interfere with pathology assessment. In the USA, guidelines recommend that any treatment modality can be used to excise AIS, provided that the specimen remains intact with interpretable margins. However, there are no high-quality studies comparing LEEP with CKC and well-designed prospective studies are needed. If such a study were to show that LEEP was non-inferior to CKC for the outcomes of post-treatment persistence, recurrence and adenocarcinoma, LEEP could be recommended as an appropriate treatment option for AIS in selected patients. This would benefit women because, unlike CKC, LEEP does not require general anaesthesia and may be associated with reduced morbidity.

Methods and analysis The proposed exploratory study is a parallel group trial with an allocation ratio of 2:1 in favour of the intervention (LEEP: CKC). Participants are women aged ≥18 to ≤45 years diagnosed with AIS on cervical screening and/or colposcopically directed biopsy in Australia and New Zealand, who are to receive excisional treatment in a tertiary level centre.

Ethics and dissemination Ethical approval for the study has been granted by the St John of God Healthcare Human Research Ethics Committee (reference number #1137).

Strengths and limitations of the study

Strengths of this pilot study include its prospective, randomised design, allocation concealment and strategies to minimise surgical performance bias. Should the pilot study demonstrate safety and feasibility, potential limitations of a subsequent phase III study include those pertaining to non-inferiority trials which lack a placebo group, can only provide an indirect assessment of the efficacy of the treatment compared with an existing standard and where the choice of non-inferiority margin can be subjective.

Results from the study will be presented at conferences and published in a peer-reviewed scientific journal.

Registration ANZCTR registration number ACTRN12617001323473 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372173&isReview=true

INTRODUCTION

Adenocarcinoma in situ (AIS) of the uterine cervix is the precursor to, and may coexist with, invasive endocervical adenocarcinoma. Current guidelines recommend that women in whom AIS is reported on screening cytology are referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or a gynaecologic oncologist, and if invasive disease is not identified at colposcopy, a cold knife cone biopsy...
(CKC) should be performed to exclude invasive adenocarcinoma.\textsuperscript{2, 3}

The role of alternative excision modalities to CKC in the investigation and management of AIS has been the subject of extensive debate. Single-specimen excision biopsies with minimal thermal damage or disruption of resection margins are essential for accurate histopathological assessment. A comprehensive review of the Australian 2005 National Cervical Screening Programme (NCSP) guidelines\textsuperscript{2} has recommended that “cold-knife cone biopsy should be considered the "gold standard" for the diagnostic assessment of glandular lesions. However, a diathermy excisional procedure may be appropriate in some circumstances and could provide an appropriate surgical specimen when performed by a gynaecologist with appropriate training, experience and expertise.”\textsuperscript{1} There is a perception that there is a greater likelihood of incomplete excision with loop electrosurgical excision procedure (LEEP) because the depth of excised tissue and the overall dimensions of the specimen tend to be smaller in comparison to CKC. It is also argued that the tissue margins in a LEEP biopsy may show significant thermal artefact, which can interfere with the pathological assessment of biopsy margins.\textsuperscript{5, 6} Some studies have shown a greater risk of a positive endocervical margin with LEEP but these have included cases in which AIS was not suspected prior to the excisional procedure.\textsuperscript{7–9} However, current American Society for Colposcopy and Cervical Pathology consensus guidelines recommend that any treatment modality can be used for diagnostic excision, provided that the specimen remains intact with interpretable margins and that there is no fragmentation, including ‘top-hat’ serial endocervical excisions.\textsuperscript{3}

Conservative treatment of women with AIS by CKC or LEEP is also controversial because AIS may co-exist with cervical adenocarcinoma\textsuperscript{10} and hence total hysterectomy has been regarded as definitive management.\textsuperscript{11} However, CKC and LEEP present fertility-preserving alternatives to hysterectomy in women of reproductive age in whom AIS is prevalent.\textsuperscript{11, 12}

Positive or close histopathological margins have been associated with an increased risk of AIS persistence and recurrence.\textsuperscript{13} A 2014 systematic review\textsuperscript{14} reported higher rates of incomplete excision with LEEP (51%) than with CKC (30%) or laser cone (28%) using pooled data and reported rates of recurrence of AIS ranging from 9% to 29% after LEEP and from 6% to 11% after CKC. This review concluded that LEEP had acceptable safety and was comparable to CKC when negative margins were achieved, and is associated with better obstetric outcomes.\textsuperscript{14} Furthermore, recent evidence suggests that CKC and LEEP are associated with similar rates of positive margins and recurrent AIS.\textsuperscript{15} Advantages of LEEP compared with CKC include the ability to perform the procedure under local anaesthesia in an outpatient setting and lower morbidity, including adverse obstetric outcomes.\textsuperscript{16, 17}

There are no prospective randomised studies of AIS treatment to inform clinical practice. More recent retrospective studies have found similar recurrence and persistence rates for LEEP and CKC.\textsuperscript{18–19} The absence of prospective randomised studies has recently been highlighted by Cancer Council Australia’s working party draft clinical management guidelines for the prevention of cervical cancer.\textsuperscript{4} There is a clear need for prospective randomised clinical trials to determine whether LEEP is associated with similar histopathological and clinical outcomes when compared with CKC in the investigation and management of cervical AIS.

The Cancer Council Australia Cervical Cancer Screening Guidelines Working Party argued that “Well-designed prospective research studies are needed to compare the use of cold knife cone biopsy with diathermy loop excision (LEEP or LLETZ) in the diagnosis and treatment of AIS. If such a study were to show that loop excision was non-inferior to cold-knife cone biopsy for the outcomes of post-treatment persistence and recurrence, and adenocarcinoma, loop excision could be recommended as an appropriate treatment option for AIS in selected patients. This would benefit women because, unlike cold-knife cone procedures, loop excision does not require hospital admission and general anaesthesia. Studies evaluating endocervical curette would provide useful evidence to determine its role in clinical practice. Long-term data from the National Cervical Screening Program should be analysed to determine the minimal effective surveillance period for women undergoing annual Test of Cure for post-treatment AIS before returning to routine 5-yearly screening.”\textsuperscript{4}

The aim of the proposed pilot study is to demonstrate the feasibility and safety of LEEP versus CKC for the treatment of cervical AIS prior to conducting a phase III prospective multicentre randomised non-inferiority trial. The specific objectives of the proposed phase I study are

1. to compare LEEP with CKC in terms of margin status and specimen dimensions
2. to compare rates of early complications at 6 weeks, for example, pain, infection, primary and secondary haemorrhage, readmission to hospital, return to the operating theatre after the two treatment modalities
3. to assess patient satisfaction following LEEP and CKC
4. to determine the costs of treatment.

If feasibility and safety are demonstrated, the objective of the subsequent phase III trial would be to determine if the treatment of cervical AIS by LEEP is non-inferior to CKC in terms of disease persistence at 12 months and recurrence at 5 years in women managed conservatively, when treatment is performed in tertiary level dysplasia and gynaecologic oncology centres.

METHODS AND ANALYSIS

The protocol conforms to the SPIRIT (Standard Protocol Items for Randomised Trials) statement.
Trial design
The proposed exploratory study is a parallel group trial with an allocation ratio of 2:1 in favour of the intervention (LEEP: CKC).

Study setting
Academic tertiary level hospitals in Australia and New Zealand.

Study sites are listed in the ANZCTR registration number ACTRN12617000132347.


Eligibility criteria
Women aged ≥18 to ≤45 years diagnosed with AIS on cervical screening and/or colposcopically directed biopsy in Australia and New Zealand, who are to receive excisional treatment in a tertiary level centre.

Inclusion criteria
► Aged between ≥18 and ≤45 years of age at time of study enrolment
► Documentation of AIS on cervical cytology and/or cervical biopsy test results
► Lesion amenable to single-pass excision (serial endocervical excisions including ‘top-hat’ will not be permitted in accordance with American Society for Colposcopy and Cervical Pathology Recommendations)7
► Proficient in English.

Exclusion criteria
► High-grade cervical abnormality prior to current AIS diagnosis
► Previous excisional or ablative treatment (LEEP, CKC, Fisher cone biopsy, laser cone, laser ablation, radical diathermy)
► Previous history of cervical cancer treated by radiation or chemoradiation
► Cytology suspicious of invasion
► Clinical/colposcopic suspicion of invasion
► Presence of a concurrent gynaecological cancer
► Patients unable to comply with follow-up evaluations
► Immunosuppression
► Pregnancy
► Lesion considered unsuitable for single-pass excision by treating specialist.

Interventions
Eligible participants will be randomised to undergo either LEEP or CKC. LEEP is the standard procedure performed for the more common high-grade squamous cervical dysplasia and the technique is described in detail in online supplementary appendix A. In Australia, CKC has been the preferred technique to excise cervical AIS and the technique is outlined in online supplementary appendix A. The interventions will be administered within the usual clinical time frames as per local practice.

Patient management will follow the National Health and Medical Research Council’s 2005 Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen-detected abnormalities and the revised 2016 guidelines. Participants randomised to the LEEP arm of the study will have their procedure performed either under local or general anaesthesia in an outpatient setting or operating theatre at the discretion of the treating specialist as per local routine practice. All participants will undergo endocervical curettage at the time of their LEEP or CKC.

Following treatment, all patients will undergo the ‘Test of Cure’ management pathway:
1. colposcopy and cervical cytology at 6 months’ postexcisional treatment
2. cervical cytology and oncogenic human papilloma virus (HPV) typing at 12 months’ post-treatment and then annually in accordance with the revised 2017 NCSP guidelines.4

Methods for protecting against sources of bias
A potential issue in surgical trials is performance bias. The study setting will be tertiary level dysplasia/gynaecologic oncology units and only the named study investigators will be performing the excisional procedures which will mitigate this bias to some extent. All clinical investigators are highly experienced providers and are certified under the Colposcopy Quality Improvement Programme in accordance with the requirements of the Royal Australia and New Zealand College of Obstetrics and Gynaecology. The requirement for a single-pass specimen will also limit surgical performance bias.

Strategies to improve adherence to intervention protocols and any procedures for monitoring adherence
It is anticipated that participants will attend for treatment and those who do not attend will be recalled as per routine clinical practice. Participants will be encouraged to complete the patient satisfaction questionnaire at 6 weeks’ post-treatment by a phone call and/or email from the site trial co-ordinators.

Outcomes
Primary outcomes: Histopathological margin status and status of the excised specimen (single specimen or more than one piece).

Rationale: Margin status has consistently been shown to predict persistence and recurrence of cervical AIS.13 Disruption to the excision specimen can make orientation and interpretation of tissue margins impossible. If there are significantly more LEEP specimens with positive margins compared with those excised by CKC, or if there are a greater number of specimens excised in more than one piece compared with CKC, then it may not be appropriate to conduct a larger phase III study.

Key secondary outcomes: Frequency of early complications (pain, infection, primary and delayed haemorrhage, readmission to hospital, return to the operating theatre),
patient satisfaction at 6 weeks’ postprocedure and costs of treatment.

Rationale: Retrospective studies have suggested that LEEP is associated with fewer early complications. Although the proposed study is underpowered to detect differences in these outcomes, the purpose of their inclusion is to determine the feasibility of data collection.

Participant timelines

Figure 1 shows a consolidated standards of reporting trials (CONSORT) flow diagram of the EXcisional treatment Comparison for In Situ Endocervical adenocarcinoma (EXCISE) study. The schedule of enrolment, interventions and assessments is presented in figure 2. Following randomisation, participants will undergo the treatment to which they are allocated (LEEP or CKC). LEEP and CKC are usually day-case procedures. Participants will have one follow-up visit with a local study co-ordinator at 6 weeks’ postprocedure. This visit may be conducted face to face or via telephone and will involve collection of information regarding complications postprocedure, return to hospital, general practitioner (GP) visits and a request to complete and return the patient satisfaction questionnaire.

We are aiming to recruit 35–40 participants for the proposed phase I study. This sample size was determined on a pragmatic basis (five patients recruited at each of seven participating sites).

Sample size

The sample size for the pilot study is pragmatic. The sample size for the potential subsequent phase III study was estimated using a two-group test of non-inferiority of proportions, where the primary end point is the AIS recurrence rate at 5 years and the comparison will be between CKC and LEEP, based on a one-sided test for

Figure 1 Consolidated standards of reporting trials (CONSORT) flow diagram of EXCISE study. CKC, cold knife cone biopsy; LEEP, loop electrosurgical excision procedure.
non-inferiority. If we assume for patients in the standard treatment arm an 8% rate of AIS recurrence at 5 years, and a 5% non-inferiority margin (so an upper 95% confidence rate of AIS recurrence of 13% is still within the non-inferiority margin), the total sample size needed is 730 (365 per group). Assuming a 10% drop-out rate, a total sample size of 810 participants (405 per group) would need to be randomised. The one-sided type I error is set at 5% with 80% power. Kaplan-Meier and log-rank tests will be used to test for non-inferiority at median follow-up of 5 years (with patient recruitment between 4 and 5 years, assuming 160–200 patients are successfully randomised per annum). Proportional hazard models will be used to test for differences between the two treatment groups controlling for confounding variables. All statistical analysis will be carried out as per CONSORT

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**Figure 2** Schedule of enrolment, interventions and assessments. AIS, adenocarcinoma in situ; BMI, body mass index; CKC, cold knife cone biopsy; HPV, human papilloma virus; LEEP, loop electrosurgical excision procedure; STI, sexually transmitted infection.
recommendations for non-inferiority randomised controlled trials using intent-to-treat as well as per-protocol populations.

Recruitment: strategies for achieving adequate participant enrolment to reach target sample size
Several of the investigators are the clinical leads of their local dysplasia units and triage patient referrals to their centres. They will be ideally placed to identify potential eligible participants. The investigators believe that it is feasible to recruit the number of participants needed for this phase I study based on the local incidence of cervical AIS and enrolment rates in previous research studies.

Assignment of interventions
Allocation: Participants will be randomised to undergo LEEP or CKC (2:1 ratio).

Generation of the allocation sequence will be by computer-generated random numbers. The allocation sequence will be implemented by central telephone (interactive voice response system) and will be generated by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney.

Participants will be enrolled by the treating specialist who will be one of the named investigators. Following randomisation, participants will be assigned to LEEP or CKC by a study co-ordinator at each site.

Blinding
All study investigators and participants will not be blinded to the intervention.

Data collection, management and analysis
A case report form (CRF) will be used to record data for each participant. The primary outcomes will be assessed as part of routine clinical care by the reporting consultant anatomical pathologists at each site. All participating sites will be required to complete synoptic/standardised histopathology reports for each study participant. All specimens will undergo centralised pathology review at Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia, by Dr Lyndal Anderson, Consultant Pathologist and Study Investigator. Data regarding early complications will be obtained via patient medical records and at patient follow-up visits and recorded on the CRF by the site study co-ordinator. Patient satisfaction will be assessed by using those aspects of the European Organization for Research and Treatment of Cancer in-patient satisfaction (EORTC IN-PATSAT32) which are pertinent to outpatient care, as well as additional questions on the ease of making appointments, clinic accessibility and waiting times.

The intervention is a surgical procedure so once performed it will not be possible for participants to deviate from the intervention protocol. Should a participant withdraw from the study postintervention then it may not be possible to obtain data regarding secondary outcomes (early complications and patient satisfaction).

Data will only be collected with the signed permission of the participant. All questionnaires/data CRFs will be given a unique identity number (de-identified data) and will not include information that would allow identification of the participant. Unique patient identification number will be generated by the interactive voice response system (IVRS) and identified patient data will only be available to the principal investigators at each participating institution. Only de-identified clinical information will be used for statistical analysis and reporting.

The original study participant CRFs will be stored securely by the relevant study site investigators. Copies of the completed CRFs accompanied with de-identified supporting source documents will be scanned by the study site researchers, saved in a PDF format and these version files will be emailed to the lead site for data entry.

The study standard operating procedures (SOP) will be used to ensure the collection of accurate, consistent, complete and reliable data. In addition, prior to the study initiation at each site, an investigator meeting and training session will be held via teleconference to prepare both the investigators and other trial staff involved and to standardise performance.

Safety reporting will be conducted according to trial specific procedures. Data management will be performed by the lead site. Accurate and reliable data collection will be assured by 100% verification and crosscheck of CRFs against the investigator’s records by the St John of God (SJOG) Gynaecological Cancer Research Group.

All data will be stored in locked offices, password-protected computer files and password-protected database, accessible only by site staff. A FileMaker Pro database will be used for the data management, and data from the CRFs will be entered into the database by the SJOG Gynaecological Cancer Research Group.

Safety monitoring
An independent medical monitor (IMM) will undertake ongoing safety monitoring throughout the trials duration assessing serious adverse events (SAE) and suspected, unexpected adverse reactions (SUSARs) reported by research sites to the Trial Steering Committee (TSC). The IMM will provide recommendations whether the study should continue as planned or that changes should be made to the protocol to improve safety. If matters of major safety are identified, for example, a higher than expected SUSARs/SAEs being reported, the IMM can recommend that the study be postponed until matters are clarified and resolved. Otherwise, if study participant safety is compromised, the study must be terminated.

Data monitoring
A systematic, prioritised risk-based monitoring schedule will be implemented by the study sponsor in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) (5.18 Monitoring) guidelines. It will encompass both on-site monitoring and centralised remote monitoring modalities. On-site
monitoring will verify that study participants have given their consent to participate voluntarily, have been fully informed of the research trial and that their rights, safety and well-being are assured. Additionally, the monitoring will verify that the data collected are accurate, complete and verifiable from source documents and that the site research personnel are conducting the trial in accordance with the Human Research Ethics Committee (HREC) approved study protocol and its ‘conditions of approval’.

Centralised monitoring will complement and reduce on-site monitoring whereby reliable data and potentially unreliable data can be distinguished, that is, omissions, inconsistencies, incongruous or anomalous data entries will be identified and queries can be clarified and where applicable, corrected and resolved in a timely manner with the relevant study sites in accordance with GCP guidelines.

Harms

The investigator is responsible for reporting all AEs and SAEs that are observed during the study, regardless of their relationship to treatment or their clinical significance. All AEs and SAEs that occur after surgery during the study must be recorded in the patient’s chart and the CRFs and followed to a satisfactory resolution or until the local Investigator deems the patient to be stable or the AE/SAE to have resolved. The description of the AE/SAE will include the onset date, duration, date of resolution, severity, seriousness, aetiology and the likelihood of relationship of the AE to study treatment. Severity of AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTC-AE v4.0).

If an AE occurs which is not contained in the CTC-AE v4.0, the following five-point scale will be used:
1. mild: discomfort noticed but no disruption of normal daily activity
2. moderate: discomfort sufficient to reduce or affect daily activity
3. severe: inability to work or perform normal daily activity
4. life threatening: represents an immediate threat to life
5. death.

Any AE considered serious by the local Investigator or which meets the previous criteria must be reported to the TSC. A CRF and SOP for SAE reporting will be provided by the lead site. If the patient is hospitalised because of, or during, an SAE, then a copy of the hospital discharge summary and any other reports/results should be emailed to the lead site (SJOG Subiaco) as soon as they are available.

Once an investigator becomes aware that an SAE has occurred in a study participant, they will immediately notify the lead site via email. The SAE form must be completed by site personnel as thoroughly as possible with all available details of the event, signed by the investigator (or appropriately qualified designee) and emailed to the lead site within 24 hours of first becoming aware of the event. The investigator will always provide an assessment of causality at the time of the initial report.

All sites are required to submit locally occurring SAEs to their reviewing ethics committee or site governance office within 24 hours of first notification of SAE occurrence or according to local HREC policy.

At every study visit, patients will be asked a standard non-leading question to obtain any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medications or changed concomitant medication regimens (prescription, over-the-counter medications and herbal supplements). In addition to patient or investigator observations, AEs will be documented from any data collected (eg, laboratory values, physical examination findings), or other documents that are relevant to patient safety.

The investigator’s assessment of an AE’s relationship to treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, until the participant is lost to follow-up or up to close out visit.

Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other healthcare professionals.

New or updated information for SAEs will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator or designee. The updated SAE form should be resent to the SJOG Gynaecological Cancer Research Group.

AUDITING

Participating sites will be audited at least once during the pilot phase by a study monitor who is an employee of the sponsor but independent of the investigators.

ETHICS AND DISSEMINATION

Ethical approval for the study has been granted by the St John of God Healthcare Human Research Ethics Committee (reference number #1137). Important protocol modifications will be submitted to the St John of God Subiaco Hospital HREC as requests to amend the approved study protocol. Informed consent will be obtained by the participant’s treating specialist. Only the investigators, data manager and trial co-ordinator at St John of God Subiaco Hospital will have access to the final
trial dataset. Participants will undergo post-trial care in accordance with NHMRC guidelines for the follow-up of women after treatment for cervical AIS. There are no provisions for those who suffer harm from trial participation as any harm would be regarded as having arisen because of routine treatment and not specifically due to trial participation.

The investigators and sponsor do not intend to communicate results directly to participants. Results from the study will be presented at national and international conferences and published in a peer-reviewed scientific journal. The authorship guidelines largely follow the rules established by the International Committee of Medical Journal Editors. The investigators do not intend to use professional writers.

DISCUSSION
In contrast to cervical squamous dysplasia, the incidence of AIS is increasing in relative and absolute terms. There is a clear need for prospective randomised clinical trials to determine whether LEEP is associated with similar histopathological and clinical outcomes when compared with CKC in the investigation and management of cervical AIS. This is the first prospective randomised study to investigate this clinical question. Limitations of the pilot study are its relatively short follow-up period (6 weeks) and small sample size, which are pragmatic. The objective of the pilot study is to demonstrate the feasibility and safety of the intervention as defined by pathological margin status, and hence long-term outcomes of interest including rates of cervical AIS recurrence and obstetric complications will be endpoints in a subsequent phase III trial. Limitations of a phase III study include those of non-inferiority trials such as defining the acceptable margin of AEs that would render the interventional treatment inferior, lack of a placebo group and allowing only an indirect assessment of the efficacy of the intervention compared with an accepted standard.

Strengths of the study include its randomised design and attempts to minimise surgical performance bias. If LEEP was found to be non-inferior to CKC for the outcomes of post-treatment persistence and recurrence, and adenocarcinoma, it could be recommended as an appropriate treatment option for AIS in selected patients. This would benefit women because, unlike cold knife cone procedures, loop excision does not require hospital admission and general anaesthesia.

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Funding This work has been supported by the Australia and New Zealand Gynaecological Oncology Group (ANZGOG) Fund for New Research grant number FNR 2016/03.

Competing interests None declared.

Ethics approval St John of God Healthcare Human Research Ethics Committee, Subiaco, Perth, Western Australia 6008, Australia.

Provenance and peer review Not commissioned; externally peer reviewed.

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Family history of cancer predicts endometrial cancer risk independently of Lynch Syndrome: Implications for genetic counselling

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HIGHLIGHTS

- Endometrial cancer risk is predicted by cancer in first and second degree relatives.
- The strongest predictor was a first degree relative with endometrial cancer < 50 y.
- Risk was significantly greater with increasing Lynch cancers reported in relatives.
- Risk associated with cancer in relatives did not differ by proband tumor MMR status.

ARTICLE INFO

Article history:
Received 20 April 2017
Received in revised form 4 August 2017
Accepted 8 August 2017
Available online 17 August 2017

Keywords:
Endometrial cancer
Family cancer history
Lynch syndrome
Mismatch repair
Risk

ABSTRACT

Objective. To determine endometrial cancer (EC) risk according to family cancer history, including assessment by degree of relatedness, type of and age at cancer diagnosis of relatives.

Methods. Self-reported family cancer history was available for 1353 EC patients and 628 controls. Logistic regression was used to quantify the association between EC and cancer diagnosis in ≤1 first or second-degree relative, and to assess whether level of risk differed by degree of relationship and/or relative’s age at diagnosis. Risk was also evaluated for family history of up to three cancers from known familial syndromes (Lynch, Cowden, hereditary breast and ovarian cancer) overall, by histological subtype and, for a subset of 678 patients, by EC tumor mismatch repair (MMR) gene expression.

Results. Report of EC in ≤1 first- or second-degree relative was associated with significantly increased risk of EC (P = 3.8 × 10^-7), independent of lifestyle risk factors. There was a trend in increasing EC risk with closer relatedness and younger age at EC diagnosis in relatives (P_trend = 4.43 × 10^-6), and with increasing numbers of Lynch cancers in relatives (P_trend ≤ 0.0001). EC risk associated with family history did not differ by proband tumor MMR status, or histological subtype. Reported EC in first- or second-degree relatives remained associated with EC risk after conservative correction for potential misreported family history (OR 2.0; 95% CI, 1.24–3.37, P = 0.004).

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1. Introduction

Endometrial cancer (EC) is the fifth most common cancer in women in developed countries, accounting for 4.8% of new cancers and 2.1% of cancer deaths. The highest incidence rates in 2012 were estimated to be 19.1 and 15.6 per 100,000 in North America and Western Europe respectively [1,2], attributed to the greater overall prevalence of obesity and metabolic syndromes in these regions [3].

Established non-genetic risk factors for EC include age and exposure to exogenous estrogens, or endogenous estrogens associated with nulliparity, early age at menarche, late-onset menopause and obesity [4]. A role for genetic factors in EC susceptibility is supported by the fact that a family history of EC is associated with a ~2–3-fold increased risk of EC [5]. Genome-wide association studies and large-scale candidate gene studies have identified common modest-risk genetic variants, currently estimated to account for ~5% of the familial relative risk of EC [6–12]. High-risk pathogenic variants in the DNA mismatch repair (MMR) genes associated with Lynch syndrome confer a high lifetime risk of EC in carriers (reported risks 18%–71%), but account for only ~5% of population-based EC (reviewed in [14,15]). Germline loss-of-function variants in the PTEN tumor suppressor gene cause Cowden syndrome, and are associated with a lifetime risk of EC of up to 28% in this context [16], but there is insufficient evidence regarding their contribution to EC risk in the population setting [17]. Variants within the exonuclease domains of the DNA replication and polymerase proof-reading genes POLD1 and POLE have also been implicated in susceptibility to EC, although the level of risk is yet to be quantified in the familial [18] or population setting. While there is convincing evidence that both carriers and non-carriers of BRCA1/2 pathogenic variants have an increased risk of EC following tamoxifen treatment [19], there remains debate about the role of BRCA1/2 in EC risk outside such settings [14].

To date the association between EC risk and number or age of affected relatives, degree of relatedness, or reported family cancer history outside the clinical definition of Lynch Syndrome has not been assessed. Here we report a comprehensive analysis of the risk of EC associated with a family history of EC and other cancers, using the well-characterised, population-based Australian National Endometrial Cancer Study (ANECS). We also considered if family history-associated risk of EC differs according to population setting. While there is convincing evidence that both carriers and non-carriers of BRCA1/2 pathogenic variants have an increased risk of EC following tamoxifen treatment [19], there remains debate about the role of BRCA1/2 in EC risk outside such settings [14].

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2. Patients and methods

2.1. Study population

All ANECS participants provided informed written consent, and approval was obtained from the QIMR Berghofer Medical Research Institute Human Research Ethics Committee, participating hospitals and cancer registries.

Women newly diagnosed with EC, and a comparable group of cancer-free women identified through the national electoral roll (enrollment to vote is compulsory in Australia) were invited to participate in ANECS, a population-based case-control study [20]. Additional details on eligibility criteria, questionnaires and data collection, including tissue and blood samples for molecular testing, have been reported previously [21]. Data were available for 1420 patients and 744 controls. Women were excluded from our analysis if they provided very little or no information about their family cancer history (48 patients, 62 controls), or if they were adopted and therefore their family cancer history was unknown (19 patients). The final analysis dataset with family cancer information comprised 1353 patients and 682 controls. This included 38 women (37 patients and 1 control) who met the Amsterdam II criteria [22] for Lynch Syndrome; of these 7 patients had undergone further testing and were proven to carry a pathogenic MMR gene variant (Supplementary Methods and Table S1). In addition, patients who reported a family history of cancer were asked permission for the study to contact their relatives; relatives of a subset of 119 patients consented to provide risk factor data and complete the same family cancer history questionnaire as patients. A total of 258 relatives (179 first, 32 second, and 47 third and fourth degree) completed the family history questionnaire.

2.2. Assessment of family history of cancer

Family history of cancer for each patient or control proband was not formally verified by medical records, but was based on each proband’s report of cancer and age at diagnosis (if known) in first degree relatives (FDR; parent, sibling, child of proband) and second degree relatives (SDR; maternal or paternal grandmother/grandfather/aunt/uncle, grandson, granddaughters, niece, nephew), as documented by questionnaire. Hereafter, cancer in a relative refers to FDR or SDR unless otherwise specified. Any cancer occurring twice in the same relative was counted as two cancers if they were diagnosed at least one year apart. Cancers reported in questionnaires as ‘fallopian tube’ were combined with ovarian cancer, ‘rectum’ with colorectal cancer, and ‘GI’ were analysed as gastrointestinal cancer. Lymphomas were variously reported as Hodgkin/Non-Hodgkin Disease/lymphoma, lymphosarcoma, or cancer of the lymph node. Reports of Hodgkin lymphoma in relatives (n = 18) were insufficient to analyse separately. We therefore analysed Non-Hodgkin lymphoma (NHL) if specifically reported as NHL, and pooled NHL with all reports of lymphoma as a secondary analysis since approximately 85% of all lymphomas are NHL [1]. Questionnaires on cancer history provided by the subset of relatives of patients invited to participate in the ANECS study were used to evaluate the concordance between patient reports of family cancer history and relative self-reports of cancer, overall, and by degree of relationship. This information was used to estimate the percentage of over-reported (e.g. benign conditions reported as malignant at a specific site) and misreported (different site) cancers by patients for the specific cancers relevant to this study.

2.3. Statistical analysis

In order to obtain population-based risk estimates for EC risk according to family cancer history, patients with known germline pathogenic MMR gene variants (n = 21) were included in analyses using the full dataset, but excluded from analyses using the subset of patients with known MMR status to assess evidence for genetic risk outside Lynch Syndrome. The association between EC and proband-reported family history of cancer was estimated using age-adjusted logistic regression models (age at EC diagnosis for patients and age at interview for controls) to obtain the odds ratios (ORs) and 95% confidence intervals (CIs) for risk of EC associated with any cancer reported in at least one FDR or SDR. Analyses assessing EC risk associated with report of non-EC cancers in relatives were additionally adjusted for report of EC in relatives to remove any potential inflation of risk estimates due to EC
in the same pedigree. We also re-analysed EC risk excluding 37 patients and 1 control who met Amsterdam II criteria, to assess whether estimates were influenced by known or possible MMR pathogenic variant status. To evaluate whether an association between family history of a specific cancer and EC risk was independent of other cancers, we performed backward stepwise regression modelling of all cancer family history variables, as well as known predictors of risk (age, parity, body mass index, age at menarche, and oral contraceptive use), using \( P > 0.05 \) for variable removal from the model.

We also conducted analyses considering the degree of relatedness of the affected relative and the relative’s age at diagnosis. We initially evaluated the risk of EC associated with age at EC diagnosis in relatives using three age categories (<50, 50–59, and ≥60 years); results suggested no meaningful difference in estimates for subgroups 50–59, and ≥60, so these two age-groups were collapsed. To evaluate the combined effect on EC risk associated with having a close relative diagnosed with EC under age 50 years, we created ordered factor variables as follows: ≥1 FDR diagnosed <50 years, ≥1 SDR-only diagnosed <50 years, ≥1 FDR diagnosed ≥50 years, and ≥1 SDR-only diagnosed ≥50 years. We hypothesize that the younger the age at EC diagnosis in a relative and the closer the degree of relatedness, the greater the risk of EC, and assessed this trend across ordered groups using the nonparametric Cuzick’s test for ordered trend.

We analysed the co-occurrence of EC and other cancer types in relatives of patients and controls. We hypothesized that if both cancers were linked to a syndrome that includes EC, the association between EC and the second cancer type would be stronger in relatives. We also explored EC risk associated with proband-reported family history variables, as well as known predictors of risk (age, parity, body mass index, age at menarche, and oral contraceptive use), using \( P > 0.05 \) for variable removal from the model.

Finally, concordance between proband- and relative-reported family cancer history was estimated from the subset of 119 patients, whose relatives consented to complete a family cancer history questionnaire. The information they provided was used to derive a correction factor to estimate the effect of reporting bias on risk estimates.

All tests for association were two-tailed and performed using STATA SE v. 13 (StataCorp, USA), and forest plots were generated using the rmeta package in the R project for Statistical Computing version 3.2.2 (http://www.r-project.org/).

3. Results

Patient characteristics including demographic, clinical and tumor pathology are summarized in Table S2.

The risks of EC associated with report of different cancer types in ≥1 FDR or SDR are presented in Fig. 1. Report of EC in at least one relative was associated with a significant three-fold increased risk of EC (OR, 3.38; 95% CI, 2.11–5.42; \( P = 3.77 \times 10^{-7} \)). Family history of colorectal cancer (OR, 1.27; 95% CI, 1.03–1.56), and stomach cancer (OR, 1.35; 95% CI, 1.01–1.80), were also associated with an increased risk of EC; adjusting for a family history of EC only marginally altered these estimates, suggesting that the risks associated with colorectal and stomach cancer were not biased by reported family history of EC in the same family (Table S3). Risk estimates for reported family history of endometrial and colorectal cancer (but not stomach) remained unchanged in stepwise regression models including all reported cancers.
and covariates using a threshold for variable removal of $P > 0.05$ (data not shown). We examined histologic subtype-specific EC risks associated with family history of endometrial, colorectal, stomach and breast cancers. There was no convincing evidence for a difference in risk of specific subtypes of EC associated with report of family history of cancer in relatives. Sample numbers were small for the non-endometrioid subgroups, and confidence intervals overlapped for risk estimates of the different EC histological subtypes (Table S4).

We further examined the relationship between various measures of relatedness and reported age at EC diagnosis of relatives and risk of EC. Fig. 2 and Table S5 show that report of at least one EC-affected FDR (regardless of affected SDRs) is associated with a 4-fold increased risk of EC (OR, 4.02; 95% CI, 2.00–8.11; $P = 0.001$), whereas report of at least one EC-affected SDR-only was associated with an almost 3-fold increased risk of EC (OR, 2.91; 95% CI, 1.56–5.43; $P = 0.001$). We also examined relatedness according to age at diagnosis of relatives, and found that patients who reported ≥1 FDR diagnosed with EC < 50 years had the highest risk of EC, although the confidence intervals reflect the smaller numbers in this subgroup (OR, 5.53; 95% CI, 1.29–23.75; $P = 0.02$); 91% of this subgroup reported having a only one FDR diagnosed with EC < 50. Models assessing trend in risk across subgroups of relatives according to degree of relatedness and age at diagnosis suggest a significant ordered trend in increasing risk for closer degree of relatedness and younger age at diagnosis ($P_{\text{trend}} = 4.43 \times 10^{-6}$, Table S5). Risk estimates associated with a report of EC in a relative remained unchanged when Amsterdam II families were removed from the analysis for all measures of relatedness and age at diagnosis of EC in relatives (Table S5).

Analysis of co-occurrence of EC and another cancer showed that patients were significantly more likely to report endometrial and colorectal, breast or stomach cancers in a FDR and/or SDR compared to controls ($P < 0.0001$; Fig. 3). Estimates from $2 \times 2$ contingency tables consistently suggest a greater likelihood that EC co-occurred with colorectal, breast or stomach cancers in patient families compared to controls ($OR_{\text{patients}} \geq 1.38$ vs. $OR_{\text{control}} \geq 0.57$; Table 1), although these differences were not statistically significant (Breslow-Day heterogeneity $P \geq 0.1$). We further evaluated cancer clustering in relatives for EC and colorectal cancers, and EC and breast cancers, as well as Lynch, Cowden and HBOC syndromes (Table S6). Risk of EC was 1.25-fold for report of one Lynch cancer in a relative, and 2-fold if three or more Lynch cancers were reported (Fig. 4). There was a significant ordered trend in increasing risk for each additional Lynch cancer up to three reported cancers in relatives ($P_{\text{trend}} < 0.0001$). There was also a significant trend in increased risk for number of Cowden cancers in relatives ($P_{\text{trend}} < 0.004$), with OR 1.83 (95% CI, 1.31–2.54) associated with ≥2 Cowden cancers in relatives. There was no evidence of a significant increased risk ($P > 0.2$) or ordered trend ($P_{\text{trend}} = 0.17$) in risk of EC associated with report of HBOC cancers in relatives. Analysis investigating risk associated with reported family history of cancers falling within established cancer syndromes (Lynch, Cowden and HBOC) showed a significant trend in increased risk according to the number of affected relatives ($P_{\text{trend}} = 0.0003$). Analyses of cancer clustering of endometrial and/or breast or colorectal cancer in relatives, and for Lynch, Cowden and HBOC cancers according to patient tumor histology also showed no differences in risk associated with specific tumor subtypes (Table S4).

Multinomial regression analysis of family history of cancer in the subset of patients with tumor MMR status, and no known pathogenic MMR variant, showed that elevation in risk associated with reported cancers in FDR and SDRs was similar for both MMR-proficient and MMR-deficient cancers (Table 2). Risk of EC associated with report of at least one FDR or SDR with EC was 3-fold for MMR proficient EC (OR, 3.17; 95% CI, 1.88–5.34), compared to a 2-fold increased risk for MMR-deficient EC (OR, 2.45; 95% CI, 1.12–5.35). Analyses of risk associated with reported family history of cancers falling within Lynch, Cowden, HBOC syndromes produced effect sizes that were generally similar to those obtained from the larger sample, although the width
of the confidence intervals reflected the variability due to smaller sample sizes of the subsets of patients with tumor MMR data (Table 2).

To assess the possible effect of bias in patient-reported family cancer history, we compared the relatives’ cancers reported by 119 patients with the self-reported cancers of 258 of their relatives who completed their own family history questionnaires (there was no equivalent information available from relatives of controls). A total of 232 (90%) responses from relatives of patients, comprising 165 (92.2%) FDRs, 26 (81%) SDRs, and 41 (87.2%) 3rd and 4th degree relatives, were concordant with those provided by patients. We also compared self-reports of specific cancer types from 211 FDRs and/or SDRs with patient reports (Table S7). For family history of EC, we found that of 10 patient reports of EC in a FDR and/or SDR, six were correctly reported, and three FDRs and one SDR were over-reported (patient reported EC where relative reported endometriosis or benign fibroids). Additionally, one patient reported cervical cancer in a SDR, where the relative self-reported EC (Table S7). We derived a conservative correction factor of 0.7 that was used to obtain an adjusted risk estimate associated with reported EC in relatives. Applying this correction factor to patients yielded a significant 2-fold risk of EC associated with report of EC in at least one FDR and/or SDR (OR, 2.0; 95% CI, 1.24 – 3.37, P = 0.004).

4. Discussion

Our analysis showed that among all familial cancers, report of EC in a FDR and/or SDR, and whether her diagnosis age was < 50 or ≥ 50 years were the strongest predictors of EC risk, regardless of other reported cancers. The effect of known predictors of EC risk (body mass index, parity, oral contraceptive use and early age at menarche) on risk estimates of reported familial cancers was explored in stepwise regression models, but the risk associated with report of EC in at least one FDR or SDR remained unchanged (OR, 3.39; 95% CI, 2.08 – 5.53). The risk of EC

Table 1
Estimates of the odds ratio of co-occurrence of endometrial and another cancer type in relatives of controls vs. patients using contingency 2 × 2 tables.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 682)</th>
<th>Patients (n = 1353)</th>
<th><em>P</em>het</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both cancer N (%)</td>
<td>Neither cancer N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Endometrial &amp; colorectal cancer</td>
<td>5 (22.7)</td>
<td>497 (75.3)</td>
<td>0.00 (0.25 – 2.58)</td>
</tr>
<tr>
<td>Endometrial &amp; breast cancer</td>
<td>4 (18.2)</td>
<td>474 (71.8)</td>
<td>0.57 (0.14 – 1.75)</td>
</tr>
<tr>
<td>Endometrial &amp; stomach cancer</td>
<td>2 (9.1)</td>
<td>587 (88.9)</td>
<td>0.80 (0.09 – 3.42)</td>
</tr>
<tr>
<td>Endometrial &amp; ovarian cancer</td>
<td>0 (0.0)</td>
<td>632 (95.8)</td>
<td>na</td>
</tr>
<tr>
<td>Endometrial &amp; thyroid cancer</td>
<td>0 (0.0)</td>
<td>651 (98.6)</td>
<td>na</td>
</tr>
</tbody>
</table>

* a A total of 132 (9.7%) patients and 22 (3.2%) controls had at least one relative with endometrial cancer.
* b N represents the number of patients or controls reporting a family history of both cancer types; both cancers may or may not occur in the same relative.
* c Odds ratio estimates are based on contingency 2 × 2 tables estimating a ratio of the odds of both cancers vs. neither cancer reported in patient and control families. The presentation in the table is simplified to show counts [N (%)] for only 2 of the 4 cells used to obtain odds ratios of co-occurrence of EC & other cancer in relatives.
* d Phet is derived from the Breslow-Day test for heterogeneity between patients and controls for distribution of counts within 2 × 2 tables. Results from the Tarone modification of the Breslow-Day test for smaller sample sizes were the same.
and reports of other cancers in relatives (Fig. 1) were similarly unchanged in models that included known predictors of risk compared to age-adjusted estimates (data not shown). These observations suggest that family history of cancer is an independent predictor of risk. Further, our results suggest that recording reported cancers in both first- and second-degree relatives with simple age stratification of \(<50\) vs. \(\geq 50\) will be valuable in a counselling setting for risk evaluation.

We also evaluated EC risk and family history of cancers that fall within the spectrum of various high risk syndromes, and observed a significant trend in increasing risk associated with all syndromes except HBOC. However, consideration of colorectal, breast and other syndrome cancers reported in relatives did not improve the risk prediction associated with report of EC in a relative, suggesting that the risk estimates and trends for combinations of cancers are mostly driven by report of EC in a relative. These results indicate that family history of EC only, or of multiple Lynch syndrome cancers, may be the most relevant for prediction of EC risk and patient management in a familial cancer setting.

Results from the sub-analysis stratified by patient MMR tumor status, and excluding patients with known pathogenic MMR gene variants, indicate that alterations in genes other than the known MMR genes are likely to contribute to familial risk of EC. There was no difference in EC risk by MMR status for association with the family history of EC, or association with family history of all other cancer combinations and syndromes (Table 2). Notably, MMR proficiency was observed for 16/18 IHC-tested patients meeting Amsterdam II clinical criteria in our ANECs sample. Cook et al. previously reported a non-significant \((P = 0.09)\) difference in EC risk associated with family history of colorectal cancer by patient tumor MMR proficiency status as defined by microsatellite instability (MSI) testing \((\text{OR}_{\text{MSI}1.1-4} = 95\%\; CI\; 1.0-2.2; \; \text{OR}_{\text{MSI}1.0-95\%\; CI\; 0.7-1.3})\) [23]; however their analysis of 459 patients excluded patients meeting Amsterdam II criteria (MSI status not provided) [23]. Based on our observation that the vast majority of patients meeting Amsterdam II clinical criteria will be MMR proficient, we hypothesize that exclusion of Amsterdam II patients from the analysis of Cook et al. would drive their risk estimate for MSI stable EC towards the null.

A recent meta-analysis of estimates from published case-control and cohort studies reported an approximately 2-fold increase in the risk of EC associated with report of EC in a first-degree relative. However, there was considerable imprecision in the study-specific estimates that contributed data to this meta-analysis, with point estimates ranging from 1.2 to 5.0 for either case-control or cohort studies [5]. The largest study included in this meta-analysis was a population-based study with data on 3911 cases from the Utah Cancer Registry which reported an approximately two-fold increased risk of ECs in a FDR \((\text{RR}, 1.81; 95\%\; CI, 1.60-2.05)\) [24].

In our study, we observed a 3-fold increased risk of EC associated with EC in a FDR and/or SDR, somewhat greater than risk estimates reported by individual studies or meta-analysis [5]. Our analysis applying a correction factor for potential misreporting of EC in their relatives by the EC patient probands, estimated a similar 2-fold increased risk of EC associated with report of EC in a FDR and/or SDR, suggesting that our uncorrected estimate of a 3-fold increased EC risk is likely inflated due to over- or misreported EC in relatives of women with EC. However, this correction factor could be considered overly stringent given that no equivalent data was obtained from relatives of control probands, and thus the correction factor derived assumed no misreport of cancer by controls. It is also interesting to note that several of the “over-reported” EC in relatives were actually self-reported by relatives as conditions of the uterus that have been reported to be associated with increased EC risk, namely fibroids [25] and endometriosis [26]. Regarding other cancer types, it is unlikely that risk estimates associated with cancer report in relatives could be similarly inflated; concordance between patient and relative reports of other cancers was high (Table S7).

The accuracy of patient reports of family cancer history has been previously evaluated and found to vary according to degree of relationship, patient ascertainment, and type of cancer. Overall, patient reports of FDRs were found to be consistently more accurate than for SDRs, and whether probands were from the general population or cancer clinic referrals [27]. Positive or negative reports of breast and colon cancer were found to be accurate if reported in a FDR, while negative reports of ovarian and ECs were less accurate [28]. Reported family history of EC by patients or individuals receiving genetic counselling had accuracy rates of 25–40% [29]. One study specifically measured inaccuracy of reported cancers among a series of women diagnosed with EC and found that 29% of cancer reports were inaccurate, with higher rates of inaccuracy observed for second or third degree relatives [30]. Multiple factors may account for these variations, including public awareness of the importance of family cancer history and media coverage of some of the more common cancers. Our comparison of reported cancer did not suggest marked differences according to degree of relatedness, but support consistency in reported colon and breast cancer.

Despite these variations and recommendations for caution in the use of reported family history, it remains the most important basis for identifying age-related cancer risk and susceptibility to family cancer syndromes [31]. Such information is clinically important as a first step in prevention, and where management including counselling and genetic testing is possible, particularly for individuals with a family history of cancer.

Our study identified a significant trend in increasing risk associated with closer relatedness and younger age at diagnosis of EC. Although

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**Table 2**

<table>
<thead>
<tr>
<th>Cancer reported in relative(s)</th>
<th>Controls ((n = 682)) N (%)</th>
<th>MMR proficient tumor status</th>
<th>MMR deficient tumor status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients ((n = 543)) N (%)</td>
<td>(^a)OR ((95%; CI))</td>
<td>P</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>22 (3.2)</td>
<td>50 (9.2)</td>
<td>3.17 ((1.88-5.34)) (1.6 \times 10^{-5})</td>
</tr>
<tr>
<td>Endometrial and/or colorectal cancer</td>
<td>185 (27.1)</td>
<td>184 (32.9)</td>
<td>1.40 ((1.00-1.79))</td>
</tr>
<tr>
<td>Lynch cancers</td>
<td>208 (30.5)</td>
<td>202 (37.2)</td>
<td>1.33 ((1.05-1.70))</td>
</tr>
<tr>
<td>Cowden cancers</td>
<td>298 (43.7)</td>
<td>275 (50.6)</td>
<td>1.34 ((1.07-1.69))</td>
</tr>
<tr>
<td>HBOC</td>
<td>235 (34.5)</td>
<td>220 (40.5)</td>
<td>1.28 ((1.02-1.62))</td>
</tr>
<tr>
<td>Any syndromic cancer ((affected relatives))</td>
<td>294 (43.1)</td>
<td>247 (45.5)</td>
<td>1.08 ((0.80-1.36))</td>
</tr>
</tbody>
</table>

\(^a\)Mismatch repair (MMR) proficient patients \((n = 543)\) were proficient in immunohistochemistry testing for endometrial tumor expression of MLH1, MSH2, MSH6 and PMS2, and were not tested for gene sequence changes - assumed to have no pathogenic variant.
\(^b\)MMR deficient patients \((n = 135)\) were deficient in immunohistochemistry for at least one of MLH1, MSH2, MSH6 or PMS2, and genetic testing suggested MMR deficient with no pathogenic or likely pathogenic variant, or MMR deficient due to somatic MLH1 methylation or other unknown somatic or germine causes.
\(^c\)Estimates are age-adjusted for categorical variables \((0\; vs.\; \geq 1\; cancers)\) from multinomial regression models.
\(^d\)Lynch cancers: bile duct, bladder, brain, colon/rectum, duodenal, endometrial, gastrointestinal/GL, ovary/FT, pancreas, PMP, renal pelvis, stomach cancers.
\(^e\)Cowden cancers: breast, thyroid, endometrial, kidney-renal cancers.
\(^f\)HBOC: breast, ovary, pancreas, prostate cancers.
\(^g\)Any syndromic cancer refers to Lynch, Cowden and HBOC cancers defined above; counts are for number of first and/or second degree relatives of the proband reported to have any syndrome (Lynch, Cowden or HBOC) cancer.

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Further studies with confirmed cancer diagnoses are needed to verify the magnitude of risk estimates, we have shown that it is important to collect information on EC and age at diagnosis in both FDRs and SDRs when assessing the family cancer history for genetic counselling and risk prediction. Importantly, we also provide evidence that a family history of EC is associated with risk of MMR proficient EC and also MMR deficient EC after excluding MMR gene pathogenic variant carriers, suggesting that other non-MMR gene susceptibility underlies familial EC. Additional studies are required to investigate underlying genetic explanations for these associations with family cancer history.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jygyno.2017.08.011.

References

This manuscript reports the consensus statements regarding the design and conduct of clinical trials in patients with newly diagnosed and recurrent epithelial ovarian cancer (EOC), following deliberation at the Fifth Ovarian Cancer Consensus Conference (OCCC), held in Tokyo in November 2015. Three important questions were identified for discussion prior to the meeting and achieved consensus during the meeting: (i) What are the most important factors to be evaluated prior to initial therapy? (ii) What are the most important factors to be evaluated specifically in recurrent disease? (iii) Are there specific considerations for special patient subpopulations? In addition, we report a list of important unmet needs compiled during the consensus process, which is intended to guide future research initiatives.

**Key words:** ovarian cancer, consensus conference, GCIG, individualized therapy, recommendations

### Introduction

At the 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup (GCIG) held in Tokyo, Japan, in November 2015, representatives of 29 cooperative research groups studying gynaecologic cancers gathered to establish international consensus on issues critical to the conduct of large randomized trials. The process focused on a series of predetermined questions. Group A addressed six questions regarding clinical and biologic factors in patients with newly diagnosed and recurrent EOC.

The consensus statements for group A are presented in Tables 1–3; all statements achieved unanimous consensus. While achieving complete consensus, a list of important unmet needs was also compiled, presented in Table 4. The statements are recommendations for development of clinical trials, to be adapted, as appropriate, to the clinical setting (including local circumstances), specific agents under investigation, and study objectives.

### What are the most important factors to be evaluated prior to initial therapy?

#### Clinical markers

Clinical trials addressing primary therapy of EOC require consideration of prognostic or predictive factors potentially confounding the interpretation of study results (Table 1).

FIGO (International Federation of Gynecology and Obstetrics) surgical stage provides a standardized basis for comparing EOC patients. The third OCCC stated that ‘surgical staging should be mandatory and performed by a gynaecologic oncologist’, again affirmed at the 4th OCCC [1]. In 2014, FIGO staging was updated, reflecting that EOC comprises at least five distinct types: High Grade Serous Carcinoma (HGSC), Ovarian Endometrioid Adenocarcinoma (OEA), Clear Cell Carcinoma, Ovarian Mucinous Carcinoma (OMC) and Low Grade Serous Carcinoma (LGSC) [2]. The majority (70%) of EOC are HGSC, however, site...
of origin was acknowledged to include the fallopian tube, and possibly the peritoneal surface, in the latest FIGO update [2]. The OCCC recognizes that surgical pathologic stage, with both primary cytoreductive surgery (PCS) and interval cytoreductive surgery (ICS) following neoadjuvant chemotherapy (NACT), might serve for stratification in study design.

After surgical stage, the extent of residual disease (RD) following PCS surgery is the next most important prognostic factor to

Table 1. What are the most important factors to be evaluated prior to initial therapy?

<table>
<thead>
<tr>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FIGO stage, surgical pathologic (applies to Ov, FT and P)</td>
</tr>
<tr>
<td>• Cytoreduction status (primary complete resection versus other)</td>
</tr>
<tr>
<td>• Primary treatment modality (surgery versus NACT)</td>
</tr>
<tr>
<td>• Performance status and associated variables</td>
</tr>
<tr>
<td>• Tumour markers (e.g. CA-125) documented prior to therapy</td>
</tr>
<tr>
<td>• Country or geographic region of treatment</td>
</tr>
</tbody>
</table>

Pathology

• Histopathology remains the gold standard for the classification of epithelial ovarian (FIGO: Ov, FT, P) cancer subgroups
• In NACT, tumour grading (and typing) should be based on the pre-chemotherapy biopsy
• Binary grading of serous carcinoma (low-grade and high-grade), with distinction of micropapillary carcinoma
• Binary grading is favoured for endometrioid carcinoma (with assignment of FIGO grade 1 to low-grade, and 2–3 to high-grade)
• Carcinosarcomas are regarded as carcinomas
• Carcinosarcoma, clear cell carcinoma and undifferentiated carcinoma should not be graded
• Mucinous carcinoma should be graded
• Access to archival tumour specimens should be documented and maintained

Biomarkers

• Germline mutation testing to include BRCA1/2 is recommended for all patients enrolled on clinical trials
• Stratification (if possible) should be performed and knowledge of mutation status should be incorporated into primary endpoint analysis
• Somatic mutation analysis for BRCA 1/2 is recommended
• Predictive biomarkers for targeted agents to be included as companion diagnostics

Table 2. What are the most important factors to be evaluated specifically in recurrent disease?

<table>
<thead>
<tr>
<th>Clinical-pathologic markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treatment-free interval following primary chemotherapy</td>
</tr>
<tr>
<td>• With reference to last dose of primary platinum agent (PFI)</td>
</tr>
<tr>
<td>• Report as a continuous variable</td>
</tr>
<tr>
<td>• Less robust markers include acquired resistance following platinum-based therapy for recurrent disease</td>
</tr>
<tr>
<td>• Report last dose of non-platinum therapy, maintenance therapy (particularly anti-angiogenic agents or PARPi)</td>
</tr>
<tr>
<td>• Outcome following most recent cytoreductive surgery</td>
</tr>
<tr>
<td>• Presence of non-measurable versus RECIST-measurable disease</td>
</tr>
<tr>
<td>• Additional recommendations</td>
</tr>
<tr>
<td>• Separate clinical trials, if available, should be utilized for different histological subtypes, although trials can include multiple subtypes</td>
</tr>
<tr>
<td>• Collection of tumour specimens at relapse is encouraged</td>
</tr>
</tbody>
</table>

Table 3. Are there specific considerations for special patient subpopulations?

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Collection, reporting and analysis of race/ethnicity categories should be incorporated in future trials</td>
</tr>
<tr>
<td>• Emerging data support differences in clinical outcomes in relationship to race/ethnicity, however, pharmacogenomics markers have not been defined, and these population-based data are not sufficient to recommend stratification</td>
</tr>
<tr>
<td>• As data are validated within specific populations, race/ethnicity could become a stratification factor within individual studies</td>
</tr>
<tr>
<td>Frail and elderly</td>
</tr>
<tr>
<td>• Older age should not be an exclusion criterion in ovarian cancer trials</td>
</tr>
<tr>
<td>• Any limitations to eligibility criteria based on performance status, comorbidities, and prior malignancies should be justified by the trial design</td>
</tr>
<tr>
<td>• Clinical trials in ovarian cancer should include measures from the geriatric assessment domains</td>
</tr>
</tbody>
</table>

of origin was acknowledged to include the fallopian tube, and possibly the peritoneal surface, in the latest FIGO update [2]. The OCCC recognizes that surgical pathologic stage, with both primary cytoreductive surgery (PCS) and interval cytoreductive surgery (ICS) following neoadjuvant chemotherapy (NACT), might serve for stratification in study design.
be considered for stratification. Several aspects beyond surgical skill and effort influence RD status, including patient medical comorbidities, tumour biology and local institutional resources. Those patients who achieve optimal cytoreduction, without macroscopic residual disease (MRD) have been shown to achieve better overall survival (OS) relative to patients with macroscopic RD [3, 4]. Stage for stage, the absence of macroscopic RD has been shown to confer a large OS benefit compared to those patients with RD [5–7]. MRD at PCS is predictive of shorter time to first (Hazard Ratio (HR) 1.50 [1.31–1.72]) and second (HR 1.48 [1.22–1.80]) recurrence [8]. When stratifying by RD, the OCCC agreed that cytoreduction status be reported as primary complete resection (PCR) of all visible disease versus other, moving away from tumour measurements of <1 cm versus >1 cm. While groups might choose to report the extent of residual disease and outcomes according to previous definitions, the presence of RD, irrespective of size, confers a poorer survival benefit relative to complete cytoreduction. Need for accuracy and standardization in reporting the extent of RD was recognized as an unmet goal. Various measurement tools have been reported; scoring of RD has largely been subjective, without objective verification [9–12]. When disease status is assessed by postoperative computed tomography (CT), it can be discordant from surgical reports and potentially of independent prognostic value, however, there are currently insufficient data mandating postoperative imaging [11, 12].

Primary treatment modality has also become an important factor to consider for stratification. Two randomized controlled trials have shown that ICS is not inferior to PCS among patients with advanced disease. Criticism of these studies has centred on poor overall survival and low levels of complete and optimal (<1 cm) cytoreduction achieved with PCS, raising questions about surgical effort and institutional expertise. The higher optimal cytoreduction rates achieved following NACT compared with PCS (CHORUS 73% versus 41%, EORTC 80.6% versus 41.6%) did not translate into a survival benefit [11, 12]. Neither the assessment of pathologic response following NACT nor the minimum surgical requirements for ICS have been standardized. The clinical impact of complete cytoreduction post-NACT is likely to be less robust than complete cytoreduction with PCS.

Retrospective series have suggested that improved survival is possible with PCS, particularly when incorporating radical surgical techniques [5–7, 13–16]. It remains difficult to control for selection bias in retrospective data. Other studies have suggested that tumour biology and initial tumour burden remain important, even with maximum surgical effort [17, 18]. These studies also highlight the need to develop better criteria to guide the selection of patients for NACT or PCS.

Performance status (PS) and associated variables should be utilized as stratification points (SP), depending on the trial design. In the CHORUS study, designed for co-analysis with EORTC 55971, anticipated OS at 3 years in the primary surgery arm was 50%, but actual median OS was only 22–24 months. Explanations for this discrepancy included a relatively poor PS among study participants (19% PS grade 2 or 3) and an older patient population (median age 65 years). PS and other variables associated with comorbidities (e.g. nutritional status) aid interpretation of study results and should be considered in future trial design [19, 20].

Prior to instituting therapy, the importance of documenting tumour markers was affirmed. Traditional tumour markers have included CA-125 and carcinoembryonic antigen (CEA), the latter to exclude gastrointestinal primary. While acknowledging that CA-125 is not truly ‘tumour-specific’, an analysis of seven GOG studies found that pre-treatment CA-125 level was an independent predictor of progression-free survival (PFS), especially in patients with serous or endometrioid histology and microscopic residual disease [21].

Another promising tumour marker is Human Epididymis Protein 4 (HE4), shown to have good sensitivity and specificity in EOC, both at initial diagnosis (differentiating EOC from benign) and in documentation of recurrence [22–24]. A failure of HE4 to normalize at completion of treatment is an indicator of poor prognosis [24, 25]. Documentation of appropriate pre-treatment tumour markers should be incorporated in future trials of primary therapy.

Country/region of treatment was determined to be an important potential stratification factor, recognizing differences in race, ethnicity, local resources and clinical practice. The EORTC 55971 study showed widespread variations in optimal PCS rates by country [26]. In the same study, however, regional OS did not correlate with cytoreduction rates, with patients from regions with the lowest rates of optimal cytoreduction achieving the best survival [27]. In the SCOTROC-1 study, patients from the UK with no MRD had less favourable PFS relative to non-UK patients [28]. Nuances in care and patient selection will impact outcomes from apparent standardized treatments. Consider country or region of treatment as a stratification factor where appropriate.

Pathologic markers
Consistent with the fourth OCCC, histopathology remains the gold standard for the classification of EOC cancer subgroups [1].
Where required, diagnostic accuracy of histopathology can be improved with standardized application of immunohistochemistry (IHC) [29]. For pathological reporting within randomized clinical trials (RCT), histological subtype and grade should not be reported separately. Following NACT, morphological features of the tumour at ICS could differ greatly from the original tumour, including necrosis, inflammation, fibrosis and altered differentiation status [30]. The OCCC determined that tumour grading (and typing) should be based on the pre-chemotherapy tissue biopsy. For serous carcinoma, there was consensus recommending a binary grading system, limited to HGSC and LGSC (incorporating micropapillary carcinoma). Discrimination between LGSC and HGSC follows the degree of nuclear atypia in combination with mitotic activity [31]. LGSC is characterized by frequent mutations in KRAS, BRAF and ERBB2 genes and infrequent TP53 mutations [32]. Whereas TP53 mutations are rare in LGSC, they are ubiquitous in HGSC. Absence of a loss-of-function molecular alteration in TP53 is inconsistent with a diagnosis of HGSC [33, 34].

The OCCC recommends that in HGSC, the fallopian tubes be intensively sampled using a Sectioning and Extensively Examining of the Fimbriated End (SEE-FIM) protocol [35]. With serous tubal intraepithelial carcinoma (STIC) and widespread peritoneal involvement, where ovarian surface involvement or parenchymal involvement is <5 mm, these tumours should be classified as tubal primaries.

When categorizing ovarian endometrioid adenocarcinoma (OEA), adoption of a binary grading system was also recommended. This differs from the 2014 WHO classification of female reproductive organs and reporting standards endorsed by the International Collaboration on Cancer Reporting (ICCR), where OEA are graded identically to uterine endometrioid carcinomas – grade 1, 2 or 3 [36, 37]. FIGO grading of endometrioid endometrial carcinoma reflects not only the presence of high-grade cytological features but also the actual percentage of high-grade solid tumour, which is less relevant in the setting of a non-endometrial primary site. High-grade endometrioid tumours demonstrate mutational profiles similar to HGSC harbouring TP53 mutations, while the low-grade tumours showed distinct mutations in CTNNB1, PTEN and/or PIK3CA [38]. Mutations in the Wnt/Beta-cat signalling pathways present in low-grade tumours were absent in high-grade endometrioid carcinoma. The consensus recommends classifying FIGO grade 1 tumours to low-grade, and grades 2 and 3 to high-grade.

Clear cell carcinoma, carcinosarcoma and undifferentiated carcinoma should be classified as high-grade epithelial malignancies [37]. Carcinosarcomas are included, despite having mixed epithelial and mesenchymal components, attributed to epithelial–mesenchymal transition [39]. Most OMC are of intestinal type, arising through a continuum from benign to borderline to malignant [31]. These are usually well to moderately differentiated (grade 1 or 2) and can exhibit expansile (non-destructive) or infiltrative (destructive) invasion, although controversy exists about the ability to prognosticate based on pattern of invasion [37]. According to WHO (2014), Mullerian and endocervical type tumours, previously classified as mucinous, and now classified as seromucinous, are thought to be more closely related to endometrioid tumours than to mucinous intestinal types [36]. Grading of OMC is recommended.

The importance of access to archival tumour specimens for future molecular studies was affirmed. Study protocols should account for the documentation and maintenance of archival specimens. One method endorsed by the ICCR is to record the origin and designation of tissue blocks in the final pathology report [37]. Collected specimens allow for extended correlative studies, where bio-specimens are linked to clinical data.

Genomic biomarkers

For patients enrolled in clinical trials, germline mutation testing to include BRCA1/2 was recommended, with stratification and incorporation of mutation status into endpoint analysis. Many series have shown that BRCA 1/2 mutation is associated with improved outcomes [40]. One large aggregated analysis has suggested that the advantage associated with BRCA1 mutations may become less favourable over time [41]. The power of a long-term retrospective analysis could be impacted by non-germline (somatic) mutations and other molecular factors within the BRCA “wild-type” cohort. There was debate whether germline testing should be limited to non-mucinous histologies; in view of the risk of misclassification, as well as concordance with published guidelines, it was recommended that within a trial, patients with EOC should undergo germline testing [40].

The consensus recommends somatic mutation analysis of tumour samples. Loss of BRCA function secondary to somatic mutations in OC accounts for 7%–13% of BRCA mutations in HGSC [42–44]. Somatic analysis from The Cancer Genome Atlas (TCGA) project demonstrated that approximately 50% of HGSC have associated homologous recombination deficiency (HRD), potentially targetable with poly (ADP-ribose) polymerase (PARP) inhibitors [45]. Extending BRCA1/2 testing to include somatic mutation analysis was recommended.

As validated predictive biomarkers become available, these should be included as companion diagnostics. Several potential biomarkers were discussed. The creation of an HRD score based on loss of heterozygosity (LOH) correlates with mutations in BRCA1/2 and other genes, while accurately predicting both OS and PFS [46]. Regardless of histology, HRD defects are associated with both platinum sensitivity and improved OS [44]. Another HRD signature based on LOH correlates with response to PARP inhibitor [45, 47].

A potentially targetable biomarker is the overexpression of Cyclin E1 (CCNE-1) seen in OC [48]. CCNE-1 amplification correlates with shorter PFS when PCS is followed by platinum/taxane chemotherapy, and it correlates with platinum resistance in HGSC [49, 50]. A third potential biomarker is represented by intratumoural T-cells in EOC tissue. In patients with stage III/IV EOC, the presence of intratumoural T cells correlates with improved PFS and OS [51]. This illustrates another area of unmet need, where immunologic functional scoring might guide the development of immunologic interventions.

What are the most important factors to be evaluated specifically in recurrent disease?

The OCCC addressed factors to consider in the design of phase III trials in the recurrent setting. Treatment-free interval (TFI)
following primary chemotherapy was identified as the most important clinical factor. As treatment with a platinum-based regimen remains standard of care in the primary setting, the platinum-free interval (PFI) should be documented and utilized to determine eligibility or serve as a stratification factor (Table 2).

Several studies have shown a differential impact of subsequent treatments based on the PFI. AGO-OVAR 2.5 comparing gemcitabine/carboplatin versus carboplatin showed differential PFS (7.9 versus 9.7 months) based on initial PFI, between partially platinum-sensitive patients (6–12 months) and those who were platinum-sensitive (>12 months) [52]. Penultimate platinum treatment should be considered at randomization. The analysis by Hanker et al. [8], addressing effectiveness of chemotherapy at recurrence, included patients on trials in the primary setting to characterize PFS/OS from the second to the sixth lines of therapy. PFI following first-line treatment was strongly prognostic for PFS up to the third recurrence (OR 0.56 [0.5–0.63] at first recurrence; OR 0.76 [0.64–0.9] at second recurrence). In the CALYPSO trial, a subset of patients with a prolonged TFI >24 months was analysed separately, reflecting their different tumour biology [53].

Considering the linear relationship between extended PFI and platinum sensitivity, we recommend reporting PFI following primary chemotherapy as a continuous variable, rather than adopting an arbitrary definition of ‘platinum-sensitive’ or ‘platinum-resistant’ disease based on a single fixed time point (such as 6 months). Future trials could define eligibility or patient cohorts according to any appropriate PFI, depending on the nature of the study, and may, therefore, not be limited to a fixed 6-month window.

Platinum-based therapy (PBT) remains the most active agent in the management of EOC, and primary PFI clearly provides important prognostic and predictive information. Many patients receive multiple lines of PBT, and the time interval following the most recent PBT can also provide prognostic information, due to acquired resistance and clonal evolution associated with intervening non-platinum treatments.

A variety of non-platinum agents have been integrated with conventional therapy, and other prognostic/predictive markers are needed to guide treatment decisions in the management of recurrence. Several trials have affirmed that targeting the vascular endothelial growth factor (VEGF) improves clinical outcomes as maintenance post-chemotherapy or in combination with chemotherapy for recurrence [54–60]. PARP inhibitors have demonstrated improved PFS as single agents in the management of recurrence and as maintenance following chemotherapy [60]. Recognizing emerging treatment strategies, the OCCC also recommended that the last dose of non-platinum agents, including maintenance therapy, be recorded.

Secondary (or subsequent) cytoreductive surgery has been increasingly utilized in selected patients with recurrent ovarian cancer, and the OCCC recommends stratification based on the outcome of the most recent cytoreductive surgery. Complete resection was associated with prolonged survival in the recurrent setting in the exploratory DESKTOP OVAR trial (45.2 versus 19.7 months, HR 3.71, \( P < 0.0001 \)), also confirmed elsewhere [61,62].

With recurrence, the presence of non-measurable versus RECIST (response evaluation criteria in solid tumours)-measurable disease should be documented, including small solid/cystic lesions and fluid collections as well as diffuse tumour implantation on vital organs without measurable solid components, depending on study eligibility. Solid tumour response was defined in RECIST version 1.1 [63], and RECIST guidelines for progression of disease can be applied to patients with non-measurable disease at enrolment. GCIG guidelines to determine tumour response and progression using CA-125 exist, and although these have not been accepted as primary endpoints by regulatory authorities, they can be utilized to provide supporting data [64].

Histological subtype remains an important factor to guide enrolment in sub-type specific trials, or as a SP. In light of different genetic risk factors, molecular abnormalities and precursor lesions, as well as variable response to chemotherapy and targeted agents across histologies, histotype must be considered [65]. Collection of tumour specimens at relapse is encouraged, with an emphasis on paired samples collected at the outset and at recurrence, enhancing the study of molecular targeting and acquired resistance.

### Race and ethnicity

Differences in outcome of cancer treatments attributable to race/ethnicity are becoming recognized, the result of both biological and environmental interactions [66] (Table 3). When comparing treatment and survival between Asian and white women with EOC in the US, age, stage of presentation, as well as histological subtype/grade differed between the groups [67]. Dividing Asians into immigrant versus US-born, 5-year disease-specific survival favoured immigrant Asians compared with US-born Asians and whites (55%, 52%, and 48%, respectively, \( P < 0.001 \)). Increases in 5-year OS over the past 30 years seen in whites (36%–45%) have been met with a decrease in blacks (43%–39%) over the same time period [68]. A positive first line maintenance trial investigating pazopanib has shown inferior outcome in Asian patients compared with placebo, meaning a drug could harm specific patient subgroups, even in a positive trial [69]. A separate study examining potential racial disparities between blacks and whites enrolled in GOG clinical trials found equivalent PFS between the two groups (37.9 and 39.7, respectively, \( P > 0.05 \)) [70].

The collection, reporting and analysis of race/ethnicity categories should be incorporated in future trials. Predefined and prospective data collection minimizes confounding and strengthens associations found in post hoc analysis of trial data. Race and ethnicity are differentially categorized by country and region; development of universal standards was recognized as an unmet need, limiting international data harmonization.

In a meta-analysis of RCTs treating advanced stage non-small cell lung cancer, a difference in the overall response rate between Asians and Caucasians was observed (65% versus 31%, \( P = 0.01 \)), where ethnicity was identified as the only independent predictor of response to treatment by multivariable analysis [71]. Several studies have shown associations or putative effects between polymorphisms and outcome/toxicity. Attempts to validate...
a previously defined set of polymorphisms from the Scottish Randomized Trial in Ovarian Cancer, no pharmacogenetics markers for outcome or toxicity were identified [72]. Until more data emerge, existing studies do not support stratification; as data are validated within specific populations, race/ethnicity could become a stratification factor within individual studies.

Frail and elderly patients

In the conduct of phase III trials in EOC, frail and elderly patients have been underrepresented. Comorbidities and physiologic factors are predictive of outcomes and toxicity, compared to age; older age should not be an exclusion criterion in EOC trials.

The improvements in cancer survival over the past decades generally seen in younger patients have not translated to elderly cohorts, with a widening gap of OS rates between younger and more elderly cohorts [73, 74]. In Germany between 1979 and 2003, age-specific OC survival remained stable for women age 75 and over, yet OS steadily increased for women aged 15–54. Women aged 55–74 experienced an increase from 1994 onwards, representing the highest age gradient seen across all tumours [75].

Outcomes for elderly patients may relate directly to the care they receive, particularly when that care deviates from the standard. Surveillance, Epidemiology and End Results Program (SEER) data investigating risk factors for early death show that the largest risk factor for death at one year was receiving non-standard treatment [76]. This is echoed by the German experience, where differential treatment in women over 70 was associated with differences in survival. Analysing patients enrolled in phase III RCTs addressing first-line treatment, women >70 (10.7% of patients) were more likely to experience discontinuation of their treatment and receive 4 or fewer cycles [77, 78]. Multivariate analysis of PFS in women 70 or older receiving 4 or fewer cycles of chemotherapy was 2.3 (P < 0.001), translating into a difference in PFS of 18.4 (P < 0.001) months and OS of 33.8 months (P < 0.001) [79].

Patients enrolled in clinical trials tend to have better outcomes based on the need to meet eligibility requirements, with healthier patients more likely to achieve enrolment. The results of some trials then become poorly generalizable, as they are not addressing the realities of patients seen in the real-world clinical domain [80, 81]. Apart from advanced age, OC patients may present with comorbidities or poor PS, which will impact OS [20, 82]. While prior cancer diagnosis is often an exclusion criterion from an RCT out of concern that it might interfere with the current study, no data exist which support this practice [83]. To improve generalizability of trial results, with the goal to make trials available to the broadest population possible, any limitations to eligibility criteria based on PS/comorbidities/prior malignancies must be justified by the trial design.

Adequately comparing patients for trial inclusion requires validated measures to minimize confounding. While elderly patients must be considered for inclusion as trials are developed, inclusion based on the age alone is insufficient. In conjunction with age and geriatric conditions, comorbidities, disability and physical reserve must be considered in consort. The goal is to differentiate elderly patients who could receive standard treatment from frail patients – those with low physiologic reserve – who are not candidates for standard therapy and could benefit from a comprehensive geriatric assessment (CGA) to help guide therapy [84]. To date, measures of frailty have failed to achieve both the high sensitivity and specificity required to ensure that patients deemed fit enough for standard treatment truly are, and to differentiate these patients from those who will benefit from a CGA [84]. The consensus recommends that clinical trials in EOC should include measures from geriatric assessment domains.

Unmet needs to support future clinical research

In the process of assigning important SP throughout the consensus process, unmet needs were identified as areas with potential to enhance clinical research but which lack direction. In regards to the issue of assessing residual disease at the time of debulking surgery, the group sees a potential role for intra-operative scoring [85] and/or post-operative imaging (see Clinical markers section) to document RD (Table 4).

Universal staging criteria in the context of NACT are needed. In CHORUS and EORTC 55971, women in the NACT arms were staged clinically using imaging [3, 4]. No validated process exists for documenting the extent of disease outside of surgery.

Treating patients with NACT will result in morphological changes to the tumour. While attempts at quantifying the chemotherapy effect on tumour morphology have been undertaken, none have proven to be prognostic. The International Collaboration on Cancer Reporting has recently published a validated chemotherapy response score (CRS) with prognostic significance for PFS [86]. There is a need for creation of a CRS that can be incorporated in primary endpoint analysis and pathological reporting.

Immunotherapy in OC represents a rapidly evolving treatment domain, with an urgent need for the standardization of immunologic assessment. Programmed cell death ligands (PD-1 and PD-L1) and CD8+ T cells are prognostic in OC, the former allowing for immune evasion of tumour cells [87]. T cell infiltration into OC tumour samples is associated with improved OS [51]. Standards for immunologic assessment, including lymphocyte infiltration scores, T cell subsets and PD-1/PD-L1, are required for comparison among studies and in order to allow for incorporation as SP in future studies.

There are important issues regarding definition and categorization of race/ethnicity that would benefit from international harmonization (see Race and ethnicity section). Older patients and/or those with compromised functional status are underrepresented in clinical trials. There is a need to define this population and perform trials to evaluate standards for this subgroup (see Frail and elderly patients section).

Acknowledgements

The Fifth Ovarian Cancer Consensus Conference was convened by the GCIG in Tokyo, Japan, from 7–9 November 2015. The authors acknowledge that all 92 delegates to this consensus conference contributed to these statements including those from the 29 member groups. The authors acknowledge the GCIG industry partners and the administrative support from GCIG,
JGOG (Japan), Jikei University (Japan) and Kitasato University (Japan).

Funding

This work was supported by unrestricted grants from Astra Zeneca UK Limited (UK); Bristol-Myers Squibb Company (USA); Clovis Oncology Inc. (USA); Eisai Co., Ltd. (Japan); F. Hoffmann-La Roche Ltd. (Switzerland); Pfizer Inc. (USA); Pharma Mar, S.A. (Spain); TESARO, Inc. (USA); and Zeria Pharmaceutical Co., Ltd. (Japan). The agenda, presentations and statements were entirely developed without involvement of these funding sources. No grant numbers apply.

Disclosure

The authors have declared no conflicts of interest.

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Foley catheter silicone versus latex for term outpatient induction of labour: A randomised trial

Therese M McGee¹,², Beata Gidaszewski³, Marjan Khajehei¹,²,⁴, Toni Tse¹ and Emma Gibbs⁵

Background: Both silicone and latex single-balloon Foley catheters are available for cervical ripening but no literature exists to compare them. Local experience suggested more frequent insertion-related accidental rupture of the membranes (acROM) with silicone.

Aims: To compare the performance of silicone versus latex catheters with respect to acROM and other outcomes.

Materials and Methods: Women undergoing outpatient Foley catheter cervical ripening were randomised to a silicone or latex catheter. Data were collected on the primary outcome, acROM, and secondary outcomes including catheter insertion failure, unplanned hospital admission and patient-reported discomfort, together with intrapartum fever and antibiotics for suspected chorioamnionitis along with general obstetric and neonatal outcomes.

Results: Among 534 recruited women, acROM was significantly more common with a silicone compared to a latex catheter at 7.2% (19/265) versus 1.5% (4/269) (relative risk (RR) 4.8; 95% CI 1.7–14.0). Insertion failure was significantly less common with silicone than latex at 2.6% (7/265) versus 9.3% (25/269) (RR 0.3; 95% CI 0.1–0.6). However, when the alternative catheter was subsequently tried, the final failure rates were 1.9% silicone (5/265) versus 2.6% latex (7/269). Insertion-related hospital admission was higher with silicone at 9.4% (25/265) than latex at 4.8% (13/269) (RR 2.1; 95% CI 1.1–4.1). All other obstetric outcomes were similar between the groups.

Conclusion: When used for cervical ripening, a silicone Foley catheter is associated with a higher rate of acROM than a latex catheter but a lower rate of insertion failure. It may, therefore, be reasonable to attempt insertion with a latex catheter initially and manage insertion failures with a silicone catheter.

KEYWORDS
accidental membrane rupture, cervical ripening, failed catheter insertion, Foley catheter, labour induction
INTRODUCTION

Induction of labour occurs in about 25% of pregnancies in high-resource countries.\(^1\) Cervical ripening is often utilised if the cervical Bishop score is below seven.\(^3\) The options for ripening include pharmacological methods using exogenous prostaglandins or mechanical methods such as extra-amniotic Foley catheters which are thought to stimulate the release of endogenous prostaglandins among other effects.\(^5\) Foley catheters are said to have been used for this purpose since 1906,\(^6\) while prostaglandin PGE\(_2\) (dinoprostone) and PGE\(_1\) (miso-prostol) analogues have been used over more recent decades.\(^7\)–\(^9\)

Current evidence suggests that a Foley catheter has equivalent efficacy to vaginal prostaglandins for caesarean birth rates\(^5\) and birth within 24 h,\(^4,10\) while having lower rates of tachysystole, with or without fetal heart rate changes.\(^3\)–\(^5\) A Foley catheter also has the advantage over PGE\(_2\) products in its low cost and stability at room temperature.\(^3\)

Reported complications with Foley catheters include vaginal bleeding, rupture of the membranes, febrile morbidity and displacement of the presenting part,\(^3\) as well as failure to achieve insertion\(^11\)–\(^13\) and the woman’s discomfort during the insertion.\(^14\)–\(^16\) There does not appear to be an increase in maternal or neonatal infection with catheter use.\(^17\)

Regarding single-balloon Foley catheters versus double-balloon catheters, the literature is contradictory about relative efficacy.\(^18,19\) While double balloon catheters are significantly more expensive and may be more uncomfortable for women.\(^20\)

Due to tachysystole concerns, in late 2014 our hospital moved from PGE\(_2\) gel to Foley catheter as the default tool for cervical ripening. Both silicone and latex Foley catheters were readily available but no evidence existed regarding their relative efficacy or complications. In fact, labour induction studies rarely mentioned the type of catheter material used.

Our experience suggested that silicone was more likely than latex to be associated with insertion-related (immediate) accidental rupture of membranes (acROM). In our unit where ripening (both PGE\(_2\) gel and Foley catheter) has been a wholly outpatient day-before-induction procedure for most women since 2007, the occurrence of acROM was important because it mandated immediate hospital admission and overnight stay rather than discharge home and presentation the next morning. Differences in other comparative outcomes between the catheters were unclear. The purpose of our study therefore, was to compare silicone and latex Foley catheters for performance during cervical ripening and labour induction, with the primary outcome being acROM.

MATERIALS AND METHODS

Design

Between May 2015 and July 2017, we conducted a randomised trial, stratified by parity, at Westmead Hospital, a large (5600 births) tertiary unit serving a multiethnic, low-to-middle income population in addition to referred high-risk pregnancies. The study protocol was prospectively approved by the Western Sydney Ethics Committee. It was also registered with the Australian New Zealand Clinic Trials Registry (ANZCTR 12615000795594) although, due to administrative oversight, this occurred 2 months into the study rather than before it.

Participants

Pregnant women were considered for participation if they required pre-induction Foley catheter cervical ripening. Eligibility criteria included age ≥16 years, gestational age ≥36 weeks and Bishop score <7. Exclusion criteria included latex allergy, Bishop score ≥7, ruptured membranes, placenta closer than 2 cm to the internal cervical os or recent undiagnosed bleeding, abnormal pre-ripening cardiotocograph (CTG), prior use of prostaglandins, active cervical or vaginal infection, lethal fetal congenital anomaly or fetal demise, and inability to consent (including inadequate English).

Randomisation and allocation concealment

A researcher away from the clinical service used a random-numbers list to determine group allocation, placing each into identical, sequentially numbered opaque envelopes, using permuted blocks of eight with 1:1 allocation. After a normal pre-ripening CTG, ascertaining eligibility, and obtaining trial consent, the clinician undertaking catheter insertion opened the next sealed envelope appropriate to the woman’s parity (parity = 0, parity ≥ 1). Trial-related counselling and data collection added 20–30 min to the usual insertion time.

Blinding

The participants were blind to the catheter type at the time of insertion but the clinician, and therefore assessment of immediate outcomes, could not be blinded. Birth/neonatal outcomes were based on independently collected hospital data, blind to treatment allocation.

Intervention

The Foley catheters were both 18F (C. R. Bard, Covington, GA, USA) and were described on the packaging respectively as 100% silicone and silicone elastomer coated latex. The latter is the standard latex catheter used in our hospital for both bladder and cervical insertion. The coating, designed to minimise bacterial colonisation and hypersensitivity, is completely invisible with the appearance and feel identical to plain latex, now considered obsolete.\(^21\) We selected 18F because it is a popular size\(^4,22\) and because the Cook cervical ripening double-balloon option is 18F silicone (Cook Medical, Bloomington, IN, USA).
Catheter insertion was performed during the daytime seven days a week in the outpatient service by trained obstetric and midwifery staff. The initial insertion mode was via speculum, without use of antiseptic cleansing, anaesthetic agents, tenaculums or styles. After insertion, the balloon was filled with 30 mL of sterile water and taped under light tension to the inner thigh. A post-insertion 60 min CTG was then performed. In the absence of abnormal CTG, regular uterine contractions, major bleeding and maternal/fetal indications for admission, the woman was discharged home to return next morning for induction as per usual hospital protocol. She was also invited to return immediately if the Foley fell out (she was asked to record the time) or if pain/contractions, bleeding, ruptured membranes or fetal movement concerns developed.

If insertion failed with the primary allocation catheter, clinicians were permitted to attempt insertion with the alternative Foley. If both insertions failed, digital insertion was attempted or the woman received PGE	extsubscript{2} gel, oxytocin or caesarean section. If acROM occurred during insertion, the catheter was left in situ but the woman was admitted rather than discharged home. Antibiotics for prophylaxis were administered to Group B Streptococcus (GBS) positive but not GBS negative women.

Estimated blood loss with insertion was recorded; if bleeding was ongoing or >5 mL, the catheter was removed and the woman admitted as per hospital protocol. All other aspects of care were determined by the obstetric team caring for the woman during labour and birth.

**Outcomes**

The pre-specified primary outcome was acROM (apparent immediately) at the time of Foley catheter insertion. Pre-specified secondary outcomes included catheter insertion failure, women’s self-reported discomfort during insertion (visual analogue score 1–10), clinician assessment of insertion difficulty (easy, moderate, difficult), and labour/birth outcomes including mode of birth, intrapartum fever ≥38°C, antibiotic administration for suspected chorioamnionitis and blood loss at delivery. Neonatal outcomes included Apgar scores, umbilical artery lactate and nursery admission. Hospital admission related to acROM and vaginal bleeding >5mL were planned outcomes at trial initiation, although not listed in our trial protocol. Routine induction outcomes such as type of Foley removal, mean Bishop score at removal, and oxytocin and epidural use in labour were also examined.

**Statistical methods**

**Sample size calculation**

In the absence of published data and from our limited experience, we estimated a likely 2% acROM rate with silicone and 0.5% with latex catheters. Based on this estimate, using an alpha of 0.05 and a power of 80%, a sample size of 870 participants in each group was needed. Because of the uncertainty surrounding this estimate, the study protocol allowed independent data/safety monitoring committee review after every 100 participants with the stopping point determined as a very significant difference in the primary outcome (≤0.001) between the cohorts.

**Statistical analysis**

Intention to treat analysis was performed using SPSS Advanced Statistics version 24.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used to summarise the demographic data; binary outcomes were summarised with a relative risk (RR) and 95% confidence intervals (CIs), and compared between the two groups using a $\chi^2$ test (or Fisher’s exact test where applicable). A t-test was used to assess continuous non-skewed variables; these are presented as means with standard deviations. For skewed ordinal data, the Mann–Whitney U-test was used; these data are presented as medians with interquartile ranges. Difference in the effect over the subgroups was assessed using logistic regression. $P < 0.05$ was considered statistically significant.

**RESULTS**

In July 2017, the independent data monitoring committee recommended early conclusion of the trial because the primary study question had been answered at a level of significance of $P = 0.001$.

Between May 2015 and July 2017, 12 727 women gave birth, 3661 were induced (28.7% induction rate) and 1058 underwent cervical ripening using a Foley catheter. Of these, 534 women were recruited to the study (371 nulliparous and 163 parous) with 269 in the latex group and 265 in the silicone group. Data for all participants were available for analysis (Fig. 1). There were no differences in baseline characteristics between the silicone and latex groups (Table 1) or between the 534 women recruited and the 524 not recruited (data not shown).

**Accidental rupture of membrane**

The primary outcome, acROM, occurred in 23 women. It was significantly more common overall in the silicone cohort at 7.2% (19/265) than the latex cohort at 1.5% (4/269) (RR 4.8; 95% CI 1.7–14.0), and also in nulliparous women (RR 5.4; 95% CI 1.6–18.1), while the number of parous women was underpowered to show a significant difference (RR 3.1; 95% CI 0.3–29.3; Table 2).

**Insertion failure**

Failure to insert the catheter was significantly less common in the silicone compared to latex cohort overall at 2.6% (7/265) versus 9.3% (25/269) (RR 0.3; 95% CI 0.1–0.6) and within both the nulliparous (RR 0.4; 95% CI 0.2–0.9) and parous subgroups (RR 0.1; 95% CI 0.01–0.9; Table 3). Of the seven silicone insertion failures, two were subsequently successful with a latex catheter, giving an overall
Silicone versus latex catheter for labour induction

Women who required Foley catheter for induction of labour and were assessed for eligibility (n = 1058)

Did not participate (n = 524)
- Staff too busy (n = 348)
- Did not meet inclusion criteria (n = 136)
  ✓ Inadequate English (n = 86)
  ✓ Non reassuring fetal status, lethal congenital anomaly or fetal demise (n = 20)
  ✓ Latex sensitivity (n = 14)
  ✓ <36/40 gestation (n = 9)
  ✓ Antepartum haemorrhage (n = 7)
- Patient declined (n = 40)

Enrolled (534)

Silicone Foley catheter (n = 265)
- Received allocated Foley (n = 258)
- Received alternative Foley after failure to insert allocated Foley (n = 2)
- Failure to insert both Foleys [n = 5 (4 PGE₂ gel, 1 oxytocin)]

Latex Foley catheter (n = 269)
- Received allocated Foley (n = 244)
- Received alternative Foley after failure to insert allocated Foley (n = 18)
- Failure to insert both Foleys [n = 7 (5 PGE₂ gel, 1 oxytocin, 1 CS)]

Analysed (n = 265)
Analysed (n = 269)

FIGURE 1  Consort flow chart showing enrolment, randomisation and follow-up of study. CS, caesarean section; ITT, intention to treat; PGE₂, prostaglandin E₂.

Failure of 1.9% (5/265). Of the 25 latex insertion failures, 18 were subsequently successful with a silicone catheter giving an overall failure of 2.6% (7/269). Route of insertion was speculum (498), digital after speculum failure (24) and complete insertion failure (12).

Other outcomes
Hospital admission directly relating to catheter insertion occurred significantly more often in the silicone than the latex group at
TABLE 1 Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Silicone Foley (n = 265)</th>
<th>Latex Foley (n = 269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>39 (15%)</td>
<td>29 (11%)</td>
</tr>
<tr>
<td>25–35</td>
<td>191 (72%)</td>
<td>190 (71%)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>35 (13%)</td>
<td>50 (19%)</td>
</tr>
<tr>
<td>Parity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous (n = 371)</td>
<td>185 (70%)</td>
<td>186 (69%)</td>
</tr>
<tr>
<td>Parous† (n = 163)</td>
<td>80 (30%)</td>
<td>83 (31%)</td>
</tr>
<tr>
<td>Australian-born, n (%)</td>
<td>99 (37%)</td>
<td>91 (34%)</td>
</tr>
<tr>
<td>BMI at first antenatal visit, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 (underweight)</td>
<td>8 (3%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>18.5–24.9 (normal)</td>
<td>127 (48%)</td>
<td>114 (42%)</td>
</tr>
<tr>
<td>25–29.9 (overweight)</td>
<td>76 (29%)</td>
<td>85 (32%)</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>54 (20%)</td>
<td>63 (23%)</td>
</tr>
<tr>
<td>Median BMI at first antenatal visit (IQR)</td>
<td>24.8 (22.3, 28.5)</td>
<td>25.6 (22.3, 29.4)</td>
</tr>
<tr>
<td>Median BMI at end of pregnancy (IQR)</td>
<td>29.9 (27.1, 33.0)</td>
<td>30.2 (27.1, 34.1)</td>
</tr>
<tr>
<td>Indication for Foley insertion, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged pregnancy (≥41 weeks)</td>
<td>82 (31%)</td>
<td>84 (31%)</td>
</tr>
<tr>
<td>Maternal indications</td>
<td>95 (36%)</td>
<td>110 (41%)</td>
</tr>
<tr>
<td>Fetal indications</td>
<td>79 (30%)</td>
<td>62 (23%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (3%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Median gestational age, weeksdays (IQR)</td>
<td>39\textsuperscript{16} (38\textsuperscript{16}, 41\textsuperscript{16})</td>
<td>39\textsuperscript{16} (38\textsuperscript{16}, 41\textsuperscript{16})</td>
</tr>
<tr>
<td>Bishop score before Foley insertion, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>167 (63%)</td>
<td>180 (67%)</td>
</tr>
<tr>
<td>5–6</td>
<td>98 (37%)</td>
<td>89 (33%)</td>
</tr>
<tr>
<td>Dilatation before Foley insertion, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>87 (33%)</td>
<td>98 (36%)</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>178 (67%)</td>
<td>171 (64%)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CS, caesarean section; IQR, interquartile range. †Of 163 parous women, 27 had a previous CS; 22 had only a previous CS (nine silicone, 13 latex); five had both a previous vaginal birth and a previous CS (one silicone, four latex). There was no significant difference between the cohorts with respect to any baseline characteristic.

TABLE 2 Primary outcome: accidental rupture of membranes with Foley catheter insertion

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Silicone n/N (%)</th>
<th>Latex n/N (%)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total women who had acROM</td>
<td>19/265 (7.2)</td>
<td>4/269 (1.5)</td>
<td>4.8 (1.7, 14.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>acROM subgroup†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>16/185 (8.6)</td>
<td>3/186 (1.6)</td>
<td>5.4 (1.6, 18.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Parous</td>
<td>3/80 (3.8)</td>
<td>1/83 (1.2)</td>
<td>3.1 (0.3, 29.3)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

acROM, accidental rupture of membranes; RR, relative risk.
†Subgroups analysis: the subgroup numbers are small and there was no evidence of a difference in the effect of the type of Foley catheter used on acROM rates between nulliparous and parous women (P = 0.66).

COMMENT

Our results demonstrate that outpatient cervical ripening with a silicone 18F Foley catheter is associated with a higher rate of acROM (and subsequent unscheduled hospital admission) than a latex 18F Foley catheter, but a lower rate of insertion failure. On all other measures, the performance appears equivalent.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Silicone (n = 265)</th>
<th>Latex (n = 269)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foley failure</td>
<td>7 (2.6%)</td>
<td>25 (9.3%)</td>
<td>0.3 (0.1, 0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Subgroup for Foley failure:†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous (n = 371)</td>
<td>6 (3.2%)</td>
<td>16 (6.8%)</td>
<td>0.4 (0.2, 0.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Parous (n = 163)</td>
<td>1 (1.3%)</td>
<td>9 (10.8%)</td>
<td>0.1 (0.01, 0.9)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Bleeding during Foley insertion, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>156 (58.8%)</td>
<td>156 (58.0%)</td>
<td>1.0 (0.8, 1.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>≤5 mL</td>
<td>103 (38.9%)</td>
<td>100 (37.2%)</td>
<td>1.0 (0.9, 1.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;5 mL</td>
<td>6 (2.3%)</td>
<td>13 (4.8%)</td>
<td>0.5 (0.1, 1.1)</td>
<td></td>
</tr>
<tr>
<td>Hospital admission directly related to Foley insertion,§ n (%)</td>
<td>25 (9.4%)</td>
<td>13 (4.8%)</td>
<td>2.1 (1.1, 4.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinician-rated difficulty of Foley insertion, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>194 (73.2%)</td>
<td>179 (66.5%)</td>
<td>1.1 (0.9, 1.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Moderate</td>
<td>53 (20.0%)</td>
<td>65 (24.2%)</td>
<td>0.8 (0.6, 1.1)</td>
<td></td>
</tr>
<tr>
<td>Difficult</td>
<td>18 (6.8%)</td>
<td>25 (9.3%)</td>
<td>0.7 (0.4, 1.3)</td>
<td></td>
</tr>
<tr>
<td>Patient-rated discomfort during Foley insertion, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>109 (41.1%)</td>
<td>107 (39.8%)</td>
<td>1.03 (0.8, 1.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Uncomfortable</td>
<td>104 (39.2%)</td>
<td>122 (45.4%)</td>
<td>0.9 (0.8, 1.3)</td>
<td></td>
</tr>
<tr>
<td>Painful</td>
<td>52 (19.6%)</td>
<td>40 (14.9%)</td>
<td>1.3 (0.9, 1.9)</td>
<td></td>
</tr>
<tr>
<td>Mean Bishop score before Foley insertion (SD)</td>
<td>3.9 (±1.4)</td>
<td>3.7 ± 1.5</td>
<td>0.2¶ (−0.04, 0.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean Bishop score after Foley removal (SD)</td>
<td>5.9 (±1.8)</td>
<td>5.9 ± 1.7</td>
<td>0.03¶ (−0.3, 0.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>Type of Foley removal, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foley fell out by itself</td>
<td>123 (46.4%)</td>
<td>137 (50.9%)</td>
<td>0.91 (0.9, 1.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Foley was removed by the clinician</td>
<td>128 (48.3%)</td>
<td>102 (37.9%)</td>
<td>1.27 (0.7, 0.9)</td>
<td></td>
</tr>
<tr>
<td>Did not receive Foley (failed insertion of both primary and secondary catheter)</td>
<td>5 (1.9%)</td>
<td>7 (2.6%)</td>
<td>0.73 (0.2, 2.3)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>9 (3.4%)</td>
<td>23 (8.5%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median time until Foley fell out or was removed hours†† (IQR)</td>
<td>14 (5.0, 22.0)</td>
<td>15 (6.0, 21.8)</td>
<td>NA</td>
<td>0.67</td>
</tr>
<tr>
<td>Antenatal/intrapartum pyrexia (temperature ≥38°C), n (%)</td>
<td>38 (14.4%)</td>
<td>32 (11.9%)</td>
<td>1.21 (0.8, 1.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Intrapartum antibiotics for suspected chorioamnionitis,‡‡ n (%)</td>
<td>36 (13.6%)</td>
<td>27 (10.0%)</td>
<td>1.33 (0.8, 1.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Oxytocin use, n (%)</td>
<td>242 (91.3%)</td>
<td>235 (87.4%)</td>
<td>1.04 (0.9, 1.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Epidural block, n (%)</td>
<td>170 (64.2%)</td>
<td>184 (68.4%)</td>
<td>0.9 (0.8, 1.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mode of birth, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vaginal birth</td>
<td>120 (45.3%)</td>
<td>126 (46.8%)</td>
<td>0.9 (0.8, 1.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Instrumental birth</td>
<td>41 (15.5%)</td>
<td>36 (13.4%)</td>
<td>1.16 (0.8, 1.7)</td>
<td></td>
</tr>
<tr>
<td>Caesarean birth</td>
<td>104 (39.2%)</td>
<td>107 (39.8%)</td>
<td>0.9 (0.8, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Postpartum blood loss (mL), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>236 (89.1%)</td>
<td>232 (86.2%)</td>
<td>1.03 (0.9, 1.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>500–1500</td>
<td>24 (9.1%)</td>
<td>34 (12.6%)</td>
<td>0.72 (0.4, 1.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;1500</td>
<td>5 (1.9%)</td>
<td>3 (1.1%)</td>
<td>1.69 (0.4, 6.9)</td>
<td></td>
</tr>
</tbody>
</table>

acROM, accidental rupture of the membranes; GBS, Group B Streptococcus; IQR, interquartile range; RR, relative risk.
††Denominators are based on the numbers in the subgroups.
‡Using Fisher exact test.
§Insertion-related indications for hospital admission rather than being discharged home: acROM (18 silicone, four latex; one silicone acROM declined admission), significant or ongoing bleeding (five silicone, eight latex) and non-reassuring CTG (two silicone, one latex).
¶Mean difference.
††Using Mann–Whitney U-test.
‡‡Additional 17 women in each cohort received antibiotics for GBS prophylaxis.
Latex has been the traditional material used for urinary catheters. However, latex catheters without a coating become readily encrusted with mineral deposits and colonised by bacteria. Silicone-elastomer coating on the latex catheter reduces these features. Pure silicone has similar advantages and can be used in women with latex allergy, but it is less flexible while the balloon tends to spontaneously deflate with prolonged bladder use.

The slightly stiffer, less flexible, nature of the pure silicone catheter probably accounts for both of our findings regarding acROM and insertion failure.

Data addressing acROM rates with Foley catheter use are limited. Baloch and colleagues reported a 0% acROM rate (0/50) while Cromi experienced a 0.8% rate (2/265); neither mentioned the catheter material but probably used latex. In a large retrospective series, Maslovitz reported abandoning the procedure and removing the Foley catheter in cases of acROM — but provided no incidence data. With respect to silicone catheters, rates of 1–2% have been reported with double-balloon silicone catheters, while Hoppe recently reported a 4% acROM rate with both double- and single-balloon silicone catheters. Although our rate of 7.2% with silicone catheters is higher than these limited reports, the reality is that the issue simply has not been adequately studied.

The consequences and optimal management of acROM are unknown. Increased antibiotic exposure is likely. While we demonstrated no difference in antibiotic use for suspected chorioamnionitis in acROM compared to non-acROM women, a significant difference would be likely in larger studies or with more liberal antibiotic use. Another negative consequence of acROM is unscheduled pre-induction hospital admission. As more hospitals consider outpatient cervical ripening, this may assume greater importance. Regarding management, we left the balloon in situ and administered antibiotics only to the minority who were GBS positive but this may not be the best approach. While no increase in intrapartum fever or nursery admission was demonstrated, the numbers are small and infection risk remains a concern. A few researchers have consciously inserted Foley catheters in situations of known ruptured membranes; in one study, a non-significant doubling of chorioamnionitis incidence was seen in the Foley cohort.

Failure of catheter insertion was about one-third as likely to occur with a silicone catheter compared to latex (2.6% vs 8.9%); however, when the alternative catheter was subsequently attempted, the final insertion failure rate was little different at 1.9% for the primary silicone group and 2.6% for the primary latex group. Insertion failure is a recognised complication of this procedure; rates as low as 0.9% have been reported in large studies where the researchers were actively involved in the insertion process with higher failures of 3–8% occurring when general clinicians performed the insertion, as in our study. We did not find that experience was a factor in insertion failure, but this is confounded by experienced staff being called on to assist in more difficult cases.

### Strengths and Limitations

The strength of our study is the exploration of aspects of Foley catheter use not previously considered and a reasonably large cohort. In addition, it shows outpatient catheter ripening has a high rate of avoiding pre-induction hospital admission.

Limitations include the impossibility of blinding the inserting clinician to catheter type. We do not believe this affected acROM rates, but it may have affected insertion failure rates with staff aware they could default to the alternative catheter if encountering difficulty. Further, with respect to insertion failure, although we demonstrated significantly different rates between the catheter types, the numbers of events were small and would have benefitted from a larger cohort.

A further limitation is clinician numbers and ranges of experience. However, in a large teaching hospital, this represents the ‘real world’ situation, and no difference in either acROM or insertion failure with experience was demonstrated. Finally, half of the eligible women were not recruited, mostly because staff were too busy, but the similarity in baseline characteristics of the recruited and non-recruited groups suggests broad generalisability of the findings.

---

**Table 4: Neonatal outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Foley catheter type</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mg/dL)</td>
<td>Silicone (n = 268)†</td>
<td>134 (126–143)</td>
<td>2.8 (2.1, 3.7)</td>
</tr>
<tr>
<td>Mean birth weight, g (SD)</td>
<td>Silicone (n = 268)†</td>
<td>3311 ± 521</td>
<td>3365 ± 503</td>
</tr>
<tr>
<td>Apgar &lt;7 at 5 min</td>
<td>Silicone (n = 268)†</td>
<td>7 (2.6%)</td>
<td>9 (3.3%)</td>
</tr>
<tr>
<td>Umbilical Cord Artery lactate ≥ 6.0 mmol/L¶</td>
<td>Silicone (n = 268)†</td>
<td>27 (10.1%)</td>
<td>26 (9.5%)</td>
</tr>
</tbody>
</table>

NICU, neonatal intensive care unit; RR, relative risk; SCN, special care nursery.
†There were seven twins (three silicone, four latex) with none admitted to the SCN/NICU.
¶Reason for NICU/SCN admission: neonatal condition including respiratory distress and high lactate (26 silicone, 20 latex), congenital condition (15 silicone, six latex), maternal gestational diabetes (10 silicone, 14 latex), infection risk (five silicone, four latex), intrauterine growth restriction / small for gestational age (four silicone, two latex).
§Mean difference.
¶Cord artery lactate ≥ 6 mmol/L is the trigger level for complete blood gas analysis in our unit.
CONCLUSION

When used for cervical ripening, a silicone Foley catheter is associated with a higher rate of acROM than a latex catheter but a lower rate of insertion failure. It may therefore be reasonable to attempt insertion with a latex catheter initially and manage insertion failures with a silicone catheter.

ACKNOWLEDGEMENT

We would like to thank the clinicians at Westmead Hospital for their valuable contribution to this study. We would also like to acknowledge statistical advice from Ms Adriende Kirby.

FINANCIAL SUPPORT

This research was conducted with the In-Kind support from the Department of Women’s and Newborn Health at Westmead Hospital.

REFERENCES

Freestanding midwifery units: Maternal and neonatal outcomes following transfer

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ARTICLE INFO

Keywords:
Childbirth
Transfer
Freestanding midwifery unit
Tertiary Hospital
Place of birth
Midwifery

ABSTRACT

Background: The viability of freestanding midwifery units in Australia is restricted, due to concerns over their safety, particularly for women and babies who require transfer.

Aim: To compare the maternal and neonatal birth outcomes of women who planned to give birth at freestanding midwifery units and subsequently transferred to a tertiary maternity unit to the maternal and neonatal outcomes of a low-risk cohort of women who planned to give birth in tertiary maternity units.

Methods: A descriptive study compared two groups of women with low-risk singleton pregnancies who were less than 28 weeks pregnant at booking: women who planned to give birth at a freestanding midwifery unit (n=494) who, transferred to a tertiary maternity unit during the antenatal, intrapartum or postnatal periods (n=260) and women who planned to give birth at a tertiary maternity unit (n=3157). Primary outcomes were mode of birth, Apgar score of less than 7 at 5 minutes and admission to special care nursery or neonatal intensive care.

Key findings: The proportion of women who experienced a caesarean section was lower among the freestanding midwifery unit women who transferred during the intrapartum/postnatal period compared to women in the tertiary maternity unit group (16.1% versus 24.8% respectively). Other outcomes were comparable between the cohorts. Rates of primary outcomes in relation to stage of transfer varied when stratified by parity.

Discussion: These descriptive results support the provision of care in freestanding, midwifery units as an alternative to tertiary maternity units for women, with low risk pregnancies at the time of booking. A larger study, powered, to determine statistical significance of any differences in outcomes, is required.

Introduction

Each year, approximately 300,000 women give birth in Australia (Australian Institute of Health and Welfare, 2015). The concept of safely giving birth in Australia has become inherently linked with immediate, onsite access to specialist obstetric, paediatric and anaesthetic support (Hunt and Symonds, 1995; Tracy et al., 2006; Australian Health Ministers' Advisory Council, 2008). As a result, many small maternity units have closed in Australia over the last 10 years, leaving a gap in a tertiary, emergency. Although FMUs play an important role in maternity services (Reiger, 2006; Kildea et al., 2010). Freestanding midwifery units (FMUs)- which are maternity units managed by midwives with no obstetric, anaesthetic or paediatric support available on site- are well placed to fill this gap. Freestanding midwifery units work within an integrative, collaborative services framework, and have an established referral pathway with a tertiary maternity unit in the event of need for medical consultation and transfer (Birthplace in England Collaborative Group, 2011; Overgaard et al., 2011; Monk et al., 2014). Despite this there are concerns over the safety of planning to give birth at a location that requires transfer via car or ambulance in the event of an obstetric emergency. Although FMUs play an important role in maternity service provision in countries including England and New Zealand (Birthplace in England Collaborative Group, 2011; Grigg et al., 2014), they barely feature in the Australian maternity landscape due to concerns over their safety (Monk et al., 2013a).

The Evaluating Midwifery Unit (EMU) study was the first study to evaluate FMUs in Australia. It was prospective cohort study of maternal and neonatal outcomes associated with the intention to give birth at a location that requires transfer via car or ambulance. This study is powered, to determine statistical significance of any differences in outcomes, is required.
birth at FMUs in New South Wales compared to the outcomes of similar low risk women who planned to give birth in tertiary maternity units (Monk et al., 2014). It formed part of a larger prospective cohort study on freestanding midwifery units in Australia and New Zealand (Grigg et al., 2015a, 2015b). The results of the study support the provision of care in FMUs as an alternative to high risk settings for women with low risk pregnancies- with FMUs associated with similar or reduced odds of intrapartum interventions (including caesarean section) and similar or improved odds of indicators of neonatal wellbeing (Monk et al., 2014). These findings concur with a broad range of international evidence that supports the provision of primary birthing services to women with low risk pregnancies (Birthplace in England Collaborative Group, 2011; Davis et al., 2011; Overgaard et al., 2011).

Transfer from FMU to tertiary maternity units is relatively common; the EMU study reported an overall rate of transfer of 51.8%, with 34% of women planning to give birth in an Australian FMU transferring during the antenatal period and 16.8% transferring during the intrapartum/postnatal period (the stage of transfer for 1% of women was unknown) (Monk et al., 2014). These findings concur with the New Zealand arm of the EMU study, which reported that a similar proportion of women transferred during the antenatal and intrapartum/postnatal periods (28.5% and 17.3% respectively) (Grigg et al., 2015b). The rates of intrapartum/postnatal transfer in other international studies were also similar to the Australian arm of the EMU study: 16.3% in Denmark (Overgaard et al., 2011), 21.9% in England (Birthplace in England Collaborative Group, 2011).

There is much concern about the safety of women and babies who require transfer, and Australia data around this issue is scant. The clinical outcomes of mothers and babies who transferred from a small rural Primary Maternity Unit in Queensland compared to routinely-collected state data (n=61,027 births in 2010) were reported by Kruske et al. (2015). This Primary Maternity Unit functioned in a very similar way to FMUs apart from the occasional increase in capacity to perform instrumental births and caesarean sections by doctors. The retrospective, descriptive study reported that 138 of the 506 women who planned to give birth at the Primary Maternity Unit transferred to the tertiary referral hospital. For the 66 women who transferred antenatally, the proportion of birth interventions including caesarean section (31.8%) and instrumental birth (6.1%) were lower than for all women who gave birth in Queensland in 2010 (33.6% and 9.6% respectively), and the rate of vaginal birth higher (62.1% versus 56.9% respectively). The inverse was the case for the 58 women who transferred during the intrapartum period, with 39.7% of women who transferred intrapartum experiencing caesarean section versus 33.6% of women in Queensland, 15.5% experiencing instrumental birth versus 6.1% in Queensland and 44.8% experiencing vaginal birth versus 56.9%. The incidence of Appgar scores of less than 7 at 5 minutes for livebirths of women who transferred was unable to be compared to state-wide data due to small cell sizes in the transfer groups. The results of this important study challenge the notion that birthing services can only be provided in rural areas with onsite surgical capacity (Kruske et al., 2015), however the generalization of these findings to maternity units that only operate within the scope of FMUs is limited.

The aim of this study was to compare the maternal and neonatal birth outcomes of women who planned to give birth at FMUs and subsequently transferred to a tertiary maternity unit, to the same outcomes in a similar low-risk cohort of women who planned to give birth in a tertiary maternity unit. It is anticipated that the findings will contribute to the evidence on the safety of FMUs.

Methods

Study design

A descriptive study compared the maternal and neonatal outcomes of women who transferred from freestanding maternity units and women who planned to give birth in tertiary maternity units.

Setting

The study was carried out in two different types of maternity units: FMUs and tertiary maternity units. Two FMUs in regional and urban areas of New South Wales participated in the study. Women received antenatal, intrapartum and postnatal care from their midwifery group practice midwives, who worked in small groups and provide 24-hour on-call midwifery care. If the need for transfer to the referral tertiary maternity unit arose, the midwifery group practice midwife often, but not always, transferred with the woman and continued to provide midwifery care in the tertiary maternity unit (Monk et al., 2013b). The referral tertiary maternity units were approximately 15–20 km away from the FMUs; and transfer time was estimated as being between 15 minutes and 65 minutes depending on traffic conditions. Intrapartum and postnatal transfers occurred via car or ambulance depending on the urgency of the transfer.

Tertiary maternity units offer care to women of all risk statuses, and are staffed by midwives, obstetricians, neonatologists and anaesthetists 24 hours a day (NSW Health Department, 2002; NSW Health Department, 2003). The two tertiary maternity units used as comparators in this study were the referral hospitals for the freestanding midwifery units described above. They had a wide catchment area, spanning 75 hospitals in New South Wales (NSW Health Department, 2010 (Reviewed 2013)) and received women and babies transferred from all other maternity units in the catchment areas. Women received antenatal, intrapartum and postnatal care from a number of models of care, including obstetric and midwifery antenatal clinics, general practitioner shared care, birth centre and midwifery group practice (Monk et al., 2013b).

Ethics

The study was approved by the Hunter New England Human Research Ethics Committee, the Northern Sydney Local Health District Ethics Committee and The University of Sydney Human Research Ethics Committee (NSW HREC reference number: HREC/09/HNE/78).

Participant and data collection

Eligible women were those with low-risk singleton pregnancies who were less than 28th weeks pregnant at the time of commencement of antenatal care who planned to give birth at a participating maternity unit during the study period. For the tertiary unit cohort, women were classified as being at low risk of developing obstetric complications if they did not have any medical or previous obstetric complications that would require ongoing care from specialist doctors, as per the Australian College of Midwives (ACM) Guidelines for Consultation and Referral (Australian College of Midwives, 2013).

The FMU cohort consisted of women who planned to give birth at a FMU during the study period, and subsequently transferred to a participating tertiary maternity unit. All women booked to give birth at the FMUs were considered low risk and were included in the study, regardless of their specific ACM risk classification (Australian College of Midwives, 2013). This was a pragmatic decision made at the beginning of the study, because midwifery and obstetric teams from the FMUs work collaboratively with women to ensure their suitability to give birth at the FMUs. They used the ACM guidelines in conjunction with other information (such as detailed medical records and physical assessment) to determine, with the women themselves, whether they would be advised to proceed to give birth in a FMU and, if necessary, when to transfer.
Data custodians from each maternity unit used a comprehensive list of data codes to identify eligible women who booked to give birth at the participating maternity units during the study period 1st April 2010 and 31st August 2011, using the ObstetriX database. The ObstetriX database is a statewide surveillance system used across New South Wales to provide point-of-care maternity data collection across the antenatal, intrapartum and immediate postnatal periods. Midwives contribute the data on each woman and her baby as soon after birth as possible.

The primary outcome measures were mode of birth, 5 minute Apgar score of less than 7 and admission to the neonatal intensive care unit (NICU) or special care nursery (SCN). Secondary outcomes on maternal and neonatal wellbeing as well as stage of transfer were collected from the ObstetriX database. A limited amount of additional data relating to transfer were collected from maternal medical records. Women who made the decision to transfer to a tertiary maternity unit prior to the onset of labour were coded as ‘antenatal transfers’ and those who transferred whilst in labour were coded as ‘intrapartum transfers’, regardless of whether they had been admitted to the FMU in labour. Neonatal data on reason for NICU/SCN admission, treatment details and perinatal mortality and morbidity recorded in data bases other than the ObstetriX database were not available for this study.

Statistical analysis

Due to the small numbers of women who transferred from FMU to tertiary maternity unit, descriptive statistics were used to examine outcomes. This study was not powered to detect clinically significant differences in outcomes in the freestanding midwifery unit group compared to the tertiary maternity unit group, and confounding factors including previous caesarean section, risk at booking, risk at the onset of labour, maternal age, smoking status, parity, risk at the onset of labour, gestation at the time of birth, induction, augmentation of labour were not controlled during analysis. Reason for transfer was also not examined.

Findings

The study sample consisted of 3413 women- 3157 women who planned to give birth in a tertiary maternity unit and 256 women who planned to give birth at a FMU and subsequently transferred to a tertiary maternity unit. Of the latter group, 168 (65.6%) women transferred during the antenatal period, 65 (25.4%) transferred during the intrapartum period and 18 (7.0%) transferred during the postnatal period. Timing of transfer was unknown for 5 women (2.0%). Of the women who transferred, 152 (58.5%) were nulliparous women, and 41.5% were multiparous. Tables 1–3 show the outcomes of women who transferred from FMU to tertiary maternity unit by stage of transfer compared to tertiary maternity unit women. Stage of transfer is stratified into antenatal and intrapartum/postnatal transfers; intrapartum and postnatal transfers were combined due to the small numbers of postnatal transfers.

Table 1 shows the primary maternal and neonatal outcomes of women who transferred from freestanding to tertiary maternity unit according to stage of transfer. Overall, the proportion of women who transferred from FMUs who had a spontaneous vaginal birth or caesarean section were similar compared to the proportion of women from the tertiary maternity unit group who had a spontaneous vaginal birth (63.9% versus 64.7% respectively) or caesarean section (23.1% versus 24.8% respectively). A slightly higher proportion of women who transferred had an instrumental birth compared to women in the tertiary maternity unit group (13.1% versus 10.5%).

The proportion of babies with an Apgar of < 7 at 5 minutes was similar between the transferred freestanding and tertiary maternity unit groups (3.1% versus 2.9% respectively), and the proportion of babies from the transferred freestanding midwifery unit group admitted to SCN/NICU (8.1%) was lower than the tertiary maternity unit group (13.7%). When looking in more detail at outcomes related to stage of transfer, 3.4% of the babies born to women who experienced intrapartum/postnatal transfer had an Apgar of < 7 at 5 minutes, which is similar to the proportion of tertiary maternity unit babies with an Apgar of < 7 at 5 minutes (2.9%). A slightly higher proportion of babies in the intrapartum/postnatal transfer group were admitted to SCN/NICU compared to the tertiary maternity unit group (16.1% versus 13.7% respectively).

The outcomes of nulliparous women and their babies who transferred from FMUs to tertiary maternity units were similar to nulliparous women who planned to give birth in tertiary maternity units (Table 2). Specifically, 51.3% of nulliparous women who transferred experienced a spontaneous vaginal birth compared to 53.9% of nulliparous women in the tertiary maternity unit group, 19.7% experienced an instrumental birth versus 19.1% in the tertiary group, and 28.9% experienced a caesarean section versus 27.1% respectively. The proportion of babies of nulliparous women who transferred with an Apgar score of less than 7 at 5 minutes was 4.6%, versus 4.0% of babies of women in the tertiary maternity unit group. In total, 12.5% of transferred babies were admitted to NICU/SN versus 15.8% of babies of mothers who planned to give birth in tertiary maternity units.

When outcomes of nulliparous women were examined in relation to timing of transfer from freestanding to tertiary maternity unit, some differences became apparent. A smaller proportion of nulliparous women who transferred antenatally had spontaneous vaginal births compared to nulliparous women who planned to give birth in tertiary maternity units (47.4% versus 53.9% respectively), however a higher proportion who transferred intrapartum/postnatally had a spontaneous vaginal birth (58.2% versus 53.9% respectively). A higher

Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timing of transfer</th>
<th>Total transfers (n=260)</th>
<th>Planned TMU (n=3157)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antenatal (n=168)</td>
<td>Intrapartum/postnatal (n=87)</td>
<td>Unknown (n=5)</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Mode of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal</td>
<td>104 (61.9)</td>
<td>59 (67.8)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Instrumental</td>
<td>20 (11.9)</td>
<td>14 (16.1)</td>
<td>0</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>44 (26.2)</td>
<td>14 (16.1)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Apgar &lt; 7 at 5 minutes</td>
<td>5 (3.0)</td>
<td>3 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>SCN/NICU</td>
<td>21 (12.5)</td>
<td>14 (16.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Special care nursery/neonatal intensive care unit.
proportion of nulliparous women who transferred antenatally experienced a caesarean section compared to tertiary unit women (32.6% versus 27.1% respectively); while a lower proportion who transferred intrapartum/postnatally experienced a caesarean section (21.8% versus 27.1% respectively). The proportion of babies born to nulliparous women who transferred during the antenatal and intrapartum/postnatal period and required admission to SCN/NICU was lower than babies of nulliparous women in the tertiary maternity unit group (12.6% and 12.7% versus 15.8%).

Table 3 compares the maternal and birth outcomes of multiparous women who transferred at any stage with multiparous women in the tertiary maternity unit group. A higher proportion of multiparous women who transferred had spontaneous vaginal birth compared to women from the tertiary maternity unit group (81.5% versus 73.0%). The proportion of women who experienced instrumental birth was similar between the two groups (3.7% versus 4.0% respectively) and the proportion of women who had a caesarean section was markedly lower (6.3% versus 23.0% respectively). A very similar proportion of babies of women transferred antenatally were admitted to SCN/NICU compared to babies of women who planned to give birth in tertiary maternity units (12.3% versus 12.1% respectively), however a greater proportion of those who were transferred during the intrapartum/postnatal period were admitted to SCN/NICU (21.8% versus 12.1%).

**Discussion**

Overall, the birth outcomes of women and babies who transferred from a FMU to a tertiary maternity unit were similar. The most marked difference in outcomes was in the proportion of women who experienced a caesarean section- with only 16.1% of women who transferred during the intrapartum/postnatal period experiencing caesarean section compared to 24.8% of women in the tertiary maternity unit group. Caution should be used when interpreting these results as timing of caesarean section was unknown for the tertiary unit group.

When the outcomes were stratified by parity, more discernable differences were seen. Lower proportions of nulliparous women who transferred from FMUs during the antenatal period and higher proportions of women who transferred during the intrapartum/postnatal period experienced spontaneous vaginal birth compared to tertiary unit women. The inverse was the case with caesarean section, with higher proportions of nulliparous women who transferred antenatally and lower proportions who transferred intrapartum/postnatally experiencing caesarean section compared to nulliparous women in the tertiary unit cohort. There may be a number of reasons that a higher proportion of nulliparous women who transferred antenatally experienced a caesarean section compared to tertiary unit women (32.6% versus 27.1% respectively); while a lower proportion who transferred intrapartum/postnatally experienced a caesarean section (21.8% versus 27.1% respectively). The proportion of babies born to nulliparous women who transferred during the antenatal and intrapartum/postnatal period and required admission to SCN/NICU was lower than babies of nulliparous women in the tertiary maternity unit group (12.6% and 12.7% versus 15.8%).

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proportion of nulliparous women who transferred antenatally experienced caesarean section than women in the tertiary unit cohort. The most common reasons for antenatal transfer from FMU to tertiary unit in the New Zealand arm of the EMU study were induction of labour, pre-eclampsia and pregnancy-induced hypertension (Grigg et al., 2015b), with the most common from a Primary Maternity Unit in Australia being prolonged pregnancy, concern for fetal wellbeing and preeclampsia/hypertension (Kruske et al., 2015). Induction of labour, pre-eclampsia and pregnancy-induced hypertension are associated with lower rates of spontaneous vaginal birth and higher rates of caesarean section (Patterson et al., 2011; American College of Obstetricians and Gynecologists & Society for Maternal-Fetal Medicine, 2014). Although data on reasons for transfer were not available, the potential presence of such risk factors may have contributed to the higher proportion of nulliparous women who transferred antenatally having caesarean sections.

The birth outcomes of multiparous women who transferred were consistently better than those from the tertiary maternity unit group, including for caesarean section, with 14.8% of all women who transferred experiencing caesarean section compared to 23% of women who planned to give birth in a tertiary maternity unit. The exception to this was that more than double the proportion of multiparous women who transferred intrapartum/postnatally experienced instrumental birth compared with tertiary maternity unit women. The reason for this is unclear, and may be related to FMU women’s preference for vaginal birth. However it may also be a chance finding, given the small numbers involved.

The antenatal outcomes of women who transferred from a Primary Maternity Unit in Queensland (Kruske et al., 2015), which has a similar scope of practice to FMUs, were similar. Kruske et al. (2015) reported that women who transferred during the antenatal period had similar rates of spontaneous vaginal birth to this study (62.1% versus 61.9% respectively) and similar rates of birth intervention, although the distribution of birth interventions differed (31.8% caesarean section versus 26.2% and 6.1% instrumental birth versus 11.9% respectively). There was more variation in the outcomes of women who transferred intrapartum, with a higher proportion of women who transferred intrapartum/postnatally in this study experiencing spontaneous vaginal birth compared to Kildea’s study (67.8% versus 44.8% respectively), a similar rate of instrumental birth (16.1% versus 15.5% respectively) and a lower proportion of women who experienced caesarean section (16.1% versus 39.7% respectively). The reasons for these variations are unclear, yet may be related to the differences in the scope of practice between the units and small sample sizes.

This is the first descriptive study of maternal and neonatal outcomes of women who transferred from freestanding midwifery units to tertiary maternity units in Australia. There was minimal loss to follow-up and minimal bias introduced due to a non-response rate due to the use of a statewide surveillance system. The study ensured that the outcomes reflect the current practice and function of FMUs in Australia by including all women who planned to give birth at a freestanding midwifery unit and then transferred, regardless of identified risks at booking or at the onset of labour.

The study rigorously judged the tertiary maternity unit group at booking to be at low risk of developing obstetric complications, which went some way in ensuring comparability of the cohorts of women. However, due to the small size of the cohort of women who transferred, known confounding factors including parity, maternal age, previous caesarean section, smoking status and risk at the onset of labour, were not controlled during analysis. A further limitation of the study was the inability to retrieve data on severe maternal and neonatal morbidity, and more detailed information on transfers, including reason for transfer. As a result this study could not provide the level of information relating reason for transfer as employed in other studies (Grigg et al., 2015b; Kruske et al., 2015).

This paper has described the birth outcomes associated with transfer from freestanding to tertiary maternity unit, and compared these outcomes to a low risk cohort of women intending to give birth at a tertiary maternity unit. The results support the provision of care in freestanding midwifery units as an alternative to tertiary maternity units for women with low risk pregnancies at the time of booking, even for those who transfer. Further study with a larger sample size is required to determine statistical significance of any differences in outcomes, to ensure better comparability of cohorts and to follow-up reason for transfer, longer-term neonatal outcomes and more complex measures of neonatal and maternal wellbeing.

Acknowledgements

The Evaluation Midwifery Units (EMU) Project was funded by the National Health and Medical Research Council (Evaluating Maternity Units- Grant Application Number 571901). The funding body did not have a role in the study design, data collection/analysis or the writing of this manuscript. The authors would like to thank the midwives, data custodians, managers and physicians at the participating maternity units for their advice and collaboration.

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GASTROCHISIS EPIDEMIOLOGY AND OUTCOME: A FIVE-YEAR REVIEW AT AN AUSTRALIAN TERTIARY HOSPITAL

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Background: Extensive resources are used in the management of infants with gastroschisis. There are no reliable predictors of outcome of fetuses diagnosed with gastroschisis. There is a paucity of local data in Australia on geographical distribution, incidence and outcomes for gastroschisis. Our aim was to investigate socio-demographics and the antenatal and neonatal factors influencing hospital length of stay (LOS) and total parental nutrition (TPN) in infants born with gastroschisis.


Results: There were 56 infants antenatally diagnosed with gastroschisis. We found no South-Asian women in the cohort. There was one stillbirth (2%), one infant with ‘vanishing’ gastroschisis, and no terminations. The mean gestation at delivery was 36⁴⁰ weeks. Of the 54 neonates who received surgical management, 61% had primary closure. The median LOS was 32.0 (IQR, 23.2-42.6) days and the median duration of TPN was 25.7 (IQR, 17.3-34.8) days. All live-born babies survived to discharge and no antenatal or postnatal variables were found that affected the primary outcomes.

Conclusions: We found no late-gestation stillbirths and a low overall rate of 2%, suggesting the risk for stillbirth associated with gastroschisis is lower than previously documented. Termination rates may be changing. Good postnatal outcomes were achieved from 30 weeks of gestation. Improved data collection across the country may reveal causative factors and enable outcome predictors.
Homologous Recombination DNA Repair Pathway Disruption and Retinoblastoma Protein Loss Are Associated with Exceptional Survival in High-Grade Serous Ovarian Cancer

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Abstract

Purpose: Women with epithelial ovarian cancer generally have a poor prognosis; however, a subset of patients has an unexpected dramatic and durable response to treatment. We sought to identify clinical, pathological, and molecular determinants of exceptional survival in women with high-grade serous cancer (HGSC), a disease associated with the majority of ovarian cancer deaths.

Experimental Design: We evaluated the histories of 2,283 ovarian cancer patients and, after applying stringent clinical and pathological selection criteria, identified 96 with HGSC that represented significant outliers in terms of treatment response and overall survival. Patient samples were characterized immunohistochemically and by genome sequencing.

Results: Different patterns of clinical response were seen: long progression-free survival (Long-PFS), multiple objective responses to chemotherapy (Multiple Responder), and/or greater than 10-year overall survival (Long-Term Survivors). Pathogenic germline and somatic mutations in genes involved in homologous recombination (HR) repair were enriched in all three groups relative to a population-based series. However, 29% of 10-year survivors lacked an identifiable HR pathway alteration, and tumors from these patients had increased Ki-67 staining. CD8+ tumor-infiltrating lymphocytes were more commonly present in Long-Term Survivors. RB1 loss was associated with long progression-free and overall survival. HR deficiency and RB1 loss were correlated, and co-occurrence was significantly associated with prolonged survival.

Conclusions: There was diversity in the clinical trajectory of exceptional survivors associated with multiple molecular determinants of exceptional outcome in HGSC patients. Concurrent HR deficiency and RB1 loss were associated with favorable outcomes, suggesting that co-occurrence of specific mutations might mediate durable responses in such patients. Clin Cancer Res; 24(3): 569–80. ©2017 AACR.

See related commentary by Peng and Mills, p. 508
Translational Relevance

By considering high-grade serous ovarian cancer patients who deviate from a common pattern of initial response, subsequent relapse, and the progressive development of chemotherapy resistance, it may be possible to identify tumor or host factors that could be modified in patients with a more typical disease trajectory. The variation seen in the clinical pattern of response and recurrence seen in the patient cohort analyzed here suggests multiple factors may influence long-term patient survival. Therefore, consideration should be given to analyzing specific clinical subgroups of long-term survivors to maximize the ability to discern causative factors. Patients who have residual disease following surgery and yet have no disease relapse following adjuvant chemotherapy are of particular interest. That these patients are enriched for loss of RB1 expression and homologous recombination repair pathway mutations indicates that unusually long survival may arise from chance co-occurrence of mutations that render tumors highly sensitive to chemotherapy.

Introduction

Variation in survival and extreme responses to treatment in cancer patients provides valuable opportunities to investigate biological determinants of therapeutic response and outcome. Exceptional survivors have recently received increased attention (1) because they may suggest novel therapeutic approaches to apply to more typical cancer patients.

Approximately three quarters of ovarian cancer deaths are associated with high-grade serous cancer (HGSC), which is typically diagnosed at an advanced stage (2). Although fewer than half of all patients with HGSC will be alive at five years, some survive much longer (3, 4). Residual disease following primary surgery is a significant negative prognostic factor for advanced-stage epithelial ovarian cancer (5, 6), but optimal debulking does not fully explain unusually good clinical outcomes, because approximately half of all long-term (10 years) survivors have residual disease following debulking surgery (4).

Inactivation of the homologous recombination (HR) DNA repair pathway is particularly important in influencing response to platinum-based therapy in HGSC (7). Mutations in BRCA1/2 (8–10), or genomic changes associated with HR-pathway inactivation (11), are also predictive of response to poly(ADP-ribose) polymerase (PARP) inhibitors. Higher response rates to chemotherapy in patients with germline BRCA1/2 mutations are reflected in increased 5-year survival (12, 13). However, survival advantage diminishes thereafter, and fewer patients with BRCA1 mutations are alive at 10 years compared with those with a BRCA2 mutation or noncarriers (14). It is unclear whether differences in response and survival in mutation-positive women are associated with the type or position of mutations in BRCA1/2, or additional genomic changes in the tumors (12, 13).

Other prognostic factors in HGSC include molecular subtype defined by gene expression profiles (15, 16) and CCNE1 (cyclin E1) amplification (17). CCNE1 amplification is mutually exclusive with BRCA1/2 mutation and thus is a biomarker of HR-intact tumors that are less likely to respond to platinum-based chemotherapy (16, 18, 19). Finally, the presence of CD8+ tumor-infiltrating lymphocytes is strongly associated with improved survival (20).

In this first detailed clinical and molecular characterization of exceptional response in HGSC, we studied three partially overlapping patient outlier groups, namely, those with progression-free survival of >36 months despite having residual disease following debulking surgery, patients with three or more complete responses to chemotherapy, and/or those who survived more than 10 years. Our findings highlight differences in clinical trajectories of HGSC patients with unusually favorable outcomes, and show that in addition to mutations in the HR pathway, high Ki-67, high CD8 and co-occurrence of RB1 and HR pathway mutations are associated with long-term survival.

Materials and Methods

Patients

Patients were identified in the population-based Australian Ovarian Cancer Study (AOCs, n = 1,776) and the Gynaecological Oncology Biobank at Westmead Hospital, Sydney (GynBiobank, n = 507; Supplementary Fig. S1). This project was conducted with Human Research Ethics Committees approval. AOCs and GynBiobank were approved by Human Research Ethics Committees at all participating centres, and written informed consent was obtained from all participants. Patient identifiers (ID) used in this article were randomly generated for the purpose of publication. Median follow-up was 9.95 years (95% confidence interval, 9.7–10.2 years) from diagnosis.

Cases were selected according to the following inclusion criteria: (i) histologically confirmed serous ovarian, fallopian or peritoneal carcinoma; (ii) International Federation of Gynecology and Obstetrics (FIGO) stage IIIIC or IV disease; (iii) high grade (grade 2 or grade 3) at diagnosis; (iv) primary treatment incorporating a platinum-based agent; and (v) an exceptionally good clinical outcome, defined by a long progression-free interval (Long-PFS), multiple complete treatment responses (Multiple Responder) and/or long survival (Long-Term Survivors). Long-PFS was defined as >36 months progression-free survival from diagnosis and restricted to cases with macroscopic residual disease after primary cytoreductive surgery. Multiple Responders had complete responses (assessed by CA125 criteria, ref. 21) to three
or more lines of platinum-based chemotherapy. Response to first line was only included in patients with residual disease after surgery. Long-Term Survivors had an overall survival period of at least 10 years (120 months) after histological diagnosis. Collectively, these three patient subgroups are referred to as Exceptional Responders. Statistical considerations for the selection of cutoff points to identify outliers in treatment response and overall survival are detailed below.

All eligible Exceptional Responder cases (n = 112; Supplementary Table S1) underwent pathology review to confirm diagnosis and histological subtype and to determine histological grade according to standardized criteria (22). Review was completed by expert gynecological pathologists using a complete set of hematoxylin and eosin (H&E)–stained diagnostic slides or H&E-stained slides from 1 to 3 representative diagnostic block/s selected by the original reporting pathologist. Previous analysis performed by the AOCS has shown the two review methods are comparable (13). We were not able to obtain slides for review of 4 patients.

High histopathological grade, TP53 mutation, abnormal p53 staining, and WT1 positivity characterize HGSC, whereas low-grade serous carcinoma (LGSC) are typically TP53 wild-type and harbor ras pathway mutations (16, 23–27). We applied these molecular criteria to the initial cohort of 112 patients: 8 cases (7%) that had features consistent with ras pathway-activated LGSC were excluded from further analyses (Supplementary Table S1). We excluded a further 8 cases for which biospecimens were not available for research, resulting in 96 patients for which blood, tissue, and/or tissue microarray cores were available. All 96 cases of Exceptional Responder cases were confirmed HGSC based on pathological features, presence of TP53 mutation, abnormal p53 expression, and/or WT1 expression (Supplementary Table S1).

Comparison control cohorts were obtained from the same patient populations as the Exceptional Responder groups. Cases were matched for stage (FIGO III/IV) and histology (serous) and included all cases, except those that met the Exceptional Responder criteria. For comparison of patient characteristics (Table 1), we analyzed the clinical data from the AOCS serous cohort (2002–2006, n = 710, i.e., 785 cases excluding cases that met Exceptional Responder criteria).

Clinical definitions
Progression-free survival (PFS) was defined as the time interval between the date of histological diagnosis and the date of disease progression, determined by CA125 serum levels or imaging according to Gynecological Cancer Intergroup criteria (21), clinical deterioration or death. Overall survival (OS) was defined as the interval between diagnosis and death from any cause, or date of last follow-up for women who were alive. Response to postrelapse lines of treatment was assessed using routine serum CA125 measurements based on Gynecological Cancer Intergroup CA125 criteria (21), and a complete response was defined as normalization of CA125 levels maintained for ≥28 days.

Statistical analyses
The Long-PFS cutoff of >36 months was based on analysis of progression-free interval for a large cohort of consecutively recruited cases with advanced stage (IIIC/IV), serous ovarian cancer (AOCS, n = 782, median PFS, 12.75 months, recruited 2002–2006). The cutoff point was determined using conditional survival analysis to define the probability of remaining progression-free, having not progressed at specified time points, based on the approach given by Harshman and colleagues (28). This was determined by calculating the probability of being progression free for a further 6 months given that patients have not progressed at 6, 12, 18, 24, 30, 36, 42, 48 to 84 months, respectively. For patients not progressing at or post-36 months, this probability of approximately 80% was constant and 10% higher than those patients not progressing at times <36 months. A similar cutoff point was found using a second method calculating two standard deviations beyond the median (>30.6 months) in the same unselected cohort. The more conservative cutoff of >36 months was used to define Long-PFS in all analyses.

Conditional survival analysis in patients with stage III/IV serous carcinoma (AOCS, n = 785) showed >84 months OS was consistent with exceptional survival. We also calculated the median OS for the same cohort and found two standard deviations beyond the median to be 118.2 months (median OS, 36.6; SD, 40.81). Both methods supported a conservative cutoff point of >10 years for Long-Term Survivors.

For molecular studies, differences in proportions between groups were assessed by χ² test and corresponding 95% confidence interval. Correlations between molecular alterations were estimated by Pearson correlation. The Kaplan–Meier product limit method was used to estimate and plot PFS and OS probabilities and the corresponding time-to-event were compared between groups using the log-rank test. All comparisons were two-sided, and a 5% level of significance was used to declare a statistical difference. The reverse Kaplan–Meier method (29) was used to quantify follow-up time. Statistical analyses were performed using IBM SPSS (version 23) and Stata 10.0 (StataCorp LP).

Molecular analyses
Germline BRCA1 and BRCA2 mutation status was available for 89 of 96 Exceptional Responder HGSC patients, through their clinical record and/or previous mutational analyses (13, 30). For cases with tumor samples available (82 of 96 Exceptional Responders), we assessed tumor DNA for pathogenic mutations in 32 genes associated with ovarian cancer, HR and DNA repair (Supplementary Table S3), including TP53, BRCA1, and BRCA2. Sequence analysis of the 32 genes was performed using two types of sequence data: (i) 66 cases were sequenced using the 32-gene panel targeted DNA sequencing approach (see Supplementary Methods for additional details), and (ii) 19 cases had previously undergone comprehensive whole-genome sequencing of primary tumor DNA and matched germline (lymphocyte) DNA (30). The same selection criteria were applied to cases sequenced using either method. Three patients were sequenced by both approaches and showed concordance between pathogenic mutations detected.

BRCA1 and RAD51C promoter methylation was assessed by methylation-sensitive high-resolution melting analyses. CD8, RB1, p16, Ki-67, WT1, and p53 protein expression was determined by immunohistochemistry.

Further experimental methods are provided in Supplementary Data.

Results
Distinct clinical patterns of exceptional survival
We considered several objective clinical, surgical and histopathologic criteria to define HGSC patient subsets with a
Table 1. Clinical characteristics by patient subgroups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Long-PFS (n = 73)</th>
<th>Multiple Responders (n = 21)</th>
<th>Long-Term Survivors (n = 43)</th>
<th>Control (n = 710)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 73)</td>
<td>(n = 21)</td>
<td>(n = 43)</td>
<td>(n = 710)</td>
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<tr>
<td>Age at diagnosis, y</td>
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<td>56 (0.04a)</td>
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<td>19 (3)</td>
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NOTE: Exceptional Responder patient subgroups were compared with unselected patients with advanced stage (stage IIIC/IV) serous ovarian cancer (control). Statistical comparisons were calculated as follows:

aMann–Whitney test.
bχ² test.
cLog-rank test.
dIncludes one case that meets the criteria for Long-PFS, Multiple Responder and Long-Term Survivor.
eIncludes 40 cases that meet the criteria for Long-PFS and Long-Term Survivor (n = 75).
fPatients who had residual disease after primary cytoreductive surgery but the size was not recorded were classified as “Size unknown,” and patients for whom it was not recorded whether or not they had residual disease were classified as “Not known.”
gInoperable chemotherapy received (number of patients indicated in brackets): Long-PFS: gemcitabine (3), topotecan (1); Multiple Responder: gemcitabine (1), liposomal doxorubicin (1); Long-Term Survivor: gemcitabine (3), topotecan (1); Control: gemcitabine (18), topotecan (18), bevacizumab (1), etoposide (1), and doxorubicin (1).
hOther chemotherapy received in addition to platinum/taxane: Long-PFS: gemcitabine (2), cyclophosphamide (1), not known (1); Multiple Responder: cyclophosphamide (1); Long-Term Survivor: cyclophosphamide (1), not known (3); Control: gemcitabine (4), topotecan (3), cyclophosphamide (1), not known (3).
iIncludes 3 patients where primary chemotherapy details are not known.

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favorable outcome, collectively termed Exceptional Responders. HGSC diagnosis was based on histopathology, presence of TP53 mutation, abnormal p53 expression, and WT1 expression (ref. 25; Supplementary Table S1).

To identify clinical and biological dependencies, we first identified patients where a favorable outcome could be associated with response to primary platinum-based chemotherapy. We identified 73 patients with an unusually prolonged PFS of >36 months (Long-PFS). This time point was based on conditional survival analysis, and a similar cutoff was found using a second method, calculating two standard deviations beyond the median (>30.6 months; Materials and Methods). We took into consideration that response to primary treatment is the combined effect of debulking surgery and chemotherapy. Therefore, to characterize patients with unambiguously chemoresponsive tumors, we restricted analysis to cases with residual disease after surgery, including 26 women who were nonoptimally debulked (>1 cm residual disease or tumor not resected), and yet had a rapid and sustained fall in serum CA125 following chemotherapy (CA125 normalization >36 months; Fig. 1A and Supplementary Fig. S2).

We also identified 21 patients with multiple responses to chemotherapy. Acquired chemoresistance is common in HGSC, and many patients experience diminished responses to each line of treatment (31). Within AOCs, less than 3% of stage IIIC/IV patients (21/785) had three or more complete responses to platinum-based chemotherapy, providing a threshold for selection of patients whose tumors appeared to have limited capacity for developing resistance (Fig. 1B and Supplementary Fig. S2).

Lastly, we identified 43 Long-Term Survivors (OS > 10 years). Of these, 29 (67%) remained progression free, and 14 (33%) had one or multiple periods of relapse and treatment-induced remission (Fig. 1C and Supplementary Fig. S2). This clinical variability illustrates that there are diverse ways leading to extended survival. Collectively, 96 HGSC patients were identified as Exceptional Responders, with partial overlap between the groups (Fig. 1D).

Clinical characteristics of Exceptional Responders

Clinical characteristics of the HGSC exceptional response groups are summarized in Table 1. Compared with unselected serous ovarian cancer patients, Multiple Responders were younger, while Long-PFS and Long-Term Survivors were a similar age at diagnosis. Patients with Long-PFS were less likely to have primary peritoneal cancer, and all three Exceptional Responder groups were less likely to have had neoadjuvant chemotherapy. Additional clinical descriptors and longitudinal CA125 profiles are provided in the Supplementary Data.

The majority of Long-PFS patients (41/73; 56%) were alive with no progression at time of analysis (Table 1). Indeed, many Long-PFS became Long-Term Survivors (40/73), although this was not always the case, with some patients having an extended progression-free interval but lack of chemoresponse upon recurrence (e.g., patient 15051; Supplementary Fig. S2). Conversely, Long-Term Survivors did not necessarily have extended PFS or sustained responses to therapy (e.g., patient 5693; Supplementary Fig. S2). Almost no Multiple Responders became Long-Term Survivors, with only one case being in both groups (Fig. 1D).
TP53 mutations in Exceptional Responders are typical of HGSC
TP53 is almost invariably mutated in HGSC (16, 24). We considered whether distinct TP53 mutations were associated with exceptional survival. Tumor tissue was available for DNA analysis in 82 of the 96 included cases. TP53 mutations were identified in 98% (80/82; Fig. 2A and Supplementary Table S4). Most TP53 mutations were missense (64%, 51/80) and the distribution and classes of TP53 mutations were similar to those previously reported (16) in HGSC (P = 0.99, χ² test; Supplementary Fig. S3A and S3B). The frequency of mutation type was not different between exceptional responder subgroups. Eleven TP53 residues were recurrently mutated in Exceptional Responders (i.e., mutated in more than one case; Supplementary Table S4), representing 39% of cases. Patients with these TP53 mutations in an unselected HGSC cohort (16) from The Cancer Genome Atlas (TCGA; n = 67/265) failed to demonstrate a significant survival advantage (median OS, 49.24 months, compared with 44.51 months for the remainder of the cohort; n = 198; P = 0.45; Supplementary Fig. S3C).

HR and DNA-repair pathway mutations
Germline BRCA1/2 mutation status was obtained for 89/96 Exceptional Responders through clinical records and/or mutational assessment (Materials and Methods). While a higher proportion of Long-Term Survivors (9/39, 23.1%, P = 0.34), Long-PFS (18/67, 26.9%, P = 0.05) and Multiple Responders (4/20, 20%, P = 0.73) had germline BRCA1/2 mutations compared with an unselected HGSC cohort (ref. 13; 98/574, 17%; Fig. 2B; Supplementary Table S6). A majority (73% (60/82)) of Exceptional Responders had evidence of HR pathway disruption, compared with 41% (128/316, P < 0.001, χ² test) in the TCGA HGSC cohort (ref. 16; Fig. 2C). The TCGA study previously reported (16) HR pathway disruption in up to 51% of cases. However, the TCGA samples underwent whole-exome sequencing, and additional putative mechanisms of HR inactivation were reported, including (i) mutations in additional Fanconi anemia genes that were not included on our panel (FANCA, FANCC, FANC1, FANCL, FANCE, FANCG, and FANCM), (ii) EMSY amplification, and (iii) missense variants of unknown or uncertain significance. For direct comparison with Exceptional Responders in this study, we only considered truncating mutations and pathogenic missense mutations in the genes in our panel (Supplementary Table S3). A greater proportion of Long-PFS patients with bulky residual disease (>1 cm) had HR defects compared with those with minimal residual disease (≤1 cm; 79% vs. 61%; P = 0.14), and the highest proportion of HR defects were found in Multiple Responders (88%, P < 0.001; Fig. 2C; Supplementary Table S6), with a predominance of BRCA1 mutations (59%), reflecting the role of HR deficiency in chemosensitivity.

RB1 loss is enriched in Long-PFS and Long-Term Survivors
A subset of 19 Exceptional Responders had whole-genome sequencing as part of our International Cancer Genome Consortium study (30), allowing us to investigate whether HR-pathway mutations were associated with other genomic aberrations. We previously observed that gene breakage results in inactivation of tumor suppressors in HGSC, including RB1 (30). Inactivation of RB1 was frequent in Exceptional Responders, particularly in Long-PFS patients with 6 of 11 cases (54.5%) affected by RB1 gene breakage or homozygous deletion (Fig. 3A). To explore this observation further, and because RB1 loss by gene breakage is not apparent in targeted sequence data, we validated RB1 protein detection by immunohistochemistry (Fig. 3B and Supplementary Fig. S4) and then assessed expression in a cohort of 313 patients, including 91 Exceptional Responders (Supplementary Fig. S1). RB1 loss was significantly more frequent in Long-PFS (35%, P < 0.001) and Long-Term Survivors (33%, P = 0.001) compared with unselected HGSC (13%; Fig. 3C and Supplementary Table S6). RB1 loss was enriched in Long-PFS patients who were nonoptimally debulked compared with those with <1 cm residual disease (48% versus 27.5%; Fig. 3C, P = 0.09). Furthermore, in an independent analysis of unselected HGSC patients (N = 1,083), low RB1 mRNA expression was associated with increased overall survival (Fig. 3D, P = 0.014).

Homogeneous p16 expression pattern is frequently used as a marker of RB1 loss. We found a significant correlation between RB1 loss and homogeneous p16 staining in Long-PFS (P = 0.001), Long-Term Survivors (P = 0.001) and control patients (P = 0.04; Pearson correlation); however, p16 staining alone was not enriched in Exceptional Responders (Fig. 4A). RB1 loss and homogeneous p16 were not correlated in Multiple Responders (P = 0.116; Pearson correlation).

Association between HR deficiency and RB1 loss
We identified enrichment for co-occurrence of RB1 loss and HR deficiency in Long-PFS (20/58, 34.5%) and Long-Term Survivor (11/33, 36.4%) groups compared with control HGSC (13/75, 17.3%) and Multiple Responders (3/17, 17.6%). The homogeneous p16 mRNA expression was associated with increased overall survival (Fig. 3D, P = 0.014). HR deficiency and RB1 loss were highly correlated in Long-PFS (P = 0.008), less so in controls (P = 0.039) and not in Multiple Responders (P = 0.486; Pearson correlation). Kaplan–Meier survival analysis of patients with HR-defective tumors demonstrated a significant survival advantage associated with concurrent RB1 loss in Exceptional Responders (Fig. 3E; P = 0.03).

Proliferative and immune cell markers reveal a heterogeneous pattern within the cohort
Immune cell infiltration, particularly in tumor epithelium, has been associated with favorable outcomes in multiple HGSC datasets (20). We scored CD8⁺ lymphocytes on tissue microarrays comprising Exceptional Responders and controls (Supplementary Fig. S1 and Supplementary Table S7). Both intraepithelial and stromal CD8 scores were significantly higher in Long-PFS and Long-Term Survivors, but not Multiple Responders, compared with controls (Fig. 4A–C and Supplementary Table S6). Elevated levels of CD8⁺ lymphocytes were associated with BRCA1 mutations (Supplementary Fig. S5A and S5B), as previously observed (32–34), but not with other predicted HR-inactivating alterations, although sample sizes were small for these other groups. CD8⁺ tumor infiltrates were also elevated in HR-intact tumors compared...
Figure 2.

HR pathway gene alterations in Exceptional Responders. **A**, Pathogenic alterations in HR and DNA repair genes detected by next-generation sequencing of tumor DNA from 82 Exceptional Responder patients. Patients are grouped by clinical subgroups, and mutated genes are listed in descending order from most to least frequently altered across the entire Exceptional Responder cohort. In addition, tissue microarrays of formalin-fixed paraffin-embedded HGSC specimens were stained with antibodies and assessed for RB1 protein loss, high Ki-67 expression, homogeneous p16 expression, and CD8+ lymphocytes in tumor epithelium (TE) and stroma (STR). **B**, Prevalence of BRCA1 and BRCA2 germline mutations in unselected HGSC Alsop cohort (13) and each clinical subgroup. **C**, Proportion of patients affected by either germline or somatic HR pathway gene alterations in unselected HGSC TCGA cohort (16) and each clinical response group as indicated. One gene mutation is counted for samples with more than one change, ranking mutations in BRCA1, BRCA2, followed by other germline, somatic and promoter methylation events respectively. In the unselected HGSC cohort, the “other HR genes” altered were ATM (1), FANC D2 (1), MSH6 (1), and RAD51 (1). The number of patients is indicated in parentheses.
Figure 3.
RB1 loss and clinical associations in HGSC patients. A, Inactivating structural variants and mutations detected in tumor suppressor genes by whole-genome sequencing in 19 Exceptional Responders (30). B, Representative immunohistochemical staining patterns are shown for tumors in which RB1 protein expression was retained or lost. C, Proportion of tumors with RB1 loss in each clinical subgroup compared with control (unselected HGSC; left) and in Long-PFS patients with >1 cm residual disease (RD) compared with those with ≤1 cm (right; \( \chi^2 \) value reported). D, In a meta-analysis of 1,083 HGSC patients using publicly available gene expression array data sets (ref. 43; http://kmplot.com), patients with low tumor RB1 mRNA expression were associated with significantly better overall survival (Affymetrix Probeset ID 203132_at; automatic cutoff). E, Kaplan-Meier estimates of overall survival for Exceptional Responders with HR-defective tumors, by RB1 protein expression.
with the control group ($P = 0.009$; Supplementary Fig. S5A), indicating that presumably HR-competent tumors can also engender immune responses.

We also evaluated proliferation status, reasoning that highly proliferative tumors may be more susceptible to chemotherapy. Ki-67 was significantly higher in Long-PFS and Long-Term Survivor groups ($P < 0.001$ and $P < 0.001$, respectively; Fig. 4A and D; Supplementary Tables S6 and S7). Ki-67 scores were highest in HR-proficient tumors (Supplementary Fig. S5C), potentially indicating a mechanism of sensitivity that is distinct from HR deficiency.

**Discussion**

The potential to stratify cancer care by molecular phenotype has focused attention on cancer patients with unusually favorable outcomes, including those with exceptional responses to systemic therapy (35). Previous analyses of cancer registry data (3) and clinical parameters (4) for factors that influence 10-year survival in ovarian cancer patients have highlighted the importance of tumor grade, histotype and optimal surgical cytoreduction. Therefore, any molecular analysis of long-term survival must also control for clinical and histopathologic factors associated with survival (36). Given the heterogeneity of ovarian cancer (2), we focused on the dominant ovarian cancer histologic subtype, HGSC, and provide the first detailed molecular characterization of patients with over 10-year survival and those with exceptional responses to chemotherapy. We compared exceptional cases with those representing the spectrum of responses seen in HGSC rather than just platinum-resistant cases, to avoid reidentifying determinants of resistance (17).

HGSC has the highest frequency of HR disruption of any cancer type, through somatic and germline mutations in $BRCA1/2$ and their protein partners, and this is a major determinant of the unusually high rates of response to platinum-based therapy compared with other solid cancers (7, 16). Accordingly, we found an increased frequency of pathogenic mutations in HR proteins in our series relative to unselected HGSC (16). $BRCA1/2$ germline mutations are not, however, sufficient to impart long-term survival; indeed, many $BRCA1/2$ carriers have average or even poor

Figure 4. Characterization of germline $BRCA1/2$ mutation, HR deficiency, immune cell infiltration and proliferative capacity of tumors in Exceptional Responders. **A,** Proportions of each molecular alteration in clinical subgroups compared with control groups. Germline $BRCA1/2$ and somatic HR pathway mutation rates were compared with those reported previously in HGSC cohorts (13, 16). The values for Ki-67 (upper quartile), RB1 (loss), p16 (homogeneous staining), and CD8 (upper quartile) are relative to unselected HGSC. Differences in proportions between groups were assessed by $\chi^2$ test. $P$ values are represented by asterisks: *, $< 0.05$; **, $< 0.01$; ***, $< 0.001$. Further details are listed in Supplementary Table S6. **B,** Density (in cells/mm$^2$) of CD8$^+$ lymphocytes in tumor epithelium (TE) and C, stroma (STR). **D,** Quantification of Ki-67 expression in tumor nuclei of different patient subgroups, detected by immunohistochemical staining. In scatter plots the horizontal lines indicate the median score. $P$ values are shown for the subgroups that had significant differences to the median score of unselected HGSC (Mann-Whitney test).
responses to therapy [13], suggesting that co-occurrence of other factors are needed to obtain durable responses to therapy and/or long-term survival. We found that RB1 loss, in conjunction with HR deficiency, was associated with particularly long survival, which is consistent with a previous analysis of RB1 expression in a large series of HGSC [37]. The highest frequency of RB1 loss was seen in nonoptimally debulked Long-PFS patients, indicating an association with extreme chemosensitivity.

RB1 loss and gene disruption has been associated specifically with BRCA1-mutated basal-like breast cancers, which are molecularly similar to HGSC [38]. Whether these are associated with response to platinum-based therapy, which is becoming more common in basal-like breast cancer, requires investigation. It is notable that loss of RB1 expression is seen in only a minority of lung adenocarcinoma patients, but is strongly associated with improved survival following cisplatin-based therapy [39]. Further studies are warranted to determine whether RB1 loss is predictive for platin, taxane, or combined sensitivity in HGSC.

We identified a subset of patients in all three clinical groups where no HR pathway disruption was detected by mutation or methylation profiling. The TCGA analysis included additional putative HR variants, and it is possible that the proportion of HR-deficient Exceptional Responders in our study may be an underestimate. Whether the HR pathway is disrupted via untested mechanisms may be revealed by an analysis of genomic scarring [40]. However, the observation of increased Ki-67 immunoreactivity in this group suggests they may be molecularly distinct and represent an opportunity to develop novel therapeutic interventions.

In addition to RB1 loss, we found higher densities of CD8+ lymphocytes in Long-PFS and Long-Term Survivors compared with selected cases. Intriguingly, this association did not apply to Multiple Responders, despite recent evidence that T-cell infiltrates can inhibit chemoresistance mediated by stromal fibroblasts in ovarian cancer [41]. Instead, Multiple Responders were highly enriched for mutations involving the HR pathway. These patients resemble the cyclic pattern of relapse and repeated response to cisplatin seen in a BRCA1 mouse model of breast cancer [42]. In that model, a large deletion of BRCA1 precludes the development of resistance by intragenic reversion. By extension, tumors of Multiple Responders may have an impaired ability to restore HR pathway activity despite the strong selective pressure of repeated platinum exposure. Few Multiple Responders became Long-Term Survivors, suggesting that while deregulation of the HR pathway can increase sensitivity to chemotherapy, it is not sufficient for a complete response leading to prolonged, 10-year survival. Cooperating factors, such as those identified in this study including immune cell infiltration, RB loss, and proliferation rate, appear to be required to confer long-term survival. One limitation in the classification of Multiple Responders is our reliance on CA125 criteria of response rather than radiological data. Serial imaging data were not available, so stringent CA125 criteria requiring normalization of CA125 were applied (Materials and Methods).

In summary, our findings suggest that distinct clinical patterns of exceptional response in HGSC are imparted by the interplay between HR pathway disruption, the chance co-occurrence of other mutations such as RB1, and immune factors. The substantial clinical, molecular, and immunological heterogeneity we observed, even within this highly selected cohort, indicates that large numbers of HGSC patients will be required to untangle these interactions. Given the rarity of Exceptional Responders, this will be possible only by international collaboration among investigators, patients, and patient advocates to identify these unusual individuals.

Disclosure of Potential Conflicts of Interest

K. Alsop reports receiving other commercial research support from AstraZeneca. Y.C. Leung is a consultant/advisory board member for Royal Australian and New Zealand College of Obstetricians and Gynaecologists. P.J. Beale reports receiving speakers bureau honoraria from and is a consultant/advisory board member for AstraZeneca, Ipsen, and Roche. A. de Fazio reports receiving commercial research grants from AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Study supervision: P. Blomfield, D.D.L. Bowtell, A. de Fazio

Other (pathology review): P. E. Allan

Acknowledgments

The Australian Ovarian Cancer Study gratefully acknowledges the cooperation of the participating institutions in Australia and also acknowledges the contribution of the study nurses, research assistants and all clinical and scientific collaborators including Gillian Mitchell, Margot Ousins, Karen Sanday, Helen Steinke, and Leanne Bowes. The complete AOC Study Group can be found at www.aocstudy.org. We would like to thank all of the women who participated in the study. We also thank Shuhong Liu from Calgary Laboratory Services, Alberta, Canada, for performing RB1 immunohistochemistry.

This study was financially supported by grants from the Department of Health and Human Services through the Victorian Cancer Agency (ECG15011, to D.W. Garsed), the National Health and Medical Research Council of Australia (NHMRC; APP631701, to D.D.L. Bowtell), Cancer Australia (APP632595, to A. de Fazio; APP1004673, to D.D.L. Bowtell), the National Breast Cancer Foundation (CG12-07), the Canadian Institutes of Health Research (MOP142436), the U.S. Army Medical Research and Materiel Command (W81XWH-08-1-0684, to P. Blomfield; W81XWH-08-1-0685), Cancer Australia and the National Breast Cancer Foundation (ID509303), and the Cancer Council Victoria. The Australian Ovarian Cancer Study was supported by the U.S. Army Medical Research and Materiel Command under DAMD17-01-01729, The Cancer Council Victoria.
Queensland Cancer Fund, The Cancer Council New South Wales, The Cancer Council South Australia, The Cancer Foundation of Western Australia, The Cancer Council Tasmania and the NHMRC (ID400413 and ID400281). The AOCS gratefully acknowledges additional support from S. Boldeman, the Agar family, Ovarian Cancer Australia and the Peter MacCallum Cancer Centre Foundation. The Gynaecological Oncology Biobank at Westmead, a member of the Australian Biospecimen Network-Oncology group, was supported by grants from the NHMRC (ID3110670 and ID628903) and the Cancer Institute New South Wales. 12/1/R/1-17 and 15/R/1-16. A. de Fazio is supported by the University of Sydney Cancer Research Fund and Cancer Institute NSW, through the Sydney West Translational Cancer Research Centre.

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Received June 8, 2017; revised August 7, 2017; accepted October 11, 2017; published OnlineFirst October 23, 2017.

References


How do different brands of size 1 laryngeal mask airway compare with face mask ventilation in a dedicated laryngeal mask airway teaching manikin?

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ABSTRACT

Background International neonatal resuscitation guidelines recommend the use of laryngeal mask airway (LMA) with newborn infants (≥34 weeks’ gestation or >2 kg weight) when bag-mask ventilation (BMV) or tracheal intubation is unsuccessful. Previous publications do not allow broad LMA device comparison.

Objective To compare delivered ventilation of seven brands of size 1 LMA devices with two brands of face mask using self-inflating bag (SIB).

Design 40 experienced neonatal staff provided inflation cycles using SIB with positive end expiratory pressure (PEEP) (5 cmH2O) to a specialised newborn/ infant training manikin randomised for each LMA and face mask. All subjects received prior education in LMA insertion and BMV.

Results 12 415 recorded inflations for LMAs and face masks were analysed. Leak detected was lowest with i-gel, with a mean of 5.1 cmH2O compared with face mask (triangular 42.7, round 35.7) and other LMAs (45.5–65.4) (p<0.001). Peak inspiratory pressure was higher with i-gel, with a mean of 28.9 cmH2O compared with face mask (triangular 22.8, round 25.8) and other LMAs (14.3–22.0) (p<0.001). PEEP was higher with i-gel, with a mean of 5.1 cmH2O compared with face mask (triangular 3.0, round 3.8) and other LMAs (0.6–2.6) (p<0.001). In contrast to other LMAs examined, i-gel had no insertion failures and all users found i-gel easy to use.

Conclusion This study has shown dramatic performance differences in delivered ventilation, mask leak and ease of use among seven different brands of LMA tested in a manikin model. This coupled with no partial or complete insertion failures and ease of use suggests i-gel LMA may have an expanded role with newborn resuscitation as a primary resuscitation device.

INTRODUCTION

Laryngeal mask airways (LMA) are listed in the International Liaison Committee on Resuscitation (ILCOR) neonatal resuscitation guidelines as a means of assisting positive pressure ventilation (PPV) during resuscitation of term and near-term infants where face mask PPV is not adequate and resuscitator skills to effect endotracheal intubation are insufficient.1 LMA may also be of assistance with newborn infants with rare significant craniofacial abnormalities such as Pierre Robin syndrome where upper airways obstruction is severe and endotracheal intubation even in expert hands may be very difficult. Simply put, the LMA may be a life-saving device when ‘you can’t ventilate and you can’t intubate’.2,3 Assessment of LMA for use by local birth attendants (physicians and midwives) in developing and developed countries in manikin models compared with face mask PPV showed the feasibility of training and use of LMA in these settings and recommended further evaluation.4–6

The 2005 Cochrane review on the use of LMA versus bag-mask ventilation or endotracheal intubation comments that evidence from observational studies suggests LMA can provide rescue airway and achieve effective PPV during newborn resuscitation if both bag-mask ventilation and intubation have been unsuccessful.7 Two recent prospective, unblinded, randomised, controlled trials comparing LMA to face mask ventilation for newborn ≥34 weeks’ gestation found there was less need for endotracheal intubation using LMA and it was more effective than face mask.8,9

What is already known on this topic?

► The International Liaison Committee on Resuscitation guidelines recommend use of LMA at newborn resuscitation if adequate face mask positive pressure ventilation or endotracheal intubation cannot be accomplished.

► Use of non-inflatable LMA in paediatric patients is beneficial due to possible cuff hyperinflation of inflatable cuff types.

► Efficacy of LMA use during neonatal resuscitation remains unclear.

What this study adds?

► Size 1 LMAs tested in this manikin study showed marked performance variation.

► The i-gel brand LMA showed superior performance for provision of peak inspiratory pressure, positive end expiratory pressure and mask leak compared with other LMAs and face masks tested.

► Inexperienced users of LMA showed higher proficiency in attaining adequate lung inflation and ease of insertion using i-gel brand LMA.
Training for use of LMA in newborn resuscitation requires leak-free manikins with anatomically correct pharyngeal structures to apply LMA cushion to seal. Size 1 LMA brands differ substantially in stiffness of angled tube, the angle of the tube, tube internal diameter, and the size, shape and type of mask cushion (inflatable with a syringe, auto inflate with PPV or non-inflatable contoured gel) (figure 1). This suggests the potential for variation in performance characteristics. Studies to date of comparisons between LMA brands have been limited to up to three LMA model comparisons. Clinical studies of LMA use in infancy by anaesthetists have been conducted in more controlled clinical situations of elective surgery with stable patients; brand comparisons have focused on ease of use, time to insert and inflation pressure at which audible leak occurs. The neonatal resuscitation focus on sufficient tidal volume (TV) with least peak inflation pressure, in newborn infants with significant lung disease, has dictated the search for devices and methods to reduce face mask leak. There is a need to guide clinicians how a range of different LMA devices perform in dedicated LMA training manikins and clinical practice at birth.

We aimed to examine delivered ventilation and airway leak to an anatomically correct manikin head designed specifically to train in LMA use attached to a neonatal test lung. This crossover study was designed to test seven size 1 LMAs compared with two face masks (round and triangular). Our null hypothesis was that there would be no differences between face mask and brands of LMA in the rate of successful insertion (LMA), delivered ventilation, maximal inflation pressure, mask leak and particularly the ability to achieve targeted positive end expiratory pressures (PEEP). Primary outcomes were the delivered ventilation to the manikin, and the secondary outcomes were the insertion failure tally and subjective assessment of ease of LMA insertion.

**METHODS**

Forty clinicians in a busy tertiary neonatal intensive care unit (9 consultants/fellows, 13 registrars and 18 nurses) agreed to participate in this study. All were experienced in bag-mask ventilation and variably less experienced with LMA use. A new AirSim Baby manikin head (JR10001, TruCorp, Belfast, Ireland) was modified by changing the supplied lung bag to a test lung (SmartLung Infant, IMT Medical, Buchs, Switzerland) with a static compliance of 2 mL/cmH₂O and resistance of 50 cmH₂O/L/s, simulating a near-term infant (figure 2). Seven internationally available size 1 LMA single-use devices were examined: (1) Ultimate (Ultimate Medical, Tianjin Medis, China), (2) PRO-Breathe (Well Lead Medical, China), (3) LMA Supreme (The Laryngeal Mask, Seychelles), (4) Unique LMA (The Laryngeal Mask), (5) air-Qsp (Cookgas, Malaysia), (6) AuroOnce (Ambu A/S, Ballerup, Denmark) and (7) i-gel (Intersurgical, Wokingham, Berkshire, UK).

Two face mask devices were compared with LMA: (1) Ambu (Ambu A/S) triangular size infant (Part No 252 052) and (2) Laerdal (Stavanger, Norway) round size 1 (Part No 851600). PPV was supplied using an Ambu self-inflating bag (SIB) (SPUR II Part No 335 102 000) with Ambu manometer and PEEP valve (0–20 cmH₂O, Part No 199 102 001). Two neonatal respiratory function monitors (RFM) (Florian, Hirzel, Acutronics, Switzerland, and Cosmo Novametrix) were used to determine the TV, flow and inflation pressures at two points. At point 1, the pneumotach of the Florian RFM was sited between the SIB and the proximal end of the device under test (LMA or face mask). At point 2, the pneumotach of the Cosmo RFM was sited between the test lung and the manikin head. Both RFMs were calibrated with an external syringe of known volume and pressure/flow via a traceable reference ventilator analyser (PF300, IMT Medical). Participants were blinded to both RFM displays. The manikin head was assessed for system leak and leak points at the base of the head where airway bifurcates and the corner of the lip was sealed with silicone. Test lung, manikin head and measurement system (RFM pneumotach’s proximal pressure lines) were pressurised to a static pressure of 50 cmH₂O, and over 120s there was no fall in pressure, indicating the system was leak-free.

A PowerLab data acquisition system (Part No ML880, ADInstruments, Sydney, Australia) with a sample rate of 200 Hz.
and a laptop computer collected analogue signals for volume, airflow and airway pressure from both RFMs. Respiratory parameters from each RFM (peak inspiratory pressure (PIP), PEEP, TV), for each breath, were determined by a customised program software algorithm (Python Software Foundation).

Leak during PPV was determined as (TV proximal (SIB) – TV distal (test lung))/TV proximal (SIB)×100.

Each subject received extensive instruction and practice with both face mask and LMA insertion/cuff inflation with each brand using the manikin head over several sessions. Competency with each method was assessed in the training phase by the instructor determining adequate test lung inflation and lack of audible leak.

Participants were asked to deliver 2 min of PPV aiming to achieve adequate test lung inflation for each randomised device; a 2 min rest period was provided between each test sequence. If the LMA device required cuff inflation, a volume of 4 mL was used, reflecting recommended maximum inflation volume. If the subject judged test lung inflation inadequate or there was no test lung movement, this was noted as an unsuccessful attempt; a second placement of the device was allowed, and two unsuccessful attempts were noted as a complete failure. Successful PPV following the second insertion was judged a partial failure (table 1). PEEP valve was set at 5 cmH\textsubscript{2}O and PIP was not specified beyond adequate test lung inflation. The inflation rate (40–60) is as per ILCOR guidelines.\textsuperscript{1} At the end of each sequence the subjects were instructed to provide four inflations of maximum SIB compression to determine if delivery of PIP up to the SIB overpressure value of 40 cmH\textsubscript{2}O (+/− 5 cmH\textsubscript{2}O) could be achieved, simulating the need to increase PIP during PPV at resuscitation.\textsuperscript{16}

### Table 1 Delivered test lung respiratory data, device insertion failures and device insertion rating

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Secondary outcomes</th>
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<tbody>
<tr>
<td></td>
<td>LM insertion\textdagger</td>
</tr>
<tr>
<td></td>
<td>Estimated mean (SE)</td>
</tr>
<tr>
<td>Face mask</td>
<td></td>
</tr>
<tr>
<td>M1. Triangular</td>
<td>43.0 (0.44)</td>
</tr>
<tr>
<td>M2. Round</td>
<td>34.9 (0.39)</td>
</tr>
<tr>
<td>Laryngeal mask</td>
<td></td>
</tr>
<tr>
<td>1. Ultimate</td>
<td>48.8 (0.38)</td>
</tr>
<tr>
<td>2. PRO-Breathe</td>
<td>64.7 (0.40)</td>
</tr>
<tr>
<td>3. Supreme</td>
<td>46.2 (0.37)</td>
</tr>
<tr>
<td>4. Unique</td>
<td>64.5 (0.40)</td>
</tr>
<tr>
<td>5. air-Q</td>
<td>58.5 (0.39)</td>
</tr>
<tr>
<td>6. AuroOnce</td>
<td>62.2 (0.41)</td>
</tr>
<tr>
<td>7. i-gel</td>
<td>4.0 (0.42)</td>
</tr>
</tbody>
</table>

*Parameters significant at p<0.001, analysis of variance for repeated measures, estimated means with SE.
†Frequency counts for LMA only tested, Fisher’s exact test, p<0.001.
‡Averaged four maximal inflations to achieve highest possible PIP.
LM, laryngeal mask; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.
Data analysis
The analysis using Stata V.14 examined the mean and SD for PIP, PEEP, TV and mask leak. Analysis of variance for repeated measures was used to determine differences between device types, with estimated means reported with their SEs (table 1) with p values-adjusted F test using Box’s conservative epsilon. p Values of <0.05 were considered significant. Pairwise comparisons between groups were assessed with Bonferroni correction. LMA insertion attempts were grouped as frequency counts of subjects (no failure, partial or complete failure), and participant impression of ease of insertion (dichotomised to easy or difficult) per device was examined by Fisher’s exact test.

RESULTS
There were 12415 inflations recorded and analysed. The i-gel LMA consistently and statistically outperformed all other devices tested (table 1). Box and whisker plots demonstrate the median and spread of values for primary outcomes (PEEP in figure 3 and leak in figure 4).
Primary outcomes
The mask leak observed with i-gel LMA of 5.7% was dramatically lower than all other devices observed, including face mask (ranging from 37.5% to 65.4%, p<0.001) (table 1 and figure 4). The i-gel LMA provided the highest mean PIP of 28.9 cmH\textsubscript{2}O compared with the other devices (ranging between 16.3 and 25.5 cmH\textsubscript{2}O, p<0.001) (table 1). The i-gel delivered PEEP was closest to the set value of 5.0 cmH\textsubscript{2}O, with others ranging from 0.6 cmH\textsubscript{2}O to 3.6 cmH\textsubscript{2}O (p<0.001) (table 1 and figure 3). Comparing the maximal average PIP for the four inflations targeting the highest peak inflation pressure possible, the i-gel LMA delivered a significantly higher mean value of 38.4 cmH\textsubscript{2}O compared with other devices, ranging from 18.5 cmH\textsubscript{2}O to 32 cmH\textsubscript{2}O (p<0.001) (table 1).

Secondary outcomes
The i-gel LMA was regarded by all 40 (100%) subjects as easy to insert, which compared with the range of subjective ratings for the other LMA from 16 (40%) with AuroOnce LMA to 38 (95%) with the Supreme LMA. All subjects were able to insert the i-gel LMA the first time with minimal leak. All other LMAs had at least one first insertion failure and four LMA brands had two failures recorded for subjects ranging from 1 to 5 in total.

DISCUSSION
We believe this is the first comprehensive study in a dedicated LMA manikin model looking at the performance of several brands (n>3) of size 1 single-use LMA devices compared with face mask PPV. The laryngeal structure of the AirSim Baby manikin head is modelled on CT scans of anatomically normal infants aged 2 months (TruCorp, personal communication 2017). Anatomically correct laryngeal structure is vital to train LMA use and allow assessment of LMA cushion leak. During the design phase, the RFM pneumotach positioned between the SIB and the LMA tube connector frequently indicated 100% leak with some brands of LMA when the test lung was clearly moving. Thus, a single point pneumotach measurement at the delivery device (SIB) may not account for differing leak characteristics during inspiratory and expiratory flow past the LMA seal. A second pneumotach sited at the test lung was required to assess system leak relative to TV (figure 2).

The superiority of the i-gel LMA to deliver ventilation compared with the other LMAs and face mask tested was unexpected given the group of experienced neonatal resuscitators. The ease of use of the i-gel LMA coupled with no insertion failure indicates the physical structure of the LMA does significantly influence performance at least in this manikin model. Many of the LMAs tested in our study were rated by the users as difficult to insert. This paralleled the higher rates of partial or complete failure to establish a useable laryngeal seal. The provision of an auto-inflate cuff with the air-Qsp LMA) may allow shorter time to PPV and be simpler to use overall. The ability to quickly adjust the inflation pressure to respond to inadequate clinical response most likely due to mask leak may be important with the use of LMA devices given the variance of ventilation performance seen in this study. The clear superiority of the i-gel LMA with dramatically less leak and stable PEEP levels, compared with the traditional face mask SIB in this study, was unexpected. In our view, this warrants human studies to confirm this finding. Our group is currently examining the comparative performance of SIB and NPIR with LMA devices, and beginning human infant studies to compare leak with face mask and i-gel LMA in the resuscitation of moderately preterm infants.

The emergency use of LMA devices during resuscitation of newborn infants is a time-critical procedure. We did not examine the additional time required for manual cuff inflation. We speculate devices that do not require manual inflation (i-gel with a solid gel cushion and the auto inflate cuff with the air-Qsp LMA) may allow shorter time to PPV and be simpler to use overall. This may be important with less experienced LMA users in the clinical setting of delivery suite or home birth.

CONCLUSION
This study has shown dramatic performance differences in delivered ventilation, mask leak and ease of use among seven different brands of LMA tested. PPV with the i-gel LMA with a solid gel laryngeal cushion had superior performance characteristics than the triangular or round face mask. This coupled with no partial or complete insertion failures and ease of use suggests i-gel LMA may have an expanded role with newborn resuscitation as a primary resuscitation device.
Acknowledgements We thank staff at Westmead Neonatal Intensive Care Unit for their participation. We also acknowledge and thank LMA and SIB suppliers for supply of devices to examine in this study, and Dr Peter Gibson paediatric anaesthetist for education and training assistance in the use of LMA.

Contributors MBT is primary researcher responsible for study design, statistical analysis, writing of manuscript and review. AP contributed to participant education, data collection, analysis, interpretation, manuscript construction and review. KL contributed to participant education, data collection and manuscript review. DG contributed to manuscript construction and review. JH contributed to programming of a customised respiratory data extraction algorithm, data interpretation and manuscript review. MH contributed by assisting in design, data collection, data analysis, writing the manuscript and review.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


Intravenous iron vs blood for acute post-partum anaemia (IIBAPPA): a prospective randomised trial

Seng Chua1,2†, Sarika Gupta2,3†*, Jennifer Curnow4, Beata Gidaszewski1, Marjan Khajehei1 and Hayley Diplock1

Abstract

Background: Acute post-partum anaemia can be associated with significant morbidity including a predisposition for postnatal depression. Lack of clear practice guidelines means a number of women are treated with multiple blood transfusions. Intravenous iron has the potential to limit the need for multiple blood transfusions but its role in the post-partum setting is unclear.

Methods/design: IIBAPPA is a multi-centre randomised non-inferiority trial. Women with a primary post-partum haemorrhage (PPH) >1000 mL and resultant haemoglobin (Hb) 5.5-8.0 g/dL after resuscitation with ongoing symptomatic anaemia who are otherwise stable (no active bleeding) are eligible to participate. Patients with sepsis or conditions necessitating rapid Hb restoration are excluded. Eligible participants are randomised to receive a blood transfusion or a single dose of intravenous iron polymaltose calculated using the Ganzoni formula. Primary outcome measures include Hb, Ferritin and C-Reactive Protein levels on Day 7. Secondary outcomes evaluate (i) Hb, Ferritin and CRP levels on Day 14, 28, (ii) anaemia symptoms on Day 0, 7, 14 and 28 using structured health related quality of life questionnaires, (iii) treatment safety by assessing adverse reactions and infection endpoints and (iv) the quantitative impact of anaemia on breast feeding quality using a hospital designed questionnaire.

Discussion: If equivalence in Hb and ferritin levels, symptom scores and safety endpoints is demonstrated, intravenous iron may become the preferred treatment for women with acute post-partum anaemia to minimise transfusion reactions and costs.

Trial registration: Australian and New Zealand Clinical Trials Registry: ACTRN12615001370594 on 16th December, 2015 (prospective approval).

Keywords: Packed cell transfusion, Intravenous iron, Post-partum anaemia

Background

Post-partum haemorrhage (PPH) commonly complicates pregnancy and can result in acute anaemia [1]. Up to 10% of women with blood loss in excess of 1000 mL will develop severe anaemia (Hb < 8 g/dL), which can be associated with lethargy, decreased mental alertness, physical weakness, poor concentration and a predisposition to post-natal depression [2–4].

Red blood cell (RBC) transfusions have traditionally been used to manage severe anaemia in the puerperium however in the absence of clear transfusion triggers many women without severe symptoms will also receive blood transfusions. This places them at an increased risk of septicaemia, haematological reactions, delayed wound healing and thromboembolism, particularly if they receive multiple transfusions [5]. Blood products are also a scarce and costly resource [5]. Recent institutional guidelines and trial data suggest blood transfusions are likely to be appropriate in patients with Hb < 7 g/dL but not necessarily if alternative therapy is available or if the individual is clinically well compensated [5, 6].
Intravenous (IV) iron therapy has been shown to reduce the requirement for allogenic blood transfusion and can restore haemoglobin levels by an average of 2.5 g/dL at day 5 post infusion with peak effects observed at 3-6 weeks [2, 7-13]. Compared to RBC transfusions, newer iron preparations excluding dextran derivatives are cheap, display a more benign side effect profile than blood transfusions (<0.5% risk of serious adverse events, 1-3% risk of mild adverse events) and have single dosing regimens [14-16].

Primary objectives
To determine if intravenous iron is non-inferior to RBC transfusion in correcting haemoglobin deficit, replenishing iron stores and improving clinical symptoms in women with acute post-partum anaemia without increasing the rate of adverse outcomes.

Secondary objectives
To determine if intravenous iron is superior to RBC transfusion in improving the quality of breast-feeding in women with acute post-partum anaemia.

Hypothesis
Intravenous iron is non-inferior to RBC transfusion in women with acute post partum anaemia in correcting Hb levels and improving clinical symptoms with no increased rate of adverse outcomes.

Intravenous iron is superior to blood transfusion in replenishing pre-pregnancy iron stores.

Design
This is a multi-centre prospective, randomised, open-label, non-inferiority trial.

Study settings
Participants will be recruited from at least three Australian hospitals, including Westmead Hospital, a tertiary teaching centre. Secondary sites are eligible if they are willing to participate and have the ability to collect and process blood tests and prepare and administer interventions according to the study protocol in a reasonable timeframe. They must be adequately staffed for recruitment, data collection (including follow-up) and treatment monitoring.

Patients will receive information about the study in antenatal clinics and recruitment will occur post-natally as hospital inpatients

Participants/eligibility criteria
The sample population will consist of women who sustain a primary post-partum haemorrhage in excess of 1000 mL with a resultant Hb drop of ≥3 g/dL and Hb of 5.5-8.0 g/dL. Asymptomatic women, as well as patients with mild signs and/or symptoms of anaemia including dizziness, increased respiratory rate to ≥ 25 on minimal exertion, HR 100-130 or a postural blood pressure drop of >10 mmHg are eligible.

Blood loss will be assessed by weighing all blood stained articles including sponges, sheets, under-pads and clothing. If delivery occurs in the operating theatre (after subtracting liquor volume) suction output will be added. Where possible all blood spillage will be mopped up, weighed and added to the total.

Evidence suggests 90% of women with PPH > 1000 mL have resultant Hb < 10 g/dL thereby defining our haemorrhage cut off [1]. Similarly the nominated minimum Hb is a conservative estimate based on levels used in previous studies evaluating expectant management in patients with acute anaemia [6, 10, 11, 17].

If applicable, enrolment must occur within 48 h of resuscitation and stabilisation. Stabilisation is defined as (1) having no active per vaginal bleeding in excess of expected post-partum losses and (2) having all vital parameters within hospital review criteria for a period of 12 h immediately prior to study recruitment (i.e. all patients having pulse <130 bpm, systolic blood pressure > 90 mmHg, diastolic blood pressure < 110 mmHg, respiration rate < 25, temperature < 38.5 degrees and oxygen saturations >90%).

Patients with significant antenatal or peri-partum complications such as severe pre-eclampsia who are now stable (as per above criteria) are eligible. Women who receive whole blood transfusion, other blood products, antibiotics (other than for sepsis) and intravenous fluid therapy prior to stabilisation will also be eligible.

Major inclusion criteria
- Age 16-50 years
- Willingness to attend follow up at Day 7, 14, 28

Major exclusion criteria
- Age < 16 or >50 years
- Refuse consent to blood transfusion or iron infusion
- Co-morbidities necessitating rapid Hb restoration including: cardiac failure, ischemic heart disease, chronic renal failure
- Known hematological malignancy
- Known hemaglobinopathies requiring regular transfusions
- Sepsis (clinical or laboratory evidence—intrapartum fever >38.5 degrees with abnormal vital signs, positive blood culture)
- Contraindications to iron polymaltose (i.e. asthma, known hypersensitivity to iron polymaltose, chronic polyarthritis, acute renal dysfunction, uncontrolled hyperparathyroidism, infectious hepatitis and iron overload (ferritin >1000 ng/L))
• Severe symptoms of anemia including dyspnoea at rest, angina pectoris, syncope or transient ischemic attacks.

Interventions
All eligible women will be approached and given information about the intervention arms of the study i.e. the blood transfusions and intravenous iron including details about the interventions themselves and other scientific and ethical considerations. Those who decline either intervention will be offered oral iron in line with standard practice. These women will be invited to participate in the trial as part of an oral iron subgroup which has an identical follow up protocol. These women will be administered 325 mg of oral iron daily. This is not a randomised arm of the study.

Patients in the intervention group will be randomised to receive cross-matched RBC transfusion or an IV iron polymaltose infusion. In patients allocated to RBC transfusion, Hb will be checked after each unit and given to achieve a Hb of at least 9.0 g/dL. Patients who received transfusions will be discharged on 325 mg of oral ferrous sulphate for a minimum of 4 weeks.

Iron polymaltose was selected instead of iron carboxymaltose as it allows for individualised dose calculations and a larger dose of iron to be administered. Iron carboxymaltose, despite having a shorter infusion time, has a maximum of 1 g that can be administered within a 7 day period.

The dose of iron polymaltose will be calculated according to the Ganzoni formula: Total iron dose (mg) = body weight (kg) x (150-baseline Hb (g/dL)) x 0.24 + 500 mg, assuming a target Hb of 15.0 g/dL which allows for ongoing normal per vaginal loss during the puerperium. For those with Thalassemia minor, the target Hb will be adjusted to reflect the patients pre-pregnancy Hb. Iron will be administered as per hospital protocol which instructs slow infusion at 20-40 mL/h for the first 50 mL, increasing to 120 mL/h based on patient tolerance.

Patients will be pre-medicated with anti-histamine (10 mg cetirizine hydrochloride) and anti-emetic (metoclopramide 10 mg) 1 h prior to the iron infusion to reduce adverse reactions [18]. During the infusion patients will be monitored for adverse affects including itch and urticaria, bronchospasm/dyspnoea, back, joint or muscle pain, nausea, indigestion, abdominal pain, headache, hypotension, tachycardia, syncope, and circulatory collapse [9].

Any patient experiencing an adverse reaction will receive appropriate medical care including additional RBC transfusion if indicated. Infusion rates will be slowed in the instance of mild to moderate reactions and ceased for severe reactions.

A new intravenous cannula will be inserted immediately prior to treatment to minimise the risk of confounding infection.

Outcomes
Primary outcomes
• Hb, ferritin and CRP levels at Day 7

Secondary outcomes
• Hb, CRP, ferritin and reticulocyte count at Day 14 and 28
• clinical symptoms at day 7, 14 and 28
• breastfeeding quality at day 7, 14 and 28
• adverse reactions

Quantifying CRP will ensure changes to ferritin levels are not the result of an acute phase response. Reticulocyte count will be used as a marker of bone marrow response [19, 20].

Statistics
To demonstrate equivalence of the interventions in restoring Hb levels at Day 7 with 90% power at 5% significance (α = 0.025), 116 women need to be recruited to each intervention group. Based on similar studies, this assumes an acceptable difference in Hb of 1 g/dL and an expected difference of 0.7 g/dL [2, 8, 12]. Hence, the final sample size, accounting for a 10% loss to follow up, is a total of 250 women.

Participants experiencing adverse reactions will remain in the trial unless they fail to meet inclusion and exclusion criteria at any point. Data will be analysed according to the intention to treat principle. Primary outcomes and secondary binary outcomes will be analysed using one sided and two group t-tests. The incidence of adverse reactions and symptom scores will be assessed by calculating rates and 95% confidence intervals. Validity of the Post Partum Symptom Scale (PPSS) will be determined at the time of analyses as part of an embedded study and if validated, correlations between subscales and primary outcomes will be analysed.

Procedures, recruitment and randomisation
Table 1 describes the schedule of enrolment, interventions and assessments during the trial.

Clinical staff at all sites will be able to contact the research team at any time to enrol participants. Research midwives at the primary site will identify women from daily birth records who have had a PPH >1000mLs. These women will be briefed on the study using a structured information sheet about the trial and interventions. Following this they will verbally consent to preliminary bloods including a group and hold, haemoglobin, creatinine (to exclude acute kidney injury), ferritin and CRP. Eligible patients will then provide written informed...
consent and be enrolled to participate in the study (intervention and follow up phases).

Participants will be stratified as per mode of delivery and randomisation will occur within these groups by a computer generated list, blocked in a 1:1 ratio to each intervention. A central telephone service will be accessed to allocate the intervention and study identification number.

Eligible women who decline participation in the trial will be offered 325 mg oral ferrous sulphate daily until iron replete, which is in accordance with current standard practice guidelines. This will be mentioned in the consent process.

Blinding during the intervention stage is practically difficult due to strict hospital protocols requiring bedside checks and regulated transparent packaging for all blood products. During the follow up phase however researchers will be blinded to the participant’s intervention and researchers who enrolled a particular participant will not be allocated to conduct their follow up interviews. Participants are reminded not to disclose their intervention to the researcher during follow up. We acknowledge that strict blinding in this phase may be difficult.

**Data collection**

Each participant will have a study file labelled with their name, medical record number, study identification number and allocated treatment. This will contain copies of their consent forms (the original will remain in their hospital file while they are an inpatient), questionnaires and comprehensive study checklists template for documenting outcome variables and other clinical data. Files will be kept in locked cabinets on the ward and in the principle researcher’s office after discharge and remain on site for 7 years before being destroyed/archived.

Baseline blood results (Hb, ferritin, CRP) for all enrolled participants will be manually transcribed by researchers from the hospital electronic database into the participant’s study file. Once allocated to an intervention, the number and coding sticker of each blood unit or the serial number and dose of the pre-packaged iron infusion will be recorded in the template.

Patient symptoms will be scored on Day 0 prior to receiving any intervention using previously validated HRQoL questionnaires: the EuroQol-5D (E-5D), the Multidimensional Fatigue Inventory (MFI-20) and our in-hospital devised Post-Partum Symptom Score (PPSS). The EQ-5D measures a patient’s activity level and emotional attitude at a single point in time, indirectly reflecting symptom severity. It consists of five items (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression) where a patient scores: 1 = no problems, 2 = more problems, 3 = extreme problems. The sixth item is a patient’s own global evaluation of their health using a visual analogue scale with a range from 0 (worst imaginable health state) to 100 (best imaginable health state) [21].

<table>
<thead>
<tr>
<th>Table 1 Schedule for enrolment, interventions and assessments</th>
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<tbody>
<tr>
<td><strong>TIMEPOINT</strong></td>
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<tr>
<td><strong>0-48 h</strong></td>
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<tr>
<td><strong>ENROLMENT:</strong></td>
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<tr>
<td>Eligibility screen</td>
</tr>
<tr>
<td>Informed consent</td>
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<tr>
<td>Randomisation</td>
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<tr>
<td><strong>INTERVENTIONS:</strong></td>
</tr>
<tr>
<td>RBC Transfusion</td>
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<tr>
<td>Intravenous Iron Polymaltose</td>
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<tr>
<td><strong>ASSESSMENTS:</strong></td>
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<tr>
<td>E-5D, MFI-20 and PPSS symptom scores</td>
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<tr>
<td>Clinical history and examination</td>
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<tr>
<td>Hb</td>
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<td>Ferritin</td>
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<tr>
<td>UEC</td>
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<tr>
<td>CRP</td>
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<tr>
<td>Reticulocyte Count</td>
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<td>Group and hold</td>
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<td>Vital Signs</td>
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</table>
The MFI is a 20-item self-report instrument designed to comprehensively measure fatigue. It evaluates: general, physical and mental fatigue and reduced motivation and activity. Patients score each dimension on a scale ranging from 4 to 20 where 4 is optimal. Hence, higher scores indicate more severe symptoms. Scales are balanced to reduce the influence of response tendencies. Each scale sub-total is interpreted independently. Questions are structured to evaluate symptoms over a period of time (5-7 days) which is particularly useful to measure treatment impacts [22]. Both the MFI and EQ-5D have previously been validated in pilot studies of obstetric cohorts [23].

The PPSS developed by clinicians at Westmead Hospital is a 27 point self-report questionnaire measuring frequency across three subscales: frequency of clinical symptoms commonly observed in anaemic patients (6 questions), feeding status indicated by changes to breastfeeding habits (7 questions) and home factors to quantify the amount of assistance received to care for the newborn (11 questions). Validity of the scale to discern a relationship between anaemia severity, treatment and breast feeding quality will be determined at the time of data analyses through an embedded study.

Prior to analysis data will be de-identified using study identification numbers and transferred from study files into an electronic database by a study researcher and re-checked by a second researcher. The database will be on a separate computer at the primary study site, accessible only by study researchers and statisticians who will sign a confidentiality agreement stipulating the terms of their use of the data.

Follow up
The follow up period consists of 4 weeks with face-to-face visits at Day 7, 14 and 28. At each of these visits women will be seen by a research midwife or doctor. Hb, ferritin and CRP will be checked and results recorded in the study file. Patients will have been discharged with completed pathology forms to facilitate compliance with follow-up laboratory testing. Women will also undergo a clinical examination following a specified checklist to assess for any features of infection or other adverse outcomes. Symptom scores using the three specified scales will be collected at each of the follow up sessions. Research midwives will make all effort to ensure compliance with follow up and can facilitate home visits, including pathology collections if required.

Monitoring/reporting of data
Given the potential for serious adverse events with each treatment, an independent Data Safety and Monitoring Board has been appointed at the primary study site consisting of a consultant obstetrician, haematologist and anaesthetist who are not directly involved with the study design or execution, as well as an independent research midwife and a statistician. Members will be provided with a charter prior to commencement of the study by study researchers requiring them to convene every 2 months for the duration of the study where they will review the data for completeness, accuracy and to identify incidences and severity of any adverse reactions and their management.

If the total incidence of severe adverse reactions (i.e. anaphylaxis, hematological reaction) exceeds 2 per 50 participants at any time in either treatment group, or if the difference in incidence of serious adverse events is greater than 50%, the study will be suspended until further review. Unscheduled DSMB meetings will be called whenever severe adverse reactions occur in either treatment group.

Conclusions and recommendations regarding study modifications will be presented to the principal researchers after each DSMB meeting and attention to these recommendations will be reviewed at subsequent meetings. Final decisions to terminate the study will be made by study researchers in consultation with the DMSB and the ethics committee.

Discussion
Moderate to severe acute post-partum anaemia is associated with a number of short and long-term adverse health outcomes hence active treatment is necessary and is commonly indicated by a combination of haemoglobin and iron deficit and symptom severity. Whilst RBC transfusion is the mainstay treatment for severe symptomatic anaemia, wide practice variations exist in the management of mild-moderate anaemia in otherwise clinically stable women. If over treated with blood products, these women are placed at risk of transfusion related adverse effects, which although uncommon, can be life threatening and are almost always associated with ongoing morbidity.

The argument supporting expectant management for these patients has been well outlined in recent studies though there is no standard definition of what expectant management entails. Some institutes advocate the use of oral iron only whilst others prescribe parenteral replacement. Long term data indicates that parenteral iron is faster and more effective than oral iron at restoring haemoglobin and total body iron deficits and has the added advantage of avoiding gastrointestinal side effects which often interrupt compliance in the post-natal cohort [2, 3, 24]. Moreover, the lag period to replenish iron stores and induce erythropoiesis is significantly contracted with IV compared to oral therapy. This, coupled with an attractive safety and tolerance profile as well as being cheaper and more available, introduces parenteral iron as an appropriate alternative to blood transfusions in selected women.

If our study hypotheses are true then intravenous iron presents as a safer, sustained and more cost-effective
alternative to blood transfusion in the management of hemodynamically stable women with acute post-partum anaemia. Our findings will be particularly useful for patients ineligible for treatment with blood products due to clinical or religious reasons and in under-resourced settings both within Australia and internationally. Ultimately we would hope these findings support the widespread implementation of parenteral iron into routine post-natal practice policies in an effort to improve patient safety and minimise resource wastage.

Abbreviations
BP: Blood pressure; CRP: C-Reactive Protein; Hb: Haemoglobin; HR: Heart rate; HRQoL: Health related quality of life; IV: Intravenous; PPH: Primary post-partum haemorrhage; RBC: Red blood cell; RR: Respiratory rate

Acknowledgements
We would like to thank and acknowledge Karen Bythe for her guidance with statistical analysis and Raj Ramakrishna for his input into study design modifications. We would also like to thank Patricia Fa and the entire Pharmacy Department at Westmead Hospital for assembling study specific medications.

Funding
This study is financed by the Department of Obstetrics and Gynaecology at Westmead Hospital, (Wentworthville, Australia) and a 3 year research grant (SAUD 27,352 per year) awarded by the National Blood Authority of Australia. Ph: +61288904629; +61261515050.

Availability of data and materials
The researchers plan to publish the study protocol in a peer-reviewed journal. Study findings will also be submitted for publication regardless of the outcome, including discontinuation of the trial. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations
The authors state that they have no competing or financial interests to declare.

Post-trial care
If any participants suffer harm that can be directly attributed to trial participation they will be entitled to free medical care from the relevant study hospital.

Authors’ contributions
SC, SG and JC were involved in study design. SC, SG, JC and MK developed the study protocol and data collection templates. SC, SG and MK prepared the submitted manuscript. BG and HD co-ordinated participant recruitment, enrolment and follow up and assisted in ethics acquisition. All authors read and approved the final manuscript. SC, SG, JC, MK, BG, and HD are all employed by Westmead Hospital and make significant contribution to the study design, data collection, management and interpretation of data, writing of the report and decision to submit the report for publication. SC, as the primary researcher will have ultimate authority over these activities.

Ethics approval and consent to participate
Ethics approval for this trial was obtained from the Western Local Health District Ethics Committee. The ethics number is: 4158. Written informed consent was obtained from all women prior to participation in the study. Any recommendations described by the DSMB will be communicated in writing to the WLHD ethics committee as necessary.

Consent for publications
Consent for publication will be obtained at enrolment, at the time of consent for participation in the study.

Competing interests
Neither the co-ordinating centre and sole funder of the study The Department of Obstetrics and Gynaecology at Westmead Hospital, nor any of the authors have any competing interests in the conduct of this study or its publication.

Publisher’s Note
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Received: 18 January 2016 Accepted: 24 November 2017

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Clinical practice

Labour and beyond: The roles of synthetic and endogenous oxytocin in transition to motherhood

Abstract
During spontaneous labour, endogenous oxytocin is released from the pituitary gland and initiates uterine contractions. In some women, it is necessary to induce or augment labour contractions. Induction or augmentation of labour using synthetic oxytocin (Syntocinon) is one of the most common interventions to facilitate the progress of labour and birth. Both Syntocinon and endogenous oxytocin affect the body through oxytocin receptors. Although the use of Syntocinon is regarded as a relatively safe intervention during labour, it works in a different way from endogenous oxytocin and has different effects on the mother and child. Syntocinon may negatively affect birth outcomes for mother and baby, interfere with the success of lactation and breastfeeding, impair the mother-child attachment and may affect the child’s development. We review the effect of endogenous oxytocin and Syntocinon on the health and wellbeing of women during labour and after birth, discuss the benefits of endogenous oxytocin and highlight some adverse effects of Syntocinon.

Keywords
Amygdala | Oxytocin | Syntocinon | Childbirth | Breastfeeding

In the course of spontaneous physiological labour, endogenous oxytocin is released from the pituitary gland and initiates uterine contractions. However, when it is deemed medically necessary to induce or augment labour contractions, synthetic oxytocin (Syntocinon) is administered intravenously. Induction or augmentation of labour using Syntocinon is one of the most common interventions for facilitating the progress of labour and birth (Wood et al, 2014). Between 30% and 50% of women receive Syntocinon for augmentation of labour, and 50–70% receive it for induction of labour (Calder et al, 2008). In addition, Syntocinon is often administered intramuscularly after the birth of the baby and during the third stage of labour to prevent post-partum haemorrhage. The administration of Syntocinon depends on a variety of reasons including, but not limited to, maternal medical conditions if they become problematic and necessitate the induction of labour (i.e. hypertension, gestational diabetes, obstetric cholestasis) and fetal indications (i.e. macrosomia, small for gestational age, oligohydramnios, abnormalities) (Declercq et al, 2007).

The use of Syntocinon is regarded as a relatively safe intervention during labour, even for patients who have had a single previous caesarean section in resource-rich developed countries such as France (Sananès et al, 2014), Greece (Rath and Tsikouras, 2015), Australia (Homer et al, 2011) and USA (Landon et al, 2006). Nonetheless, it has been suggested that Syntocinon works differently from endogenous oxytocin, and its effects can be unpredictable (Uvnäs-Moberg, 1998). Animal studies also suggest that the effect of Syntocinon varies depending on the administration site, route, frequency, dose and time (Mota-Rojas et al, 2006). It has been proposed that the unpredictable effects of Syntocinon may interfere with the mother-child attachment, bond and breastfeeding and may affect the child’s development (Feldman et al, 2010; Fernández et al, 2012). Here, we review the effect of endogenous oxytocin and Syntocinon on the health and wellbeing of women and their children during labour and after birth, and discuss the benefits of endogenous oxytocin and some adverse effects of Syntocinon.

Endogenous oxytocin and Syntocinon
Endogenous oxytocin and its receptors were first discovered because of their role in inducing labour contractions, the delivery of the baby and stimulating lactation (Fuchs et al, 1984). Endogenous oxytocin is primarily synthesised in the hypothalamus and is then stored in the posterior pituitary gland, where it is released into the bloodstream (Russell et
The blood–brain barrier prevents the released endogenous oxytocin from re-entering the brain (Mens et al, 1983). This hormone is also synthesised in the amnion and the chorionic layer of the placenta, and in the decidual layer of the uterus during labour and birth (Cunningham et al, 2010). The release of endogenous oxytocin can be provoked by a variety of stimuli including sexual and reproductive stimuli (i.e. copulation, genital and breast stimulation, birth, olfactory stimuli and sucking) (Baskerville and Douglas, 2008) and nonsexual stimuli (i.e. grooming, massage and contact with offspring) (Gimpl and Fahrenholz, 2001). The central and peripheral actions of endogenous oxytocin are mediated by its receptors (Russell et al, 2003; Leng et al, 2008).

Endogenous oxytocin has a complex role in the body. It acts as a neurotransmitter in the brain and applies a wide range of central and peripheral physiological effects in women (Cunningham et al, 2010). The spectrum of its effects varies from modulating neuroendocrine reflexes to establishing social and bonding behaviours, such as facilitating milk ejection, uterine contractions, birth, copulation, maternal behaviours, partner and offspring preference and social contacts (Feldman et al, 2010).

Endogenous oxytocin has unique interactions with the body and does not act in the same way as Syntocinon. Although Syntocinon has a well documented role during labour and can be a life-saving intervention for many women (Cunningham et al, 2010), it can impede the delicate orchestration of natural hormones of the mother and baby during and after birth, which is not free of risks (Fernández et al, 2012; Weisman et al, 2015). We discuss details of these changes in the following sections.

Preparation of fetal neurons for birth

Maternal endogenous oxytocin may help prepare the fetus for birth and may have a role in protecting the fetal brain during labour and birth. According to animal studies (Tyzio et al, 2006; Khazipov et al, 2008), maternal oxytocin crosses both the placental barrier and fetal blood–brain barrier during labour. It enters the fetal brain and prompts a transient switch in the action of the neurotransmitter gamma-aminobutyric acid (GABA) (Khazipov et al, 2008), changing GABA from having an excitatory to an inhibitory effect. GABA then inhibits fetal cortical neurons, reduces fetal brain activity for the duration of labour and delivery, and helps decrease the vulnerability of the fetal brain to hypoxic damage during birth. These changes start the day before the onset of physiological labour and have maximal effect during the second stage of labour. The effects of these GABA-induced changes include decreased central blood flow, decreased oxygen requirement and reduced vulnerability to hypoxic brain damage (Tyzio et al, 2006; Khazipov et al, 2008).

There is, however, disagreement about whether peripherally administered Syntocinon has the same effects, crosses the fetal blood–brain barrier and alters the neuronal actions of the fetal nervous system (Churchland and Winkielman, 2012). In theory, based on the pharmacological properties of Syntocinon, this drug is not able to cross the blood–brain barrier because of its large molecular size and hydrophilic nature. However, some animal studies have found low levels of Syntocinon in the fetal brain after parenteral administration, and that administration of high-dose synthetic oxytocin (Ceanga et al, 2010) or the oxytocin antagonist atosiban (Tyzio et al, 2006) block the oxytocin receptors, reducing...
the neuroprotective effects of endogenous oxytocin and increasing the fetus’ vulnerability to hypoxic brain damage.

**Uterine contractions and pain management**

The role of endogenous oxytocin in stimulating uterine contractions during the expulsive phase of labour and delivery is very well known (Russell et al, 2003; Leng et al, 2008). According to animal studies (Young et al, 1997), during the body’s preparation for the physiological onset of labour, the rising oestrogen level during the last weeks of pregnancy increases the number and sensitivity of oxytocin receptors in the uterus leading up to birth. These changes are accompanied by an increase in the oxytocin receptors in the hypothalamus and olfactory bulbs. This increase, in turn, raises the sensitivity of the hypothalamic and olfactory neurons to endogenous oxytocin and prepares the body for birth. It has been shown that the descent of the baby during labour stimulates stretch receptors in the lower vagina and cervix. This triggers a pulsatile release of endogenous oxytocin from the posterior pituitary gland into the bloodstream and stimulates uterine contractions (also known as the Ferguson reflex) (Russell et al, 2003; Leng et al, 2008).

Endogenous oxytocin blocks the β-adrenergic receptors and decreases clearance of endorphins, especially the β-endorphin. This process raises the level of plasma endorphins, increases their binding to opioid receptors on the uterus and results in pain reduction. This can relieve some of the pain associated with uterine contractions and labour (Saisto et al, 2004).

During natural labour, endogenous oxytocin reaches a peak at birth, when it stimulates the fetal ejection reflex and allows for an easier delivery, as shown in animal studies (Gilbert et al, 1994). In addition, an increase in the number of oxytocin receptors and in uterine contractility helps the uterus to contract after delivery, resulting in placental separation and expulsion (Blanks and Thornton, 2003).

Endogenous oxytocin and Syntocinon are similar in terms of binding to oxytocin receptors on the uterine muscles, but Syntocinon can have unpredictable effects on the body. This could be partly due to the physiological differences in oxytocin receptors during induction of labour with Syntocinon. Unlike endogenous oxytocin, Syntocinon is administered continuously at various doses via an intravenous cannula (Cunningham et al, 2010). If labour has not started physiologically, fewer oxytocin receptors exist in the uterine muscles and, therefore, higher doses of Syntocinon (10–16 mU/minute) are administered to induce labour (Fuchs et al, 1983). This is markedly higher than the dose required for augmentation of labour (4–6 mU/minute) when physiological labour has already started and enough oxytocin receptors exist (Fuchs et al, 1983).

Large doses of Syntocinon can increase the resting tone of the uterine muscle by creating more frequent, longer and stronger contractions. An increased resting tone of the uterine muscle can reduce blood flow to the uterus and placenta, as shown in preliminary animal studies (Brotanek et al, 1969) and result in myometrial ischemia and increased pain sensation (Lowe, 1996). The ischemia may in turn compromise fetal replenishment of blood and oxygen between contractions and result in abnormal fetal heart rate patterns, fetal distress and even uterine rupture (Bell et al, 2014). These events may occur because the constant administration of Syntocinon does not allow its levels to decrease between contractions as much as would occur for endogenous oxytocin in physiological labour. The physiological pulsatile secretion of endogenous oxytocin, along with increased oxytocinase production, helps the uterine muscles rest between contractions and improves fetal blood supply (Nomura et al, 2005).

The increased pain sensation that occurs with Syntocinon use is not only because of vigorous myometrial ischemia but may also be due to the inhibitory effects of Syntocinon on the release of endorphins in the brain. Genazzani et al (1985) compared β-endorphin levels in women in spontaneous labour with women who received Syntocinon to stimulate uterine contractions. They found that in women in spontaneous labour, the plasma levels of β-endorphin increased significantly throughout labour until delivery. However, the β-endorphin levels remained constant or lower in women who received Syntocinon. Genazzani et al reported that the lower levels of β-endorphin in women who received Syntocinon to stimulate uterine contractions could have been related mostly to the primary uterine hypocontractility rather than to intravenous Syntocinon administration. However, they pointed out that using Syntocinon to augment or induce labour can result in tocophobia (anxiety and fear of childbirth) which might be associated with lower β-endorphin levels in those women. Results of the study by Genazzani et al were supported by a later study (Petraglia et al, 1986) suggesting that administration of Syntocinon (0.4 μg/min for 120 min) could inhibit the rise of β-endorphin in stressful situations in healthy humans.

**Lactation and breastfeeding**

Endogenous oxytocin continues to play an important role in lactation and breastfeeding after stimulating uterine contractions during labour and delivery. Pulsatile secretion of endogenous oxytocin stimulates the release of ochytoxin.
of prolactin, a hormone produced by the lactotroph cells in the pituitary gland. Prolactin is responsible for milk production (Nissen et al, 1996). Nipple stimulation during breastfeeding sends a signal via the spinal cord to the hypothalamus. This results in the release of oxytocin from the pituitary gland into the bloodstream. Endogenous oxytocin then binds with its receptors on the smooth muscle cells of alveoli in the mammary glands, resulting in the milk-ejection reflex, also known as the forceful let-down reflex, with milk ejected from the mammary glands into the ducts and cisterns (Leng et al, 2008).

Endogenous oxytocin facilitates breastfeeding by making the mother more relaxed and more confident about successfully breastfeeding her baby. Research has shown that women who breastfeed their babies are calmer and report lower stress levels than women who formula-feed their babies, which has been attributed to higher levels of plasma oxytocin in breastfeeding women (Schwarze et al, 2014). In addition to the psychological benefits of breastfeeding, the release of endogenous oxytocin during breastfeeding induces mild but often painful uterine contractions that help decrease the size of the uterus and postpartum lochia (Cunningham et al, 2010).

Syntocinon can affect the mother and alter initiation of breastfeeding. Administration of high doses of Syntocinon during labour impairs the pulsatile secretion of endogenous oxytocin, desensitises or downregulates oxytocin receptors, decreases their responsiveness, and finally alters the maternal neural architecture. In the study by Phaneuf et al (2000), myometrial samples were taken from women before the onset of labour, after the onset of spontaneous labour and after induced or augmented labour, and were tested for the quantity and sensitivity of oxytocin receptors. Results showed that although receptor desensitisation occurred in both spontaneous and induced or augmented labour, in women who had undergone induced or augmented labour there was a significant reduction in oxytocin binding that was associated with a longer duration of Syntocinon infusion. In addition, the concentration of oxytocin mRNA was much lower in induced or augmented labour than in spontaneous labour.

Syntocinon molecules resemble vasopressin (an antidiuretic hormone). Since Syntocinon is often administered in relatively high doses during labour and after birth, it can have antidiuretic effects and can lead to breast engorgement and complicated breastfeeding. Another way that Syntocinon can affect breastfeeding success is that the strong, painful contractions it initiates during labour can raise the level of stress and anxiety in the mother (Jonas et al, 2009). The study by Jonas showed that oxytocin infusion uplifts the reactivity of the hypothalamic–pituitary–adrenal (HPA) axis, which controls the body’s stress response (Jonas et al, 2009) and results in delayed onset of lactogenesis and unsuccessful breastfeeding (Matias et al, 2010).

The association between Syntocinon and impaired breastfeeding is believed to be dose-dependent (Olza Fernández et al, 2012). Fernandez et al reported an association between higher Syntocinon doses during labour and impaired infant sucking after birth. In addition, the rate of exclusive breastfeeding for babies at 3 months of age was higher in women who had received a markedly lower average dose of Syntocinon during labour (Fernández et al, 2012). The study by Beebe et al (2007) revealed that compared with spontaneous labour and birth, the Apgar score at one minute was more likely to be less than three in induced labour. Matias et al (2010) reported that a low Apgar score can delay the onset of lactogenesis and interfere with successful breastfeeding. Similarly, a multinational study (Guerra et al, 2009) found that children born during induced labour are at greater risk of a low Apgar score at five minutes than children born during spontaneous labour. This study suggested that inducing labour when labour is not indicated may be the likely cause of adverse fetal outcomes. Nevertheless, these findings are not supported by reports of other research indicating no significant association between the use of Syntocinon for induction of labour and low Apgar scores at 5 minutes after birth (Gülmezoglu et al, 2006).

The negative impacts of Syntocinon on breastfeeding may be due to a low Apgar score and also a result of other adverse neonatal outcomes associated with induction or augmentation of labour, such as hyperbilirubinaemia (Trotman and Henny-Harry, 2012), admission to the neonatal intensive care unit (NICU) (Clark et al, 2009). These impacts may be because successful breastfeeding requires the child to be alert with coordinated sucking, swallowing and breathing and not being separated from the mother (Romano and Lothian, 2008).

**Maternal behaviours and child development**

Human studies suggest that central oxytocin may be involved in behavioural adaptations to the maternal role, parenting behaviour, social development and affectionate touch (Feldman et al, 2010). It enhances positive feelings and memory for facial identity that will help mother to recognise her newborn. This system, which depends not only on the release of oxytocin but also on oxytocin receptor distribution, becomes particularly important at birth, when the primary bond is formed between mother and baby (Savaskan et al, 2008).

Administration of Syntocinon during labour hinders the pulsatile secretion of endogenous oxytocin, which may have a lasting effect. Animal studies have shown that the brain is sensitive to hormonal imprinting effects. Therefore, the manipulation of the hormone system at
birth may predict lifelong changes in social behaviours and their associated repertoire (Bales et al, 2013). This theory is supported by other animal studies indicating that hormonal imprinting takes place in neonates when the developing receptors and their target hormones meet for the first time (Csaba, 2000). Evidence suggests that exposure to Syntocinon during birth may change the infant’s DNA methylation, and these changes may affect the neuropeptide systems of the child’s brain (Emberti Gialloreti et al, 2014). Animal studies have also shown that patterns of maternal behaviour, such as licking and grooming, shape the neurochemical organisation of oxytocin in the infant’s brain during the early stages of life (Kappeler and Meaney, 2010).

Low levels of plasma endogenous oxytocin during the first and third trimester of pregnancy, as well as inhibited endogenous oxytocin during labour, have been shown to correlate with maternal postpartum anxiety and depression symptoms (Kroll-Desrosiers et al, 2017), minimal affectionate touch and low levels of attachment behaviour and social synchrony (Feldman, 2012). This extragenomic dissemination explains a bio-behavioural feedback circle: maternal oxytocin regulates the mother’s care-giving behaviours, which in turn outlines the infant’s oxytocin through distinctive parenting behaviour (Champagne, 2008).

Statistical analysis of more than half a million births in the USA revealed a link between induction or augmentation of labour and increased odds of the child attending an educational programme for children with special needs, particularly autism spectrum disorders (Gregory et al, 2013). The researchers, however, suggested further research on the association of induction and/or augmentation of labour with autism, as it was unclear whether this association was because of induction or augmentation of labour, the medications used during labour, the underlying medical and obstetric conditions, or acute intrapartum events (Gregory et al, 2013). In contrast to these findings, two earlier studies showed no association between antepartum use of Syntocinon and a subsequent diagnosis of autism in the child (Fein et al, 1997; Gale et al, 2003). It is difficult to interpret the validity and generalisability of the results of the two latter studies because of the small sample size in one study (Gale et al, 2003), and missing data on gender as a variable in data analysis of the other study (Fein et al, 1997), as risk has been reported to be higher in male children (Weisman et al, 2015).

As mentioned earlier, the risk of a low Apgar score is higher in newborns whose mothers have received Syntocinon during labour. A low Apgar score is associated with a higher chance of admission to the NICU and postpartum separation of mothers and infants. This early separation can have negative short- and longer-term effects, such as disruption of successful initiation of breastfeeding, lack of skin-to-skin contact, increased levels of stress hormones, hypoglycaemia and hypothermia in the infants, and shortfalls in maternal hormones and role adaptations affecting the mother–infant attachment (Moore et al, 2012).

**Conclusion**

Endogenous oxytocin has extensive effects on the brain and body during reproduction. In labour and birth, it optimises the transition to the postpartum period in the mother and infant. Endogenous oxytocin is released into the maternal bloodstream and causes rhythmic uterine contractions, imposes soothing and analgesic effects on the mother and infant, and facilitates the initiation of lactation and maternal-child bonding.

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**Table 1. Summary of the activities of endogenous oxytocin and Syntocinon**

<table>
<thead>
<tr>
<th>Endogenous oxytocin</th>
<th>Syntocinon</th>
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</thead>
<tbody>
<tr>
<td>Modulating neuroendocrine reflexes</td>
<td>Uterine contractions</td>
</tr>
<tr>
<td>Preparation of fetal neurons for birth</td>
<td>Birth of the baby</td>
</tr>
<tr>
<td>Uterine contractions</td>
<td>Potentially increasing the fetus’s vulnerability to hypoxic brain damage</td>
</tr>
<tr>
<td>Birth of the baby</td>
<td>Myometrial ischemia</td>
</tr>
<tr>
<td>Facilitating milk ejection and breast-feeding</td>
<td>Increased sensation of pain</td>
</tr>
<tr>
<td>Maternal behaviours (behavioural adaptations to the maternal role; positive feelings and memory for facial identity)</td>
<td>Likelihood of abnormal fetal heart rate patterns, fetal distress and uterine rupture</td>
</tr>
<tr>
<td>Bonding and attachment</td>
<td>Impaired lactation and breast-feeding</td>
</tr>
<tr>
<td>Establishing social behaviours</td>
<td>Maternal postpartum anxiety and depression symptoms</td>
</tr>
<tr>
<td>Partner and offspring preference</td>
<td>Minimal affectionate touch and low levels of attachment behaviour and social synchrony</td>
</tr>
</tbody>
</table>

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British Journal of Midwifery, April 2017, Vol 25, No 4
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effects in mothers and infants throughout labour and the postpartum period, has positive feedback on its release, accelerates the progress of labour, increases postpartum maternal adaptations, and enhances satisfaction with infant care and contact. The pre-labour rise in oxytocin receptors in the brain and the uterine muscles maximises these effects.

Intravenous Syntocinon administered during labour can facilitate the birth of the baby, but it has some adverse effects on mothers and their infants (Table 1). Although there is a lack of high-quality up-to-date human research, it has been suggested that Syntocinon hinders the pulsatile secretion of endogenous oxytocin and may disrupt the beneficial effects of endogenous oxytocin. Syntocinon use may have short- and long-term effects in mothers and babies, such as increased perception of pain during labour, impaired breastfeeding, disturbed maternal behaviours and changes in the child development. Considering these potentially life-changing effects on women, further human studies are required.

Further to this, midwives and other childbirth professionals need to exercise caution in using this drug. They should keep their knowledge about Syntocinon up to date, and inform pregnant women about the similarities and differences between endogenous oxytocin and Syntocinon and their powerful role through labour, birth and beyond. In order to minimise the consequences of Syntocinon use, pregnant women should be told about the potential effects of Syntocinon. This will allow women to make informed choices about induction of labour and to seek support when required. Pregnant women should, however, know that some women need induction or augmentation of labour due to fetal, maternal or obstetric indications and there may be few alternatives to Syntocinon (Mishanina et al, 2014).

Childbirth should be a positive experience for women and their families. It is the responsibility of healthcare providers to equip themselves and women with appropriate knowledge to minimise negative outcomes and promote quality of life for women and their families. To this end, healthcare professionals should promote normality and help labouring women boost their endogenous oxytocin levels to facilitate the birth. Breast/ nipple stimulation and sexual activity have been suggested to help promote natural physiological labour and birth. Oxytocin is known as the hormone of love and is secreted during sexual activity. Although research into the role of sexual intercourse as a method of induction of labour is tentative (Kavanagh et al, 2001), it has been shown that breast/nipple stimulation and having sex or an orgasm are positively correlated with higher plasma levels of oxytocin (Salonia et al, 2005). The level of vaginal lubrication and sexual arousal in women, which is correlated with higher levels of oxytocin, is enhanced by stimulating the nipples and breasts (Levin and Meston, 2006). Furthermore, the release of oxytocin into the bloodstream reaches a peak during orgasm resulting in involuntary rhythmic uterine contractions (Komisaruk et al, 2006). In addition to the release of oxytocin during sexual activity and orgasm, semen contains prostaglandins (PGs) that act as modulators, fine-tuning the system (Hertelendy and Zakár, 2004). Research has shown that the concentration of PGs in cervical mucus samples taken within several hours of sexual intercourse is 10–50 times greater than normal (Huleihel et al, 1999). In addition, the amount of PGE delivered into the vagina during sexual intercourse is similar to the amount of the PGs that stimulate cervical ripening and onset of labour (Nuutila and Kajanoja, 1996). These findings, on the other hand, are interesting because a Cochrane review has reported that sexual intercourse does not promote cervical ripening (Kavanagh et al, 2001). It seems logical to conclude that any recommendations given to pregnant women should be on a case by case basis and according to individual circumstances.

Other activity that may assist with natural physiological labour and birth is walking or ambulating during labour. Systematic review of the literature has shown that the duration of first stage of labour is almost 1 hour and 20 minutes shorter for women who are in upright position or walk around during labour (Lawrence et al, 2013). Although there is a need for further research to validate these results for all women in labour, it seems acceptable to advise women to ambulate during labour if they feel comfortable doing so and there are no maternal or fetal concerns requiring the women to stay in bed.

Complementary therapies have attracted the attention of health professionals during recent decades. Despite their popularity, there are controversial reports in the literature regarding their efficacy in inducing labour contraction and decreasing the duration of labour. Acupressure has been reported in clinical trials to reduce the length of the first stage of labour (Mollart

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**Table 1**

<table>
<thead>
<tr>
<th>Complementary Therapies</th>
<th>Evidence of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>Yes</td>
</tr>
<tr>
<td>Massage</td>
<td>Yes</td>
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<tr>
<td>Yoga</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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**Key points**

- Intravenous Syntocinon used to assist with the birth of the baby during labour hinders the pulsatile secretion of endogenous oxytocin
- Intravenous Syntocinon can result in increased perception of pain during labour, impaired breast-feeding, disturbed maternal behaviours, and developmental problems in the child
- Pregnant women should be informed of the potential effects of intravenous Syntocinon in order to make informed decisions about how to manage their labour in consultation with their midwives or doctors
- Midwives and other childbirth professionals should encourage and support a normal physiological birth free of interventions and side effects, when possible
et al, 2015). Nevertheless, further research is required to explore its efficacy in the onset of labour, duration of labour and uterine contractions. Similarly, results of systematic reviews have shown very limited benefit from acupuncture (Smith et al, 2013) and no benefit from homeopathy (Smith, 2003) to induce labour. Their effectiveness has not been shown and there is insufficient evidence to support their use as methods of induction of labour. Before suggesting implications for clinical practice, well-designed trials are required to investigate the role of complementary therapies in labour induction.

In conclusion, providing pregnant women with enough appropriate information will help them make informed decisions about how to manage their labour. In consultation with their midwives or doctors, it can help them choose practical ways of working with their body and hormones, in particular endogenous oxytocin, to maximise their chance of having a physiological birth, free of interventions and side effects. BJM

**CPD reflective questions**

- What knowledge of Syntocin will you need to adequately explain the risk to pregnant women?
- How does the use of Syntocin affect the pulsatile secretion of endogenous oxytocin?
- What are the chief risks of using Syntocin for facilitating labour?


Labour pain relief in women with assisted conception and its effects on labour and birth outcomes

With the improvement of assisted reproduction technology, and greater public awareness, a growing number of children are born to women with a history of infertility (Sutcliffe and Ludwig, 2007). Despite its high success rate, there are concerns about the impact of assisted conception on maternal and neonatal wellbeing. Compared with women who spontaneously conceive, women who undertake assisted conception experience greater levels of depression (Fisher et al, 2012), more negative pregnancy outcomes, unfavourable birth experiences and more negative neonatal outcomes (Giallo et al, 2011; Cooklin et al, 2012; Giallo et al, 2014). Several studies have suggested an association between assisted conception and an increased rate of gestational diabetes, pre-eclampsia and caesarean delivery. Neonatal outcomes have also been reported to be poor: babies born as a result of assisted conception are more likely to be admitted to the neonatal intensive care unit, and have an increased risk of congenital abnormalities, low birth weight and preterm delivery (Hammarberg et al, 2008a; 2008b; McGrath et al, 2010). However, controversial results have been reported by Shevell et al (2005), who indicated no association between assisted conception and fetal growth restriction, or fetal anomalies.

Childbirth has a reputation for being one of the most painful events in a woman’s life (Lowe, 2002). A variety of non-pharmacological complementary approaches have been proposed to assist with the progress of physiological labour through effective pain management. These include, but are not limited to: massage therapy (Hosseini et al, 2013; Bolbol-Haghighi et al, 2016), transcutaneous electrical nerve stimulation (Sluka and Walsh, 2003), acupuncture (Tempfer et al, 1998), acupressure (Lee et al, 2004), yoga and relaxation (Field, 2011), exercise, visualisation, controlled breathing (Levett et al, 2016), reflexology (Smith et al, 2012), music therapy (Taghinejad et al, 2010), water immersion (Benfield et al, 2010), heat therapy and the use of a birth ball (Taavoni et al, 2016). A meta-analysis of 57 studies published from January 1990–December 2012 (Chaillet et al, 2014) showed that non-

Abstract

**Background** Increased use of assisted reproduction technology has resulted in concerns about its impact on maternal and neonatal wellbeing.

**Aims** To evaluate the labour and birth outcomes in women who had and had not undertaken assisted conception and how the use of labour pain relief affected their outcomes.

**Methods** Women who had and had not undertaken assisted conception were studied, and the effects of labour pain relief on labour and birth outcomes evaluated.

**Findings** The results showed that women who had undertaken assisted conception were more likely to have had epidural analgesia during labour. However, after adjusting for country of birth, body mass index (BMI), maternal age, model of care during pregnancy and gestational hypertension, this difference was not statistically significant. Regression analysis showed no differences between the groups in use of oxytocin, mode of birth, episiotomy or tear, postpartum blood loss, Apgar score at 5 minutes and neonatal complications at birth ($P>0.05$).

**Conclusions** These findings demonstrate the factors leading to poor outcomes in women who undertake assisted conception, and will help to reduce obstetric complications in this population.

**Keywords** Assisted conception | Birth | Epidural | Labour | Outcomes | Pain relief

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pharmacological methods to relieve labour pain could offer benefits to women and their newborns without additional harm.

Some women choose to use epidural analgesia to help decrease their stress and pain (Thomas et al, 1982). Use of opiate drugs for epidural analgesia has been reported to prolong second-stage labour (Agrawal et al, 2014) and to be associated with an increased risk of caesarean section (Herrera-Gómez et al, 2017). In contrast, Cochrane reviews (Anim-Somuah et al, 2011; Sng et al, 2014) have shown that early or late initiation of epidural analgesia for labour does not affect labour and birth outcomes.

Despite the increasing rate of assisted conceptions, research comparing labour pain relief in women who had and had not undertaken assisted conception is scarce, and the effect of epidural analgesia on birth outcomes in women who have undertaken assisted conception has been under-studied. Data derived from assisted reproduction technology registries only provide results for overall pregnancy outcomes, not on women’s mode of labour pain relief. To address this existing gap in the literature, this study aimed to evaluate the labour and birth outcomes in women who had and had not undertaken assisted conception and how the use of labour pain relief affects their outcomes.

Methods
Design and ethics approval
This was a retrospective cohort study. Ethics approval was granted from the Human Research Ethics Committee at the Western Sydney Local Health District before the commencement of the study.

Setting and participants
Data for evaluation and analysis were collected from women who gave birth at Westmead Hospital between 1 July 2010 and 30 June 2017. Inclusion criteria were that the woman must have had a singleton pregnancy; given birth to a live, term baby between complete 37 and 43 weeks; and been primiparous. Data from multiparous women, twins or triplets and preterm births were excluded from the study.

Figure 1. Cohort selection

Total number of women who gave birth, 1 July 2010–30 June 2017
(n=39994)

Excluded data (n=28859)
- Parous women (n=22420)
- Pregnancies at 36+6 weeks or earlier (n=3996)
- Twin or triplets (n=1911)
- Incomplete data (n=532)

Analysed data (n=11135)

Primiparous women, spontaneous conception
(n=10560)

Primiparous women, assisted conception
(n=575)
Procedure
Women’s records were selected from the ObstetriX database, an obstetric information system based on the clinical dataset developed in Australia by the New South Wales OBSTET consortium. It is a unique clinical data management tool and is used in most New South Wales Local Health Districts to collect obstetric data. The recorded data were collectively reported as an archetype report and were saved in a Microsoft Excel spreadsheet. The variables extracted from the ObstetriX database were demographic data; obstetric and gynaecological history; medical history; pregnancy, labour and birth outcomes; and the newborns’ characteristics and outcomes.

Statistical analysis
The data were downloaded from the Excel spreadsheet to SPSS Advanced Statistics version 24.0. Descriptive statistics were used to summarise the demographic data. Associations between contributing factors and outcomes were examined using the $\chi^2$-test (or Fisher exact test if applicable) and Student $t$ tests, where appropriate. Univariate and multivariate regression modelling were used to estimate crude and adjusted effects of factors of interest. Gaussian, logistic or multinomial logistic link functions were used for continuous, dichotomous or multicategorical outcome variables, respectively. Odds ratios (ORs) were calculated to report the effect size for logistic models. Differences were considered significant when $P<0.05$. Data preparation and cleaning were performed in Excel and validated through visual review, value range checks, field type checks, and logical checks by researchers. Statistical analyses were performed in R, version 3.1.2.

Results
During the period of data review, there were 39,994 births in the hospital. Data were collected from 11,135 records for the analysis (575 women who had undertaken assisted conception and 10,560 women who had conceived spontaneously) (Figure 1).

The baseline characteristics of the women are shown in Table 1. Compared to women who had spontaneously conceived, women who had undertaken assisted conception were more likely to be older, non-
smokers, under obstetrician or GP-led care during their pregnancy and have a larger body mass index (BMI) \((P<0.001)\). Although the difference in rate of gestational diabetes was statistically significant between the two groups \((P=0.043)\), it was not clinically significant \((0.5\% \text{ vs } 0.1\%)\). There were no differences between the two groups when comparing other baseline characteristics \((P>0.05)\) (Table 1), nor were there differences between the two groups for other medical conditions including renal, endocrine, neurological and autoimmune diseases, or for other antenatal complications, such as abnormal placental site, antepartum haemorrhage after 20th week of pregnancy, fetal growth restriction, fetal anomaly and threatened premature labour \((P<0.05)\) (results not shown in the Tables).

The percentage of women receiving epidural analgesia was higher in women who had undertaken assisted conception \((54.6\%)\) than women who had spontaneously conceived \((46.6\%)\), with significant differences between the two groups \((P<0.001)\). However, after adjusting for country of birth, BMI, maternal age, model of care during pregnancy and gestational hypertension, this difference was not statistically significant \((OR=0.86; 95\% CI=0.72–1.03)\) (Table 2).

Women who had undertaken assisted conception were more likely than women who had spontaneously conceived to undergo cervical ripening before labour \((8.3\% \text{ vs } 4.5\%, \text{ respectively})\), receive oxytocin for induction or augmentation of labour \((67.7\% \text{ vs } 57.5\%, \text{ respectively})\), have an instrumental birth \((35.7\% \text{ vs } 29.4\%, \text{ respectively})\) and have postpartum blood loss more than 500 ml \((16.8\% \text{ vs } 13.3\%, \text{ respectively})\) \((P<0.001)\) (Table 3). No significant differences were found between the two groups in terms of other labour, birth and neonatal outcomes (Tables 3 and 4).

To investigate the role of labour pain relief in maternal and neonatal outcomes, a regression analysis was performed, adjusted only for labour pain relief. Primary results showed that ORs of stage 1 labour duration \((OR=0.10; 95\% CI=0.00–0.03; P=0.023)\), instrumental birth \((OR=0.81; 95\% CI=0.67–0.98; P=0.027)\) and postpartum blood loss of 500–1500 ml \((OR=0.6; 95\% CI=0.39–0.91; P=0.016)\) were less in women who did not receive labour pain relief (results not shown in Tables). However, after adjusting for maternal age, BMI, model of care during pregnancy, cervical ripening before labour and labour pain relief, no statistically significant differences were found between the two groups in terms of use of oxytocin for induction or augmentation of labour, mode of birth, episiotomy or tear, postpartum blood loss, Apgar score at 5 minutes and neonatal complications at birth (Table 5).

**Discussion**

This study investigated labour and birth outcomes in women who had given birth after spontaneous conception and women who had given birth after undertaking assisted conception. The authors evaluated how the use of labour pain relief affected maternal and neonatal outcomes. Results of the study showed that a greater number of women who had undertaken assisted conception were older, overweight or obese and non-smokers. These findings were not surprising, because previous research has shown an association between infertility, obesity (Gesink Law et al, 2007) and older age (Tendais and Figueiredo, 2016).

The findings showed that women who had undertaken assisted conception were more likely than women who had spontaneously conceived to be in the care of an obstetrician or GP. It could be assumed that women with a history of infertility might have other concurrent medical conditions (Palomba et al, 2016) that require them to be in the care of an obstetrician or GP due to a high-risk pregnancy; however, these findings did not support this assumption, as there were no significant differences in the women’s medical conditions and antenatal complications when the two groups were compared. Despite this, it may not be possible to rule out this assumption because women who gave birth before the 37th week of pregnancy were excluded from data collection, and preterm birth might have been due to their antenatal complications.

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**Table 2. Pain management in labour**

<table>
<thead>
<tr>
<th>Type of analgesia</th>
<th>Type of conception</th>
<th>Crude OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assisted (n=575)</td>
<td>Spontaneous (n=10560)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-pharmacological† or no first stage</td>
<td>214 (37.2%)</td>
<td>4520 (42.8%)</td>
<td>Reference</td>
<td>–</td>
<td>Reference</td>
</tr>
<tr>
<td>Intramuscular or intravenous narcotics</td>
<td>47 (8.2%)</td>
<td>1117 (10.6%)</td>
<td>1.13 (0.82–1.55)</td>
<td>0.473</td>
<td>1.04 (0.75–1.44)</td>
</tr>
<tr>
<td>Epidural</td>
<td>314 (54.6%)</td>
<td>4923 (46.6%)</td>
<td>0.74 (0.62–0.89)</td>
<td>0.001</td>
<td>0.86 (0.72–1.03)</td>
</tr>
</tbody>
</table>

Ref. = reference value. OR = odds ratio. * Adjusted for country of birth, BMI, maternal age, model of care during pregnancy and gestational hypertension. † Included breathing and relaxation techniques, massage, water immersion, subcutaneous sterile water injection and nitrous oxide gas.
Table 3. Labour and birth outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Type of conception</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assisted (n=575)</td>
<td>Spontaneous (n=10560)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical ripening before labour, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (prostaglandin gel, Foley catheter)</td>
<td>48 (8.3%)</td>
<td>479 (4.5%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Use of oxytocin for induction of labour, n (%)</td>
<td>389 (67.7%)</td>
<td>6077 (57.5%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Antenatal/intrapartum antibiotics, n (%)</td>
<td>4 (0.7%)</td>
<td>95 (0.9%)</td>
<td>0.780</td>
<td></td>
</tr>
<tr>
<td>Mean duration of first stage of labour ± SD</td>
<td>5.5 ± 3.7</td>
<td>5.7 ± 3.8</td>
<td>0.215</td>
<td></td>
</tr>
<tr>
<td>Mean duration of second stage of labour ± SD</td>
<td>1.5 ± 1.2</td>
<td>1.4 ± 1.4</td>
<td>0.156</td>
<td></td>
</tr>
<tr>
<td>Mode of birth, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vaginal birth</td>
<td>344 (59.8%)</td>
<td>7008 (66.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrumental birth</td>
<td>205 (35.7%)</td>
<td>3109 (29.4%)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Caesarean birth</td>
<td>26 (4.5%)</td>
<td>443 (4.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episiotomy/tears, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No tear</td>
<td>237 (41.2%)</td>
<td>4012 (38.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second degree tear/episiotomy</td>
<td>168 (29.2%)</td>
<td>3215 (30.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third–fourth degree tear</td>
<td>41 (7.1%)</td>
<td>600 (5.7%)</td>
<td>0.099</td>
<td></td>
</tr>
<tr>
<td>Other tears (first degree, clitoral, labial, parauretal, etc)</td>
<td>129 (22.4%)</td>
<td>2733 (25.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpartum blood loss (ml), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>478 (83.1%)</td>
<td>9156 (86.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500–1500</td>
<td>25 (4.3%)</td>
<td>271 (2.6%)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>&gt;1500</td>
<td>72 (12.5%)</td>
<td>1133 (10.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; differences statistically significant at \( P < 0.05 \)

Table 4. Neonatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Type of conception</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assisted (n=575)</td>
<td>Spontaneous (n=10560)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>281 (48.9%)</td>
<td>479 (4.5%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>294 (51.5%)</td>
<td>6077 (57.5%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>19 (3.3%)</td>
<td>282 (2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2500–4000</td>
<td>529 (92%)</td>
<td>9697 (91.8%)</td>
<td>0.481</td>
<td></td>
</tr>
<tr>
<td>&gt;4000</td>
<td>27 (4.7%)</td>
<td>581 (5.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 minutes</td>
<td>9 (1.6%)</td>
<td>154 (1.5%)</td>
<td>0.976</td>
<td></td>
</tr>
<tr>
<td>Neonatal complication at birth</td>
<td>99 (17.2%)</td>
<td>1575 (14.9%)</td>
<td>0.148</td>
<td></td>
</tr>
</tbody>
</table>

Differences statistically significant at \( P < 0.05 \)
The other assumption that could be made is that nulliparous women who undertake assisted conception are likely to be more concerned about their birth outcomes than women who spontaneously conceive, and may be more likely to request a caesarean section, which is also more likely to occur when a woman is in the care of a private obstetrician (Roberts et al, 2000; Gillet et al, 2011). Research has shown that women who undertake assisted conception have a 2.95 times higher risk of planned caesarean birth (Chien et al, 2015); however, the results of this study did not support this association and showed no difference between the two groups in their mode of birth and the rate of their caesarean section. Because this was a retrospective study using patient records, it was not possible to investigate the reason why women who had undertaken assisted conception were more likely to be in the care of an obstetrician or GP. Further prospective studies are needed to clarify this.

This study showed that 54.6% of women who had undertaken assisted conception used epidural analgesia, compared with 46.6% of women who had spontaneously conceived. However, after adjusting for several confounding variables, including country of birth, BMI, maternal age, model of care during pregnancy and gestational hypertension, the odds of having an epidural did not differ between the two groups. This indicated that the type of pain relief used during labour was not solely affected by the type of conception and there were other factors that affected labour pain management techniques. For example, research has shown that giving...
birth without epidural analgesia was associated with unfavourable social and organisational factors, such as labour occurring too quickly, medical contraindication and unavailability of anaesthetists (Le Ray et al, 2008). Another study (Jeschke et al, 2012) reported that first-time labour, the desire for birth without pain, and previous use of epidural analgesia were independent predictors of the use of epidural analgesia in labour. Because this was a retrospective study using patient records, the authors were unable to investigate the social situations of patients, their desire for labour pain relief and the availability of anaesthetists. Nevertheless, it is acknowledged that the choice of labour pain relief is affected by many factors, not only the type of conception.

The χ²-test showed that women who undertook assisted conception were more likely to receive oxytocin during labour, undergo instrumental birth and have postpartum haemorrhage. However, regression analysis adjusted for maternal age, BMI, model of care and epidural analgesia showed no significant difference between women who undertook assisted conception and women who spontaneously conceived, indicating that the dynamics of labour and birth were affected not only by the type of conception, but also by other confounding factors contributing to labour and birth outcomes. For example, research by Adams et al (2015) investigated the role of labour analgesia and showed that women’s use of non-pharmacological pain management decreased the likelihood of their baby being admitted to a special care nursery, and the use of epidural analgesia increased the likelihood of instrumental birth and neonatal complications at birth necessitating admission to a special care nursery. In other research, Carlson et al (2017) evaluated the association between model of care, BMI, and maternal and neonatal outcome. Their study showed that, compared to women with high BMI who were in the care of obstetricians, women with high BMIs who were cared for by a nurse–midwife were less likely to have an operative vaginal birth and a third- or fourth-degree perineal tear, and were more likely to have labour anaesthesia and synthetic oxytocin augmentation. Nevertheless, they reported that the rates of unplanned caesarean birth, postpartum haemorrhage, maternal intrapartum fever and neonatal intensive care unit admission were similar between the two groups.

Implications for practice
The results of this study confirmed that the type of conception was not the sole indicator of the labour and birth outcomes, and that there were many other factors that contributed to the wellbeing of mothers and their newborns. These findings will help inform best practice to support labouring women who undertake assisted conception and provide them with the most appropriate information about the factors that can affect their perinatal outcomes, such as their country of birth, BMI, model of care, medical history and labour analgesia. The results can also help facilitate shared decision-making to help women who undertake assisted conception to receive appropriate care during labour and birth and achieve the most favourable outcomes. This will in turn help to promote the general health and quality of life of these women, followed by significant effects on the wellbeing of the community and society.

Limitations and strengths of our study
This study had limitations that are inherent in the use of administrative data. The retrospective design of the study necessitated the use of routinely collected data. The authors relied on information entered by clinical midwives into a database not purpose-built for this research, and excluded the records of women with missing data, although no difference was found in the baseline demographics (age and country of birth) between excluded and included women. Records of multiparous women, which might have yielded different outcomes, were also excluded from analysis. Despite these shortcomings, the large sample size of this study (11 135 women) adds further evidence of labour and birth outcomes in women who do and do not undertake assisted conception, and how labour pain relief modulates this association. Future research needs to investigate labour and birth outcomes in multiparous women with a history of infertility and assisted conceptions, and should evaluate the use of labour pain relief in these women and how it affects their outcomes.

Conclusion
Use of labour pain relief is associated not only with the type of conception, but also with other factors, such as country of birth, BMI, maternal age, model of care during pregnancy and gestational hypertension. In addition, having undertaken assisted conception is not the sole indicator of oxytocin use during labour, instrumental birth and postpartum haemorrhage, as factors such as maternal age, BMI, model of care and epidural analgesia facilitate this association. These findings provide a better understanding of the management of factors leading to poor outcomes in women who undertake assisted conception, and will help to develop better strategies to reduce obstetric complications in this population.

Declaration of interests: The authors have no conflicts of interest to declare.

Ethical approval: Ethics approval was granted from the Human Research Ethics Committee at the Western Sydney Local Health District.
Women who had undertaken assisted conception were more likely to be older, non-smokers, under obstetrician or GP-led care during their pregnancy and have a larger body mass index (BMI).

The percentage of women receiving epidural analgesia was higher in women who had undertaken assisted conception than women who had spontaneously conceived.

The type of pain relief used during labour was not solely affected by the type of conception and there were other factors that affected labour pain management techniques including country of birth, BMI, maternal age, model of care during pregnancy and gestational hypertension.

The dynamics of labour and some birth outcomes, such as receiving oxytocin during labour, undergoing instrumental birth and having postpartum haemorrhage, were affected not only by the type of conception but also by other confounding factors including maternal age, BMI, model of care and epidural analgesia.

**Funding:** This research was conducted with in-kind support from the Department of Women’s and Newborn Health at Westmead Hospital.

**Review:** This article was subject to double-blind peer review and accepted for publication on 19 February 2018.

**Acknowledgement:** The authors thank the Department of Women’s and Newborn Health at Westmead Hospital for their support to conduct this study.


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CPD reflective questions

- How does assisted conception affect birth outcomes?
- What are factors affecting women’s use of epidural pain relief during labour?
- What are the factors affecting labour and birth outcomes in women who undertake assisted conception?
Late diagnosis of hepatic mesenchymal hamartoma and placental mesenchymal dysplasia

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Abstract
Placental mesenchymal dysplasia (PMD) is a rare condition characterised by placental enlargement, oedematous villi and multiple anechoic cysts. Hepatic mesenchymal hamartoma (HMH) is a benign proliferation of mesenchymal tissue, commonly seen in infants below the age of 2. We report the case of a 28 years old female who was noted to have a fetus with a well-circumscribed cyst on the liver, suggestive of HMH and a large, thickened placenta, with multiple anechoic cysts, consistent with PMD during the third trimester. There were no other structural abnormalities and at 38 weeks she underwent an induction of labour with normal vaginal delivery of a live female infant. While the aetiology is poorly understood, the increased incidence of HMH with PMD and the morphological similarities of the changes seen in both the placenta and liver, suggests a possible common developmental mechanism. There are only 12 other cases of this concurrent pathology in the literature and only one of these had resulted in a term delivery, and ours is the second one to date.

Keywords: anechoic cysts, fetal liver cysts, hepatic mesenchymal hamartoma, placental mesenchymal dysplasia.

A 28-year-old female, gravida 4 para 2, with two previous term spontaneous vaginal deliveries, and no prior history of any medical or surgical conditions, was referred to our tertiary centre for evaluation of a fetal cystic abdominal mass at the level of the cord insertion that was noted at 34 weeks’ gestation. She had an uneventful early pregnancy with a normal morphology scan at 19 weeks’ gestation. The morphology scan images were independently reviewed by a Maternal Fetal Medicine specialist to confirm that there was no prior evidence of this cystic mass that may have been missed.

A formal tertiary scan was performed at 36 weeks which confirmed a large well-circumscribed, heterogeneous, septated cyst in the right lobe of the fetal liver, measuring 4.0 cm × 3.0 cm × 4.0 cm (Figure 1 & 2). The scan also revealed a large, thickened placenta, 17 cm in width, with multiple anechoic spaces, the largest which was 3.0 cm in diameter (Figure 3 & 4). The fetus was otherwise normal with no evidence of hydrops, intra-uterine growth restriction or polyhydramnios. The association of the fetal liver cyst with anechoic placental cysts raised the suspicion of a liver hamartoma in the fetus with associated placental mesenchymal dysplasia. She was monitored closely with weekly serial growth scans which

Figure 1: Axial view of fetal abdomen at 34 weeks showing well-circumscribed, multi-septate nature of the liver cyst, measuring 4 cm × 3 cm × 4 cm in size.
demonstrated that the liver cyst remained stable in size and there was good fetal interval growth.

At 38 weeks' gestation she underwent an induction of labour with an uncomplicated normal vaginal delivery of a live female infant born in good condition. The birthweight was 2.7 kg and the infant was admitted to the special care nursery for observation. She was breastfeeding well and was discharged home day 2 postpartum.

The placental histopathology reported a markedly enlarged placenta, weighing 1.97 kg (>95th centile) with typical features of placental mesenchymal dysplasia.

Post-natally, the infant has been monitored closely by paediatric surgeons and the liver harmartoma was noted to be stable in size. Liver function tests and tests of hepatic synthetic function were all normal. Serial measurements of alpha-fetoprotein levels in the infant, which can be raised with some liver neoplasms, have also remained normal since birth. Currently, there is a plan to operate on the lesion at 1 year of life.

Placental mesenchymal dysplasia (PMD) is a rare condition characterised by sonographic features of a thickened and enlarged placenta with multiple hypoechoic, grape-like cystic areas. The diagnosis can only be confirmed histopathologically as PMD can often be mistaken for gestational trophoblastic disease due to their similar sonographic features. Other fetal anatomical conditions can often co-exist with PMD including Hepatic Mesenchymal Hamartomas (HMH), with up to a dozen cases reported in the literature.

HMH is a rare, benign, proliferative lesion of mesenchymal tissue of the liver, with the majority being diagnosed in infants below the age of 2 years. The striking feature is the morphological similarity of the oedematous, myxoid changes seen in both the placenta and liver with these two conditions. While the aetiology is poorly understood, the increased incidence of HMH with PMD does suggest a possible common developmental mechanism.

Although it was not clearly noted in our case report, current data does imply that the placental changes precede the development of HMH. One possible theory suggested by Lennington et al., is that the multiple thrombi present in the placental vasculature embolise to the fetal liver resulting in the development of HMH as a reactive process to the associated ischaemia.

Androgenetic/biparental mosaicism has also recently come to light as a possible cause for the synchronous development of PMD and HMH. The nature of the mutation and relative proportion of androgenetic cells present may explain the large spectrum of disease that exists and why these two conditions may occur together, but not always.

Owing to the rarity of these conditions, particularly in conjunction with each other, there is limited data on the antenatal and long term post-natal outcomes for these fetuses. However, it does appear that the co-occurrence of PMD and HMH is associated with worse outcomes than if these conditions were
to occur individually and could potentially result in prematurity, hydrops, IUGR and fetal demise.\textsuperscript{2,5}

While there is no consensus on how to manage these cases antenatally, it can be agreed that heightened surveillance with serial growth scans and fetal wellbeing assessments, is required in the perinatal period to reduce fetal morbidity and mortality. There may also be a role for consideration of early delivery and ultrasound guided percutaneous decompression of the HMH if other concerning features such as rapid enlargement with associated mass effect, hydrops, or growth abnormalities are also present.\textsuperscript{6}

In conclusion, we describe a case of a late diagnosis of PMD with HMH in which there was a good outcome for the fetus. There are only 12 other cases in the literature and only one of these had resulted in a term delivery, and ours is the second one to date. This may be a reflection of the poor prognosis or a publication bias and this requires further clarification.

References
MANAGEMENT OF HEREDITARY FRUCTOSE INTOLERANCE IN PREGNANCY

Araz Boghossian1*, Indika Alahakoon1, Michel Tchan1

1Westmead Hospital

Background: Hereditary fructose intolerance (HFI) is a rare autosomal recessive disorder of metabolism, caused by deficiency of Aldolase B activity in the liver and kidney. Ingestion of fructose results in hypoglycaemia and symptoms of abdominal pain and vomiting. Repetitive fructose exposure leads failure to thrive, renal and hepatic failure and increased mortality. Large exposures are potentially fatal.

Method: Case review.

Results: This 24 year-old woman was diagnosed with HFI at eight years of age. She presented in her first pregnancy at eight weeks gestation. Her pregnancy was managed by the maternal fetal medicine team in conjunction with a clinical geneticist and an endocrinologist. Early pregnancy was complicated by hypoglycaemic episodes that required hospitalisation. These were treated with dietary modifications and mannose supplementation. The patient had a body mass index of 27 and weight gain of 16 kilo-grams in pregnancy. Antenatal pharmacy review of all potential medications was undertaken, revealing many potentially dangerous medications. The patient presented in spontaneous labour at 39 weeks gestation and progressed to a Ventouse delivery of a 3735 g male infant. Post-partum haemorrhage of 2200 ml occurred secondary to uterine atony. The infant was transferred to the neonatal intensive care unit following an episode of hypoglycaemia at four hours.

Conclusions: HFI is a rare medical condition and management in pregnancy requires multidisciplinary input with unique considerations and close monitoring.
MANAGEMENT OF SEVERE IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION IN THIRD TRIMESTER PREGNANCY: A CASE REPORT

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Background: Idiopathic Pulmonary Arterial Hypertension (IPAH) is a rare, progressive disease with significant morbidity and mortality. Exacerbated by pregnancy, this life-threatening illness is associated with greater than fifty percent mortality in pregnancy.

Methods: We present rare, multi-disciplinary management of a 28-year-old nulliparous woman, who was diagnosed with severe IPAH and subsequently achieved a vaginal birth. The women presented with a significant reduction in exercise tolerance and orthopnoea in the third trimester. A trans-thoracic echocardiogram identified severe pulmonary hypertension, severe right ventricular dilatation, impaired systolic function and a pulmonary pressure of 101mmHg at thirty-six weeks gestation. Under guidance of a highly skilled, multi-disciplinary team consisting of ICU, Anaesthetic, Cardiology, Respiratory, Maternal Fetal Medicine and Midwifery staff, the patient was medically stabilised. A pulmonary artery catheter was inserted to measure pressures accurately prior and during delivery.

Results: A holistic delivery plan was formulated and a successful labour and vaginal delivery (via ventouse) was undertaken in an operating theatre with ECMO capacity. Post-partum both mother and child recovered well. The woman was commenced on tadalafil, macitentan and prostacyclin. Her pulmonary pressures and exercise tolerance were seen to improve. She was discharged home and is stable in her cardiac status.

Conclusions: Multi-disciplinary, holistic approach to management can achieve positive outcomes in complex maternal cardiac conditions such Idiopathic Pulmonary Arterial Hypertension.

References:
Neonatal endotracheal intubation is commonly accompanied by significant disturbances in physiological parameters. The procedure is often poorly tolerated, and multiple attempts are commonly required before the airway is secured. Adverse physiological effects include hypoxemia, bradycardia, hypertension, elevation in intracranial pressure and possibly increase in pulmonary vascular resistance. Use of premedications to facilitate intubation has been shown to reduce but not eliminate these effects. Other important preventative factors include adequate training of the operators and guidelines to limit the duration of attempts. Pre-intubation stabilisation with optimal bag and mask ventilation should allow for better neonatal tolerance of the procedure. Recent research has described significant mask leak and airway obstruction compromising efficacy of neonatal mask ventilation. Further research should help in elucidating mask ventilation techniques which minimise mask leak and airway obstruction.

Key words: endotracheal intubation; mask ventilation; neonate; premedication.

Introduction

Endotracheal intubation is one of the most commonly performed procedures in neonatal intensive care units. Indications include neonatal resuscitation, management of respiratory failure, surfactant administration and securing the airway preoperatively or in encephalopathic neonates. This procedure is commonly complicated by a number of serious adverse physiological effects. Endotracheal intubation randomised into three groups (no premedications, atropine, muscle relaxant and anticholinergic drug. Published studies have documented following adverse physiological effects of this procedure (summarised in Table 1):

<table>
<thead>
<tr>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Endotracheal intubation is commonly required in preterm neonates. This skill is difficult to master, and the procedure is commonly accompanied by significant hypoxemia and bradycardia. Other reported adverse physiological changes include systemic and intracranial hypertension with a potential for intraventricular haemorrhage in preterm neonates.</td>
</tr>
<tr>
<td>• Use of premedications for elective/semi-elective intubations reduces the duration and magnitude of these adverse physiological events. Premedications commonly include an analgesic, muscle relaxant and anticholinergic drug.</td>
</tr>
<tr>
<td>• Adequate training of operators and supervision of the procedure with strict limits placed on the duration of an attempt should help in minimising the effects on heart rate and oxygenation. Pre-intubation stabilisation with bag and mask ventilation minimising mask leak and airway obstruction should lead to improved neonatal tolerance of the procedure.</td>
</tr>
</tbody>
</table>

Physiological Effects of Laryngoscopy and Endotracheal Intubation

Direct laryngoscopy can be a distressing procedure often triggering autonomic reflexes leading to apnoea, bradycardia, hypoxemia and systemic as well as intracranial hypertension. Distortion of the pharynx and upper airway can occur leading to airway obstruction. Oxygen desaturation commonly occurs with intubation, and its severity may relate to these iatrogenic factors combined with the patient’s underlying illness. If the neonate is awake and vigorous, the attempts are resisted leading to increased intrathoracic pressure impeding venous return. This can lead to intracranial hypertension. For the purpose of this article, an ‘awake’ intubation is defined as a procedure performed without any premedication or with vagolytic agent only. Published studies have documented following adverse physiological effects of this procedure (summarised in Table 1):

Elevation in intracranial pressure

Multiple studies have documented that ‘awake’ intubation is associated with a rise in intracranial pressure (ICP). Raju et al. studied ICP by using a fibreoptic transducer placed over the anterior fontanelle (AF) in 10 infants undergoing surgery. Four had ‘awake’ intubation. Others had D-tubocurarine. Both the groups had increase in ICP although this was of a much greater magnitude in the ‘awake’ group. They suggested causative factors such as hypoxia (±hypercapnia), extension of the head causing venous obstruction and increased intrathoracic pressure due to infant struggle. Kelly et al. studied 30 neonates undergoing nasotracheal intubation randomised into three groups (no premedications, atropine only, atropine and pancuronium). All three groups had significant increase in ICP measured by a fibreoptic sensor over the AF.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient ages</th>
<th>Patient no</th>
<th>Study type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raju et al.¹</td>
<td>7 days–10 months</td>
<td>10</td>
<td>Monitoring of ICP during intubation prior to surgery (Half ‘awake’, half had curare)</td>
<td>Rise in ICP in both the groups, much greater in the ‘awake’ group</td>
</tr>
<tr>
<td>Kelly et al.²</td>
<td>Neonates 25–40 weeks GA</td>
<td>30</td>
<td>Randomised study comparing atropine, atropine + pancuronium and control prior to intubation</td>
<td>Atropine + pancuronium group had least changes in ICP and HR</td>
</tr>
<tr>
<td>Friesen et al.³</td>
<td>Premature neonates</td>
<td>12</td>
<td>Monitoring of ICP during intubation. Six received atropine only; six received atropine, pancuronium and an anaesthetic</td>
<td>All groups had rise in BP and fall in TcPO₂</td>
</tr>
<tr>
<td>Stow et al.⁴</td>
<td>Infants (&lt;8 weeks of age)</td>
<td>24</td>
<td>Monitoring of ICP, HR and BP during intubation</td>
<td>Rise in AF pressure only in the former group</td>
</tr>
<tr>
<td>Barrington et al.⁵</td>
<td>Preterm neonates</td>
<td>20</td>
<td>Randomised study comparing atropine with atropine + suxamethonium for intubation</td>
<td>Both groups had rise in ICP with greater rise in the &quot;awake&quot; group</td>
</tr>
<tr>
<td>Millar et al.⁶</td>
<td>1–34 days</td>
<td>13</td>
<td>Randomised study comparing ‘awake’ intubation with thiopentone + suxamethonium, Both groups had atropine</td>
<td>No significant change in HR and BP</td>
</tr>
<tr>
<td>Marshall et al.⁷</td>
<td>Preterm neonates</td>
<td>10</td>
<td>Observational study of physiological parameters during intubation</td>
<td>Bradycardia, hypoxemia and hypertension observed</td>
</tr>
<tr>
<td>Bhutada et al.⁸</td>
<td>Term neonates</td>
<td>30</td>
<td>Randomised study comparing thiopentone with placebo for intubation</td>
<td>Less effects on HR and BP in the medicated group</td>
</tr>
<tr>
<td>Lemyre et al.¹⁰</td>
<td>Term and preterm neonates</td>
<td>34</td>
<td>Randomised study comparing morphine with placebo for intubition</td>
<td>Longer hypoxemia in the morphine group</td>
</tr>
<tr>
<td>Oei et al.¹¹</td>
<td>Neonates 25–40 weeks GA</td>
<td>20</td>
<td>Randomised study comparing intubation with morphine, atropine and suxamethonium with ‘awake’ intubation</td>
<td>Faster intubation in premedicated neonates, greater bradycardia in the ‘awake’ group</td>
</tr>
</tbody>
</table>

AF, anterior fontanelle; BP, blood pressure; GA, gestational age; HR, heart rate; ICP, intracranial pressure; TcPO₂, transcutaneous oxygen tension.
The group receiving pancuronium had the least increase. Friesen et al.\textsuperscript{3} measured AF pressure in 12 neonates undergoing intubation. Six received atropine, and six received pancuronium and an anaesthetic in addition. A significant rise in ICP was seen only in the first group. Stow et al.\textsuperscript{3} studied ICP in awake and anaesthetised infants undergoing intubation and concluded that AF pressure increased significantly during intubation and this was partially attenuated in the anaesthetised group. Barrington et al.\textsuperscript{5} studied 20 preterm neonates randomised into two groups (atropine only and atropine + suxamethonium). Intracranial hypertension was prevented by premedication with suxamethonium. Millar et al.\textsuperscript{6} compared ICP in ‘awake’ intubation and intubation under thiopentone and suxamethonium. There was a significant rise in ICP in ‘awake’ intubations only.

Duration of raised ICP was generally brief with one study reporting a mean duration of 28 s.\textsuperscript{1} Many of these studies comment on the potential increased risk of intra-ventricular haemorrhage with raised ICP.\textsuperscript{1,3,5,6} although none have documented this. It is unclear if this brief rise can contribute to intra-ventricular haemorrhage and we could not find any study exploring this link.

In summary, ‘awake’ intubations are associated with a significant rise in ICP. This is largely counteracted by premedication with neuromuscular relaxants with or without an anaesthetic. Muscle relaxation works by abolishing the infant struggle which can lead to an increase in cerebrovenous pressure.\textsuperscript{2}

### Elevation in systemic blood pressure

Marshall et al.\textsuperscript{7} noted a significant rise in systolic blood pressure (BP) with laryngoscopy and ‘awake’ intubation in preterm neonates. They attributed this to infant struggle and increased sympathoadrenal activity. In a randomised trial\textsuperscript{10} to evaluate thiopentone for intubation, a rise in mean BP was reported in the placebo group only. Khammash et al.\textsuperscript{9} studied 28 infants randomised to four groups (atropine, atropine + suxamethonium, atropine + fentanyl, atropine + suxamethonium + fentanyl) and noted rise in mean BP of ≥20% in the first two groups. In six neonates with ‘awake’ intubation, authors noted significant increase in systolic BP which was not seen with the use of pancuronium and an anaesthetic. Rise in mean BP with intubation was also seen by other investigators.\textsuperscript{2,5} Lemyre et al.\textsuperscript{10} noted bradycardia with greater severity in the ‘awake’ group. Bhutada et al.\textsuperscript{6} noted bradycardia in the ‘awake’ group but gradual increase in HR in the thiopentone group.

Other different patterns of changes in HR have been noted. Millar et al.\textsuperscript{6} recorded significantly elevated HR in the ‘awake’ group with laryngoscopy and decrease in HR in the medicated group. Barrington et al.\textsuperscript{5} showed expected tachycardia with atropine but no changes with laryngoscopy. Stow et al.\textsuperscript{3} did not show any significant changes in HR with the procedure.

In conclusion, bradycardia is commonly seen with intubation as a result of vagal stimulation and if the procedure is prolonged, then as a consequence of hypoxemia as well.

### Elevation in pulmonary vascular resistance

Measurements of pulmonary vascular resistance have not been reported in neonates undergoing endotracheal intubation likely because of the technical difficulty inherent in such a measurement. Pulmonary hypertensive responses have been reported in older infants and children with congenital heart disease\textsuperscript{13,14} with intubation or tracheal suctioning. It is uncertain whether neonates have this type of response with tracheal intubation.

### Development of hypoxemia

In their study on ‘awake’ intubations in preterm neonates, Marshall et al.\textsuperscript{7} noted a significant drop in transcutaneous oxygen (TcO\textsubscript{2}) tension with the procedure. This was thought to be due to apnoea resulting from vagal stimulation or airway obstruction because of neck extension and mechanical pressure on the laryngopharyngeal region. Similar findings were reported by Kelly et al.\textsuperscript{2} Profoundly low levels of oxygen saturation have been reported with intubation with mean values of 58% and 60% in ‘awake’ and premedicated groups, respectively.\textsuperscript{11} Pokela et al.\textsuperscript{12} report the lowest recorded SpO\textsubscript{2} value of 28% in the ‘pethidine’ group and 45% in the ‘alfentanil + suxamethonium’ group. Majority of studies have not shown prevention of hypoxia by using premedication.\textsuperscript{2,8,11} Lemyre et al.\textsuperscript{10} noted longer duration of hypoxemia in the morphine group as compared with the placebo group. Barrington et al.\textsuperscript{5} found less decrease in oxygenation with the use of suxamethonium.

To summarise, laryngoscopy and intubation are associated with significant falls in oxygen saturation in neonates. Measures to reduce the duration and number of intubation attempts may be beneficial in limiting this adverse effect.

### Changes in heart rate

Laryngoscopy and intubation are frequently accompanied by decrease in heart rate (HR) which can be as much as 43% decline from baseline in ‘awake’ intubation with levels as low as 41 beats per minute (bpm).\textsuperscript{11} No data could be found regarding duration of bradycardias. Marshall et al.\textsuperscript{7} described changes in HR (predominantly bradycardia) thought to be due to vagal stimulation and concomitant hypoxemia. Bradycardia during intubation has also been noted by other investigators.\textsuperscript{2,8,10} Significant bradycardia was noted during intubation by Kelly et al.\textsuperscript{2} which was prevented with the use of pancuronium and atropine. It is notable that in the group receiving atropine alone, HR still decreased significantly. Bradycardia during the procedure has been noted in a majority of neonates\textsuperscript{10} without improvement with morphine premedication. Oei et al.\textsuperscript{10} noted both the groups (‘awake’ and medicated) having bradycardia with greater severity in the ‘awake’ group. Bhutada et al.\textsuperscript{6} noted bradycardia in the ‘awake’ group but gradual increase in HR in the thiopentone group.

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### Physiological Effects With InSurE (Intubation, Surfactant Administration and Extubation) Procedure

In recent years, practice of InSurE has increased in an effort to minimise duration of mechanical ventilation in preterm neonates. Van den Berg et al.\textsuperscript{15} studied changes in regional cerebral oxygenation and amplitude integrated electroencephalography during...
the procedure. An opioid was used as premedication. Whilst no adverse effect on cerebral oxygenation was seen, the authors noted a sustained negative effect on the electrical activity on the amplitude integrated electroencephalography.

**Strategies to Reduce Physiological Disturbances Associated with Intubation**

In view of the preceding discussion, it is desirable to reduce these perturbations of homeostasis associated with intubation. In the following section, we summarise the available literature about the strategies used to achieve this objective.

**Use of premedications**

As can be gleaned from the preceding discussion, multiple studies have evaluated various classes (sedative-analgesic, muscle relaxants, anaesthetic agents and anticholinergic) of medications either singly or in combination prior to intubation to see if it facilitates the process. Given the beneficial effects of premedication in majority of these studies, current guidelines recommend using premedications for all non-urgent endotracheal intubations in newborns. Another review concluded that routine premedication for elective intubation in neonates produces more optimal intubation conditions (fewer attempts and shorter times) and less potentially harmful physiological fluctuations and pain. They recommend using a potent opiate or thiopentone as the drug combination of choice. An anticholinergic has also been used to counteract the vagal stimulation in many studies.

Given this evidence, there has been a significant increase in the use of premedications prior to non-urgent neonatal intubations. In a telephonic survey conducted in the UK, it was noted that only 37% of the neonatal units gave any sedation before intubation. In a similar survey conducted in 2007, 93% of the units provided premedication prior to intubation. Similar findings have been reported in another telephone survey performed in the UK. However, the rate of haemodynamic complications with one of the most commonly used drug regimens (morphine, atropine and suxamethonium) still remains high, suggesting that additional measures are required to facilitate intubation.

**Training of operators**

Neonatal intubation is a difficult skill to master. Studies have shown that success rates for the procedure improve as trainees progress through their training in paediatrics or emergency medicine. One study noted higher success rates and decreased duration of successful attempts as the level of experience of the operators increased. The study included residents, fellows and consultants.

In light of these findings, it is clear that adequate training should be provided to paediatric trainees to learn this important skill. However, real-life opportunities are getting limited now as continuous positive airway pressure is used more often as respiratory support for preterm neonates and routine endotracheal suctioning of neonates born through meconium stained amniotic fluid is no longer recommended. Recent literature has emphasised the value of simulation-based training in enhancing resuscitation skills. Availability of manikins with airway anatomy resembling that of term, very preterm and extremely preterm neonates, is highly desirable. This alone may not be sufficient, however, as improved performance in the simulation environment may not be transferable to the clinical setting. In a recent randomised trial, videolaryngoscopy has shown promise in improving success rates of neonatal trainees for endotracheal intubation. Videolaryngoscopy allowed an instructor to share the view and guide the trainee as needed.

**Limiting the duration of intubation attempts**

Neonatal resuscitation guidelines recommend limiting the intubation attempts to 20 s to minimise the physiological disturbances. Studies have suggested that majority of intubation attempts exceed this limit even in expert hands. It may be prudent to individualise this time limit guided by observations of HR and oxygen saturation (SpO2) as timing of deterioration can be highly variable. No evidence-based recommendation can be made at this stage as to when to resort to mask ventilation in the event of a difficult intubation when HR/SpO2 start falling. Until more data are available, units should devise their own guidelines in this regard (e.g. abandon an attempt when HR/SpO2 decrease by >20% from the baseline).

**Stabilisation with optimal mask ventilation prior to intubation**

O’Donnell et al. showed that the pre-intubation condition of the neonate had a great bearing on the likelihood of deterioration during the procedure. The more unwell the neonate at the time of intubation (as indicated by lower HR and SpO2), the more likely they were to deteriorate during the procedure. It stands to reason then that pre-intubation stabilisation with optimal bag and mask ventilation should lead to a smoother procedure. It must be emphasised that bag and mask ventilation is a difficult skill to master and often poorly performed unwittingly. Research in the last few years has highlighted the issues of mask leak and airway obstruction during mask ventilation. These can be difficult to identify clinically. Hence, attempts to recognise these are required to optimise mask ventilation so that corrective actions could be taken for example repositioning the neonate and reapplying the mask. In this regard, use of a respiratory function monitor is exceedingly helpful. Finer et al. have also used a colorimetric CO2 detector to identify airway obstruction.

There is evidence that educational workshops on neonatal resuscitation improve outcomes. Conducting these workshops and emphasising on pre-intubation stabilisation with mask ventilation for paediatric and emergency medicine trainees are likely to lead to decreased instability during intubation.

In a neonatal manikin study, Tracy et al. showed that mask leak could be halved with a two-person technique as compared with one-person method whilst using a t-piece resuscitator. Wood et al. have shown that participant instruction coupled with demonstration improves mask leak. They also identified the optimal mask hold in this manikin study for two different types of masks. Wilson et al. compared three different types of mask hold in a manikin study without significant differences in mask leak. O’Shea et al. have studied dimensions of the faces of preterm infants and...
concluded that the smallest size of some brands of mask is too large for the tiniest of infants. This research may stimulate development of smaller masks.

Dawson et al. compared self-inflating bag with a positive end-expiratory pressure (PEEP) valve, a T-piece resuscitator and a flow inflating bag to evaluate the delivery of peak inspiratory pressure and PEEP in a manikin model. They concluded that a T-piece provides the most accurate and consistent peak inspiratory pressure and PEEP during the positive pressure ventilation. Figure 1 illustrates a suggested schema for neonatal tracheal intubation in neonatal intensive care unit.

**Strategies for intubation in delivery room**

Intubation in the delivery room can be very different from a controlled intubation in the neonatal intensive care unit as it is often needed on an emergent basis, and premedications are usually not feasible. Training of operators in optimal mask ventilation and intubation, as given in the previous discussion, is critical in facilitating this skill. Availability of a person to monitor HR and SpO₂ and call for halting the procedure with a significant deterioration is also vital.

**Summary**

A variety of adverse physiological effects are commonly seen with laryngoscopy and intubation in neonates. Use of premedications helps in facilitating the procedure. Supervised training of junior doctors is needed so that the procedure can be performed in a shorter time frame. For non-emergent intubations, it is essential that the neonate is stabilised with optimal bag and mask ventilation prior to the procedure to improve their tolerance. Further research is required to refine neonatal mask ventilation techniques. Studies on the impact of neonatal intubation (including InSurE technique) on cerebral oxygenation are also warranted.

**References**


Neonatologist performed point-of-care bowel ultrasound: Is the time right?

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Abstract

Introduction: This review acquaints neonatal clinicians using point-of-care ultrasound with a range of pathological bowel ultrasound findings, with the aim to promote utility of this skill as a diagnostic assessment tool in diseased neonatal intestinal states.

Overview: A range of normal and pathological bowel ultrasound findings are illustrated with case examples from our neonatal intensive care unit. The technical challenges of lack of familiarity with sonographic appearance of bowel (healthy and diseased), occurrence of gas artefacts and requirements of high-resolution linear transducer probes are described to allow the development of skills amongst neonatologists trained in point-of-care ultrasound. Plain abdominal radiography continues to remain the standard investigation to differentiate benign bowel states such as continuous positive airway pressure (CPAP) belly syndrome in preterm infants from life-threatening pathological intestinal states such as necrotising enterocolitis. Although plain radiography is the gold standard modality in the evaluation of neonatal diseased bowel states, real-time point-of-care bowel ultrasound performed in conjunction can provide valuable information on bowel peristalsis, bowel wall thickness and bowel vascularity. Abnormal configuration of superior mesenteric vessels on colour Doppler can alert the clinician to the diagnosis of neonatal intestinal malrotation-a time critical emergency.

Conclusion: Further research is needed to explore true-negative and true-positive predictive values of bowel ultrasound. However, with expansion of knowledge, appropriate training of techniques, neonatologists will be able to enhance their diagnostic acumen by performing point-of-care bowel ultrasound in conjunction with plain radiography in the evaluation of broad array of neonatal intestinal states.

Keywords: neonatologists, bowel ultrasound, point of care.

Introduction

The potential for use of bowel ultrasonography (BUS) in the evaluation of paediatric diseased bowel states has been well recognised. Whilst plain abdominal radiography is the gold standard modality for diagnosis, monitoring and guiding management of suspected diseased bowel state in neonates, there is a growing interest in the utility of BUS. The use of BUS in the diagnosis of necrotising enterocolitis (NEC) has steadily increased worldwide over the last 12 years, particularly in the hands of the radiologists.1 There is compelling evidence correlating with clinical presentation and pathological bowel findings intraoperatively.2,3

In 2011, neonatal clinician-performed ultrasound (CPU) was formalised in Australia and New Zealand in association with The Australian Society of Ultrasound in Medicine (ASUM). Neonatal trainees undergo rigorous hands-on training in performing cranial and cardiac ultrasound for 2 years or more to obtain certification in clinician-performed ultrasound (CCPU).4 Point-of-care ultrasound, performed by trained neonatologists, now has an established role in the clinical management of sick neonates. Whilst assessment of functional changes in cardiac state, intracranial structural injuries such as intraventricular haemorrhage using point-of-care ultrasound is well established, knowledge of point-of-care BUS is a growing area of interest amongst neonatologists.
Identifying gastrointestinal obstruction or perforation presents as critical, time-sensitive scenarios for neonatal clinicians. Also, a common scenario faced by neonatologists is the occurrence of abdominal distension, feed intolerance in preterm infants on respiratory support with continuous positive airway pressure (CPAP) ventilation. This benign gaseous abdominal distension is called CPAP belly syndrome and often necessitates differentiation from life-threatening bowel conditions such as NEC. The use of point-of-care abdominal ultrasound can be a very valuable clinical tool in these scenarios. BUS can enhance diagnostic accuracy of diseased neonatal bowel states in conjunction with clinical assessment and findings from plain abdominal radiography.

BUS studies in adult patients have shown that diseased bowel is easier to image than healthy normal bowel. Similar findings have been reported in diseased neonatal bowel states such as NEC. In diseased neonatal bowel states, often motility is decreased, bowel wall thickened, which appears larger and easier to see. Familiarity with the sonographic appearance of the normal bowel pattern, meticulous use of technique (e.g. use of high-resolution linear transducer probes) and using techniques to obscure the gas artefacts are essential to identify pathological appearance of the bowel on ultrasound. Despite these challenges, real-time BUS provides crucial information on bowel peristalsis, vascularity, bowel wall thickness, the presence of free fluid within the abdominal cavity, all of which can help differentiate healthy from diseased bowel state and without any ionising radiation effects.

The objective of this review was to firstly discuss BUS as a clinical tool in neonatal bowel assessment. Secondly, we describe a range of pathological BUS findings obtained when performing point-of-care BUS in our Neonatal Intensive Care Unit for a range of acute intestinal emergencies.

**Technical aspects for performing BUS**

One of the technical challenges in performing BUS in neonates is the difficulty in evaluating bowel in its physiological state. Ongoing enteral feeds with the use of respiratory support such as CPAP in preterm infants often result in reverberation gas artefacts. These artefacts appear as transverse lines on the imaging screen obscuring the sonographic appearance of the bowel.

Clear anatomical appearance of the bowel is often difficult to obtain until these gas shadows resolve. Gentle compression of the abdominal wall using the transducer probe and repositioning the infant to the lateral side can improve bowel visibility.

Meticulous technique and following a structured protocol are vital to reproduce the imaging findings and maintain reliability. Recently, Faingold (2018) published on the technical aspects of performing abdominal ultrasound and colour Doppler assessment of bowel viability in NEC, providing a comprehensive description of the technique and sharing his practical experience.

High-resolution liner probes 12–20 MHz are desirable to perform BUS. In our cases, BUS was performed using the 15 MHz linear transducer probe to obtain grey scale images of the bowel, portal venous gas, free fluid within abdominal cavity and locate the superior mesenteric vessels. Colour Doppler assessment was then performed to determine bowel vascularity and confirm the anatomical location of the superior mesenteric vessels.

**Appearance of normal neonatal BUS pattern**

**The normal bowel appearance**

The normal sonographic appearance of the bowel also called as the ‘gut signature’ describes typically the appearance of alternating hyperechoic and hypoechoic layers on ultrasound imaging that arise from its highly stratified histological appearance of the bowel wall. Anatomically, these layers from innermost to outermost are superficial mucosa (echogenic); muscularis mucosa (hypoechoic); submucosa is the thickest layer (echo-genic); muscularis propria (hypoechoic); and the outermost layer serosa (echogenic). Sonographic pattern recognition of the normal gut signature distinguishes bowel from the adjacent structures. Disruption of this sonographic pattern aids in the diagnosis of bowel pathology. Normal neonatal bowel appearance (gut signature) shows a particularly prominent hypoechoic halo, which is thought to represent the muscularis propria.

Highly echogenic dots seen within the lumen of the bowel are produced due to the presence of intraluminal gas which is a normal finding within the bowel lumen. Although there are five layers of the bowel wall described in the literature, only three layers are usually identifiable on BUS in a neonate, the most prominent being the hypoechoic layer formed by the muscularis propria (Figure 1).

**Bowel wall thickness**

Bowel wall thickness varies with gestational age. Faingold et al. (2005) reported bowel wall measurements ranging from 1.1 to 2.6 mm in 30 infants (gestational age 24–41 weeks) with healthy bowel. Bettina Bohnhorst (2013) reported similar findings of normal bowel wall measurements ranging from 1.3 to 2.0 mm in healthy preterm infants. Bowel wall thinness <1 mm is highly suggestive of bowel ischaemia in diseased infants with NEC. A recent meta-analysis by Cuna et al. (2018) described cut-off values to define bowel wall thickening as >2.5 to >2.7 mm in various studies.

We conclude then that normal bowel wall thickness ranges from 1 to 2.6 mm. Bowel wall measurements of >2.6 mm would classify as thickened, and any measurement <1 mm would classify as thinned, both suggesting pathological bowel states. Bowel wall thinning <1 mm results from ischaemia or necrosis. In neonates, thickening of the bowel wall >2 mm should be considered suspicious; this thickening is usually accompanied by an increase in echogenicity. Bowel wall measurements should be taken in relaxed bowel segments (Figure 2).
Bowel motility dysfunction remains a major concern in preterm neonates. Examination using traditional auscultation of bowel in neonates is limited by examiner skill, inability to reproduce and objectivity of assessing peristalsis quality. Recently, it has been feasible to use automated assessment of bowel sounds using digital stethoscopes for extended periods to assess gut peristalsis. However, noise interference is a limitation of this method.\(^1\)\(^,\)\(^2\) Ultrasound is a valuable tool in the detection of bowel peristalsis. Normal bowel peristalsis appears more than 10 times per minute\(^3\) and can be visualised in real time as a ‘worm-like motion’. This characteristic opening and closing of the bowel lumen ‘swirling movement’ displacing the echogenic dots within the lumen seen in real-time represents normal bowel peristalsis on BUS and is often easily appreciated despite gas artefacts.

**Vascularity on BUS**

Real-time BUS has the added advantage of assessing bowel wall vascularity, which cannot be assessed on plain abdominal radiography. Faingold *et al.*\(^8\) assessed bowel wall perfusion (BWP) by counting the number of dots on colour Doppler (CD) signal/cm\(^2\) and forming standardised squares on areas of interest on the bowel images using a four-quadrant approach. Normal BWP was classified as 1–9 CD signal dots detected per square cm. Bowel wall perfusion is considered to be present when these CD signals are reproducible or confirmed on pulsed Doppler waveforms.\(^1\) BWP is interpreted to be absent when no CD signal is detected at the slowest possible velocity.\(^9\) The slowest possible velocity on Colour Doppler reported in the study by Faingold *et al.* was 0.029 m/s.\(^8\) Interpretation of absent colour Doppler signal, suggestive of avascular bowel wall, is potentially prone for observer error. Reduction to the lowest possible velocity on the colour Doppler is crucial to confirm this finding. Considering that oxygenation and perfusion are both likely to be reduced in the event of absent bowel wall perfusion; no study so far has compared absent bowel wall perfusion to regional oxygen saturation using near-infrared spectroscopy (NIRS) to detect intestinal viability. The absence of BWP as evidenced by no CD signals on Doppler Ultrasound, in the hands of an experienced operator using standardised techniques, is highly suggestive of severe intestinal disease.

**Appearance of neonatal BUS pattern in some of the acute intestinal diseased states**

Identifying developmental obstructions of the intestine is a diagnostic challenge to the neonatologist with a myriad of possible underlying pathologies ranging from complete to incomplete obstructions such as stenosis, atresia and malrotation resulting in volvulus.
Intestinal atresia
BUS can be utilised in the early diagnosis of intestinal atresia as natural contrast (air) is not present in the bowel at birth. A transit time of about 3 h is usually required for gas to traverse the small intestine and approximately 8–9 h for the gas to appear in the sigmoid colon. Movement of gas through the intestines takes several hours to generate a contrast with fluid levels (air-fluid levels) to be apparent on plain abdominal radiographs in order to make a diagnosis of intestinal obstruction. Most plain abdominal radiographs appear as gasless abdominal films in neonates with intestinal obstruction, as opposed to air-fluid levels seen in paediatric patients pathognomonic of intestinal obstruction. On a plain abdominal radiograph, significant ascites also appears as a gasless abdomen (Figures 3 and 4).

Necrotising enterocolitis
A plain abdominal radiograph with detection of pneumatosis intestinalis in the clinical setting of feed intolerance raises the suspicion of NEC. In this clinical setting, detection of free abdominal air heralds the possibility of intestinal perforation. BUS findings in conjunction with plain abdominal radiographs are valuable in the early detection of NEC severity. Real-time BUS can provide information on the presence of bowel thickening, thinning, portal venous gas, pneumatosis intestinalis, increased bowel wall echogenicity, disturbances in BWP and the presence of free fluid or air. The presence of three out of these seven sonographic features has a sensitivity of 0.82 and specificity of 0.78 in the diagnosis of NEC. BUS is a valuable tool in complicated cases of NEC which have a poor response to medical treatment with non-specific plain abdominal radiographs. One such scenario is extreme preterm infants presenting with NEC without the presence of pneumatosis on plain abdominal radiography (Figure 9). In a recent review by Staryszak et al., the pathognomonic sign of NEC which is pneumatosis intestinalis was seen more frequently on BUS (44%) than plain abdominal radiographs (11%). Absent bowel wall perfusion seen on Doppler may suggest severe NEC. This

Figure 2: (a, b) Bowel Ultrasound Image Showing Bowel Wall Thickening and Thinning.

Figure 3: (a) Plain Abdominal Radiograph Performed on a 27-week Preterm Infant at 48 h of Life for Abdominal Distention. The Plain Radiograph Image Showing Non-specific Dilatation of the Bowel Loops. (b) Bowel Ultrasound Performed Concurrently Showed a Localised Bowel Segment with Loss of Gut Signature with Significant Dilatation and Thinning of the Surrounding Bowel Loops. There was Free Fluid Noted in the Abdominal Cavity. This Patient was Diagnosed with Ileal Atresia on Diagnostic Laparoscopy, Underwent Surgical Resection of the Atretic Segment with End to End Ileal Anastomosis.
sonographic appearance of thinned out bowel wall with absent vascular flow may herald the onset of spontaneous intestinal perforation, an indication for surgical intervention. Increased bowel wall perfusion, seen during bowel inflammation, produces specific hyperaemic flow patterns based on the area of increased vascularity such as mucosal folds of the small intestine (zebra pattern CD signals); subserosal lines and mesenteric artery (Y-shaped CD signals); and circumferential flow across the entire bowel wall (ring-shaped CD signals).^{2}\text{ Free air seen on abdominal ultrasound is suggestive of intestinal perforation (Staryszak et al.) (Figure 5).}^{10}\text{ Thus, the wall of the bowel cannot be clearly defined. PI in NEC, seen as echogenic dots along the side of the bowel wall, does not change with position. This can be tested by gently applying pressure on the transducer probe over the abdominal wall. Intraluminal gas will move and can be easily displaced by applying gentle pressure. This differentiates the fixed echogenic dots seen in PI (intramural gas) from intraluminal gas. Detection of PI is time sensitive. PI is present only for few hours during the disease process in NEC and may not be seen in advanced NEC as the disease progression worsens.}^{16}\text{ Follow-up BUS can be performed in the assessment of PI. This has the advantage of preventing radiation exposure from repeated plain abdominal radiography assessments. Kim et al. (2005) reported that PI was detectable in 100% of their 40 patients with early NEC (Bell stage 1) using BUS with no PI seen on plain radiographs. Thus, although PI is seen more impressively on plain abdominal radiograph compared to BUS, PI visibility is improved by real-time BUS in the detection of early NEC (Figure 6).}\text{Portal venous gas}\text{Portal venous gas (PVG) is produced when the entrapped intramural gas escapes through the portal vein only to get trapped in the portal microcirculation. Similar to intramural gas, this finding is also time sensitive and can be seen as bubbles}
Figure 5: (a, b) Bowel Colour Doppler (CD) Study Images in a 24-week Infant Diagnosed to have NEC Requiring Surgical Intervention on day 24 of Life. Increased Bowel Wall Perfusion seen During Bowel Inflammation in NEC Producing the Specific Hyperaemic Flow Pattern Y-shaped CD Signals. (c) Bowel Colour Doppler Study Image in a 27-week Infant Diagnosed to have NEC Requiring Surgical Intervention on day 33 of Life Showing Increased Bowel Wall Perfusion. (d) Bowel Colour Doppler Study Image in the Same 27-week Infant Diagnosed to have NEC Requiring Surgical Intervention on Day 33 of Life Showing Increased Bowel Wall Thickening and Increased Vascularity. (e) Normal Bowel Wall Perfusion on Colour Doppler.
(echogenic dots) migrating rapidly through the portal vein on real-time BUS. In the diagnosis of NEC, most studies report sensitivity of detection of portal venous gas ranging from 2.6%...
to 58% on plain abdominal radiographs vs. 16%-45% on BUS (Figure 7).

**Bowel wall thickness and thinness**

The sonographic appearance of bowel wall thickness (>2 mm) pathologically correlates with mucosal haemorrhage and oedema and is often associated with increased bowel wall echogenicity. Bowel wall thinness (<1 mm, however, pathologically correlates with ischaemia and or necrosis and may alert to the sequelae of impending intestinal perforation (Figures 8 and 9).

**Free abdominal air and free abdominal fluid**

The presence of free abdominal air on plain abdominal radiographs is diagnostic of bowel perforation. Free air on BUS is seen as bright echogenicity between the abdominal wall and the anterior surface of the liver obscuring the normal views. This requires meticulous placement of the transducer on the abdominal wall with least compression, so as not to displace the free air. The presence of localised fluid collection or echogenic material seen between the bowel loops on sonography is highly suggestive of bowel perforation, an indication for surgical intervention.

**Malrotation and volvulus**

Malrotation is a congenital malformation with incidence estimated to be present in one in 500 live births. Seventy-five per

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**Figure 8:** BUS Image in the Same 27-week Infant Diagnosed to have NEC Requiring Surgical Intervention on Day 33 of Life Showing Increased Bowel Wall Thickening (Bowel Wall Thickness Measured 3.2 mm).

**Figure 9:** (a) Plain X-Ray Showing Paucity of Gas with no Evidence of Pneumatosis Intestinalis in 24-week Infant Diagnosed to have NEC Requiring Surgical Intervention on Day 24 of Life. (b, c) BUS Performed at the Time of Plain Radiograph Assessment as Shown in Figure a Detected Significant Dilatation of the Intestinal Loops with no Visible Peristalsis and Absent Bowel Wall Perfusion.
cent present in the neonatal period with midgut volvulus.\(^{18}\)

Malrotation is caused when normal rotation and fixation of the gut have been arrested or deviated at various developmental stages in early embryological period. Intestinal malrotation can go unnoticed and predispose the infant to have a narrow base midgut mesentery resulting in twisting of the bowel loop around itself and occurrence of volvulus. This results in arterial strangulation with resultant gut ischaemia. Delay in diagnosis can result in necrotic bowel requiring surgical resection. The need for frequent paediatric surgical reviews and opinion from experienced radiologists may warrant transfer of the neonatal patient to a surgically specialised centre to rescue ischaemic bowel loops. Point-of-care BUS conducted by neonatologists allows more rapid assessment and diagnosis to allow timely surgical decompression of twisted bowel loops and restoration of the bowel wall perfusion.

The diagnosis of malrotation is conventionally made on Upper Gastrointestinal (GI) contrast study, to demonstrate abnormal configuration of duodenal C-loop or duodenojejunal flexures located on the right side of the vertebral bodies.\(^{19}\) On sonography, the normal anatomy of the superior mesenteric vessels is seen as the superior mesenteric vein (SMV) lying left and superior of the superior mesenteric artery (SMA).\(^{20}\) That is, the SMV lies at 11 o’clock position to the SMA. Chao et al.\(^{21}\) studied the sensitivity and specificity of detection of intestinal malrotation and volvulus on BUS. Their study results demonstrated a 100% sensitivity in detecting neonatal intestinal malrotation based on the inversion of the SMV and SMA (with no SMV seen at 11 o’clock position to the SMA), whilst the whirlpool sign (SMV winding around the SMA) had a sensitivity of 86% and specificity of 92% in the detection of volvulus. It is imperative to note that a normal anatomical configuration of the SMA and SMV does not exclude malrotation; however, their abnormal anatomical configuration is diagnostic. Characteristic signs of midgut volvulus include duodenal dilatation with distal tapering, fixed midline bowel on contrast study and the whirlpool sign with dilatation of the SMV on sonography (Figures 10 and 11).\(^{21}\)

Although plain abdominal radiography in preterm infants with bile stained aspirates showing normal gas pattern can be reassuring, the most common finding on plain radiography in neonate with malrotation is normal bowel gas pattern.\(^{18}\) BUS can be used to determine the position of the superior mesenteric vessels and their relationship to the third portion of the

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**Figure 10:** (a) Plain Abdominal Radiograph Showing a Distended Gastic Bubble with Paucity of Gas Beyond the Gastic Bubble in a 36-week Infant Diagnosed with Malrotation on Laparotomy. (b) Normal Anatomical Orientation of the Superior Mesenteric Vessels. The Superior Mesenteric Vein Seen at 11 o’clock Position to the Superior Mesenteric Artery. (c) Colour Doppler Study Showing the Superior Mesenteric Vein Swirling Around the Superior Mesenteric Artery, the Whirlpool Sign’ Diagnostic of Malrotation.
duodenum. Normal orientation of the superior mesenteric vessels does not completely exclude malrotation but makes the diagnosis less likely.

**CPAP belly syndrome**
A particularly frequent clinical presentation to neonatologists’ is the occurrence of CPAP belly syndrome.\(^5\) Benign gaseous distension of the bowel, due to CPAP support, exacerbates the physiological gastrointestinal dysmotility seen in preterm infants. Clinically, this presents as feed intolerance that is manifested in the form of abdominal distension and significant pre-feed aspirates, sometimes with bile. This clinical scenario necessitates urgent evaluation to rule out potentially life-threatening conditions such as NEC or volvulus. The characteristic features of CPAP belly syndrome on plain radiography include (i) Distended abdominal cavity (cross-diameter); (ii) Almost symmetrical polygonal gas/air spaces with thin walls spread homogeneously with the presence of rectal gas; (iii) Non-thickened bowel wall; and (iv) The absence of pneumatosis intestinalis, portal venous gas and non-moving (stagnant) parallel sausage-shaped loops. These findings are reassuring to the clinician, although often the findings are non-specific. In the context of feed intolerance, inconclusive plain radiology clinical decision to withhold feeds with potential antibiotic administration is justified. BUS can add to diagnostic accuracy in these clinical settings by differentiating healthy bowel that has normal gut signature, peristalsis and normal vascularity.

**Conclusion**
Surviving extremely low-birthweight infants have prolonged periods of noninvasive ventilation (nCPAP, biPAP) with varying degrees of gastrointestinal tract dysmotility, CPAP belly syndrome. Frequently, feed intolerance with low-grade bilious aspirates triggers appropriate concerns of possible life-threatening pathological gastrointestinal diseases such as NEC or intestinal obstruction and the ability of the clinician to perform point-of-care BUS may enhance timely management. With expansion of knowledge and appropriate training of ultrasound techniques, neonatologists will be able to enhance their diagnostic acumen by performing point-of-care BUS in addition to plain radiography for a broad array of diseased bowel states in neonates.

Thus, to conclude, BUS has the added ability to measure bowel wall thickness, provide real-time evaluation of peristalsis, intestinal perfusion, free abdominal air/fluid and can detect pneumatosis intestinalis, portal venous gas and pneumoperitoneum similar to abdominal radiographs.

**Future directions and research areas**
Further studies to characterise bowel motility (swirls) using computerised vectorial analysis and measurements of vascularity by percentage (%) of colour pixels to luminance (intensity) of each colour pixel using novel computer-based software are underway to develop quantitative assessments (personal communication: Parson et al., unpublished data, University Hospitals, Coventry and Warwickshire NHS trust hospitals). Such studies will determine bowel wall thickness and its variation with gestational age in healthy preterm infants with no diseased bowel states.

The role of BUS in reassuring the clinicians trained for point-of-care BUS to reassure with a diagnosis of CPAP belly syndrome as opposed to NEC will require further delineation.

We are undertaking a study to determine normal peristalsis in healthy preterm and term infants to define normal peristaltic movements—a sign of healthy bowel and comparing it with various methods to detect peristalsis clinically.
The objective of this review was thus to acquaint point-of-care neonatal clinicians with the range of normal and pathological BUS findings, the findings of which can be used to guide the need for any further acute medical or surgical intervention. The authors plan to examine in a prospective cohort study, the true-negative and true-positive predictive value of using point-of-care BUS to reassure clinicians of the low likelihood of diseased bowel states. Despite these challenges, it is feasible for neonatologists to enhance diagnostic accuracy of diseased neonatal bowel by using point-of-care BUS in conjunction with clinical assessment and performing plain abdominal X-rays.

Acknowledgements
The authors would like to thank parents for granting permission to use the bowel images of their infants for the purpose of this review. We would like to thank Dr Traci-Anne Goyen, PhD, Department of Neonatology, Westmead Hospital, for her contribution in editing the manuscript.

Funding
None.

Conflict of interests
None.

Disclosure statement
None.

Authorship declaration
We certify that this manuscript is original, has not been previously published or submitted elsewhere for publication, is not currently under consideration by another journal and will not be submitted elsewhere until we have received your final decision. The authorship listing conforms with the journal’s authorship policy and that all authors are in agreement with the content of the submitted manuscript. None of the authors have any financial or other relationships that could lead to a conflict of interest.

References
Neopuff T-piece resuscitator: does device design affect delivered ventilation?

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ABSTRACT

Background The T-piece resuscitator (TPR) is in common use worldwide to deliver positive pressure ventilation during resuscitation of infants <10 kg. Ease of use, ability to provide positive end-expiratory pressure (PEEP), availability of devices built into resuscitaires and cheaper disposable options have increased its popularity as a first-line device for term infant resuscitation. Research into its ventilation performance is limited to preterm infant and animal studies. Efficacy of providing PEEP and the use of TPR during term infant resuscitation is not established.

Aim The aim of this study is to determine if delivered ventilation with the Neopuff brand TPR varied with differing (preterm to term) test lung compliances (Crs) and set peak inspiratory pressures (PIP).

Design A single operator experienced in newborn resuscitation provided positive pressure ventilation in a randomised sequence to three different Crs models (0.5, 1 and 3 mL/cmH₂O) at three different set PIP (20, 30 and 40 cmH₂O). Set PEEP (5 cmH₂O), gas flow rate and inflation rate were the same for each sequence.

Results A total of 1087 inflations were analysed. The delivered mean PEEP was Crs dependent across set PIP range, rising from 4.9 to 8.2 cmH₂O. At set PIP 40 cmH₂O and Crs 3 mL/cmH₂O, the delivered mean PIP was significantly lower at 35.3 cmH₂O.

Conclusions As Crs increases, the Neopuff TPR can produce clinically significant levels of auto-PEEP and thus may not be optimal for the resuscitation of term infants with healthy lungs.

BACKGROUND

The T-piece resuscitator (TPR) is a device widely used to provide positive pressure ventilation during resuscitation of infants ≤10 kg.1 The device requires an interface to the patient via face mask, laryngeal mask airway or endotracheal tube (ETT). The Neopuff (Fisher & Paykel New Zealand) TPR is a gas flow-dependent resuscitator consisting of three operator-adjusted valves. These are set with the aid of a built-in manometer to the desired level for peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP) and safety pressure limit required to provide intermittent positive pressure ventilation (IPPV). Driving gas of 5–15 L per minute (LPM) is provided by blended gas, air or oxygen flowmeter.

Two control dials located on the Neopuff provide adjustable ranges for PIP of 2–75 cmH₂O and safety pressure limit of 40–80 cmH₂O. PEEP is adjusted by changing a variable orifice flow resistor located at the distal end of the patient circuit. The adjustable PEEP pressure range is 1–25 cmH₂O.

Setting delivery pressures must be carried out in the correct sequence stated in manufacturer documentation; otherwise, delivery of adequate ventilation will not be successful.1,2 Any alteration to the gas inflow rate after the initial setting and start of IPPV requires recalibration by the user, which requires disconnection from the patient.2,3 Hawkes et al4 showed that adjustment of circuit gas inflow from 5 to 15 LPM without recalibrating the delivery pressures resulted in an inadvertent increase in PEEP (300%), PIP (40%) and safety over pressure (33%) from the initial set value.

IPPV is started by occluding the gas outlet located on the PEEP valve assembly. The operator determines inflation rate and inspiratory:expiratory ratio (I:E ratio). If IPPV is not initiated and circuit seal is maintained, a continuous positive airway pressure is delivered to the patient at the same set PEEP value.

The use of the Neopuff for preterm resuscitation is well published.5–7 Although it is widely used for resuscitation in term infants,8 limited data support its use in infants with weight 3.5–10 kg. We tested the hypothesis that the delivered ventilation of the Neopuff TPR is not different between low and normal newborn lung compliance (Crs) (0.5–3.0 mL/cmH₂O).9
The aim of this study was to determine whether the delivered ventilation with the Neopuff TPR varied with differing test Crs (0.5, 1 and 3 mL/cmH2O) and different set PIPs (20, 30 and 40 cmH2O).

METHODS AND DESIGN
A single Neopuff TPR (Part Number: RD900AEU) and delivery circuit (Part Number RD 1300-10) with a measured compliance of 0.4 mL/cmH2O and tubing flow resistance of 6 cmH2O/L/s at 30 LPM were used in this bench study.

Two different leak-free test lungs were used (1) a 50 mL Draeger test lung (Draeger, Lubeck, Germany) with measured compliance of 0.5 mL/cmH2O; resistance 50 cmH2O/L/s and (2) a 200 mL IMT newborn test lung (Smart Lung Infant, IMT medical, Buchs, Switzerland) with adjustable measured compliances of 1.0 and 3.0 mL/cmH2O; resistance 50 cmH2O/L/s. A Floranian respiratory function monitor (RFM) (Accutronics, Medical Systems AG, Zug, Switzerland) was connected via the hot wire pneumotach and pressure sensor line sited between the Neopuff TPR and the test lung. The Floranian monitor was calibrated with an external syringe of known volume and pressure/flow via a traceable reference ventilator analyser (PF300, IMT Medical, Buchs, Switzerland). The analogue signals output from the RFM were collected and digitzed at 200 Hz with analysis software (Grove Medical, London, UK). The test lungs and monitoring system were pressurised to static pressure of 40 cmH2O.

RESULTS
A total of 1087 inflations were analysed. Inspiratory times were statistically different across all sequences (mean=0.53, SD=0.04 s, p≤0.001) but not considered clinically significant.

The measured PIP as a percentage of set PIP ranged from 100% to 101% with Crs of 0.5 and 1 mL/cmH2O, which were not significantly different and was lowest at 88% with set PIP of 40 cmH2O and Crs 3 mL/cmH2O (p<0.001) (table 1, figure 1). The measured PIP as a percentage of set PEEP ranged from 98% to 106% for Crs of 0.5 mL/cmH2O, 106% to 110% for Crs of 1 mL/cmH2O and 122% to 164% for Crs of 3 mL/cmH2O across set PIP range (p<0.001), this was highest at set PIP of 40 cmH2O and Crs of 3 mL/cmH2O (table 1, figure 2). The mean delivered Vt increased significantly with increasing Crs for each set PIP level, ranging from 8.5 mL (CI 0.5 mL/cmH2O at set PIP 20 cmH2O) to 66 mL (Crs 3 mL/cmH2O at set PIP 40 cmH2O) (p<0.001) (table 1, figure 3).

DISCUSSION
The results of this bench study show when using Neopuff TPR to provide IPPV, there is a significant difference between set and delivered Vt, with higher Crs requiring higher PIP to achieve target Vt. The increase in PIP and Vt is consistent with previous studies showing increasing Crs impeding gas output and increasing PEEP during IPPV.

| Table 1 | Measured respiratory parameters with differing set peak inspiratory pressures (PIP) and test lung compliance |

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<td>16.3</td>
<td>0.14 (0.19)</td>
<td>21.8</td>
<td>0.21 (0.17)</td>
</tr>
</tbody>
</table>

PEEP, positive end-expiratory pressure; Vt, tidal volume.
delivered pressures as Crs increases. The unintended rise in delivered PEEP (auto-PEEP) at compliance of 3.0 mL/cmH₂O was clinically important.

Auto-PEEP can impair the reduction in pulmonary vascular resistance important to circulatory adaptation immediately after birth and increase risk of air leaks in term infants with meconium aspiration syndrome. We suspect the auto-PEEP observed in our study is due to circuit-imposed expiratory resistance of the Neopuff PEEP valve and delivery circuit compliance, increasing the system time constant, thus increasing lung deflation time. Similarly, the observed inability to attain set PIP of 40 cmH₂O at Crs of 3 mL/cmH₂O during inspiration may be due to insufficient fill time at the circuit inflow rate of 10 LPM and inflation rate of 60 IPM (figure 4). The compliance setting that we chose for our term lung model of 3 mL/cmH₂O may be typical of a term infant of 3500 g birth weight, a recent human study by McEvoy et al suggested higher term infant values of 4–5 mL/cmH₂O.

The development of auto-PEEP is tied to the time constant of the lung and airway. The lung time constant is proportional to the product of airway resistance (RAW) and Crs.

Increasing RAW for a given Crs and volume results in a longer time for gas to exit the lung. Imposed resistance due to ventilator device design has been shown to increase patient work of breathing and change the overall respiratory system time constant. Wald et al showed that the expiratory resistance of the Neopuff TPR varied with gas in flow rate from 40.1 cmH₂O/L/s at 15 LPM to 104.8 cmH₂O/L/s at 6 LPM.

Finer et al detailed eight occurrences in a 12-month period (n=120) of inadvertent increase in PEEP using TPR device from set 5 cmH₂O (min 6.7; max 15.8 cmH₂O); IPM <60 during resuscitation of infants <1000 g which he attributed to possible movement of the PEEP control knob. It is notable that both the recordings of actual resuscitations illustrated have a starting PIP of 40 cmH₂O. Circuit gas inflow rate was not reported, Finer concluded ‘the Neopuff has the potential to cause an inadvertent and potentially toxic increase of PEEP which might not be noticed by the operator’. We have excluded PEEP valve positional changes contributing to rise in PEEP in our study by checking there was no change in a marker point on the PEEP valve during the experiment. Bennett et al examined increasing PIPs with the Neopuff TPR in a manikin model to 40 cmH₂O as escalation to these levels may be required with diseased or immature lungs.

Limitations of our study are shared with other manikin and test lung studies of the ability to generalise to actual human resuscitations at birth. Changes in inflation rate and circuit gas flow rate were not examined in this study and may contribute to the level of device imposed auto-PEEP. The performance of other brands of TPR’s may be different.

Preliminary data by our group in a piglet study (n=10) comparing self-inflating bag (SIB) and Neopuff TPR delivered ventilation has confirmed our bench test results that the TPR device can contribute to the production of clinically significant auto PEEP during IPPV compared SIB with PEEP valve.

Adaptive changes in pulmonary and circulatory physiology and establishment of a functional residual capacity of the lung during birth are complex. Detecting and adjusting for Crs changes during resuscitation with either SIB or TPR devices is difficult. The presence of leak during mask resuscitation is common and can also influence Neopuff performance. Mask leak that may be variable might obscure TPR generated auto-PEEP by providing a path of least resistance for expired gas. Mask ventilation by more experienced clinicians using improved mask techniques or the presence of ETT may...
provide a patient/device interface that is closer to leak free, increasing device imposed auto PEEP from TPR devices.

The efficacy of the T-piece device for term resuscitation is not established, and terms describing the device as the ‘gold-standard’ should be viewed with caution. Our data suggest that in contrast to previous studies using Neopuff TPR in preterm lung models, delivered pressures are not consistent and vary from those preset as Crs increases.

CONCLUSION
We have shown in a test lung with compliance similar to that of a term infant that use of Neopuff TPR may result in increasing auto PEEP and decreasing PIP values. This is likely to be greater with higher Crs and higher inflation rates. Lower inflation rates may mitigate this effect. Operator finger position over PEEP valve orifice during lung deflation may also contribute to unintended PEEP. Clinicians using Neopuff to resuscitate term infants should be alert to these potential consequences.

Contributors MH is the primary researcher responsible for conceiving, designing, data collection, statistical analysis and writing manuscript. PJ contributed to data collection, interpretation, manuscript construction and review. AP and AM contributed to interpretation, manuscript construction and review. MT contributed by assisting design, statistical analysis, manuscript writing and review.

Competing interests None declared.

Ethics approval This study was approved by the Western Sydney Local Health District Human Ethics and Scientific committee approval number SAC2014/5/6.9 (3999)QA.

Provenance and peer review Not commissioned; externally peer reviewed.

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Neopuff T-piece resuscitator mask ventilation: Does mask leak vary with different peak inspiratory pressures in a manikin model?

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Aim: The aim of this study was to compare mask leak with three different peak inspiratory pressure (PIP) settings during T-piece resuscitator (TPR; Neopuff) mask ventilation on a neonatal manikin model.

Methods: Participants were neonatal unit staff members. They were instructed to provide mask ventilation with a TPR with three PIP settings (20, 30, 40 cm H₂O) chosen in a random order. Each episode was for 2 min with 2-min rest period. Flow rate and positive end-expiratory pressure (PEEP) were kept constant. Airway pressure, inspiratory and expiratory tidal volumes, mask leak, respiratory rate and inspiratory time were recorded. Repeated measures analysis of variance was used for statistical analysis.

Results: A total of 12,749 inflations delivered by 40 participants were analysed. There were no statistically significant differences (P > 0.05) in the mask leak with the three PIP settings. No statistically significant differences were seen in respiratory rate and inspiratory time with the three PIP settings. There was a significant rise in PEEP as the PIP increased. Failure to achieve the desired PIP was observed especially at the higher settings.

Conclusions: In a neonatal manikin model, the mask leak does not vary as a function of the PIP when the flow rate is constant. With a fixed rate and inspiratory time, there seems to be a rise in PEEP with increasing PIP.

Key words: mask leak; mask ventilation; neonatology.

What is already known on this topic

1 Positive pressure ventilation by a face mask is recommended for neonatal resuscitation in case of apnoea or bradycardia if tactile stimulation is ineffective.
2 Mask leak is common and often of a large magnitude even in experienced hands with the potential of compromising the response to resuscitation.
3 Mask leak is more pronounced with a T-piece resuscitator as compared to a self-inflating bag likely due to constant gas flow.

What this paper adds

1 Provided the flow rate is constant, the mask leak does not change significantly in a neonatal manikin model with the change in peak inspiratory pressure (PIP) with a T-piece resuscitator.
2 Inadvertent positive end-expiratory pressure is generated as the PIP is increased in a compliant lung model at the respiratory rates usually used in neonatal resuscitation.
3 With the respiratory rates used in this study, there was a failure to achieve the set PIP at the higher end.

Neonatal resuscitation is a common and life-saving procedure required in 6–10% of all neonates at birth enabling them to make the transition from an intra-uterine fluid-filled environment to an independent air-breathing existence.1,2 The ‘healthy’ infant is born with spontaneous regular effective respirations, a normal heart rate and a timely move from cyanosed to acyanosed state. The ill newborn exhibits abnormalities principally of these features. Broadly, resuscitation is required with features of depressed respiration and secondary bradycardia. Bradycardia and true asystole are secondary hypoxic/ischaemic events, which require immediate correction by assistance with appropriate alveolar ventilation with positive pressure ventilation (PPV).3,4 An international consensus statement recommends that PPV can be provided with a face mask and self-inflating bag (SIB) or a flow-inflating bag (FIB) or a T-piece resuscitator (TPR).5 The purpose of PPV is to establish effective gas exchange by adequate alveolar ventilation.6 Mask leak however has been shown to be common, variable and often of a large magnitude in both manikin and human studies7–10 with the potential of inadequate ventilation and unnecessary escalation in therapy.

The history of development of resuscitation methods has shown progression from uncontrolled positive pressure breaths without positive end-expiratory pressure (PEEP) with SIBs, to operator-delivered variable PPV with PEEP (FIBs) to pre-set peak inspiratory pressure (PIP) and PEEP with TPR devices. More control in delivered PIP and PEEP is merging with the standard function of mechanical ventilators.11 Whilst the mechanical properties of a ventilator with an intubated infant are well known, performance of TPRs is less well-documented particularly with the
added complexities of ensuring adequate mask seal and airway patency. In a previous manikin-based study using a TPR, Tracy et al. reported a strong relationship between mask leak and measured expired tidal volume (VTe). In this study, 50% of the variation in the VTe was explained by linear changes in PIP. That study was however not designed to examine the relationship of differing PIPs and mask leak. On the other hand, in previous human and manikin studies, only a weak relationship was found between PIP and VTe with a wide range of VTe at any given PIP. No studies published to date have examined the impact of differing PIPs on mask leak. In resuscitation of very ill infants, PIPs may be increased to improve alveolar ventilation assuming the initial poor response reflected inherent lung disease and not operator error with a large mask leak. It is vital to determine if mask leak worsened with higher pre-set PIPs with a TPR.

The aim of this study was to examine the relationship between differing PIPs and mask leak in a neonatal manikin model using a TPR. The null hypothesis was of no change in the degree of mask leak with an individual operator as PIP increased. A prospective randomised crossover study was designed to test the hypothesis in a manikin simulation.

Methods

Setting

Staff members working in a neonatal intensive care unit at a major metropolitan teaching hospital (Westmead Hospital) in Western Sydney, Australia were invited to participate in this study. All staff tested had extensive training in neonatal resuscitation course using the American Academy of Pediatrics Neonatal Resuscitation Program (NRP).

Resuscitation device

The TPR used was Neopuff infant resuscitator (Fisher and Paykel Health Care, Auckland, New Zealand). This device requires a compressed gas supply. The Neopuff has manual settings for PIP and PEEP with a pressure dial to display delivered pressures. The settings were as recommended by the manufacturer with a flow rate of 10 L/min and PEEP of 5 cm H₂O. Each staff member was required to use three different PIP settings (20, 30, 40 cm H₂O) in a random sequence. A Research Randomizer computer program downloaded from http://www.randomizer.org/form.htm was used to generate the random sequence for each participant. A Laerdal 0/1 round mask was used.

The model

We used the Laerdal Advanced Life Support Training (ALST) baby manikin (Laerdal Medical, Oakleigh, Australia) in this study. This device has dual lung ‘bags’ connected to the ‘trachea’. The Laerdal ALST manikin has a closed system with lung and stomach bags with no intended leak as the oesophageal tube was blocked for this study. The Laerdal ALST manikin has a hinged mandible allowing a realistic jaw thrust. The static compliance of the model was calculated by measuring the inspired volume of the system with oesophageal tube blocked; when pressurised to 25 cm H₂O, this was 3.9 mL/cm H₂O. This is comparable to that of a term newborn with healthy lungs. A Florian Respiratory Monitor (Acutronics Medical Systems, Zurich, Switzerland) pneumotach was placed between the Laerdal mask and the resuscitation device. Percentage mask leak, using the Florian measurements, was defined as:

\[
\text{Tidal volume inspired (TVi)} - \text{tidal volume expired (TVe)} / \text{TVi} \times 100
\]

Recording equipment

Data from the Florian monitor were collected, via an analogue to digital converting device, using Spectra software (Grove Medical, London, UK). Respiratory mechanics data (PIP, PEEP, inspired and expired tidal volumes, respiratory rate and inspiratory time) for each inflation were determined via Spectra software and exported to the statistical package, and averaged data for each subject were calculated. The Florian monitor was calibrated with an external syringe of known volume and pressure/flow via a venti lator calibration analyser with a pressure resolution of 0.1 cm H₂O with a pressure accuracy of ±0.5% and flow calibration with a resolution of 0.1 L/min with an accuracy of ±1% (RT-200, Timeter Instrument, Allied Healthcare Products, St Louis, MO, USA). The Florian pneumotach was re-zeroed at the start of session of data collection from each participant.

Participants

Participants performed three mask ventilation sessions on the manikin each lasting 2 min with a 2-min rest period between each session. Flow and PEEP were constant at 10 L/min and 5 cm H₂O, respectively, for the three sessions. The PIP was the only parameter changing for each of the three sessions. The three PIP settings chosen were 20, 30 and 40 cm H₂O. A random sequence of these three pressure settings was generated for each participant. The study investigator set all the Neopuff settings. Participants were instructed to ventilate at a rate of 40–60 breaths per minute in keeping with the Australian Resuscitation Council guidelines. Participants were blinded to the Florian monitor and the Neopuff dial and were instructed to achieve adequate chest excursion. The reason for this instruction was the conclusion from our previous study where the mask leak was the same whether the participants were blinded to the Neopuff dial or the manikin chest wall movements. As described by Wood et al., the mask hold recommended was the two point top hold. Written informed consent was taken from the participants.

Statistical analysis and ethical approval

Data were analysed using Stata V.MP12 (StataCorp, College Station, TX, USA). Analysis of variance (ANOVA) for repeated measures was used to determine differences in delivered ventilation between different pressure settings. Differences between means determined by ANOVA were reported with P values adjusted F test using Box’s conservative epsilon. P values <0.05 were considered significant. The ANOVA for repeated measures allows a valid statistical comparison between different pressures delivered by the same individual when the repeat measurements between individuals are not independent. Bonferroni corrections of estimates were made to adjust for multiple comparisons. This study...
was approved by the Sydney West Area Health Service Research and Ethics Committee.

Results

Forty experienced neonatal staff members participated in this study including 4 staff specialists, 4 fellows, 7 registrars and 25 neonatal nurses. A total of 12 749 inflations were analysed with 4228 inflations for PIP of 20 cm H$_2$O, 4221 inflations for PIP of 30 cm H$_2$O and 4300 inflations for PIP of 40 cm H$_2$O.

Table 1 summarises the respiratory mechanics data at the three different PIP settings. There were no statistically significant differences ($P > 0.05$) in the mask leak with the three different PIP settings (Table 1 and Fig. 1). The expired tidal volume increased significantly with increasing PIP. No statistically significant differences could be seen in respiratory rate, inspiratory time and expiratory time with the three different PIP settings. On the other hand, there was a significant rise in PEEP as the PIP increased despite the fact that the PEEP was not increased manually and flow rate remained constant (Fig. 2). Also, failure to achieve the desired PIP was observed especially at the higher settings (Fig. 3).

Table 1  Respiratory mechanics data

<table>
<thead>
<tr>
<th></th>
<th>PIP/PEEP: 20/5 cm H$_2$O Mean (95% CI)</th>
<th>PIP/PEEP: 30/5 cm H$_2$O Mean (95% CI)</th>
<th>PIP/PEEP: 40/5 cm H$_2$O Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mask leak (%)</td>
<td>15.4 (7.8–23.0)*</td>
<td>14.9 (8.4–21.4)*</td>
<td>19.4 (12.8–26.0)*</td>
</tr>
<tr>
<td>PIP (cm H$_2$O)</td>
<td>19.1 (18.6–19.6)</td>
<td>28.1 (27.2–29.1)</td>
<td>34.4 (32.9–35.9)</td>
</tr>
<tr>
<td>PEEP (cm H$_2$O)</td>
<td>5.8 (5.5–6.1)**</td>
<td>6.5 (6.2–6.8)**</td>
<td>7.0 (6.7–7.3)**</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>52.8 (49.8–55.9)*</td>
<td>52.8 (49.6–55.9)*</td>
<td>53.8 (50.7–56.8)*</td>
</tr>
<tr>
<td>Inspiratory time [s]</td>
<td>0.57 (0.51–0.64)*</td>
<td>0.54 (0.49–0.6)*</td>
<td>0.53 (0.48–0.58)*</td>
</tr>
<tr>
<td>Expiratory time [s]</td>
<td>0.56 (0.55–0.56)*</td>
<td>0.59 (0.57–0.60)*</td>
<td>0.59 (0.58–0.60)*</td>
</tr>
<tr>
<td>Expired tidal volume (mL)</td>
<td>25.7 (25.5–25.9)**</td>
<td>39.9 (39.7–40.3)**</td>
<td>47.4 (47–47.7)**</td>
</tr>
</tbody>
</table>

* $P > 0.05$; ** $P < 0.0001$. CI, confidence interval; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

Fig. 1  Mask leak (mean with 95% confidence interval (CI)) with three different peak inspiratory pressure (PIP) settings (20, 30, 40 cm H$_2$O). ANOVA, analysis of variance.

Fig. 2  Positive end-expiratory pressure (PEEP) (mean with 95% confidence interval (CI)) with three different peak inspiratory pressure (PIP) settings (20, 30, 40 cm H$_2$O). ANOVA, analysis of variance.

Fig. 3  Achieved peak inspiratory pressure (PIP) (mean with 95% confidence interval (CI)) with three different PIP settings (20, 30, 40 cm H$_2$O). ANOVA, analysis of variance.
Discussion

Our study demonstrates that during mask ventilation with a fixed flow rate in a manikin model with a TPR, mask leak does not vary as a function of the PIP. The study also revealed two interesting findings, namely significant increase in PEEP with increasing PIP and failure to achieve the set PIP especially at the higher setting of 40 cm H₂O.

The lack of increase in the mask leak with higher PIP is reassuring. As far as we are aware, this is the first study to report on the level of mask leak with different PIPs. Clinically, this would mean linearly high tidal volume delivery with increasing PIP and our data supports this with the caveat that this is a manikin-based study. Overall, the mask leak in this study was comparable to a previous manikin-based study by Tracy et al.18 Much higher levels of mask leak have been reported from other studies.7,17 The higher leak in those studies could be explained by the reduced lung compliance in their manikin model whereby the Laerdal ‘lung’ bags were replaced with a Drager 50 ml test lung with compliance equivalent to that of a newborn with acute respiratory distress syndrome. Our study intentionally used the manufacturer supplied ‘lung bag’, which provides normal newborn lung compliance. The majority of newborn infants requiring PPV are term having some degree of hypoxic stress with normal lung compliance.

Despite the TPR’s ability to provide consistent PEEP,19 we found increasing PEEP with increase in PIP without any change in flow rate or ‘set PEEP’. This increase of up to 2 cm H₂O is of potential clinical significance. In an earlier study20 in extremely low birthweight infants, mean PEEP delivered (with Neopuff) was 5.6 cm H₂O with a set PEEP of 5 cm H₂O. The set PIP was 30 cm H₂O; however, respiratory rate was not mentioned. Our finding could relate to the high time constant of the system due to the highly compliant circuit and lungs leading to relative inadequacy of the expiratory time at the rates and inspiratory times provided in this study. Presumably, higher expiratory times are required for the PEEP to return to the baseline as the PIP and delivered tidal volume are increased. As the expiratory times were similar across the three PIPs, this may explain increasing inadvertent PEEP. Despite the low level of mask leak, we were not able to achieve the desired PIP and this finding was most apparent at a set PIP of 40 cm H₂O. Similar finding has been reported in an earlier study.6 The delivered mean PIP was 26.3 cm H₂O in that study with a set PIP of 30 cm H₂O. This was conducted in human infants and 75% of the infants had a TPR used. Failure to achieve high PIP may be related to the high compliance of the Neopuff circuit. We plan to test this hypothesis in a separate study comparing two circuits with different compliance levels.

We have recently examined the relationship between test lung compliance, inflation rate and PIP in greater detail21,22 and these findings of unintended rise in PEEP and inability to achieve the desired PIP have been noted consistently signifying the role of lung compliance and time constant in delivery of the pressures.

The strength of this study lies in the large number of inflations analysed in an expert group of users in addition to the minimal alteration of the Laerdal ALST baby manikin, which may allow better extrapolation of our results to the unaltered commercial Laerdal ALST baby manikins. Limitations are shared with other manikin studies to the extent one can generalise to actual human newborn resuscitation; however, practice in simulation model is the best system of teaching and strongly advocated.23 The other limitation was the inability to achieve the desired PIP whilst the objective was to compare the mask leak at different PIP levels. We still feel, however, that the pressures used in this study are representative of the pressures used in clinical practice and the results in terms of lack of variation in mask leak remain valid. Keeping the participants blinded to the Neopuff dial may be considered as a limitation as, in real life, practitioners do see the dial and make adjustments.

Conclusions

In a neonatal manikin model, the mask leak does not vary as a function of the PIP when the flow rate is constant. With a fixed rate and inspiratory time, there is unintended rise in delivered PEEP with increasing PIP.

References

Newborn self-inflating manual resuscitators: precision robotic testing of safety and reliability

Mark B Tracy,1,2 Robert Halliday,3 Sally K Tracy,4 Murray K Hinder1,5

ABSTRACT

Aim A controlled bench test was undertaken to determine the performance variability among a range of neonatal self-inflating bags (SIB) compliant with current International Standards Organisation (ISO).

Introduction Use of SIB to provide positive pressure ventilation during newborn resuscitation is a common emergency procedure. The United Nations programmes advocate increasing availability of SIB in low-income and middle-income nations and recommend devices compliant with ISO. No systematic study has evaluated variance in different models of neonatal SIB.

Methods 20 models of SIB were incrementally compressed by an automated robotic device simulating the geometry and force of a human hand across a range of precise distances in a newborn lung model. Significance was calculated using analysis of variance (ANOVA) and repeated measures to determine the relationship between distance of SIB compression and delivered pressures generated and functional compression distance.

Results Ten out of the 20 models of SIB failed our testing methodology. Two models could not provide safe minimum tidal volumes (2.5–5mL); six models exceeded safety inflation pressure limit (>45cm H2O, representing 6% of their inflations; five models had excessive coefficient of variation (across all compression distances); peak pressures generated and functional compression distance.

Conclusion Compliance of SIBs with ISO standards may not guarantee acceptable or safe performance to resuscitate newborn infants.

INTRODUCTION

Resuscitation at the time of birth is a common emergency procedure.1 The transition from in utero to an independent ex utero state can be complicated by failure to establish adequate respiration with bradycardia or asystole. The self-inflating bag (SIB) is the most commonly used device worldwide to provide positive pressure ventilation (PPV). It is well suited to resource-constrained countries given that it is a manual device, which can be used without a compressed gas source.2 3 In 2012, the United Nations (UN) Commission on Life-Saving Commodities for Women and Children identified the need to increase access to neonatal resuscitation devices in 50 of the world’s poorest countries.4 The provision of SIBs to birth attendants for all newborns requiring resuscitation in the low-income and middle-income countries has been a recent major world health initiative.5 6 These initiatives have identified the need for a significant boost in the production of SIBs in order to meet the global demand for the device. In addition to the production of SIBs, training, education, device maintenance and distribution are crucial elements in this health initiative.

A programme funded by USAID, the ‘Programme for Appropriate Technology in Health’ (PATH), examined a range of internationally available SIBs focusing on cost and manufacturing aspects with a view to supplying the device in resource-constrained birth settings.7 8 No data on biomechanical performance were available for the PATH review. Instead, the recommendations relied on statements of compliance outlined by the International Standards Organisation (ISO) and American Section of the International Association for Testing Materials.9 10 The WHO document on technical specifications for neonatal resuscitation devices published in 2016 recommends SIB devices for newborn resuscitation that are compliant with the current ISO standard but advises: ‘There is a gap between
physiology and available equipment specifications, and discrepancies among existing standards and professional association guidelines.¹⁰

Manufacturers of SIBs are guided by international standards as to the ventilation performance required to provide effective ventilation at birth. The current International Standard Organisation (ISO) document for manual resuscitators ISO 10651.4-2002 (reviewed 2013), advises that SIB ventilation performance (section 6.7), for ≤5 kg body weight should be able to deliver a minimum 20 mL volume into a test lung (compliance 1 mL/cm H₂O, resistance 400 cm H₂O/L/s), at I:E ratio 1:1, 60 inflations per minute and provide a safety pressure relief at 45 cm H₂O. It also warns that delivered volume may bypass the patient when bag is compressed. This is termed forward leakage of the patient control valve (PCV).

A poor response to initial resuscitation with SIB compression should prompt the resuscitator to first adjust the way the mask is held in position on the face to avoid or eliminate potential mask leak, reposition airway and assess the airway for obstruction. Only then should bag compression be increased to generate higher pressures to increase the delivered ventilation.² ¹¹ Too vigorous bag compression may cause lung injury (pneumothorax, chronic lung disease in the preterm) due to excessive pressures and tidal volumes (VT), overventilation and hypocarbia.¹²⁻¹⁵ There is a general assumption that when using SIBs there is a consistent relationship between distance compressed and delivered VT for any given lung compliance.

A recent review by Hooper et al proposes a three-phase sequence of interdependent physiological changes in the transitional process at birth, and that the type of respiratory support provided should vary to optimise the underlying physiological lung state at each phase: 1) liquid clearance, possibly aided by sustained inflation (SI), 2) liquid re-entry/temporary accumulation, aided by continuous positive airway pressure and 3) respiratory support/gas exchange, aided by PPV with positive end-expiratory pressure. They also state that current resuscitation approach is ‘unidimensional’ and focuses on ‘strategies applicable for an already aerated lung that is not water-logged’.¹⁶ Term animal studies have found very low compliance levels (<0.1 mL/cm H₂O/kg) in fluid-filled lungs.¹⁷ ¹⁸ Ersdal et al have recently presented measured compliance data from 1053 apnoeic term and near-term newborns resuscitated in Tanzania. The measured average static compliance of <1 mL/cm H₂O at up to 2 min of life supports the Hooper hypothesis, and the need for manual SIB devices providing PPV to be sufficiently responsive to the operator reacting to ventilation breath by breath.¹⁹

There is currently no data on the evaluation of differences in mechanical performance, delivered tidal ventilation and intrabatch variance in different brands of single use and reusable SIB resuscitators designed for use on newborns. We aimed to examine the dynamic ventilation performance of SIBs in a low compliant leak free lung model. This model reflects term asphyxiated infants in the first minutes of life who are apnoeic with fluid-filled low compliance lungs and surfactant-deficient preterm infants.¹⁷ ¹⁸ To provide a stable, precise and repeatable testing method, a robotic ‘hand’ replicating the geometry and force delivered by a standard human hand was developed.²⁰

**METHODS**

A computer-controlled two-armed robotic mechanism simulating ‘standard hand compressions’ provided incremental compressions to SIBs across a precise range of distances. The relationship between distance of bag compression, delivered VT and airway pressure were examined. Twenty different models of SIB (n=173) resuscitators were examined with an average of nine units per model summarised in online supplementary table S1. Some manufacturers produced multiple SIB models with differing part numbers and physical characteristics. A test lung (Drager Lubeck, Germany) of known compliance (0.5 mL/cm H₂O) and resistance (50 cm H₂O/L/s) was attached to the SIBs with a respiratory function monitor (RFM) (Acutronics, Medical Systems, Zug, Switzerland). All SIB units were functionally checked according to each manufacturer’s insert instructions, and tested for compliance to ventilation performance as specified in the current ISO standard before our testing model was applied, all devices complied.

The robotic mechanism was programmed to mimic forces generated by a human hand compressing an SIB at an inspiratory time of 0.5 s, I:E ratio 1:1 and an inflation rate of 60 per minute (IPM) as recommended in the ISO standard at all distances tested (see online supplementary data: robothand.pdf). The programme sequence was designed to provide 40 compressions at each defined distance starting at 15 mm at a rate of 60 IPM. The robotic mechanism automatically increased compression distance in increments of 5 mm (±0.03 mm) after the previous run of 40 inflations. This sequence continued to a maximum distance of 60 mm (which corresponds to approximately 82% of maximal bag compression distance averaged across the models (see online supplementary table S1). Overpressure valves were left in their normal operating position during testing.

The RFM hot wire pneumotach and pressure sensor line were sited between the SIB under test and the test lung where the airway pressures and flows were measured. System was calibrated with an external syringe of known volume, and pressure/flow via a traceable reference ventilator analyser (PF300, IMP Medical, Buchs, Switzerland). Analogue signals output from the RFM were collected and digitised at 200Hz with data acquisition and analysis software (Spectra, Grove Medical, London UK). The pneumotach was re-zeroed before each SIB was tested.

Our primary outcome was a ‘pass’ or ‘fail’ assessed as passing all four criteria determined a priori: safe minimum average VT for the smallest expected newborn infant between 5 and 10 mL/kg² (2.5–5 mL); <30% average coefficient of variation (CV) in volume delivered over compression distance per device and SIB model; 99% of delivered peak inflation pressures (PPIs) are <45 cm H₂O as recommended by the ISO standards and a functional compression distance where the device starts delivering average tidal inflations ≥2.5 mL before 50% (≤30 mm) of total bag compression is reached.

**DATA ANALYSIS**

Analysis was conducted using Stata (V.13 MP, StataCorp, College Station, Texas, USA). The measured parameters included the mean, %CV, maximum PIP and VT. Analysis of variance (ANOVA) for repeated measures was used to determine differences between models and units for VT delivered at each distance. ANOVA were reported with p values adjusted F test using Box’s conservative epsilon, p values of <0.05 were considered to be statistically significant.

**RESULTS**

A total of 67 540 compressions from 20 different models (173 individual SIB units) provided 48 493 compressions with volumes ≥2.5 mL, and 2191 compressions with volumes <2.5 mL. There were 16 856 compressions where the SIB failed to deliver a measurable volume when compressed. Based on the
a priori ‘composite pass’ criteria, 10 of 20 models passed on all four predetermined characteristics (table 1). Of those models passing all criteria, 30,963 (81.6%) compressions provided VT≥2.5 mL. This was compared with 17,530 (59.2%) compressions of models failing one or more criteria. Variations in delivered PIPs are detailed in online supplementary figure S1.

Minimum average tidal volumes
Medtrin and Hudson SIBs could not provide the minimum safe volumes for a 500 g infant. Of note, start volumes for these models were at >50% total compression distance (table 1 and online supplementary table S1). Detailed results of VT per compression distance per SIB model batch are presented in online supplementary table S2. Figure 1 shows box and whisker plots of delivered VT per SIB model batch at each compression distance.

Average coefficient of variation
Five models had average %CV exceeding 30% ranging from 34% to 46.7%. The overall mean VTs were 2.0 mL lower for those models with %CV>30% than not (95%CI −2.2 to −1.9 mL) (table 1 and Supplementary data table S2).

Peak inflation safety limit
Eight hundred twenty-one inflations exceeded the safety limit of 45 cm H₂O (mean 48, range 45.1–53.0 cm H₂O) in six models (table 1). This represented approximately 6% of all inflations of these models. Six models were found to be unsatisfactory by exceeding the peak inflation safety limit criteria (figure 2).

Functional compression distance
Three models did not deliver measurable inflation volumes until 40 mm compression distance corresponding to approximately 67% of maximum bag compression (table 1). These three models also failed on at least two a priori criteria. The Medtrin exhibited a variance in starting distance from 40 to 55 mm and one unit was unable to deliver measurable volume at any compression distance.

Intrabatch variability
The Hsiner 60 113P SIB was notable in that 5 of 10 units did not deliver a minimum usable volume until the 55 mm starting distance was reached in contrast with the 3 units that started at 25 mm compression distance.

Discussion
This is the first study to examine relationships between the compression distance of a SIB and delivered volume. The robotic bag compression and pass/fail scoring methodology described is an innovative, independent and repeatable method of assessment. It gives a new level of rigour beyond that used to set current ISO standard for manual ventilation performance for infants<5 kg. Given the ventilation performance, model
and intrabatch variance shown, it is crucial to accurately define mechanical performance necessary for the provision of safe life-saving manual ventilation for infants. Such a system was proposed as long ago as 1975 by Dick and Ahnefeld but not implemented in subsequent ISO standards.22

Limitations of this study are the use of a low compliance test lung model of ill newborn infants. Many of the SIB models tested are rated for use up to 10 kg body weight, which reflects infant/paediatric use (see online supplementary table S1).23 The performance issues found in this study are similar to those found by Kain et al in a paediatric SIB bench study using higher test lung compliance (10 mL/cm H₂O).24 A potential limitation is the generalisability of the two-armed robotic mechanism compared with a human 2–5 fingered hand compression. However, Basinni et al have shown no difference in delivered volume between 2/3/4 and 5 finger hand compressions.25 The inflation time would be <0.5 s of compression time when forward leakage was present.

The inability of the safety pressure limiting valve to prevent PIP in excess of 45 cm H₂O and the wide intrabatch variation (CV) in delivered volumes seen in some models is of serious concern. In vivo, potential exists for SIBs with faulty safety pressure limiting valves to allow higher PIPs than seen in this simulation study under uniform compression force.26

Our results indicate compliance to the ISO standard by SIB manufacturers may not guarantee the efficacy of the device to deliver a safe or uniform volume of gas when the SIB is compressed. Non-delivery of volume to the patient connection when the SIB is compressed is termed forward leakage in the ISO standard.20 Forward leakage cannot be routinely detected by the operator during resuscitation (figure 4 and online supplementary video1.mpg).

Munford and Wishaw described adult SIB failure due to forward leakage characteristics of the PCV.27 The PCV valve did not move fully into the inspiratory position and much of the VT bypassed the patient. Importantly, it was noted that users may lack the experience to detect failure to inflate the lungs. Kain et al in 1993 examined the performance of six different brands of both reusable and disposable paediatric SIB and also observed that the PCV can be placed inadvertently in an intermediate position giving rise to life-threatening hypoventilation during resuscitation.24

The current ISO standard warns: 'If forward leakage is a design feature of a resuscitator, this should be disclosed so that the user does not confuse this leakage with a malfunction’ (page 20 Rationale B.6.5).20 Notwithstanding, we found no testing methodology to detect or quantify forward leakage described in the
standard, and there was no disclosure in any of the product literature supplied with the devices examined in this study. Forward leakage does not appear to have any beneficial characteristics that we can determine.

Resende et al in 2006 examined 10 experienced neonatologists ventilating intubated preterm lambs with SIB (Hudson Lifesaver) showing great variation in delivered PIP and excess VT/kg (median 17.8 mL/kg IQR 14.1–22.4). Resende et al concluded their results are explained by operator variation. Our results of the same model of Hudson Lifesaver SIB alternatively suggest forward leakage of PCV as a major potential contributing factor.

The ability of some of the SIB models tested to safely deliver ventilation to a low compliant newborn lung (term apnoeic or preterm <1 kg) is questionable. As all units in this study passed the ventilation performance testing detailed in the current ISO standard (section 6.7<5 kg), the results suggest the standard may be inadequate to detect models of SIB that have manufacturing issues causing serious deficiencies in biomechanical performance. The estimated number of SIBs required for implementation of UN programmes in eight identified low-resource countries is approximately 400,000 units alone. Most of these countries are without an established regulatory authority to oversee the quality and safety of medical devices. The likelihood of the distribution of inferior devices with poor performance and unacceptable intrabatch variation is great.

In the absence of evidence from in vivo studies, the results of this study of SIB device performance provide valuable data for those making decisions regarding the brands and models that are most suitable for resource-constrained countries in the effort to reduce neonatal mortality.

A major concern arising from this study is that significant forward leakage via the PCV can lead to a complete lack of VT reaching the patient. The operator being unaware of this issue would likely react to poor clinical response by increasing the compression distance. At some point, the PCV closes resulting in delivery of a potentially excessive, harmful VT to the patient.

CONCLUSION
Half the SIBs examined in this study failing our testing method exhibited unacceptable performance variation between units despite all models passing current ISO standard criteria for delivered ventilation <5 kg. We conclude that the current ISO standard 10 651.4–2002 (reviewed 2013) for life-saving manual inflation devices specific to SIBs may need substantial revision. SIBs that were shown in this robotic simulation study to fail our testing methodology may potentially be unsafe for use with vulnerable newborn infants.

Acknowledgements The authors would like to thank the self-inflating bag suppliers for provision of devices to examine in this study.

Contributors MB conceptualised and designed the study, drafted initial manuscript, carried out statistical analysis of data, literature search and reviewed...
and revised manuscript. RH programmed software for robotic SIB compression device, data interpretation and reviewed and revised manuscript. ST assisted in writing manuscript, data interpretation and critically reviewed the manuscript. MKH assisted in study design and writing initial manuscript, design and construction of robotic SIB compression device, data collection, analysis and interpretation, reviewed and revised manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the Western Sydney Local Health District Human Ethics and Scientific Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

Outpatient cervical ripening: discomfort/pain during speculum and Foley catheter insertion

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ARTICLE INFO

Article history:
Received 8 June 2018
Revised 29 August 2018
Accepted 16 September 2018

Keywords:
Cervical ripening
Discomfort
Foley catheter
Outpatient
Pain
Speculum

ABSTRACT

Objective: To examine discomfort/pain associated with the Foley catheter insertion process and explore factors affecting discomfort/pain.
Design: This cohort study conducted in the context of larger randomised clinical trial comparing silicone and latex Foley catheters.
Setting: A tertiary hospital in Western Sydney.
Participants: Outpatient pregnant women (eligible participants in the main study).
Interventions: We asked about the discomfort/pain expectations and experience during the digital vaginal examination and insertion of the speculum, insertion of the Foley catheter and while the catheter was in situ.
Measurements: We used visual analog scale and a purposefully designed questionnaire to measure outcomes.
Findings: We found digital vaginal examination and speculum insertion (mean pain score = 4.6–4.7/10) to be significantly more uncomfortable than Foley catheter insertion (mean pain score = 3/10), while having the catheter in situ for a median of 14 h was mid-way in discomfort (mean pain score = 3.7/10). Only 12–13% of women experienced no discomfort during digital vaginal examination and speculum insertion, while about 40% experienced no discomfort during Foley catheter insertion. We identified no factors that influenced the experience of discomfort during speculum insertion. However, being overseas-born (odds ratio = 1.91, 95% CI 1.10, 3.33) and experiencing discomfort during the speculum insertion (odds ratio = 8.15, 95% CI 3.19, 20.79) increased the chance of discomfort on catheter insertion. Women’s discomfort was not influenced by inserter designation or experience.
Key conclusions: Digital vaginal examination and speculum insertion were moderately uncomfortable while insertion of a Foley catheter and having the catheter in situ for several hours were less uncomfortable procedures.
Implications for practice: Only 8% of insertions were rated as difficult by staff while 70% were rated easy. This, together with the fact that the inserter’s level of experience had no influence on women’s discomfort, are reassuring for midwives who wish to teach and learn this common procedure.

Introduction

Induction of labour is performed in about 25% of pregnancies in high-resource countries (Martin et al., 2017; Australian Institute of Health and Welfare, 2016). If the cervix is unfavourable for labour (defined by a Bishop score < 7 based on the length, dilata-

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https://doi.org/10.1016/j.midw.2018.09.012
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American College of Obstetricians and Gynecologists, 2009). It is therefore more suitable for outpatient use where the woman goes home with the catheter in situ and returns for the formal induction the following morning rather than being admitted to hospital overnight.

Foley catheters are usually inserted under vision via a vaginal speculum. The vaginal speculum is a medical tool used by healthcare professionals to access and visualize the vaginal canal and cervix. The current design of a typical speculum was updated in 1870 by Thomas Graves and has since only been slightly modified. In general, each speculum is comprised of two blades (the posterior usually slightly longer) with a hinged joint that can be opened and locked into position to allow hands-free visualization of and access to the vagina (Taylor et al., 2017). After fixing the speculum inside the vagina, the catheter is fed into the external cervical os, up the vaginal canal and beyond the internal cervical os with the catheter balloon inflated when it is above the internal cervical os (Prager et al., 2008; Joziak et al., 2011; Pennell et al., 2009). In this location it abuts the amniotic membranes and fetal head.

A large body of research exists on Foley catheter cervical ripening, including many randomised trials, but almost all of it has focused on labour, birth and newborn outcomes, with little attention given to women's experience of the procedure (Joziak et al., 2011; Diederen et al., 2018). While the routine cervical screening speculum examination undergone by non-pregnant women is widely-recognised as uncomfortable (Gungorduk et al., 2015; Asiedu et al., 2017; Bakker et al., 2017) especially in the popular media (Beli, 2018), little attention has been given to the speculum discomfort of late-pregnancy women or the additional discomfort associated with Foley catheter insertion. A few Foley catheter studies (Sciscione et al., 2001; Gadel Rab et al., 2015; Pennell et al., 2009; Policano et al., 2017) have briefly mentioned that mild discomfort may be experienced. Other papers (Jonsson et al., 2011; Diederen et al., 2018) have described more significant discomfort in some women with one study (Maslovitz et al., 2010) reporting pain necessitating removal of the catheter in almost 2% of women. We have been unable to locate any studies that have explored factors which influence a woman's experience of discomfort or pain during this procedure aside from a very small study which looked at speculum versus digital insertion in women with a Bishop score of at least 3 (Jonsson et al., 2011).

The growing use of Foley balloon catheters for cervical ripening necessitates a more detailed investigation of the late-pregnancy woman's experience of this procedure. The aim of this study, therefore, is to examine the level of discomfort/pain associated with both speculum insertion and Foley catheter insertion in term pregnant women undergoing outpatient cervical ripening to explore factors that may influence their discomfort/pain.

**Ethical approval**

Our study protocol was approved by the Western Sydney Human Research Ethics Committee prior to commencement.

**Study size**

The sample size was calculated for the parent study. In the absence of published data and from our limited experience, we estimated a likely 2% acROM rate with the stiffer silicone catheter and 0.5% rate with the more flexible latex catheter. Based on this estimate, using an alpha of 0.05 and a power of 80%, a sample size of 870 participants in each group was needed. Because of the uncertainty surrounding this estimate, the study protocol allowed independent data/safety monitoring committee review after every 100 participants with the stopping point determined as a very significant difference in the primary outcome \( p < 0.001 \) between the cohorts. The study did conclude early, after the recruitment of 534 women, as the primary study question had been answered at that level of significance (McGee et al., 2018).

**Participants**

Eligible pregnant women who required Foley catheter cervical ripening before induction of labour were recruited after assessment of Bishop score and a normal pre-induction cardiotocograph (CTG). Inclusion criteria were as follows: (a) aged \( \geq 16 \) years; (b) intact amniotic membranes; (c) placenta not closer than 2 cm from internal os; (d) absence of undiagnosed vaginal bleeding; (e) reassuring pre-ripening CTG; (f) Bishop score \( < 7 \); and (g) gestational age \( \geq 36 \) weeks at the time of intervention.

Exclusion criteria were (a) prior use of prostaglandin gel or Foley catheter for ripening in the current pregnancy; (b) active or purulent infection of the lower genital tract; (c) lethal congenital anomaly or fetal demise; (d) allergy to latex; (e) unable to speak English

**Variables**

Variables of interest included demographic characteristics (parity, age, country of birth and BMI), clinical characteristics (indication for Foley insertion, gestational age, bishop score before and after the intervention), women's self-reported knowledge of the procedure and expectation and experience of discomfort or pain during the initial digital vaginal, insertion of speculum insertion and Foley catheter, as well as clinicians rating of difficulty of Foley insertion.

**Intervention**

All women booked for outpatient Foley catheter cervical ripening underwent a digital vaginal examination at presentation to confirm the Bishop score was still \( < 7 \). After this assessment, the insertion of the speculum and Foley catheter took place with the woman in dorsal lithotomy position. A lubricated metal Graves vaginal speculum was inserted to provide sufficient visualization of the external cervical os to permit catheter insertion. The cervix was not cleaned with antiseptic solution. An 18F Foley catheter was then introduced as described earlier, the balloon inflated with 30 mL sterile water and the catheter taped under light tension to the inner thigh. A post-insertion, 60-minute CTG was then performed. If the CTG result was normal, there were no regular uterine contractions, bleeding was minimal, and there were no maternal or fetal indications for hospital admission, the woman was discharged home according to hospital protocol. She was advised to return the following morning for formal induction of labour.
or to return immediately if pain, contractions, bleeding, ruptured membranes or concerns about fetal movements developed. Women were requested to record the time if the catheter fell out at home.

If catheter insertion via speculum failed, digital Foley catheter insertion was attempted. If insertion failed altogether, the woman received PGE2 gel, oxytocin or underwent a Caesarean section. If accidental rupture of membranes occurred during insertion, the catheter was left in situ, but the woman was admitted to hospital rather than allowed home.

Estimated blood loss on insertion > 5 mL also required admission but in those cases the catheter was also removed. All other aspects of management after catheter insertion, including the conduct of the labour, were decided by the obstetric team caring for the woman.

Prior to the speculum/catheter insertion but after the initial digital vaginal examination to assess the Bishop score, women were asked by the researcher not performing the procedure about their knowledge of the speculum/catheter procedure (well-informed or needed more information) and their expectation of the discomfort/pain it may cause (no discomfort, uncomfortable, painful). After the procedure was completed, women were also asked about their discomfort/pain during the speculum examination and Foley insertion. To avoid bias, these questions were asked by the researcher not performing the procedure, after the clinician inserting the Foley catheter had left the room.

After the completion of the Foley catheter insertion procedure, the clinician who performed Foley insertion rated the difficulty of the procedure as easy, moderate or difficult.

**Discomfort assessment**

Women were asked to self-rate the discomfort during the three steps of the procedure, namely the insertion of the speculum, the insertion of the Foley catheter and the hours while the catheter was in situ. The level of discomfort was rated on a visual analogue score 1–10. After the commencement of the study, the value of adding a question about a fourth possible cause of discomfort, namely the initial Bishop-score digital vaginal examination, became apparent and was therefore included. The self-rated discomfort/pain experienced during the digital vaginal examination, speculum insertion and Foley insertion were scored once the catheter insertion was complete and the speculum removed. Discomfort associated with the hours, the catheter was in situ was scored when the woman presented for formal induction, usually the following day.

**Statistical analysis**

We performed statistical analysis using SPSS Advanced Statistics, version 24.0 (IBM, Chicago, IL, USA). Descriptive statistics were used to summarise the demographic data and calculate means with standard deviations. Univariate and multivariate logistic regression analyses were conducted to identify variables predictive of pain and discomfort during speculum and catheter insertion. \(p < 0.05\) was considered statistically significant.

**Results**

A total of 534 women were recruited to the study with 98% having successful Foley catheter insertion (93% speculum insertion, 5% digital insertion after failed speculum). Table 1 shows the demographic and clinical characteristics of the women. Only 318 women were questioned about their expectations of the speculum/catheter procedure because the contextual value of this information was appreciated only after the study was underway with these questions added at that time. Almost all (93%, 294/318) reported themselves well-informed, while 90% (241/318) expected some discomfort or pain with the mean expected pain score being 5/10 (Table 1).

The four aspects of self-reported discomfort are shown in Table 2. The digital vaginal examination (investigated in 330 women) and speculum insertion (534 women) were almost equally uncomfortable (rate 87% (286/330) and 88% (472/534); mean pain score 4.6/10 and 4.7/10, respectively) while fewer (60%, 318/534) experienced discomfort with the actual catheter insertion (mean pain score 3/10) or while it was in situ (mean pain score 3.7/10). The mean pain scores for digital vaginal examination and specu-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics of women.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td>(n = 534)</td>
</tr>
<tr>
<td><strong>Parity n (%)</strong></td>
<td>163 (30%)</td>
</tr>
<tr>
<td>Parous</td>
<td>371 (70%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal age, years, n (%)</strong></td>
<td>68 (13%)</td>
</tr>
<tr>
<td>(&lt;25)</td>
<td>81 (15%)</td>
</tr>
<tr>
<td>25–35</td>
<td>381 (71%)</td>
</tr>
<tr>
<td>(&gt;35)</td>
<td>85 (16%)</td>
</tr>
<tr>
<td><strong>Country of birth, n (%)</strong></td>
<td>190 (36%)</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
</tr>
<tr>
<td><strong>BMI at first antenatal visit, n (%)</strong></td>
<td>15 (3%)</td>
</tr>
<tr>
<td>(&lt;18.5) (underweight)</td>
<td>241 (45%)</td>
</tr>
<tr>
<td>18.5–24.9 (normal)</td>
<td>161 (30%)</td>
</tr>
<tr>
<td>(≥25.9) (overweight)</td>
<td>117 (22%)</td>
</tr>
<tr>
<td><strong>Mean BMI at the end of pregnancy ± SD</strong></td>
<td>31.2 ± 6.1</td>
</tr>
<tr>
<td><strong>Indication for Foley insertion, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Prolonged pregnancy ((≥41)weeks)</td>
<td>166 (31%)</td>
</tr>
<tr>
<td>Maternal indication</td>
<td>205 (38%)</td>
</tr>
<tr>
<td>Fetal indication</td>
<td>141 (26%)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (4%)</td>
</tr>
<tr>
<td><strong>Median gestational age, weeks±days (IQR)</strong></td>
<td>30.5 (28.6–41.1)</td>
</tr>
<tr>
<td><strong>Pre-induction Bishop score</strong></td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>187 (35%)</td>
</tr>
<tr>
<td>(≤4)</td>
<td>347 (65%)</td>
</tr>
<tr>
<td><strong>Dilatation before Foley insertion, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1–2 cm</td>
<td>349 (65%)</td>
</tr>
<tr>
<td>(&lt;1) cm</td>
<td>185 (35%)</td>
</tr>
<tr>
<td><strong>Self-reported knowledge of the Foley insertion procedure, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Well-informed</td>
<td>294/318 (93%)</td>
</tr>
<tr>
<td>Needed more information</td>
<td>24/318 (7%)</td>
</tr>
<tr>
<td><strong>Expected discomfort/pain during Foley insertion, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Expected no discomfort</td>
<td>31/318 (10%)</td>
</tr>
<tr>
<td>Expected discomfort</td>
<td>210/318 (66%)</td>
</tr>
<tr>
<td>Expected pain</td>
<td>77/318 (24%)</td>
</tr>
<tr>
<td><strong>Mean score of expected discomfort/pain expectation during Foley insertion ± SD</strong></td>
<td>5.01 ± 2.6</td>
</tr>
<tr>
<td>(the highest, 0 the lowest)</td>
<td></td>
</tr>
<tr>
<td><strong>Experiencing speculum insertion for first time</strong></td>
<td>210 (39%)</td>
</tr>
<tr>
<td>Foley insertion technique</td>
<td></td>
</tr>
<tr>
<td>Speculum</td>
<td>498 (93%)</td>
</tr>
<tr>
<td>Digital after failed speculum attempt</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>Both methods failed (didn’t receive Foley)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td><strong>Inserter’s level of experience with Foley insertion</strong></td>
<td></td>
</tr>
<tr>
<td>Inexperienced (≤5 insertions)</td>
<td>105 (20%)</td>
</tr>
<tr>
<td>Mid-level experience (6–10)</td>
<td>123 (23%)</td>
</tr>
<tr>
<td>Experienced (≥20 insertions)</td>
<td>302 (57%)</td>
</tr>
<tr>
<td><strong>Number of insertions by clinicians</strong></td>
<td></td>
</tr>
<tr>
<td>Registered midwives</td>
<td>365 (68%)</td>
</tr>
<tr>
<td>Obstetrics trainees</td>
<td>169 (32%)</td>
</tr>
<tr>
<td><strong>Type of Foley</strong></td>
<td></td>
</tr>
<tr>
<td>Latex</td>
<td>246 (46%)</td>
</tr>
<tr>
<td>Silicone</td>
<td>276 (52%)</td>
</tr>
<tr>
<td>Did not receive Foley</td>
<td>12 (2%)</td>
</tr>
</tbody>
</table>

\(\theta\) Percentages may not add up to 100 due to rounding.

BMI, body mass index; SD, standard deviation; IQR, interquartile range; CS, Caesarean section.

*Data for the first 216 women were not available.

Table 2
lum insertion were statistically significantly different from the mean score of discomfort/pain during the Foley catheter insertion (p = 0.001). No patient requested removal of the catheter for pain.

We conducted univariate and multivariate regression analysis to investigate associations between demographic and clinical variables and the experience of discomfort/pain during speculum insertion (Table 3) and Foley catheter insertion (Table 4). There was no statistically significant association between any variable and discomfort/pain during speculum insertion (Table 3), while multivariate regression showed that the odds of experiencing discomfort/pain during Foley catheter insertion were greater in women who were born overseas (OR = 1.91, 95% CI = 1.10–3.33), and those who experienced pain during the speculum insertion (OR = 8.15, 95% CI = 3.19–20.79) (Table 4).

Regarding the role of feeling well-informed, the odds of experiencing discomfort/pain in women needing more information compared to feeling well-informed was not significantly different at 3.91 (95% CI = 0.42–24.49) for speculum insertion and 1.21 (95% CI = 0.55–3.03) for Foley catheter insertion.

Seventy-three discrete clinicians, comprising registered midwives (n = 365 insertions) and obstetric trainees (n = 169) performed the insertions with the median number of insertions being 3 and the range being 1–83 per clinician. Only 8 insertions (1.5%) were carried out by male staff. Four midwives performed the largest number of insertions (83, 67, 54 and 50 each, 254 total). There was no difference in the rate of patient discomfort/pain according to staff designation (obstetric trainee or midwife) for either speculum insertion or Foley catheter insertion (Table 3, 4).

There were no differences in pain scores for insertions performed by the four ‘super-inserter’ midwives versus other inserters with the rate of discomfort/pain experienced during speculum insertion being 89% (227/254) and 88% (245/280), respectively (p = 0.50), and that during Foley catheter insertion being 57% (144/254) and 62% (174/280), respectively (p = 0.20). Similarly, the mean pain scores did not differ between the two groups for digital vaginal examination (super-inserters = 4.59 ± 2.41; others = 4.50 ± 2.49; p = 0.76), speculum insertion (super-inserters = 4.91 ± 2.50; others = 4.49 ± 2.35; p = 0.05) and catheter insertion (super-inserters = 3.18 ± 2.59; others = 2.78 ± 2.71; p = 0.08).

Clinicians rated 70% of Foley catheter insertions easy and only 8% difficult; patient discomfort was not significantly affected by inserters’ difficulty assessment with OR 1.68 (95% CI 0.94–3.01) for moderate-difficult versus easy insertion.

Discussion

We found digital vaginal examination and speculum insertion (mean pain score = 4.6–4.7/10) to be significantly more uncomfortable than Foley catheter insertion (mean pain score = 3/10), while having the catheter in situ for a median of 14 h was mid-way in discomfort (mean pain score = 3.7/10). Only 12–13% of women experienced no discomfort during digital vaginal examination and speculum insertion, while about 40% experienced no discomfort during Foley catheter insertion. We identified no factors that influenced experience of discomfort during speculum insertion. However, being overseas-born increased the chance of discomfort on catheter insertion, as did a painful experience during the speculum insertion. Clinician designation and experience played little role in women’s discomfort. Prior to the insertion procedure, 93% of women reported being well-informed and 90% expected some discomfort.

Factors associated with discomfort on speculum insertion and vaginal examination in non-pregnant women include woman’s physical factors including previous genital trauma, psychological factors such as expectations, embarrassment, anxiety and fear of pain (Taylor et al., 2017; Yanikkerem et al., 2009), the difficulty of the procedure (Wyttenbach, 1998; Jaeger, 2010) and clinician factors such as gender (Galasiński and Ziółkowska, 2007) and communication skills (Yanikkerem et al., 2009; Wendt et al., 2004). In our study in term pregnant women, we found no significant association between speculum insertion discomfort and woman’s BMI, expectation of pain or knowledge of the procedure, or with the inserter’s recorded difficulty with the procedure. We did not explore previous genital trauma, psychological factors or clinician communication skills, and had too few male inserters to examine the impact of gender.

Being overseas-born was associated with increased discomfort during Foley catheter insertion but not during speculum insertion. Although it is difficult to explain this variance, research by Christiaens et al. (2010) on Belgian and Dutch women showed that acceptance of pain during birth and approach to pain relief can vary between nationalities. In addition, studies have shown that overseas-born pregnant women experience more anxiety and fear than those locally-born (Nicolaou, 2011; Renzaho and Ol-

Table 2
Women’s self-rated discomfort during the procedure including vaginal examination, speculum insertion, Foley catheter insertion and while catheter in situ.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women’s self-rated discomfort during vaginal examination n (%)</th>
<th>Women’s self-rated discomfort during speculum insertion n (%)</th>
<th>Mean pain score during vaginal examination ±SD (10 the highest, 0 the lowest)</th>
<th>Mean pain score during speculum insertion ±SD (10 the highest, 0 the lowest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No discom EI</td>
<td>44/330 (13%)</td>
<td>193/330 (58%)</td>
<td>4.8 ± 2.4</td>
<td>4.7 ± 2.4</td>
</tr>
<tr>
<td>Uncomfortable discom EI</td>
<td>193/330 (58%)</td>
<td>93/330 (28%)</td>
<td>4.8 ± 2.4</td>
<td>4.7 ± 2.4</td>
</tr>
<tr>
<td>Painful discom EI</td>
<td>93/330 (28%)</td>
<td>4.8 ± 2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pain score during vaginal examination</td>
<td>4.8 ± 2.4</td>
<td>4.7 ± 2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women’s self-rated discomfort during Foley catheter insertion n (%)</td>
<td>216/534 (40%)</td>
<td>226/534 (42%)</td>
<td>3.7 ± 2.1</td>
<td>14.4 (5.6–21.9)</td>
</tr>
<tr>
<td>No discom EI</td>
<td>216/534 (40%)</td>
<td>226/534 (42%)</td>
<td>3.7 ± 2.1</td>
<td>14.4 (5.6–21.9)</td>
</tr>
<tr>
<td>Uncomfortable discom EI</td>
<td>92/534 (17%)</td>
<td>92/534 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful discom EI</td>
<td>92/534 (17%)</td>
<td>92/534 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pain score during catheter insertion</td>
<td>3.0 ± 0.65</td>
<td>3.7 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 the highest, 0 the lowest)</td>
<td>3.0 ± 0.65</td>
<td>3.7 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pain score while catheter was in situ</td>
<td>4.91 ± 2.50</td>
<td>4.91 ± 2.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD) (10 the highest, 0 the lowest)</td>
<td>4.91 ± 2.50</td>
<td>4.91 ± 2.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median insertion-to-balloon removal/expulsion (hour)</td>
<td>14.4 (5.6–21.9)</td>
<td>14.4 (5.6–21.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data for the first 204 women were not available.
Table 3
Univariate and multivariate associations for demographic and clinical variables and pain during speculum insertion.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Discomfort/pain during speculum insertion</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman experiencing speculum insertion for first time</td>
<td>n/N (%)</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>No</td>
<td>285/324 (88%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>187/210 (89%)</td>
<td>1.11 (0.64, 1.92)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>82/97 (85%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥25 or older</td>
<td>390/437 (89%)</td>
<td>1.52 (0.81, 2.85)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parous</td>
<td>142/163 (87%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>330/371 (89%)</td>
<td>1.19 (0.68, 2.09)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>168/190 (88%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>304/344 (88%)</td>
<td>1.01 (0.58, 1.74)</td>
<td>0.99</td>
</tr>
<tr>
<td>Pre-induction Bishop score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>156/187 (83%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤4</td>
<td>316/347 (91%)</td>
<td>2.03 (1.18, 3.45)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Dilatation of cervix before Foley insertion (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>306/350 (87%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;1</td>
<td>166/184 (90%)</td>
<td>1.33 (0.74, 3.37)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Length of cervix before Foley insertion (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>337/376 (90%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥2</td>
<td>135/158 (85%)</td>
<td>0.68 (0.39, 1.18)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Position of cervix before Foley insertion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior/middle</td>
<td>160/185 (86%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Posterior</td>
<td>312/349 (89%)</td>
<td>1.32 (0.77, 2.67)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Consistency of cervix before Foley insertion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft/average</td>
<td>123/149 (83%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Firm</td>
<td>349/385 (91%)</td>
<td>2.05 (1.19, 3.53)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Station of cervix before Foley insertion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–1–2</td>
<td>211/242 (87%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥3</td>
<td>261/292 (89%)</td>
<td>1.23 (0.73, 2.10)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>BMI at first antenatal visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24.9 (normal or underweight)</td>
<td>218/256 (85%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥25 (overweight or obese)</td>
<td>254/276 (91%)</td>
<td>1.85 (1.07, 3.17)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Self-reported knowledge of the procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-informed</td>
<td>258/294 (88%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Needed more information</td>
<td>23/24 (96%)</td>
<td>3.21 (0.42, 24.49)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Expected discomfort/pain during the procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected no discomfort</td>
<td>24/31 (77%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Expected discomfort/pain</td>
<td>257/287 (90%)</td>
<td>2.50 (0.99, 6.29)</td>
<td>0.05</td>
</tr>
<tr>
<td>Inexperienced (&lt;5 insertions)</td>
<td>94/109 (82%)</td>
<td>0.80 (0.41, 1.53)</td>
<td>0.46</td>
</tr>
<tr>
<td>Inexperienced (≥5 insertions)</td>
<td>268/302 (89%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Insertions by clinicians</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered midwives</td>
<td>323/365 (88%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Obstetrics trainees</td>
<td>149/169 (88%)</td>
<td>0.97 (0.55, 1.71)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Type of Foley</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicone</td>
<td>240/276 (87%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Latex</td>
<td>221/246 (90%)</td>
<td>1.33 (0.77, 2.28)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

OR — odds ratio. CI — Confidence Interval. **The procedure referred to both speculum and catheter insertion.**

** Data for the first 216 women were not available.

While we did not explore anxiety associated with the procedure, it is possible that overseas-born women may have held more concerns about possible harm to the baby from the introduction of a foreign body close to the baby’s head. Alternatively, despite all women speaking English, there could have been subtle language misunderstandings with overseas-born women (and the staff attending them) finding it harder to separately distinguish the question/answer for speculum discomfort from that for Foley discomfort. An Australian study (McLachlan and Waldenström, 2005) suggested that descriptions of pain could be influenced by language barriers together with cultural traditions and beliefs.

The biggest predictor of pain on catheter insertion was pain on speculum insertion, which is unsurprising. Both steps of the procedure will be influenced by woman’s physical or psychological features, procedure difficulty and inserter technique. In addition, it is likely that discomfort during the speculum insertion would influence the woman’s assessment of the catheter insertion which follows immediately after the speculum insertion. This association has been shown in earlier research on invasive urodynamic bladder studies indicating that painful sensations reported during the different steps are strongly correlated with each other (Yiou et al., 2015).

Staff designation and level of experience appear to play no significant role in the rate of discomfort experienced during either speculum or Foley catheter insertion. These data and the inserters’ report that 70% of insertions were ‘easy’ suggest that both steps are relatively simple to perform regardless of experience.

The odds of discomfort/pain were non-significantly greater in the small group of women (7%) who reported needing more information about the procedure (OR = 3.91 for speculum insertion and OR = 1.21 for catheter insertion). With larger numbers this could possibly be significant.

Strengths and limitations

The main strength of the study is that it provides a large, prospective and detailed examination of the rates of discomfort ex-
Table 4
Univariate and multivariate associations for demographic and clinical variables and pain during Foley catheter insertion.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Discomfort/pain during catheter insertion</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discomfort/pain during catheter insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>50/97 (52%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25 or older</td>
<td>269/437 (61%)</td>
<td>1.49 (0.96, 2.32)</td>
<td>0.08</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parous</td>
<td>108/163 (66%)</td>
<td>0.66 (0.45, 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>210/371 (57%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>102/190 (54%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>216/344 (63%)</td>
<td>1.45 (1.02, 2.09)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pre-induction Bishop score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>100/187 (54%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≤4</td>
<td>218/347 (63%)</td>
<td>1.47 (1.03, 2.11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Dilatation of cervix before Foley insertion (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>210/350 (60%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≤1</td>
<td>108/184 (59%)</td>
<td>0.95 (0.66, 1.36)</td>
<td>0.77</td>
</tr>
<tr>
<td>Length of cervix before Foley insertion (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>231/376 (61%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2–3</td>
<td>87/158 (55%)</td>
<td>0.77 (0.52, 1.12)</td>
<td>0.17</td>
</tr>
<tr>
<td>Position of cervix before Foley insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior-middle</td>
<td>104/185 (56%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Posterior</td>
<td>214/349 (55%)</td>
<td>0.81 (0.56, 1.16)</td>
<td>0.125</td>
</tr>
<tr>
<td>Consistency of cervix before Foley insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft</td>
<td>79/149 (53%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Average-Firm</td>
<td>239/385 (62%)</td>
<td>1.45 (0.99, 2.12)</td>
<td>0.06</td>
</tr>
<tr>
<td>Station of cervix before Foley insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1/−2</td>
<td>131/242 (51%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>−3</td>
<td>187/292 (64%)</td>
<td>1.24 (0.87, 1.77)</td>
<td>0.25</td>
</tr>
<tr>
<td>BMI at first antenatal visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24.9 (normal or overweight)</td>
<td>142/256 (56%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 25 (overweight or obese)</td>
<td>176/278 (63%)</td>
<td>1.39 (0.98, 1.96)</td>
<td>0.07</td>
</tr>
<tr>
<td>Self-reported knowledge of the Foley insertion procedure*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-informed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needed more information</td>
<td>152/244 (63%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Expected discomfort/pain during the procedure*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected no discomfort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected discomfort/pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experience of discomfort/pain during speculum insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No discomfort</td>
<td>13/62 (21%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Uncomfortable/painal</td>
<td>305/472 (65%)</td>
<td>6.88 (3.63, 13.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinician's rating of Foley insertion difficulty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>204/373 (55%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate-difficult</td>
<td>184/317 (57%)</td>
<td>2.01 (1.35, 2.99)</td>
<td>0.001</td>
</tr>
<tr>
<td>Inserter's level of experience with Foley insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced (≥20 insertions)</td>
<td>171/302 (57%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Inexperienced (≤5 insertions)</td>
<td>73/109 (67%)</td>
<td>1.55 (0.98, 2.46)</td>
<td>0.06</td>
</tr>
<tr>
<td>Insertions by clinicians</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered midwives</td>
<td>114/169 (67%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Obstetrics trainees</td>
<td>204/365 (56%)</td>
<td>1.63 (1.12, 2.40)</td>
<td>0.01</td>
</tr>
<tr>
<td>Type of Foley</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicone</td>
<td>161/276 (59%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Latex</td>
<td>145/246 (59%)</td>
<td>1.00 (0.70, 1.41)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

OR = odds ratio. CI = Confidence Interval. *The procedure referred to both speculum and catheter insertion. ** Data for the first 216 women were not available.

Experienced by term pregnant women during a procedure commonly performed in late-pregnancy. While other studies have briefly considered discomfort during Foley catheter insertion, to the knowledge of authors, this is the first study to investigate in detail the factors contributing to term pregnant women’s experience of discomfort/pain during pre-labour cervical ripening using a Foley catheter.

There are some limitations to our study. The first is that the questions about discomfort for both speculum and catheter insertion were asked only after the catheter was in situ and the speculum removed. Clinically, it was appropriate to order the actions in this way while it was also necessary so that an independent person could ask about the discomfort experienced after the clinician inserter had left the room. However, although there was demonstrated capacity among women to score the steps separately and allocate significantly different mean pain scores, the discomfort reported for speculum insertion may have influenced that recorded for catheter insertion. The second limitation is that we introduced questions about women’s expectation of pain and their experience of discomfort during the initial digital vaginal examination partway through the study as we came to appreciate the added perspectives they provided. This resulted in a smaller, though still quite large, cohort for assessment of these aspects. Finally, the clinicians performing the insertions comprised a large group with varying experience. However, in a busy teaching hospital, this represents the ‘real world’ situation. This feature therefore also constitutes a strength of the study in that it allowed us to demonstrate that women’s discomfort was not influenced by inserter designation or experience indicating that the both speculum and Foley catheter insertions are simple to perform regardless of experience.
Conclusion

Term pregnant women undergoing cervical ripening prior to induction of labour found digital vaginal examination and speculum insertion to be moderately uncomfortable while insertion of a Foley catheter and having the catheter in situ for several hours were less uncomfortable procedures. No demographic or clinical variables influenced discomfort on speculum examination while being overseas-born increased discomfort on Foley insertion. Only 8% of insertions were rated as difficult by staff while 70% were rated easy. This, together with the fact that the inserter's level of experience had no influence on women's discomfort, are reassuring for those who wish to teach and learn this common procedure.

Conflict of interest

The authors declare no conflict of interest.

Funding sources

This research was conducted with the In-Kind support from the Department of Women's and Newborn Health at Westmead Hospital.

Ethical approval

Our study protocol was approved by the Western Sydney Human Research Ethics Committee prior to commencement.

Acknowledgements

We would like to thank the clinicians at Westmead hospital for their valuable contribution to this study. We would also like to acknowledge statistical advice from Ms Adrienne Kirby.

References

PSANZ SANDA /Stillbirth Centre for Research Excellence/University of Queensland: PSANZ Clinical Practice Guideline for Care Around Stillbirth and Neonatal Death, 2018

Author: Susan Heath
ORIGINAL ARTICLE

Point-of-care measurement of fetal blood lactate – Time to trust a new device

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Conflict of interest: All test strips were paid for by Westmead Hospital Women’s and Newborn Health. Lactate Pro 1 and Lactate Pro 2 test meters were hospital property while StatStrip temporarily loaned two test meters.

Received: 26 April 2017; Accepted: 14 June 2017

Background: Point-of-care lactate devices are used worldwide for intrapartum decision making. Current practice is often based on Lactate Pro (Arkray) but its imminent product discontinuation necessitates determination of an optimal replacement device.

Aims: To evaluate the performance of Lactate Pro and two other point-of-care devices, Lactate Pro 2 (Arkray) and StatStrip (Nova Biomedical), and to derive scalp lactate cut-offs equivalent to the current intervention trigger of >4.8 mmol/L.

Materials and methods: Paired umbilical cord arterial and venous blood samples from 109 births were tested on the three point-of-care products (two devices each), cross-compared with the reference method blood gas analyser.

Results: All brands deviate from the blood gas analyser, with Lactate Pro and StatStrip results consistently lower and Lactate Pro 2 consistently higher. Standard deviation from the blood gas analyser was smallest for StatStrip (0.78 mmol/L, cord artery), and largest for Lactate Pro 2 (1.03 mmol/L, cord artery). Within-brand variation exists and is similar for all brands (mean absolute difference on cord artery 0.23–0.30 mmol/L). Equivalent values to the 4.8 mmol/L intervention threshold based on Lactate Pro are 4.9–5.0 mmol/L for StatStrip and 5.3–5.9 mmol/L for Lactate Pro 2, calculated by receiver-operating characteristic analysis.

Conclusions: StatStrip appears superior to Lactate Pro 2 to replace the original Lactate Pro. Using StatStrip, the 4.8 mmol/L intervention threshold equivalent was 4.9–5.0 mmol/L. The variation in accuracy of point-of-care lactate devices may exceed the small increments (eg <4.2 mmol/L vs >4.8 mmol/L) that guide obstetric decisions.

KEYWORDS
fetal blood, fetal monitoring, lactate, point-of-care testing

INTRODUCTION

Intrapartum cardiotocography (CTG) has poor specificity for fetal compromise¹ so utilising fetal scalp blood testing to confirm fetal acidosis may reduce the intervention rate compared to CTG alone.² Consequently, such tests are popular and supported by national guidelines in many countries.³⁻⁵

Lactate is a direct product of anaerobic glucose metabolism with animal studies demonstrating that levels rise earlier during hypoxia⁶ and persist longer⁷ than a low pH. While limited randomised trial data suggest scalp pH and lactate are equivalent in predicting neonatal compromise,⁶⁻¹⁰ other data suggest prediction superiority for scalp lactate¹¹⁻¹⁴ and also cord lactate¹⁵ over pH.
Both pH and lactate can be measured by arterial blood gas (ABG) machines while lactate can also be measured by hand-held point-of-care (POC) devices. For scalp lactate testing, such devices require considerably smaller volumes of blood, necessitate fewer incisions and have greatly reduced failure rates than ABG machines.\(^8\,9\) They are also cheaper, can be used at the bedside, and give a result within seconds. These advantages have seen scalp lactate supersede scalp pH testing in many units.

Lactate levels vary between POC devices depending on calibration and the chemical process for measurement; the accuracy of various devices has been the source of extensive research.\(^3\,5\,13\,16\)–\(^21\) While several brands exist, Lactate Pro (Arkray) is the only POC lactate device with fetal scalp lactate interpretation parameters in wide clinical use (<4.2 mmol/L normal, 4.2–4.8 mmol/L pre-acidaemia, >4.8 mmol/L acidaemia on a fetal scalp sample), tested in a randomised controlled trial (RCT)\(^6\) and endorsed by guidelines.\(^3\,5\)

Lactate testing also occurs after birth, with umbilical cord artery lactate having good sensitivity and specificity for predicting neonatal neurological outcome. Although no agreed cut-off yet exists,\(^22\) a level of around 6.0 mmol/L is used in several studies;\(^15\) in our unit, such a level, even in a well baby, may result in neonatal unit admission for observation. Additionally, an umbilical artery lactate above 5.2 mmol/L is a mandatorily reportable state government health indicator.\(^23\)

Lactate Pro is used for all these assessments in many departments. However, the manufacturer ceased its production in 2016 with test strips for meters still in use unavailable after 2017; it is being replaced by a new version, Lactate Pro 2 (Arkray).

Our initial clinical experience demonstrates higher lactate readings using Lactate Pro 2 compared to the original Lactate Pro. This is consistent with recently published findings reporting that the >4.8 mmol/L scalp lactate acidaemia cut-off level with Lactate Pro corresponds to >7.3 mmol/L using Lactate Pro 2. Another POC lactate meter, StatStrip (Nova Biomedical, USA), is also available for consideration. Reports suggest that StatStrip correlates well with standard ABG machines\(^25\) and is superior to the original Lactate Pro in this respect.\(^13,17\) One study reports that the >4.8 mmol/L acidaemia decision-making cut-off may equate to >5.6 mmol/L using Statstrip.\(^17\)

Since key peripartum decisions depend upon POC lactate results in many units, the primary objective of this study is to determine a suitable device to replace the original Lactate Pro. We examined three POC devices: the original Lactate Pro, Lactate Pro 2 and StatStrip, cross-compared with our routine laboratory analyser, to answer three clinical questions. First, how accurate are Lactate Pro 2 and StatStrip when measured against the ABG machine, and is one product superior? Second, how much within-brand variation exists between two devices from the same company? Finally, can cut-off levels equivalent to 4.8 mmol/L on the original Lactate Pro be established for the new devices, and do these results confirm the cut-off values of the studies mentioned above?

**MATERIALS AND METHODS**

We conducted a prospective quality assurance study between December 2016 and February 2017 at Westmead hospital, Sydney, Australia, a large tertiary centre with about 5600 births per year. Pragmatically, to ensure a sufficient sample, umbilical cord blood was used, rather than scalp blood which is generally of small volume and may be mixed with tissue fluid.\(^13,17\) Umbilical cord blood is fetal blood (low oxygen, high haematocrit) and therefore an appropriate alternative to scalp blood. While umbilical cord artery lactate best reflects the condition of the newborn, the vein was also analysed on the basis that scalp lactate levels should lie between those of the umbilical vein and artery.

Paired cord blood samples were collected by the accoucheur at birth when indicated (testing is not universal but performed at a low threshold of concern). As soon as the baby was born, samples were drawn from a double-clamped segment of umbilical cord into pre-heparinised syringes and immediately tested on a bedside Lactate Pro meter. The remainder of the sample in the syringe was immediately taken to the neonatal intensive care unit (NICU) by the study researchers for simultaneous testing on seven machines assembled in parallel: two each of the three types of POC meter (Lactate Pro, Arkray, Japan; Lactate Pro 2, Arkray, Kyoto, Japan; LP2; and StatStrip Xpress, Nova Biomedical, Waltham, MA, USA) together with the reference blood gas analyser (Radiometer ABL800 Series; ABG). Results from the test POC meters were not available to the clinical team, nor were the clinical team’s bedside lactate results used in the study. When required for clinical care, the ABG result was provided to the NICU team.

The POC lactate devices all require less than 5 μL of blood and report in less than 60 s, while the ABG machine requires 95 μL and reports in 2 min. The three POC devices measure in the range of 0.8–20.0 mmol/L, which covers the range of neonatal blood lactate. All POC devices and the ABG machine were calibrated as per the manufacturers’ instructions.

Statistical analysis was performed in Stata Version 14.0 (Statacorp, College Station, TX, USA) with arterial and venous samples separately analysed. Accuracy of POC devices with regard to the ABG machine was assessed by paired t-test and Bland–Altman analysis. Since two devices were tested for each of the three POC brands, a command in the statistical software was used to randomly select one of two samples from each brand to be used for this analysis. Within-brand reliability was assessed by Bland–Altman analysis. To establish LP2 and StatStrip values corresponding to the LP1 lactate values of 4.2, 4.8 and 6.0 mmol/L, receiver-operating characteristic (ROC) curves in conjunction with the Youden’s J statistic were used.

The Western Sydney Human Research Ethics Committee gave approval for the study as a quality assurance review of the test devices. Patient consent was deemed unnecessary.
RESULTS

Cord blood arterial and venous samples were collected from 110 patients (220 samples), of which 109 artery and 109 vein samples were of sufficient volume to test all six POC meters, while 104 artery and 107 vein samples were sufficient to also test the ABG machine. The median, mean and range of lactate results were 5.1, 5.2 and 1.7–15.0 mmol/L for the umbilical artery, and 4.3, 4.5 and 1.4–12.0 mmol/L for the umbilical vein, respectively, as measured on the ABG.

Accuracy of POC devices compared against the ABG

LP1 and StatStrip recorded significantly lower mean lactate than the ABG machine on both cord artery and vein samples (Table 1). LP2 recorded a significantly higher mean result on the artery sample and no difference from the ABG on the vein sample. The standard deviation of difference from the ABG machine was highest for LP2 (1.03 mmol/L artery; 0.88 mmol/L vein) and lowest for StatStrip (0.78 mmol/L artery; 0.49 mmol/L vein); this translated to considerably closer limits of agreement for StatStrip compared to LP2 (Fig. 1).

Within-brand variation

Two devices of the same brand varied with a mean absolute difference (MAD) of 0.16–0.30 mmol/L with neither StatStrip nor LP2 being superior (Table 2). The within-brand standard deviation (SD), which describes the extent of variation around the mean difference, was smallest for LP2 on the arterial sample (0.38 mmol/L) and smallest for LP1 and StatStrip on the venous sample (0.29 mmol/L). The within-brand variation in lactate measurement was therefore similar for the three POC brands.

TABLE 1 Accuracy of point-of-care (POC) lactate devices compared to the ABG

<table>
<thead>
<tr>
<th>Group for comparison</th>
<th>Mean difference† (mmol/L)</th>
<th>P-value</th>
<th>Standard deviation of difference (mmol/L)</th>
<th>Limits of agreement‡ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord artery (n = 104)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LP1 – ABG</td>
<td>-0.82</td>
<td>&lt;0.001</td>
<td>0.90</td>
<td>-2.57 0.94</td>
</tr>
<tr>
<td>LP2 – ABG</td>
<td>+0.59</td>
<td>&lt;0.001</td>
<td>1.03</td>
<td>-1.44 2.61</td>
</tr>
<tr>
<td>StatStrip – ABG</td>
<td>-0.56</td>
<td>&lt;0.001</td>
<td>0.78</td>
<td>-2.10 0.98</td>
</tr>
<tr>
<td>Cord vein (n = 107)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LP1 – ABG</td>
<td>-0.70</td>
<td>&lt;0.001</td>
<td>0.66</td>
<td>-1.99 0.58</td>
</tr>
<tr>
<td>LP2 – ABG</td>
<td>-0.05</td>
<td>0.557</td>
<td>0.88</td>
<td>-1.78 1.68</td>
</tr>
<tr>
<td>StatStrip – ABG</td>
<td>-0.69</td>
<td>&lt;0.001</td>
<td>0.49</td>
<td>-1.66 0.28</td>
</tr>
</tbody>
</table>

ABG reference, arterial blood gas machine; LP1 Lactate Pro 1, LP2 Lactate Pro 2.
†Mean difference: The mean lactate for the POC device subtracted by the mean lactate for the ABG machine. It is a measurement of negative or positive bias in the POC devices compared with the ABG. The standard deviation (SD) and limits of agreement are measured from this point.
‡Limits of agreement: mean ± 2 SD. Encompasses 95% of results.

Intervention thresholds for newer POC devices equivalent to established clinical cut-offs based on Lactate Pro

Using ROC curve analysis (Fig. 2), the lactate values equivalent to 4.8 mmol/L on LP1 were determined as 5.9 mmol/L (artery) and 5.3 (vein) using LP2, and 5.0 (artery) and 4.9 (vein) using StatStrip (Table 3). Equivalent LP2 and StatStrip levels for LP1 4.2 and 6.0 mmol/L were also determined (Table 3).

DISCUSSION

Of the three brands tested, our study found similar within-brand variation for all, but narrowest overall variation in accuracy for StatStrip. Additionally, intervention cut-off levels comparable to that of 4.8 mmol/L currently used with LP1 were more consistent across arterial and venous samples with StatStrip (4.9–5.0 mmol/L) than with LP2 (5.3–5.9 mmol/L).

Performance of POC devices and implications of this

Within-brand variation existed and was similar for all three POC products, with two devices from the same company differing on average by 0.23–0.30 mmol/L for the same cord artery sample. Another study using LP1 found a smaller within-brand variation.¹⁸

Both LP1 and StatStrip measured lactate concentration systematically below ABG values, while LP2 results were systematically above the ABG. Other studies have shown similar negative bias in LP1¹⁶ and StatStrip¹⁷,²⁶ and positive bias in LP2.²⁴

To a large extent, the degree of deviation of mean POC lactate from an ABG machine is less important than it appears since POC lactate clinical cut-off levels derived from perinatal outcomes are
specific for the brand of lactate device used in the study. Lactate measurements are not well standardised across brands due to differing technologies, producing results with good correlation but differing absolute value. Therefore, lactate cut-off levels for fetal scalp and neonatal cord blood must be determined for each device and cannot simply be assumed to apply to a different brand without independent confirmation. Our findings support this.

This does not limit POC lactate device usefulness as long as brand-specific lactate cut-offs are used. The scalp lactate levels established for Lactate Pro were based on retrospective examination of neonatal acidosis and neurological outcomes which suggested that scalp lactate predicted these more reliably than scalp pH and that a scalp lactate of 4.8 mmol/L gave reasonable sensitivity and specificity for such outcomes. This level was then validated in an RCT which allocated women to scalp pH (intervention cut-off pH <7.21; pre-acidaemia 7.21–7.25) or scalp lactate using Lactate Pro (intervention cut-off >4.8 mmol/L; pre-acidaemia 4.2–4.8 mmol/L) where the overall neonatal acidosis rates were the same in both groups (3.6% and 3.2%, respectively) for the same intervention rates (CS/Instrumental 66.2 and 65.6%, respectively). Of importance, in the sub-cohort where a baby was born within 60 min of scalp sampling, no baby with scalp lactate <4.8 mmol/L was born with cord artery pH of <7.0, while six babies with scalp pH >7.21 were born with this level of acidosis.

Even so, the degree of error in accuracy of lactate measurements and within-brand variation must be appreciated by the clinician. On cord arterial samples, 68% of the time (1 SD), a result obtained with StatStrip was within ±0.8 mmol/L of the true result and 95% of the time (2 SD) within ±1.6 mmol/L. With LP2, the variation was ±1.0 mmol/L and ±2.0 mmol/L, respectively. Even allowing for the differences in mean lactate between products, the standard deviations are quite wide for perinatal application, given that decisions are made across small ranges such as those separating <4.2 mmol/L and >4.8 mmol/L. Graphs from other researchers demonstrate similar findings.

**POC equivalent values to Lactate Pro established clinical cut-offs**

Using ROC and Youden’s Index analysis to examine cut-off levels we found the lactate level equivalent to LP1 4.8 mmol/L was 4.9–5.0 mmol/L using StatStrip and 5.3–5.9 mmol/L using LP2. We
Fetal blood lactate point-of-care devices

note that previous attempts to find a conversion from LP1 cut-off levels to these POC lactate machines have used linear regression analysis; Orsonneau found LP1 lactate 4.8 mmol/L equivalent to 5.6 mmol/L using StatStrip on umbilical vein samples,17 while Birgisdottir found it to be equivalent to 7.3 mmol/L using LP2 on scalp samples.24 However, linear regression and correlation analysis are inappropriate for comparing two quantitative methods that measure the same parameter, as they do not provide information about the degree of agreement between the two quantitative methods.30

Preferred alternative device to Lactate Pro

Of the two alternatives tested, this study favours StatStrip over LP2 as a replacement device for LP1. StatStrip demonstrates less variability in readings overall and more consistent cut-off levels across artery and vein in ROC analysis than LP2. Additionally, the StatStrip result is close to the original LP1 which affords reasonable confidence in continuing with the long-established >4.8 mmol/L scalp lactate intervention cut-off for now, acknowledging a likely small increase in intervention with StatStrip at this level. Ideally, outcomes-based data will shortly provide further guidance.

TABLE 2 Within-brand variation of duplicate readings for the three point-of-care devices

<table>
<thead>
<tr>
<th>Group for comparison</th>
<th>Mean absolute difference† (mmol/L)</th>
<th>Standard deviation of the difference (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord artery (n = 109)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate Pro (device A – device B)</td>
<td>0.23</td>
<td>0.45</td>
</tr>
<tr>
<td>Lactate Pro 2 (device A – device B)</td>
<td>0.27</td>
<td>0.38</td>
</tr>
<tr>
<td>StatStrip (device A – device B)</td>
<td>0.30</td>
<td>0.54</td>
</tr>
<tr>
<td>Cord vein (n = 109)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate Pro (device A – device B)</td>
<td>0.16</td>
<td>0.29</td>
</tr>
<tr>
<td>Lactate Pro 2 (device A – device B)</td>
<td>0.22</td>
<td>0.33</td>
</tr>
<tr>
<td>StatStrip (device A – device B)</td>
<td>0.19</td>
<td>0.29</td>
</tr>
</tbody>
</table>

†Mean absolute difference (MAD): mean of all differences, taking differences in either direction as positives. For example, if in the first sample tested, Device A’s result is 0.5 mmol/L higher than Device B, while in the second sample Device A’s result is 0.3 mmol/L lower than Device B, the MAD is 0.4 mmol/L ((0.5 + 0.3)/2).

FIGURE 2 Receiver operating characteristic curves for determining a cut-off equivalent to 4.8 mmol/L on Lactate Pro with potential replacement devices Lactate Pro 2 and Statstrip, using cord artery (top row, n = 104) and vein samples (bottom row, n = 107).
TABLE 3  ROC curve analysis determining key Lactate Pro cut-off levels with Lactate Pro 2 and StatStrip

<table>
<thead>
<tr>
<th>Corresponding equivalent value (mmol/L)</th>
<th>Lactate Pro 2</th>
<th>StatStrip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>Vein</td>
<td>Artery</td>
</tr>
<tr>
<td>ROC derivation for Lactate Pro readings (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2†</td>
<td>5.2</td>
<td>4.3</td>
</tr>
<tr>
<td>4.8‡</td>
<td>5.9</td>
<td>5.0</td>
</tr>
<tr>
<td>6.0§</td>
<td>7.3</td>
<td>6.1</td>
</tr>
</tbody>
</table>

ROC, receiver operating characteristic.
†4.2–4.8 mmol/L: scalp lactate level using Lactate Pro indicating pre-acidaemia.
‡4.8–5.2 mmol/L: scalp lactate level using Lactate Pro indicating acidaemia; commonly triggers immediate intervention for delivery.
§6.0 mmol/L: cord artery lactate level using Lactate Pro that may prompt neonatal admission for observation.

Strengths and limitations of the study

The strengths of our study include over 200 umbilical cord samples tested across a relevant clinical range of lactate values on the two devices currently considered most likely to be Lactate Pro replacements. The samples were tested immediately and simultaneously, wholly within the clinical setting, rather than being sent to a central laboratory. Additionally, duplicate POC device testing provides within-brand assessment.

Limitations include the use of fetal umbilical cord blood rather than scalp blood to allow sufficient volume, as others have;16,19,20 studies using both have shown greater variation in scalp than cord samples, possibly due to mixture with tissue fluid.13,26 Only two alternative POC meters which have undergone recent obstetric investigation13,17,24 were included in the study, although other lactate devices are currently being studied for obstetric use, including Roche Accutrend PlusTM,21 together with a range of devices in the sporting world.31 Finally, the study was based on laboratory performance of devices against the obstetric benchmark, Lactate Pro, rather than perinatal outcomes, but this was the only feasible option given its imminent unavailability.

CONCLUSION

StatStrip was more consistent and accurate compared to the ABG and had more consistent Lactate Pro-equivalent cut-off levels across arterial and venous samples. Within-brand variation was similar for all three POC devices tested. StatStrip is therefore the more suitable replacement for Lactate Pro at the present time. The StatStrip level equivalent to Lactate Pro 4.8 mmol/L was 4.9–5.0 mmol/L. The variation in accuracy of point-of-care lactate devices may exceed the small increments (eg <4.2 mmol/L vs >4.8 mmol/L) that guide obstetric decisions.

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Prediction of intraventricular haemorrhage in preterm infants using time series analysis of blood pressure and respiratory signals

Jacqueline Huvanandana1, Chinh Nguyen2, Cindy Thamrin2, Mark Tracy3,4, Murray Hinder1,3 & Alistair L. McEwan1

Despite the decline in mortality rates of extremely preterm infants, intraventricular haemorrhage (IVH) remains common in survivors. The need for resuscitation and cardiorespiratory management, particularly within the first 24 hours of life, are important factors in the incidence and timing of IVH. Variability analyses of heart rate and blood pressure data has demonstrated potential approaches to predictive monitoring. In this study, we investigated the early identification of infants at a high risk of developing IVH, using time series analysis of blood pressure and respiratory data. We also explore approaches to improving model performance, such as the inclusion of multiple variables and signal pre-processing to enhance the results from detrended fluctuation analysis. Of the models we evaluated, the highest area under receiver-operator characteristic curve (5th, 95th percentile) achieved was 0.921 (0.82, 1.00) by mean diastolic blood pressure and the long-term scaling exponent of pulse interval (PI $\alpha_2$), exhibiting a sensitivity of >90% at a specificity of 75%. Following evaluation in a larger population, our approach may be useful in predictive monitoring to identify infants at high risk of developing IVH, offering caregivers more time to adjust intensive care treatment.

Intraventricular Haemorrhage (IVH) remains a serious threat to survival for preterm infants and neurodevelopmental outcomes1. Despite advances in modern neonatal care such as antenatal steroids, artificial surfactant treatment and the use of neuroprotective agents such as magnesium sulphate given to mothers in labour, rates of IVH, particularly high grade, remain unchanged. Prematurity, respiratory-distress syndrome and mechanical ventilation are among the factors that may predispose infants to IVH. Recent studies have also suggested an association between IVH and cerebral pressure passivity, that is, where changes in cerebral blood flow correspond to changes in blood pressure2. The need for resuscitation and cardiorespiratory management of preterm infants within the first 24 hours of life play an important role in the development and timing of IVH3,4, where the majority of these cases can be detected at their full extent by the end of the first postnatal week5. The potential to identify infants at high risk of developing IVH is thus, particularly important.

Retrospective studies of premature infants after the diagnosis of IVH have highlighted altered autonomic functions which are reflected by heart rate variability analysis6,7. In particular, one study showed that these differences could be detected using electrocardiogram data from the first 24 hours of life6. Variability of beat-to-beat systolic blood pressure and mean arterial pressure has also been shown to offer useful information in distinguishing infants who later developed IVH from those who did not8. Such distinctions were demonstrated using detrended fluctuation analysis (DFA), a non-linear time domain technique that is able to quantify long-range power law correlations in a given time series. Its application is characterised by a scaling exponent ($\alpha$) which can be calculated over different time scales and indicates the corresponding degree of correlation9,11. More recent work in this area by Fairchild et al. has demonstrated associations between a heart rate characteristic index and adverse neurodevelopmental outcomes or white matter damage12. Models for early prediction of IVH have explored either clinical risk factors, as in the case of Luque et al.13 with an AUC of 0.79, or employed

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time series analysis techniques and physiological signals as in Tuzcu et al. who reported a sensitivity of 70% and specificity of 79% for their model using heart rate variability.

The objective of this study was twofold; firstly, to explore means of improving prediction of IVH from DFA through pre-processing, and secondly, to evaluate the potential of multivariable or multimodal models in the prediction of IVH. The latter objective focused specifically on combinations of blood pressure and respiratory features and inherently involved an evaluation of robustness as applied in a clinical context. The features evaluated comprised of the mean (μ) as well as short- and long-term scaling exponents derived from DFA (α₁ and α₂, respectively), extracted from five different time series. These were: mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse interval (PI) series as derived from the arterial blood pressure data, as well as the interbreath intervals (IBI) from the respiratory air flow data.

### Results

#### Study Population

The study cohort consisted of 27 low birth-weight (<1500 g) infants, 8 of which subsequently developed IVH. We examined the differences in physiological characteristics and other metadata between the two groups, as summarised in Table 1. Although the IVH and non-IVH groups did not exhibit significant differences in the collected metadata, certain clinical characteristics, namely, the mean DBP values were observed to be significantly different for the two groups after non-linear trend removal (p < 0.05). This established a foundation for fitting the univariate logistic regression models, though evaluation of their overall performance requires reference to leave-one-out cross-validation (LOOCV) results.

#### Effect of Detrending

In the initial stages of model fitting, we observed that in certain instances, the arterial blood pressure was subject to non-linear drift. We examined the effect of detrending the arterial blood pressure signal and noted that prediction performance of the fitted logistic regression models could be improved. This detrending affected the linear blood pressure features in particular, which also propagated to the beat-to-beat blood pressure values and thus the scaling exponents derived from DFA (α₁ and α₂, the short- and long-term scaling exponents, respectively). The Mann-Whitney U-test comparisons of the non-detrended features are shown in Table 2, where the effect of detrending was characterised by the changes in AUC and p values from the two-sided Mann-Whitney U-test. For example, the AUC scores of the mean DBP model improved from 0.757 to 0.807 subsequent to detrending. A similar increase from 0.757 to 0.771 was also observed for the univariate model of the long-term scaling exponent of DBP (DBP α₂), motivating the inclusion of this pre-processing step for the subsequent analyses. The histograms of mean DBP and DBP α₂ are also shown in Fig. 1.

#### Univariate Predictors of IVH

We fitted univariate logistic regression models using various linear and DFA features, taking the mean across all qualifying time windows of data for each subject. We evaluated the AUC, the 95% confidence interval (5th, 95th percentile) according to the Delong method for determining standard error, as well as the positive likelihood ratio and threshold corresponding to a specificity of 75%. These results are summarised in Table 3. Overall, the short-term fractal exponents (α₁) derived from the MAP, SBP and DBP signals as well as the mean DBP yielded the highest AUCs. Respiratory variables were not found to be strongly predictive.

#### Multivariable Predictors of IVH

It was also observed that model performance could also be improved through combination of the predictors extracted for the univariate models, as shown in Table 4. Predictor combinations that were significantly correlated were excluded to mitigate effects of collinearity. Many of the multivariable models exhibited higher AUC scores than univariate models, with the highest being the combination of mean DBP and PI α₂.

### Table 1. Comparison of physiological variables between infants who later developed intraventricular haemorrhage (IVH) and those who did not (non-IVH).

<table>
<thead>
<tr>
<th>Variable</th>
<th>IVH (n = 7)</th>
<th>Non-IVH (n = 20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>26.8 ± 1.2</td>
<td>26.9 ± 1.8</td>
<td>0.781</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>1120 ± 282</td>
<td>1029 ± 293</td>
<td>0.580</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>57.1 ± 49.5</td>
<td>65.0 ± 47.7</td>
<td>0.741</td>
</tr>
<tr>
<td>CRIBII</td>
<td>9 ± 1</td>
<td>9 ± 2</td>
<td>1.000</td>
</tr>
<tr>
<td>PDA (%)</td>
<td>85.7 ± 35.0</td>
<td>80.0 ± 40.0</td>
<td>0.774</td>
</tr>
<tr>
<td>RDS</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Apgar 1-min</td>
<td>6 ± 1</td>
<td>6 ± 2</td>
<td>0.696</td>
</tr>
<tr>
<td>Apgar 5-min</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
<td>0.421</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>32.5 ± 6.1</td>
<td>35.2 ± 4.7</td>
<td>0.422</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>25.0 ± 3.9</td>
<td>29.0 ± 4.6</td>
<td>0.050</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>32.1 ± 5.6</td>
<td>35.5 ± 4.2</td>
<td>0.234</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>24.6 ± 3.5</td>
<td>29.4 ± 4.1</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD. *Denotes detrended features. CRIBII is the Clinical Risk Index for Babies score II, PDA is Patent Ductus Arteriosus and RDS is Respiratory Distress Syndrome. p values are derived from a two-sided Mann-Whitney U-test where significance is defined as p < 0.05.
Similar results were obtained when evaluating all qualifying windows and with the inclusion of gestational age. Note however that the comparisons with the best performing univariate model (i.e. mean DBP, Table 3) were not statistically significant ($p > 0.05$) due to high degree of overlap. The ROC curves for a number of these models are displayed in Fig. 2, where the non-linear detrending process to obtain the DBP $c_\mu$ feature is illustrated in Fig. 3.

Leave-One-Out Cross-Validation. The models were further evaluated using LOOCV, where the probability estimates of each testing sample were used to construct a receiver-operator characteristic (ROC) curve\textsuperscript{15,16}, as summarised in the latter column of Table 4. Delong comparison of these LOOCV ROC curves with the corresponding LOOCV mean DBP model did not exhibit statistically-significant results ($p > 0.05$), with the exception of the mean DBP and SBP $\alpha_1$ combination.

Sensitivity Analysis. The models used to obtain these results were based on the mean feature(s) calculated from all qualifying 10 min windows for each subject, with a 30 sec overlap. To evaluate how robust these results were, we examined the effect of including all individual windows rather than the mean feature per subject, of using non-overlapping windows and of including gestational age. The first two cases involved use of a mixed-model allowing for repeated measures while the latter involved the addition of gestational age as a predictor in the existing multivariable models. In all three cases, we found that mean DBP and PI $\alpha_2$ remained the most predictive combination for IVH (where AUC = 0.88, 0.86 and 0.85 for the three cases, respectively, compared to the AUC = 0.92 reported in Table 4).

Discussion

Summary of findings. This study evaluated the blood pressure and respiratory features in discerning infants with IVH from those without. The highest AUC achieved was 0.921 (95% CI 0.82, 1.00) by the model fitted with PI $\alpha_2$ and mean DBP. The results of cross-validation also supported this, with an AUC\textsubscript{LOOCV} of 0.821 (0.66, 0.99). This model exhibited a sensitivity of >90% at a specificity of 75% which is greater than that reported for the heart rate variability-based model from Tuzcu et al. (70% sensitivity, 79% specificity)\textsuperscript{8}. This latter cohort was of a similar

<table>
<thead>
<tr>
<th>Variable</th>
<th>IVH</th>
<th>Non-IVH</th>
<th>AUC</th>
<th>AUC$^{c}$</th>
<th>$p$</th>
<th>$p^{c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP $\mu$</td>
<td>32.5 ± 6.1 mmHg</td>
<td>35.2 ± 4.7 mmHg</td>
<td>0.607</td>
<td>0.657</td>
<td>0.422</td>
<td>0.234</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>0.96 ± 0.17</td>
<td>0.78 ± 0.19</td>
<td>0.779</td>
<td>0.779</td>
<td>0.033</td>
<td>0.033</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>1.10 ± 0.06</td>
<td>1.00 ± 0.18</td>
<td>0.671</td>
<td>0.65</td>
<td>0.194</td>
<td>0.257</td>
</tr>
<tr>
<td>SBP $\mu$</td>
<td>41.9 ± 9.7 mmHg</td>
<td>42.7 ± 5.4 mmHg</td>
<td>0.564</td>
<td>0.55</td>
<td>0.638</td>
<td>0.719</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>0.83 ± 0.11</td>
<td>0.69 ± 0.15</td>
<td>0.764</td>
<td>0.771</td>
<td>0.043</td>
<td>0.038</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>1.04 ± 0.08</td>
<td>0.97 ± 0.16</td>
<td>0.643</td>
<td>0.664</td>
<td>0.281</td>
<td>0.213</td>
</tr>
<tr>
<td>DBP $\mu$</td>
<td>25.0 ± 3.9 mmHg</td>
<td>29.0 ± 4.6 mmHg</td>
<td>0.757</td>
<td>0.807</td>
<td>0.05</td>
<td>0.019</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>0.85 ± 0.12</td>
<td>0.68 ± 0.20</td>
<td>0.786</td>
<td>0.807</td>
<td>0.029</td>
<td>0.019</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>1.05 ± 0.06</td>
<td>0.93 ± 0.16</td>
<td>0.757</td>
<td>0.771</td>
<td>0.05</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Table 2. Effect of Detrending. Values are reported as mean ± SD, $p$ values are from Mann-Whitney U-tests from the non-detrended data. AUC is the area under the ROC curve for prediction of IVH. Note that AUC$^{c}$ and $p^{c}$ are obtained from the detrended data.

Figure 1. Normalised histograms of (a) mean DBP and (b) DBP $\alpha_1$ for IVH and non-IVH groups. The distributions for each group were based on features extracted from all individual windows which met the quality criteria.
informative proxy of cerebral perfusion pressure distribution of mean DBP is of particular importance, given previous assertions that linear features alone were not an aspect of signal quality, may confound the results from DFA as well as linear parameters. The significant improvements suggest that long-term drift and/or baseline wander of the blood pressure signals, among other models fitted with these features increased from 0.757 to 0.807 and 0.771, respectively (Tables 2 and 3). These improvements represent the mean of all qualifying 10 min windows across the recording, rather than a single segment. In the clinical application of DFA to monitored signals, we strongly recommend examination of signal data to determine including the quality control measures for window selection and the evaluation process; the features extracted not explicitly evaluated in the previous studies. Aside from the detrending, this analysis differed in other aspects Pulse pressure, seen in symptomatic patent ductus arteriosus. It is necessary to note however that this feature was not previously reported for the AUC are derived from the Delong approach for determining standard error and comparison with the reference ROC of the non-detrended mean MAP model.

size (n = 24), though it was limited to very low birthweight infants (< 1000 g) as opposed to our low birthweight cohort, potentially contributing to the difference in IVH representation observed (41.7% compared to 29.6%). Although the univariate model fitted with mean DBP exhibited an AUC of 0.807 in the initial analysis, results from LOOCV cautioned its use as a sole predictor, with an AUC of 0.607 and a non-significant 95% confidence interval of (0.38, 0.88).

**Effect of detrending.** Out of all the factors we examined, detrending as part of the pre-processing phase of analysis resulted in the greatest improvement in prediction of IVH. It rendered both mean DBP and DBP α₂ significantly different (p < 0.05) between the IVH and non-IVH groups, where the AUC scores for two univariate models fitted with these features increased from 0.757 to 0.807 and 0.771, respectively (Tables 2 and 3). These improvements suggest that long-term drift and/or baseline wander of the blood pressure signals, among other aspects of signal quality, may confound the results from DFA as well as linear parameters. The significant contribution of mean DBP is of particular importance, given previous assertions that linear features alone were not an informative proxy of cerebral perfusion pressure and reports that such features were not significantly different between the IVH and non-IVH groups. This relationship to DBP may also have been a reflection of a widened pulse pressure, seen in symptomatic patent ductus arteriosus. It is necessary to note however that this feature was not explicitly evaluated in the previous studies. Aside from the detrending, this analysis differed in other aspects including the quality control measures for window selection and the evaluation process; the features extracted represent the mean of all qualifying 10 min windows across the recording, rather than a single segment. In the clinical application of DFA to monitored signals, we strongly recommend examination of signal data to determine whether overall detrending is necessary prior to analysis.

**Use of bivariate models.** Subsequent to detrending, a further increase in AUC achieved through fitting of bivariate models, where the combination of mean DBP with MAP α₁ and PI α₁, for example, exhibited respective scores of 0.871 and 0.921. This would suggest that relevant, non-redundant information may be captured using linear and DFA-based approaches in the prediction of IVH. The short-term scaling exponents for the beat-to-beat MAP and SBP, along with mean DBP were shown to be relatively robust markers in prediction of IVH for the studied cohort. Although all of the studied infants had triggered ventilation modes (synchronised intermittent positive pressure ventilation), breathing termination was not employed and so the potential for adverse patient-ventilator asynchrony interaction was possible. Previous work examining the impact of patient-ventilator asynchrony indicates the significant potential for IVH with this phenomenon. These results align with those previously reported and the altered vagal nerve activity in infants with IVH. From further evaluation of the bivariate models, it was clear that the initial analysis did not necessarily translate to robust and consistent performance in leave-one-out cross-validation. The model with the highest AUC in the initial analysis achieved an AUC of 0.821 (0.66, 0.99), though it did not exhibit a statistically significant improvement on the univariate

### Table 3. Univariate Logistic Regression models.

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC (95% CI)</th>
<th>p</th>
<th>Threshold</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μ</td>
<td>0.657 (0.37, 0.95)</td>
<td>0.218</td>
<td>31.72 mmHg</td>
<td>2.29</td>
</tr>
<tr>
<td>α₁</td>
<td>0.779 (0.60, 0.96)</td>
<td>0.359</td>
<td>0.92</td>
<td>2.86</td>
</tr>
<tr>
<td>α₂</td>
<td>0.650 (0.44, 0.86)</td>
<td>0.839</td>
<td>1.08</td>
<td>2.40</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μ</td>
<td>0.550 (0.20, 0.90)</td>
<td>0.389</td>
<td>37.96 mmHg</td>
<td>2.29</td>
</tr>
<tr>
<td>α₁</td>
<td>0.771 (0.58, 0.96)</td>
<td>0.382</td>
<td>0.81</td>
<td>2.86</td>
</tr>
<tr>
<td>α₂</td>
<td>0.664 (0.43, 0.90)</td>
<td>0.792</td>
<td>0.94</td>
<td>1.60</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μ</td>
<td>0.807 (0.62, 0.99)</td>
<td>0.022</td>
<td>26.34 mmHg</td>
<td>2.86</td>
</tr>
<tr>
<td>α₁</td>
<td>0.807 (0.64, 0.97)</td>
<td>0.278</td>
<td>0.79</td>
<td>3.43</td>
</tr>
<tr>
<td>α₂</td>
<td>0.771 (0.59, 0.95)</td>
<td>0.415</td>
<td>1.02</td>
<td>2.80</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μ</td>
<td>0.543 (0.25, 0.83)</td>
<td>0.759</td>
<td>50.10 ms</td>
<td>1.40</td>
</tr>
<tr>
<td>α₁</td>
<td>0.607 (0.38, 0.84)</td>
<td>1.000</td>
<td>0.42</td>
<td>1.40</td>
</tr>
<tr>
<td>α₂</td>
<td>0.707 (0.45, 0.97)</td>
<td>0.709</td>
<td>1.08</td>
<td>2.29</td>
</tr>
<tr>
<td>IBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μ</td>
<td>0.707 (0.46, 0.96)</td>
<td>0.643</td>
<td>115.88 ms</td>
<td>2.40</td>
</tr>
<tr>
<td>α₁</td>
<td>0.500 (0.25, 0.75)</td>
<td>0.568</td>
<td>0.52</td>
<td>1.14</td>
</tr>
<tr>
<td>α₂</td>
<td>0.557 (0.26, 0.85)</td>
<td>0.813</td>
<td>0.45</td>
<td>0.40</td>
</tr>
</tbody>
</table>
It was interesting to note the inclusion of pulse interval-based features in the highest-scoring model in both the initial analysis and cross-validation, given its use as an estimate of heart rate variability and the reported high correlation between the two. The accuracy of this estimation, however, has not been clarified, particularly in the neonatal context, though electrocardiogram-based heart rate variability has been found to offer useful information in distinguishing infants with and without IVH.

Addition of respiratory signals.
In this study, we found that the addition of respiratory signals did not considerably improve model performance. The fractal dynamics of respiration have been applied in the context of preterm infants, though not with respect to IVH. As for the models fitted with interbreath interval (IBI) features, mechanical ventilation may have contributed to their observed lack of predictability, despite the relevance of respiration mechanics in the development of IVH. It is also possible that the IBI-based features were not suited to characterising patient-ventilator asynchrony.

Clinical significance and application.
Hypercarbia, high ventilator pressure and patency of the ductus arteriosus are among the factors and events that may influence the fluctuation of blood pressure of preterm infants in the neonatal intensive care unit. Infants who later developed IVH exhibited lower mean DBP and a higher DBP_α (p < 0.05) across the entire recording in this study. Recent studies have reported a range of observations pertaining to blood pressure and IVH, with the main focus on characterising cerebral perfusion. It is also possible that the IBI-based features were not suited to characterising patient-ventilator asynchrony.

Table 4. Multivariable logistic regression models. Features included mean (µ), short- and long-term scaling exponents (α_1 and α_2, respectively) for mean arterial (MAP), systolic (SBP) and diastolic (DBP) blood pressure, as well as pulse interval (PI) time series. LR denotes the positive likelihood ratios, the 95% confidence intervals (CI) are reported for the AUC. p values are derived from the Delong comparison with the non-detrended mean MAP model. The corresponding AUCs from leave-one-out cross-validation (AUC_{LOOCV}) are also reported, where * denotes a statistically-significant (p < 0.05) difference from the Delong comparison of the LOOCV mean DBP model.

---

<table>
<thead>
<tr>
<th>Feature 1</th>
<th>Feature 2</th>
<th>AUC (95% CI)</th>
<th>p</th>
<th>LR</th>
<th>AUC_{LOOCV}</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP α_1</td>
<td>DBP µ</td>
<td>0.843 (0.68, 1.01)</td>
<td>0.009</td>
<td>2.86</td>
<td>0.721 (0.50, 0.94)*</td>
</tr>
<tr>
<td>PI α_1</td>
<td>DBP µ</td>
<td>0.843 (0.69, 1.00)</td>
<td>0.014</td>
<td>2.86</td>
<td>0.645 (0.40, 0.89)</td>
</tr>
<tr>
<td>DBP α_1</td>
<td>DBP µ</td>
<td>0.864 (0.72, 1.00)</td>
<td>0.022</td>
<td>2.86</td>
<td>0.750 (0.56, 0.94)</td>
</tr>
<tr>
<td>PI α_2</td>
<td>MAP µ</td>
<td>0.864 (0.72, 1.01)</td>
<td>0.068</td>
<td>3.43</td>
<td>0.679 (0.46, 0.89)</td>
</tr>
<tr>
<td>MAP α_1</td>
<td>DBP µ</td>
<td>0.871 (0.74, 1.01)</td>
<td>0.027</td>
<td>3.43</td>
<td>0.743 (0.55, 0.94)</td>
</tr>
<tr>
<td>PI α_2</td>
<td>DBP µ</td>
<td>0.921 (0.82, 1.02)</td>
<td>0.035</td>
<td>4.00</td>
<td>0.821 (0.66, 0.99)</td>
</tr>
</tbody>
</table>

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Figure 2. Receiver-Operator Characteristic Curves. These show the ROC curves for the non-detrended univariate mean DBP (DBP_µ) model, the impact of detrending this feature (DBP_ν), the addition of a respiratory feature (IBI_α_2) as well as two of the highest-scoring models (DBP_µ combined with MAP_α_1 and PI_α_2, respectively).
could flag infants at high-risk of developing IVH. Further model evaluation requires validation on a larger and more balanced cohort to estimate the prediction error and support its potential application in a clinical context.

Limitations. We acknowledge that this study was limited by the size of the dataset ($n = 27$) as well as representation of IVH (29.6%), slightly lower than the referenced 35–45% of incidence reported in neonatal care facilities. Model evaluation was also limited by the low number of IVH cases ($n = 8$), though our LOOCV and sensitivity analyses showed the main findings to be consistent. Another limiting factor was the signal quality of the recordings which was managed by implementing quality control measures as part of the feature extraction process.

Conclusion

In conclusion, this study found mean DBP and short-term scaling exponents from beat-to-beat MAP, DBP and SBP to be useful markers in the prediction of IVH in preterm infants. Non-linear trend removal and the inclusion of additional features such as the short-term scaling exponent ($\alpha_1$) of MAP was able to improve model performance. Of the models evaluated, the one that performed consistently in both the initial analysis and cross-validation was fitted with mean DBP and PI $\alpha_2$. In a clinical context, such an approach to signal processing and predictive monitoring could be applied, where a running 10 min window could continuously evaluate the relevant features from qualifying segments of data. Following evaluation in a larger population, these features may be helpful in identifying infants at high-risk of developing IVH, offering caregivers more time to adjust intensive care treatment.

Methods

Data Collection. Physiological data was collected from the infants within 1–3 hours of birth as part of a prospective clinical investigation at a large tertiary neonatal intensive care unit in Sydney, Australia. The study was approved by the Sydney West Area Health Service Human Research and Ethics and conducted according to the World Medical Association Declaration of Helsinki. Informed parental consent was obtained in all cases.

Inclusion criteria for the cohort comprised low birthweight ($< 1500$ g), gestational age ($< 30$ weeks) and an absence of significant congenital anomalies. Of the 46 infants enrolled, 27 infants had arterial blood pressure and air flow wave recordings with sufficiently long, artefact-free segments. The average (SD) length of recording was 156 (34) mins. Intra-arterial blood pressure was measured using an umbilical or peripheral arterial catheter, following single-point calibration to atmospheric pressure, collected using a bedside patient monitor (Philips Agilent Systems, Philips Healthcare, North Ryde, Australia), while the raw air flow wave was acquired from a ventilator (Babylog 8000, Drägerwerk, Lübeck, Germany). Both signals were sampled at 1 kHz and recorded by an analog data acquisition system (ADInstruments, Sydney, Australia). Cranial ultrasounds were performed at 2, 12, 24 and 36 hours then daily for the first week. The presence and grade of IVH was determined according to the Papile system.

Signal Processing and Data Analysis. Signal processing and feature extraction was completed in Python (Python Software Foundation, version 2.7. https://www.python.org/). Each of the arterial blood pressure and air flow signals were down-sampled to 125 Hz prior to analysis for computational efficiency. This frequency was sufficient for peak detection in both respiratory and blood pressure signals. From the downsampled signals, the following time series were extracted; the beat-to-beat MAP, SBP, DBP and PI, as derived from arterial blood pressure, as well as IBIs derived from air flow data. The signal quality constraints of the air flow data limited extraction of other respiratory features such as peak flow.

Only the arterial blood pressure signal was found to exhibit significant drift, defined by non-linear trends in the diastolic and systolic blood pressure ranges. Thus, the detrending was applied solely to this signal, as
shown in Fig. 3. Such a correction would also minimally impact the derivation of the IBI-based features from the air flow signal. The overall trend of each signal was determined using a large-window median filter (window width = 1000 ms) on a further downsampled signal and the mean-centred trend was subsequently removed from the original arterial blood pressure signal. This approach was similar to the baseline wander removal that has been applied widely prior to feature extraction from the electrocardiogram signal\(^{28}\). An example of this detrending process is shown in Fig. 3.

The features used in IVH prediction were extracted from a running 10 min window of arterial blood pressure and air flow data, shifted in 30 sec increments across the total recording length. This approach was adopted to simulate the application of these techniques in a clinical setting, where windows which fulfilled the quality criteria were included for feature extraction. This criteria comprised defined ranges for the allowable number of beats and breaths in a given window (40–250 beats per minute and >20 breaths per minute), a maximum limit for an absence of detected beats (15 sec) as well as an absence of large spikes in the arterial blood pressure signal (range

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**Figure 4.** Arterial blood pressure data and the predicted probability for IVH using the highest scoring model, mean DBP and PI $\alpha_2$ for correct classification of (a) IVH and (b) non-IVH, as well as incorrect classification of (c) IVH and (d) non-IVH. The threshold for classifying IVH, designated by the dashed line was defined at 90% specificity and 85% sensitivity. Red and blue markers represent windows that exceeded and did not exceed the threshold, respectively.
of beat-to-beat SBP <30 mmHg). For each respective time series, outliers were removed by imposing a maximum change of 150% from the previous data point and also a maximum loss of 30% for each window. Features including the mean (μ), short- and long-term scaling exponents (α1, α2, respectively) from DFA of the five time series (MAP, SBP, DBP, PI and IBI) were subsequently extracted.

Developed by Peng and co-workers11, DFA is able to quantify long-range power law correlations and accommodate for confounding non-stationarities often seen in real-world signals. It does this through the detrending, that is, linear trend removal, step prior to calculating the root-mean squared fluctuation as defined in equation 1.

\[
F(n) = \frac{1}{N} \sum_{k=1}^{N} (y(k) - y_n)^2
\]

where \(y(k)\) is any given time series, \(y_n\) the local linear trend for a given segment, and \(N\) the number of data points in the series for a given round of analysis. The application of DFA is further explained by Thamrin et al.11.

The scaling exponent \(\alpha\) is calculated from the gradient of the line fitted to the Log-Log relationship between \(n\) and \(F(n)\). In this case, the short-term scaling exponent was defined over 4–15 beats, as aligned with similar observations of this data and similarly defined for heart rate variability analysis of preterm infants8. The long-term scaling exponent was determined across 15–50 beats.

**Model Fitting and Evaluation.** Statistical analysis was completed using R 3.3.1 software29. Logistic regression models were used to fit the mean of extracted predictors across all qualifying 10 min windows, while the AUC was used to assess accuracy in predicting IVH. Fitted models were evaluated using leave-one-out cross-validation, where the predicted probability of each test sample was subsequently compiled and used to generate a ROC curve for performance comparison.

**References**


**Acknowledgements**

We would like to thank the Charles Perkins Centre for initiating the collaboration between the authors. The authors thank the professional biostatistician (Alun Pope) for his advice. J.H. was supported by an Australian Postgraduate Award and a Norman I. Price scholarship. C.T. is supported by an NHMRC R.D. Wright Biomedical Career Development Fellowship.

**Author Contributions**

A.M. and M.T. conceived the experiment(s), M.T. and M.H. collected the data, J.H., C.N. analyzed the results with technical advice from C.T. All authors reviewed and provided scientific input on the manuscript.

**Additional Information**

**Competing Interests:** The authors declare no competing financial interests.

**How to cite this article:** Huvanandana, J. *et al.* Prediction of intraventricular haemorrhage in preterm infants using time series analysis of blood pressure and respiratory signals. *Sci. Rep.* **7**, 46538; doi: 10.1038/srep46538 (2017).

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Pregnancy in a patient with congenital analbuminaemia

Hillary Hu, Roshini Nayyar, Lucinda Jean Berglund, Elizabeth Anne Anderson

SUMMARY

Congenital analbuminaemia is a rare autosomal recessive disorder that is characterised by a severe reduction or total absence of serum albumin. This condition has implications for therapeutics as a large proportion of commonly used drugs are plasma protein bound where albumin is the primary component of plasma protein. This is the first case report of pregnancy in a patient with congenital analbuminaemia in the medical literature. In the absence of drug dosage guidelines for patients with congenital analbuminaemia, a list of drugs which may be required for this patient during pregnancy, delivery and/or emergency situations were compiled by a multidisciplinary team. Our patient suffered from polyhydramnios during her pregnancy which was successfully managed with albumin transfusions and had a normal vaginal delivery with no complications in the intrapartum or postpartum period. The management and unique challenges of pregnancy in a patient with congenital analbuminaemia are discussed.

BACKGROUND

We report the management and outcome of a pregnancy in an Australian patient with congenital analbuminaemia, whose condition was first reported in 2015. Congenital analbuminaemia is extremely rare, with about 70 cases described worldwide, and an estimated prevalence of less than one in a million. Despite its rarity, lessons from managing this disorder in pregnancy may also apply to management of individuals with severe hypoalbuminaemia due to other causes.

Analbuminaemia is suspected when there is very low serum albumin combined with normal liver function and absence of protein loss from other sources. The diagnosis is confirmed by plasma protein electrophoresis and the identification of mutations in the gene encoding albumin on chromosome 4. Heterozygotes exhibit a mildly reduced serum albumin (33–34 g/L). Twenty-two different mutations of the albumin gene have been identified so far including mutations that cause non-sense mutations or splicing defects with about one-third of individuals affected estimated to have the Kayseri mutation.

Congenital analbuminaemia is usually asymptomatic in adults although they may suffer from fatigue, lower limb oedema, hypotension and disfiguring lipodystrophy affecting the lower limbs. Management, if required, includes statins, liposuction and albumin transfusion in some circumstances. Whether these individuals are at risk of premature atherosclerosis and cardiovascular disease is controversial due to the lack of long-term follow-up. Increased serum coagulation factors may theoretically increase risk of thrombotic events. Of ~70 documented cases, only 4 have recorded cause of death: 2 cases of cancer, 1 of pneumonia and 1 of cardiac failure. Clinical manifestations in children have included respiratory distress in a newborn, tetany crisis, oedema, diarrhoea and increased infections.

Albumin is the primary component of plasma protein and contributes to 80% of plasma colloid osmotic pressure, which prevents systemic oedema. In the absence of albumin, the human body compensates through the synthesis of immunoglobulins and other serum proteins including globulins, transferrin, coagulation factors and apolipoprotein-B. Patients subsequently have hypercholesterolaemia, with elevated plasma low-density lipoprotein (LDL) cholesterol levels and normal or reduced high-density lipoprotein cholesterol levels.

Changes in maternal physiology during pregnancy include increased maternal fat and total body water and decreased plasma protein concentrations, especially albumin. This is due to increased maternal blood volume, cardiac output and blood flow to the renal system, leading to increased urinary excretion of plasma proteins. The physiological hypoalbuminaemic state combined with congenital analbuminaemia has implications for therapeutics, as a large proportion of commonly used drugs are highly protein bound. Frohlich et al have reported in analbuminaemic children, a 10-fold increase in the unbound fraction of warfarin and diazepam. Demirsoy et al reported no observed changes in pharmacokinetics of perioperative drugs; however, their patient was given perioperative albumin.

Ions and hormones also show altered protein binding in analbuminaemia. The level of protein-bound calcium is low while free active ionised calcium levels are normal. Conversely the protein-bound portion of thyroxine usually increases due to high thyroxine binding globulin and patients develop increased total thyroxine levels with a normal free fraction. Vitamin D is also usually increased due to an increase in the level of vitamin D-binding globulin. It has been suggested that there is an increased risk of osteoporosis associated with the condition although this has not been found in subsequent cases.

Analbuminaemia may significantly impact antenatal development, which could explain the low incidence of pregnancy reports for patients with
analbuminaemia. Neonates with analbuminaemia are often born ‘small-for-gestational-age’ and there is a significantly increased prevalence of neonatal death and maternal miscarriage.1

**CASE PRESENTATION**

A 24-year-old primigravida was referred to the Westmead Hospital High Risk Antenatal clinic by her immunologist for management of her pregnancy. The patient had been diagnosed with congenital analbuminaemia ∼18 months prior to her pregnancy. She initially presented with several years history of oedema and lipodystrophy of her lower limbs. She was found to have a very low serum albumin but elevated serum cholesterol, LDL cholesterol, triglycerides, globulins, transferrin and fibrinogen.

Diagnosis was confirmed via protein electrophoresis and genetic evaluation where she was found to have the Kayseri mutation—homozygous AT deletion at the 91st and 92nd bases of exon 3 on chromosome 4.3 Investigations of her close family members revealed that they were heterozygous for the mutation in that region of the molecule and also had elevated serum proteins similar to the patient.

Table 1 Medications which may be required in obstetric patients and their possible risk in patients with congenital analbuminaemia*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding</th>
<th>Acid/base†</th>
<th>Possible risk if normal dosage is used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>95%20</td>
<td>Weak base</td>
<td>Low</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>80–85%21</td>
<td>Weak base, but protein-binding behaviour different to basic drugs</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>Concentration dependent</td>
<td>Basic</td>
<td>Low</td>
</tr>
<tr>
<td>Morphine</td>
<td>20–36%21</td>
<td>Basic</td>
<td>Low</td>
</tr>
<tr>
<td>NSAIDs (sulindac, diclofenac, ibuprofen)</td>
<td>&gt;90%</td>
<td>Acidic</td>
<td>High</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>45%22</td>
<td>Basic</td>
<td>Low</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>∼20%23</td>
<td>Unionised</td>
<td>Low</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>20%24</td>
<td>Acidic</td>
<td>Low</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Up to 85%24</td>
<td>Acidic</td>
<td>Unknown</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>80–93%</td>
<td>Can act as acid or base</td>
<td>High</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0–30%</td>
<td>Basic</td>
<td>Low</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>10–20%</td>
<td>Unionised</td>
<td>Low</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>80%25</td>
<td>Acidic</td>
<td>Moderate/high</td>
</tr>
<tr>
<td>Heparin</td>
<td>More protein bound than low molecular weight heparin</td>
<td>Acidic</td>
<td>High</td>
</tr>
<tr>
<td>Antiemetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Primarily bound to α-1-acid glycoprotein21</td>
<td>Basic</td>
<td>Low</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>70–76%26</td>
<td>Acidic27</td>
<td>Moderate</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>88–90%29</td>
<td>Basic20</td>
<td>Unknown, possibly low</td>
</tr>
<tr>
<td>Labetalol</td>
<td>52%</td>
<td>Can act as acid or base</td>
<td>Unknown</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>25–30%</td>
<td>Weak base</td>
<td>Low</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Negligible</td>
<td>Acidic</td>
<td>Low</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>95%</td>
<td>Unionised</td>
<td>Unknown</td>
</tr>
<tr>
<td>Emergency medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Unknown</td>
<td>Acidic</td>
<td>Unknown</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>96%21</td>
<td>Basic</td>
<td>Unknown</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>83%21</td>
<td>–</td>
<td>Unknown</td>
</tr>
<tr>
<td>Naloxone</td>
<td>50%28</td>
<td>–</td>
<td>Unknown</td>
</tr>
<tr>
<td>Postpartum haemorrhage medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboprost</td>
<td>Unknown</td>
<td>Acidic</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ergometrine</td>
<td>Unknown</td>
<td>Basic</td>
<td>Unknown</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>81–88%</td>
<td>Unionised, then converted to free acid</td>
<td>Unknown</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Very low</td>
<td>–</td>
<td>Low</td>
</tr>
<tr>
<td>Prostaglandin F2α</td>
<td>∼50–60% bound to albumin in studies</td>
<td>–</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

General guidance—
concern about drug dosage and requirements for dosage reduction is greatest for drugs that are:
I. highly protein bound and
II. acidic or neutral.

*The assessed risks in this table are based on theoretical predictions due to lack of clinical experience in humans.
†Based on the parent molecule.

NSAID, non-steroidal anti-inflammatory drug.
She was first reviewed in the high-risk antenatal clinic in her 11th week of pregnancy where an antenatal care plan was established for her. This included deep vein thrombosis (DVT) prophylaxis (compression stockings and enoxaparin) during any hospital admissions and postpartum, and formal growth scans at 28 and 34 weeks gestation. The patient had normal antenatal serology as well as a low-risk first trimester screening test at 13+1 weeks and a normal morphology scan at 19+5 weeks. Her early and repeat fasting glucose tolerance tests were negative for gestational diabetes. Her thyroid function and vitamin D levels were within normal limits.

**TREATMENT**

The patient underwent her first growth scan in her 27th week where she was found to have polyhydramnios (amniotic fluid index (AFI) 27) with a shortened cervix of 9 mm. The estimated fetal weight (EFW) was just over 1 kg (just below 50th centile) with a normal umbilical artery Doppler ratio. She was asymptomatic for her shortened cervix and denied any tightenings or contractions. There was no abnormal vaginal discharge with good fetal movements.

She was admitted for monitoring and started on sulindac 200 mg twice daily, 25 mg glyceryl trinitrate (GTN) patch daily, progesterone 200 mg pessary nightly, a course of steroids (two intramuscular doses of betamethasone 11.4 mg, 24 hours apart to stimulate fetal lung growth), DVT prophylaxis as well as albumin infusions. Sulindac is a prostaglandin synthetase inhibitor that was given to reduce the amniotic fluid volume by reducing fetal urine production thereby potentially reducing the risk of rupture of membranes and preterm labour. The GTN patch was given as a tocolytic and the progesterone was given as a management for the shortened cervix.

The polyhydramnios was postulated to be secondary to her low oncotic pressure as a result of her condition and therefore there may have been a theoretical benefit of giving albumin to manage this. She was given twice daily albumin infusions and received a total of 11 x 100 mL concentrated albumin 20% during her admission. Her serum albumin improved from <6 to 18 g/L after receiving the albumin. A growth scan was repeated just over a week later and her polyhydramnios had resolved with her AFI decreasing to 21.

After receiving two doses of 200 mg sulindac 12 hours apart the patient reported a burning sensation and flushing of the face. Sulindac was ceased and the facial burning sensation and flushing resolved spontaneously within 1 day.

In the absence of drug dosage guidelines for patients with congenital analbuminaemia a list of drugs which may be required for this patient during pregnancy, delivery (vaginally or caesarean section) and/or emergency medications were compiled by a multidisciplinary team. These medications were researched with respect to protein binding and acid/base properties in order to assess potential drug administration risks for this patient and to consider alternatives (see table 1).

During her 34th week she underwent another growth scan which redemonstrated polyhydramnios (AFI 30). Again she had normal umbilical artery Doppler ratio with an EFW just below the 50th centile. She was transfused with albumin—a total of 4 x 100 mL concentrated albumin 20%. An informal bedside ultrasound scan performed a week later showed an AFI of 16. The progesterone pessaries were ceased in her 34th week.

In her 35th week she presented to hospital with constant backache and intermittent uterine tightenings. On speculum examination her cervix was closed and there was no pooling of liquor. The cardiotocography tracing remained reassuring throughout. She was monitored and given simple analgesia (paracetamol only). The cervical activity and back pain settled after a few hours and she was discharged home.

**OUTCOME AND FOLLOW-UP**

The patient presented to the birth unit at 36+5 weeks gestation with spontaneous rupture of membranes and delivered a healthy live male infant vaginally, weighing 2.58 kg, after 3 hours of labour. It was an uncomplicated delivery with minimal blood loss and the patient only required paracetamol and 10 units of oxytocin (active third stage management). She suffered a very small second-degree tear in the posterior vaginal wall and this was repaired under local anaesthetic (15 mL of 1% lidocaine).

Postpartum she was given paracetamol and isapaghula husk as well as 1 week of prophylactic 40 mg enoxaparin daily. She was discharged day 2 post normal vaginal delivery with routine postpartum midwifery follow-up as well as review with her immunologist at 6 weeks postpartum.

**DISCUSSION**

For highly protein-bound drugs, changes in plasma protein concentration affects the concentration of free drug available for pharmacological action. Acidic or neutral drugs primarily bind to albumin, while basic drugs tend to bind to α-1-acid glycoprotein. Therefore, the highest risk of adverse reactions exists for medications that are highly protein bound and acidic when used in normal dosage in patients with analbuminaemia. Caution should be taken with drugs such as non-steroidal anti-inflammatory drugs and unfractionated heparin which are both acidic and protein bound.

In the absence of published guidance for pregnant patients with congenital analbuminaemia and knowing that changes in plasma protein concentration affects the concentration of free drug available for pharmacological action of highly protein-bound drugs, a literature review was conducted using MEDLINE, EMBASE, Journals at Ovid Full Text and internet searches. Search terms used (as Emtree or MEDLINE terms where appropriate, or as mapping or textword terms) included ‘hypoalbuminemia’, ‘hyopabulminemia’, ‘analbuminemia’ or ‘analbunimaemia’. This very general search enabled a broad view of the literature. The available literature from this search was scanned specifically for drug dosage recommendations. Articles about pregnant patients with this condition were not located; however, a number of articles about protein-bound drugs were located including studies in mutant Nagase analbuminaemic rats (an animal model for human familial albuninaemia).

This is the 71st case of congenital analbuminaemia reported in the literature since the first case was identified in 1954. The reported patients are diverse in age and geographical location, ranging from birth to 61 years old from Africa, Europe, Asia and North America. Fourteen patients were asymptomatic for the condition, 45 patients suffered from oedema to varying degrees, 11 patients suffered from lipodystrophy and 3 patients suffered from fatigue. Decreased oncotic pressure exerted by the lower levels of serum albumin is postulated to cause oedema and perhaps polyhydramnios in pregnancy. Albumin transfusions have been used successfully in patients in perioperative settings and in this patient with congenital analbuminaemia, during pregnancy.

The primary concern for patients with this condition in clinical practice is the unpredictable drug pharmacokinetics as a result of the reduced albumin and subsequent increase in other lipoproteins. Care should be taken when administering...
medications that are highly protein bound and/or acidic in nature. An assessment of the patient’s risk versus benefit with consideration of each drug’s safety margin is required.

### Learning points

- Congenital analbuminaemia is a rare, congenital disorder characterised by very low or absent serum albumin.
- The primary concern for patients with this condition in clinical practice is possible unpredictable drug pharmacokinetics as a result of the reduced albumin.
- Care should be taken when administering medications that are highly protein bound and/or acidic in nature to this patient group.
- Decreased oncotic pressure in congenital analbuminaemia exerted by the lower levels of serum albumin is postulated to cause oedema and perhaps polyhydramnios in pregnancy. Albumin transfusions have been used successfully in patients in perioperative settings and in pregnancy.
- Specialist multidisciplinary care is recommended for management of rare conditions such as described here.

### Contributors
RN was responsible for the conception and design of this paper. All authors were responsible for the acquisition of data and interpretation of the data. HH was responsible for drafting the article. All authors were responsible for critical revision of the article as well as for giving final approval of the version of the article to be published. All authors are in agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

### Competing interests
None declared.

### Provenance and peer review
Not commissioned; externally peer reviewed.

### REFERENCES

Prenatal diagnosis and implications of microphthalmia and anophthalmia with a review of current ultrasound guidelines: two case reports

A. Searle1*, P. Shetty1, S. J. Melov1 and T. I. Alahakoon1,2

Abstract

Background: Microphthalmia and anophthalmia are rare congenital fetal abnormalities. The combined incidence is estimated at 1 in 10,000 births. These two conditions arise from complex and incompletely understood genetic and/or environmental causes. Prenatal diagnosis is neither frequent nor easy and relies on precise, high-quality ultrasonography. Current antenatal ultrasound protocols for imaging of the fetal eye are inconsistent and inadequate to screen for the spectrum of ocular malformations, and there are no clear guidelines on detection of these rare abnormalities. Our study of two cases highlights the importance of early detection, and we review current practice and suggest a definitive fetal imaging protocol.

Case presentation: We present two antenatal cases, one each of microphthalmia and anophthalmia, both diagnosed at the morphology scan at our tertiary fetal medicine unit. In both cases, the parents (a 36-year-old woman of Mauritanian ethnicity and a non-consanguineous partner of Nepalese descent, and a 31-year-old Caucasian woman and non-consanguineous Caucasian partner) elected to terminate their pregnancies and made unremarkable recoveries. Subsequent fetal autopsy confirmed the ultrasound scan findings.

Conclusions: We recommend that antenatal ultrasound guidelines are updated to specify use of a curvilinear transducer (2–9 MHz) to image both orbits in the axial and coronal planes, aided by use of a transvaginal probe when the transabdominal approach is inadequate to generate these images. When applicable, three-dimensional reverse-face imaging should be obtained to aid the diagnosis. The presence, absence, or non-visualization of lenses and hyaloid arteries should be documented in reports and these cases referred for a tertiary-level ultrasound scan and fetal medicine review. Imaging of the orbits should occur from 12 weeks’ gestation. Magnetic resonance imaging and amniocentesis with chromosome microarray testing may provide additional genetic and structural information that may affect the overall morbidity associated with a diagnosis of microphthalmia or anophthalmia.

Keywords: Microphthalmia, Microphthalmos, Anophthalmia, Anophthalmos, Guidelines, Ultrasound

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Background
Microphthalmia and anophthalmia are rare congenital abnormalities, occurring on a spectrum of congenital ocular disorders including congenital cataracts, cryptophthalmos, cyclopia/synophthalmia, congenital cystic eye, and coloboma. Microphthalmia and anophthalmia have both genetic and non-genetic causes, may be unilateral or bilateral, and may be found in isolation or as one component of a syndrome.

There is a general paucity of data on the prevalence of the conditions, and a lack of consistent, widely applied ultrasound guidelines for prenatal diagnosis. We discuss the diagnosis and current international ultrasound protocols for imaging fetal ocular structures. We also discuss ultrasound techniques and resources required for definitive identification of the associated morphological abnormalities. A brief overview of relevant early fetal development and the complex etiology of this serious prenatal diagnosis provides further useful context for treating clinicians.

Case presentation
We present two cases of fetal ocular abnormalities referred to our tertiary center with unilateral anophthalmia and microphthalmia.

Patient A
Patient A was a 36-year-old woman of Mauritanian ethnicity who presented for an initial hospital-booking visit at 13 weeks' gestation. She had no known medical conditions and a non-consanguineous partner of Nepalese descent. Her obstetric history included a 35-week morphologically normal stillbirth of unknown etiology. The pregnancy with which she presented had a low-risk result for the first-trimester aneuploidy antenatal screening in the nuchal translucency program. A fetal morphology scan attended at 19 weeks identified potential fetal anomalies, leading to a tertiary referral for review. A detailed sonogram at 21 weeks’ gestation confirmed left microphthalmia (Fig. 1a) and a small biparietal diameter (< fifth centile).

A range of investigations and management options were offered and consented to, including: genetic counseling, amniocentesis, single nucleotide polymorphisms (SNP) array testing, placental histopathological testing, preservation of cell line, and a full postmortem. A magnetic resonance imaging (MRI) examination was declined by the parents. Amniocentesis and chromosomal microarray showed a chromosomally normal male and genetic counseling was organized. The couple had significant concerns regarding the uncertain prognosis, leading to a decision for an elective termination. The fetal postmortem showed left-sided microphthalmia (Fig. 1b), with associated persistent hyperplastic primary vitreous, probable hypoplasia to the left side of the face, and a thin left optic nerve compared to the right. Placental histopathological results were normal.

Patient B
Patient B was a 31-year-old Caucasian woman with a non-consanguineous Caucasian partner and a history of a term normal birth followed by a first trimester miscarriage. She had no significant medical or family history and stated no illicit substance use. She presented with an uncomplicated pregnancy with a low-risk screening result on nuchal translucency for aneuploidy. At the 20-week fetal anomaly morphology scan, an absent right globe was identified (Fig. 2) with mild bilateral ventriculomegaly. Fetal MRI at 20 weeks further delineated the absent right globe, dysplastic ventricular system (Figs. 3 and 4), and confirmed diagnosis.

A screen for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, listeria, parvovirus, and human immunodeficiency virus (HIV) (TORCH screen) completed at the time of diagnosis was negative. Our patient had no family history of fetal anomalies. Amniocentesis and microarray results showed no chromosomal anomalies in a male fetus. Our patient chose not to continue the pregnancy and a termination was performed without complication. An autopsy
revealed right-sided anophthalmia with right optic nerve atrophy and mild bilateral ventriculomegaly. Placental histopathological results were normal. Genetic counseling and testing was organized.

Methods
In both the cases, a Voluson E10 scanning machine was used (General Electric Medical System, Zipf, Austria) equipped with a convex 2–9 MHz, and a three-dimensional convex, 2–6 MHz volumetric transducer. In case A, we produced the images in two-dimensional ultrasound. In case B, both two-dimensional and three-dimensional ultrasound techniques were used, including the three-dimensional reverse-face technique. Images were obtained at the level of the orbits, from cranial to caudal end in axial as well as coronal planes. Orbits were examined for shape, intra-orbital and bi-orbital distance, as well as presence of lenses and hyaloid arteries. The fetal face was also examined in sagittal, axial, and coronal planes for any associated abnormalities.

Discussion
Anophthalmia refers to complete absence of the globe in the presence of ocular adnexa (eyelids, conjunctiva, and lachrymal apparatus), and microphthalmia is defined as a globe with a total axial length that is at least two standard deviations below the mean for age [1]. Microphthalmia can be classified according to the anatomic appearance and severity of the reduction of the globe: severe microphthalmia refers to a globe with a corneal diameter less than 4 mm and a total axial length less than 10 mm at birth [2]. These ocular malformations can be unilateral or bilateral, and can be isolated or occur with other malformations as part of a syndrome. A normal ultrasound is not a guarantee that vision will be intact in an eye that appears normal.

The reported incidence of microphthalmia and anophthalmia varies in the literature and reflects a general paucity of reliable epidemiological data about this rare congenital abnormality. Based on hospital admissions of live babies, UK statistics from 1999 to 2011 describe the incidence of congenital anophthalmia as 0.04–0.24 per 10,000, and of congenital microphthalmia as 1.00–1.08 per 10,000 [3]. The estimated incidence from a retrospective cohort study of the Danish national patient registry in Denmark from 1995 to 2012 of microphthalmia and anophthalmia was 1.2 per 10,000 live births. Extra-ocular abnormalities were observed in 32.1% of

![Fig. 2](image1) Case B. a Two-dimensional ultrasound findings of anophthalmia. b Three-dimensional ultrasound view of the face showing unilateral anophthalmia. The triangular arrow-head represents anophthalmia. The simple wide arrow-head represents the normally formed eye.

![Fig. 3](image2) Magnetic resonance images of the fetus with anophthalmia, showing axial views of the fetal head at the level of the eyes. The triangular arrow-head represents anophthalmia. The simple wide arrow-head represents the normally formed eye.
these cases [4]. These data have the limitation of not including the number of women with a prenatal diagnosis of fetal microphthalmia or anophthalmia who chose to terminate the pregnancy, so the real incidence is likely to be higher. The 1989–1997 data from the California birth defects monitoring program identified the prevalence of anophthalmia in live births and stillbirths as 0.18 per 10,000 and for bilateral microphthalmia as 0.22 per 10,000 [5]. Unilateral microphthalmia was excluded from the data. The available data suggest that microphthalmia and anophthalmia are rare presentations, with upper estimates of incidence around 1 per 10,000 births.

As a spectrum of disorders, the etiology of anophthalmia and microphthalmia is complex and relates to the precise stage of embryological development affected by infection and/or gene mutation. Eye development commences around the third embryological week, with the development of two small grooves on the forebrain (optic grooves or sulci). Lengthening from the forebrain to the surface ectoderm, these optic grooves become the optic vesicles. The optic vesicles continue to grow, with narrowing of the proximal tissue connected to the forebrain forming the optic stalk and finally the optic nerve. The origin for the lens, the lens placode, is formed in the fifth and sixth week of gestation, and becomes complete by week eight. The double-layered optic cup is formed in weeks five and six, by an invagination of the optic vesicle to ultimately form the iris, ciliary body, and retina. The mesenchyme on the external surface of the optic cup forms the choroid and sclera in week six or seven [6, 7].

The pathogenesis of microphthalmia and anophthalmia is heterogenous and incompletely understood. Environmental agents have been implicated, with genetic factors and vascular disruption [1]. Chromosomal abnormalities (aneuploidy, deletions, rearrangements, single-gene disorders) are responsible for an unknown proportion of the presentations, and may be inherited or isolated. Single-gene deletions and mutations affecting the ability to produce proteins and enzymes such as SOX2, MFRP, ALDH1A3, STRA6, PAX2, and OTX2, have been identified as causing isolated microphthalmia and anophthalmia and syndromic forms [8–13]. SOX2 and PAX6 mutations may cause lens induction failure, FOXE3 mutations are associated with lens agenesis, and OTX2, CHX10, and RAX may cause failure of retinal differentiation. All these mutations may cause organ dysgenesis, leading to microphthalmia or anophthalmia [1]. This list of causative genes is not comprehensive but highlights some of the commonly identified genes, and indicates the significant complexity of the genetics of anophthalmia and microphthalmia.

Syndromic forms are more likely to be associated with intellectual impairment. Known syndromes associated with anophthalmia and microphthalmia include X-linked recessive Lenz microphthalmia syndrome [14, 15], microphthalmia with linear skin defects syndrome [16], and anophthalmia–esophageal–genital syndrome [17]. Other authors implicate intra-uterine infection with TORCH organisms as causes for microphthalmia [7, 18]. The known environmental causes include alcohol, thalidomide, vitamin A deficiency, and hydantoin [1, 19, 20].

Patients with anophthalmia and microphthalmia experience a spectrum of visual impairment from mild impairment to complete blindness. The anomaly also presents cosmetic problems, which are treated variably with surgery and ocular prostheses [21]. As previously noted, patients may also suffer from intellectual disability, particularly if the anomaly presents as part of a syndrome. Prognosis is varied and patients usually require the support of a multidisciplinary team to manage the vision, plastic surgery, and intellectual and psychological aspects of the condition [1].
The use of ultrasound for diagnosis of fetal ocular defects was first described in 1991 [22]. The capacity for diagnosis has paralleled technical advancements in ultrasound. A diagnosis of anophthalmia can be made by two-dimensional ultrasonography when eyeballs and lens are absent. More information can now be gained with the advent of three-dimensional ultrasonography, especially when the fetal head position is unfavorable for two-dimensional ultrasound [2, 23]. The use of three-dimensional ultrasound is well known for prenatal diagnosis of fetal facial abnormalities [23]. In 2005, the ultrasound technique of three-dimensional reverse-face view was first described by Campbell et al. [24] for the diagnosis of cleft palate. Subsequently in 2012, Araujo et al. [25] described the reverse-face imaging technique to diagnose anophthalmia at a gestation of 30 weeks, with the advantage of not being affected by shadowing [2]. It is necessary to take a satisfactory three-dimensional volume, with adequate inclusion of both orbits [23]. The sagittal plane of the face of a fetus is rotated 180° in the z-axis, and the green line (region of interest) is placed at the level of fetal orbits. This results in the image of a three-dimensional reverse-face view. Other authors have noted the use of transvaginal ultrasound at approximately week 13 to assist in the early diagnosis of microphthalmia and anophthalmia in fetuses with parents or older siblings who have the condition [18].

Fetal MRI is an adjunct tool to ultrasound in diagnosing fetal anomalies, and can be particularly useful in identifying malformations of the central nervous system, providing detailed evaluation of the brain sulci, gyri, ventricles, cerebellum, corpus callosum, and other structures. MRI can confirm the absence of eye tissue, the optic nerve, and extra-ocular muscles, in cases of anophthalmia [25–27].

**International ultrasound protocols for identifying microphthalmia and anophthalmia**

We searched international ultrasound protocols to review the current prenatal screening practices for microphthalmia and anophthalmia. We identified four commonly used protocols and suggested protocol guidelines in journal articles, which are summarized below.

**International Society of Ultrasound in Obstetrics and Gynecology, 2010 guidelines [28]**

These guidelines note the following in relation to imaging of the fetal face:

- Minimum evaluation of the fetal face should include an attempt to visualize the upper lip for possible cleft lip anomaly. If technically feasible, other facial features that can be assessed include the median facial profile, orbits, nose and nostrils.

**Fetal Medicine Foundation, 2002 guidelines [29]**

These guidelines relate to the 18–23-week morphology scan, and note the need to image the orbits, specifying that the sagittal, transverse, and coronal planes are required. The coronal planes are described as the most important to view the orbits and face. A series of transverse scans from the top of the fetal head, moving caudally allows examination of various facial structures, including the orbits. These guidelines also discuss the orbit measurements and how these relate to the diagnosis of microphthalmia. The diagnosis depends on identifying a decreased intra-orbital diameter and then carefully identifying and defining the intra-orbital structures including lens, pupil, and optic nerve.

**American Institute of Ultrasound in Medicine, 2013 guidelines [30]**

These guidelines do not mention having a detailed examination of the orbits in the head, neck, and face category.

**Australasian Society for Ultrasound in Medicine, 2014 guidelines [31]**

The protocol for the 18–20-week obstetric scan was reviewed and now includes identification and measurement of the orbits. The protocol includes charts for the expected orbital measurements, by gestation. There is no specification on the depiction of lenses and the views needed to be obtained for optimal measurements.

**Protocol literature review**

The published literature on ultrasound protocols for identification of microphthalmia and anophthalmia includes an original article on early sonographic detection of recurrent fetal eye anomalies. Mashiach et al. [18] described how transvaginal sonography at 14–16 weeks was helpful in detecting the eye abnormality in five cases in which at least one previous child in the family had the same congenital eye anomaly. The orbital region was best visualized using the coronal plane. These authors recommended offering a detailed targeted ultrasound survey with a special focus on the orbital region to pregnant women who have children with congenital eye anomalies. Achiron et al. [32] reported on axial growth of the fetal eye and the importance of evaluation of the hyaloid artery, its blood flow, and regression.

**Conclusions**

These presented cases are examples of rare fetal pathological abnormalities when early diagnosis allowed pregnancy continuation or termination options for parents. Intrauterine diagnosis is not easy or frequent, but ultrasound plays a vital role, complemented by MRI and amniocentesis with chromosome microarray testing.
Advances in ultrasound technology, including the use of three-dimensional images, are key to early diagnosis. In both cases, the early diagnosis and recognition of these ocular abnormalities assisted in counseling and support to the patients, and appropriate information could be provided about possible treatment options in neonatal and pediatric life.

A clear diagnosis of microphthalmia was made in Case A. The ultrasound images, however, did not identify thinning in the optic nerve, nor mid-face hypoplasia. MRI is considered to provide a more appropriate imaging modality to identify thinning of the optic nerve, which Patient A declined. In Case B, the right-sided anophthalmia and mild ventriculomegaly was clearly identified on ultrasound. The use of an MRI scan in Patient B was useful to confirm the ultrasound diagnosis and screen for other associated intracranial abnormalities.

The prognosis for fetuses with a prenatal diagnosis of microphthalmia or anophthalmia is complex and frequently uncertain. We recommend chromosomal microarray testing either as an antenatal invasive testing or on a fetal cord sample after delivery. This will provide useful information on possible genetic-associated conditions, and informs future family planning. When a genetic cause is identified, it is prudent to offer formal genetic counseling and parental testing. The use of MRI to image possible anomalies in the fetal brain provides a further indication of whether significant mental impairment can be expected. However, none of these investigations can be undertaken without first diagnosing the condition. The current guidelines for imaging the fetal face, as discussed above, vary from no recommendations for imaging of the orbits, to a simple recommendation to image the orbits, with only the Fetal Medicine Foundation guidelines recommending that internal structures of the eyes are imaged [29].

The sophistication of the latest generation of ultrasound machines and software, combined with the seriousness of a diagnosis of microphthalmia or anophthalmia, are such that it is time to include a robust, consistent protocol for the detailed examination of intraocular structures. We suggest using a curvilinear transducer (2–9 MHz) and imaging orbits in both axial and coronal planes. This can be aided by using a transvaginal probe in selected cases if it is difficult to visualize structures via the transabdominal method. Three-dimensional reverse-face imaging should be obtained in suspected cases of anophthalmia or microphthalmia. The presence or non-visualization of lenses and presence or absence of hyaloid arteries should be documented in reports so that cases can then be appropriately referred for a tertiary ultrasound scan and fetal medicine review.

Abbreviations
MRI: Magnetic resonance imaging; SNP: Single nucleotide polymorphisms; TORCH: Toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, listeria, parvovirus, and HIV

Funding
The publication fee for this journal was funded from the research budget for the Westmead Hospital Fetal Maternal Medicine Department.

Availability of data and materials
All data generated for the case report and conclusions are included within this published article.

Authors’ contributions
TIA, AS, and PS designed the study. Review of literature was completed by AS and PS. TIA provided specialist consultant review. TIA, AS, SJM, and PS contributed to drafting, revision, and preparation of the manuscript. All authors read and approved the final version.

Ethics approval and consent to participate
The two patients discussed in this case report gave their full and free consent for the research and publication of details of their case, including images and pathology results. The research was approved by the Western Sydney Local Health District Human Research Ethics Committee.

Consent for publication
Written informed consent was obtained from both patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Received: 2 January 2018 Accepted: 12 June 2018
Published online: 29 August 2018

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Radiation-induced vaginal stenosis: current perspectives

Abstract: Treatment of gynecological cancer commonly involves pelvic radiation therapy (RT) and/or brachytherapy. A commonly observed side effect of such treatment is radiation-induced vaginal stenosis (VS). This review analyzed the incidence, pathogenesis, clinical manifestation(s) and assessment and grading of radiation-induced VS. In addition, risk factors, prevention and treatment options and follow-up schedules are also discussed. The limited available literature on many of these aspects suggests that additional studies are required to more precisely determine the best management strategy of this prevalent group after RT.

Keywords: gynecological cancer, radiation therapy, vaginal stenosis, brachytherapy, vaginal dilators

Introduction

Treatment of uterine, cervical, vaginal and anorectal cancers commonly involves pelvic radiation therapy (RT). A commonly observed side effect of pelvic RT is radiation-induced vaginal stenosis (VS), defined as abnormal tightening and shortening of the vagina due to the formation of fibrosis.\(^1\,^2\) VS may occur following external beam radiation therapy (EBRT) or brachytherapy or both delivered in the definitive, adjuvant or palliative setting. It is well recognized that RT-induced VS may have negative impacts on patient well-being, in particular sexual dysfunction and dyspareunia and implications for limiting physical examination in the posttreatment surveillance period.

Incidence of RT-induced VS

The reported incidence of RT-induced VS is highly variable and may depend on patient, tumor and treatment factors. These factors include site of disease, RT modality, dose, dose fractionation schedule, concurrent chemotherapy and other patient factors including age and inherent radiosensitivity of tissues, and whether the side effect was specifically assessed. The existing data regarding the incidence of VS are largely based on retrospective evidence and small cohorts, and there is a wide variation between investigators in measurement techniques and reported grading of VS. This variation is reflected in the literature, with cited rates of VS ranging from 1.25% to 88%.\(^3\,^4\) Furthermore, it is noted that in the clinical setting, the discussion of VS and associated sexual dysfunction may be limited due to various issues including age, marital status and cultural factors. Therefore, incidence rates of VS and sexual dysfunction are likely underreported.\(^6\)

Nevertheless, modern data suggest that RT-induced VS is a common toxicity following pelvic RT. In a retrospective study of women with Stage 1B to Stage 4 cervical cancer treated with pelvic RT and/or brachytherapy, the prospectively recorded incidence...
of RT-induced VS was reported as 38%. Furthermore, it has been reported that VS most commonly occurs within the first year posttreatment. Another prospective study of 54 patients also reports that VS gradually increases with time, with grade 1 stenosis occurring within the first year of follow-up and the time to occurrence of moderate-to-severe stenosis gradually increasing up to 3 years following treatment.

The incidence seems to be highest in women undergoing definitive treatment for locally advanced cervical cancer. Recent data from the multicenter international EMBRACE trial demonstrated that VS was the most frequently observed vaginal toxicity in women undergoing definitive chemoradiation and brachytherapy. In this study, 630 patients were prospectively assessed for VS every 3 months in the first year following treatment and every 6 months in the second and third year. Grade 2 VS was defined as vaginal shortening/narrowing interfering with function and grade 3 as complete vaginal obliteration not surgically correctable, according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 as shown in Table 1. Grade 2 VS occurred in 29% of patients and grade ≥3 in 3.6%, with the majority occurring within 6 months. However, several small study series suggest that RT-induced VS may be less likely in the setting of adjuvant treatment for endometrial cancer using vaginal vault brachytherapy. One retrospective study of 54 patients reports no patients with grade ≥2 vaginal toxicity, including stenosis. Similar data investigating the use of vaginal dilators in 60 patients with a variety of gynecological cancers showed that surgery and adjuvant RT may also predict a lower risk of VS as compared with definitive RT alone.

Although less commonly reported in the literature, VS following pelvic RT for rectal and anal cancer is also recognized. One study reports over two-thirds of women experiencing degree of VS post-RT for anal or rectal tumors. Although the study involved a relatively small cohort of 54 patients, this rate of VS has a plausible radiobiological basis, given the authors report a mean vaginal doses of 50.0 and 36.8 Gy for anal and rectal cancer patients, respectively. Another larger prospective study investigating rates of VS in 94 female patients with anal squamous cell cancer treated with definitive chemoradiation reported a VS grade distribution of 27.1% for grade 2 and 37.1% for grade 3 (as defined by CTCAE v3.0).

### Pathogenesis

The vagina is lined by stratified squamous epithelium overlying the lamina propria and longitudinal muscle fibers. Acute RT reactions are defined as those occurring during or immediately after RT. Following either EBRT or brachytherapy, these acute reactions may include mucosal inflammation, hyperemia and epithelial denudation leading to ulceration and endothelial injury causing small-vessel thrombosis, edema and smooth muscle necrosis.

Delayed or late RT reactions are defined as those occurring later than 3 months post-RT. VS is considered a late reaction and is due to damage to the vaginal mucosa caused by increased collagen production in the submucosal fibroconnective tissue layer. This leads to atrophic changes of the vaginal mucosa and obliteration of the muscle and vasculature resulting in hypoxia, tissue atrophy and fibrosis. Clinically, this results in the development of telangiectasia, mucosal pallor, adhesions and occlusion of the vaginal canal, loss of elasticity and fragility of the vaginal wall.

### Clinical manifestation of RT-induced VS

RT-induced VS is commonly associated with sexual dysfunction, including dyspareunia and postcoital bleeding. In severe cases, an inability to have intercourse may occur. It is recognized that the severity of the impact of VS may be multifactorial and partly due to other accompanying symptoms and side effects such as vaginal dryness and atrophy due to damage to the epithelium. These may be further exacerbated by posttreatment ovarian failure or menopausal status resulting in further decreased lubrication and thinning of vaginal tissues. It has been suggested that VS may also predispose to increased trauma and infection, although the true prevalence of this is not known. Overall, VS can impact negatively on quality of life and represent a long-term source of psychological and physical distress.

### Table 1: Common Terminology Criteria for Adverse Events v3.0 grading for vaginal stenosis

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Short name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal stenosis/length</td>
<td>Vaginal stenosis</td>
<td>Vaginal narrowing and/or shortening not interfering with function</td>
<td>Vaginal narrowing and/or shortening interfering with function</td>
<td>Complete obliteration; not surgically correctable</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: Data from Common Terminology Criteria for Adverse Events (CTCAE). Version 3.0.
Assessment and grading of RT-induced VS

Several grading systems and methods for assessing VS exist, none of which have been uniformly adopted.

The National Cancer Institute CTCAE v3.0 defines VS as a disorder characterized by the narrowing of the vaginal canal; the corresponding definitions of all grades are outlined in Table 1. This has now been replaced with CTCAE v4.0.

The first three grades of vagina stricture are as follows: grade 1 – “asymptomatic, mild vagina shortening or narrowing,” grade 2 – “vaginal narrowing and/or shortening not interfering with physical examination” and grade 3 – “vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination.”

The Late Effects in Normal Tissues-Subjective, Objective, Management and Analytic Score (LENT SOMA) grading scale for vaginal injury due to radiation and/or chemotherapy is based on the assessment of subjective symptoms, observed clinical features, management strategies required and analytical tests (Figure 1). VS and length is listed as one of the numerous symptoms that may be graded according to this scale.

Risk factors

Multiple risk factors for the development of RT-induced VS have been identified in the literature. Reported risk factors include patient age, RT dose and volume of vagina treated, combination of EBRT and brachytherapy and tumor extension to the vagina.

Increasing dose and volume of vagina treated is associated with all grades of VS. In the setting of locally advanced cervical cancer, patients from the EMBRACE study were prospectively assessed to identify risk factors for VS. Factors identified were tumor extension into the vagina at diagnosis, plus an EBRT dose exceeding 45 Gy in 25 fractions and total EBRT and brachytherapy rectovaginal reference point dose. Similarly, in women treated with image-guided brachytherapy alone for cervical or endometrial cancer, vaginal dose and

<table>
<thead>
<tr>
<th>Subjective</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspareunia</td>
<td>Occasional and minimal</td>
<td>Intermittent and tolerable</td>
<td>Persistent and intense</td>
<td>Refractory and excruciating</td>
</tr>
<tr>
<td>Dryness</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Occasional</td>
<td>Intermittent and tolerable</td>
<td>Persistent and intense</td>
<td>Refractory</td>
</tr>
<tr>
<td>Pain</td>
<td>Occasional and minimal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objective</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis/length</td>
<td>&gt;2/3 normal length</td>
<td>1/3–2/3 normal length</td>
<td>&lt;1/3 normal length</td>
<td>Obliteration</td>
</tr>
<tr>
<td>Dryness</td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
<td>Secondary dysfunction</td>
<td>Fistulae</td>
</tr>
<tr>
<td>Ulceration/necrosis</td>
<td>Superficial, ≤1 cm²</td>
<td>Superficial, &gt;1 cm²</td>
<td>Deep ulcer</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Patchy</td>
<td>Confluent</td>
<td>Nonconfluent</td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>Telangiectasia without bleeding</td>
<td>Telangiectasia with gross bleeding</td>
<td>Partial</td>
<td></td>
</tr>
<tr>
<td>Synchieae</td>
<td></td>
<td></td>
<td>On contact</td>
<td>Complete</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td>Intermittent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspareunia/pain</td>
<td>Occasional nonnarcotic</td>
<td>Regular nonnarcotic</td>
<td>Regular narcotic</td>
<td>Surgical intervention</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Occasional hormone cream</td>
<td>Intermittent hormone cream</td>
<td>Regular hormone cream</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Iron therapy</td>
<td>Occasional dilution</td>
<td>Frequent transfusions</td>
<td>Surgical intervention</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Occasional dilation</td>
<td>Intermittent dilution</td>
<td>Persistent dilatation</td>
<td>Surgical reconstruction</td>
</tr>
<tr>
<td>Dryness</td>
<td>Hormone replacement</td>
<td>Artifical lubrication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>Conservative</td>
<td>Debridement</td>
<td>HBO₂</td>
<td>Graft, surgical repair</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analytic</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Assessment of wall thickness, sinus and fistula formation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Assessment of wall thickness, sinus and fistula formation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUA</td>
<td>Assessment of wall diameter and length and mucosal surface</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology/biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 LENT SOMA grading scale for vaginal injury. Reprinted from Int J Radiat Oncol Biol Phys. 1995;31(5):1049–1091. LENT SOMA scales for all anatomic sites. With permission from Elsevier. Copyright ©1995 Published by Elsevier Inc.

Abbreviations: LENT SOMA, Late Effects in Normal Tissues-Subjective, Objective, Management and Analytic Score; HBO₂, HyperBaric Oxygen therapy; MRI, magnetic resonance imaging; EUA, examination under anesthesia.
volume were also associated with an increased risk of VS. However, no single approach to using vaginal dilator is uniformly utilized, and advice about when and how dilators should be used is highly variable. There is a lack of consensus on multiple aspects of using dilator including the frequency and duration of dilator use, the appropriate time interval following RT in which to commence use, size of dilator, insertion technique and the necessity of dilators in sexually active patients. The primary site of disease and the RT modality used also impact on whether clinicians advised the use of vaginal dilators.

In terms of patient factors, age >50 years has been associated with an increased risk of VS in patients treated with pelvic and/or vaginal RT for cervix cancer. Pallor reaction of vaginal tissues has also been proposed as a predisposing factor for late VS as both have a pathophysiological basis related to mucosal thinning and dryness, atrophy, inflammation and fibrosis. An assessment of grade 2 vaginal pallor reaction at 6 months was reported as predictive of late VS of grades 2 and 3 at 3 years after treatment with high-dose rate brachytherapy for cervical cancer. Cigarette smoking has also been proposed as a possible patient-related factor predisposing to VS. This is certainly plausible given the widely recognized synergistic effect of cigarette smoking and late radiation effects on normal mucosal tissues of the aerodigestive tract observed in a number of tumor sites including cervical, lung and head and neck cancer.

### Prevention strategies and outcomes

#### Vaginal dilatation

The rationale for vaginal dilatation is to stretch the vaginal mucosa and break down adhesions to maintain vaginal patency. A concurrent or alternative strategy is to also encourage regular sexual intercourse.

A recent Cochrane review concluded that there is no reliable high-level evidence to show that regular vaginal dilatation prevents radiation-induced VS. However, observational data indicate that regular use of dilator following RT is associated with lower rates of self-reported VS. Further clinical trials are ideally needed; however, the difficulties of designing appropriate trials to establish a causal relationship are widely acknowledged. There is no evidence to support the use of dilators during RT, which in fact may be harmful. Despite a lack of high-level evidence, vaginal dilators are continued to be used widely in clinical practice as an accepted prevention strategy for VS. Numerous international reviews and guidelines recommend the use of dilators.

### Topical therapies

Given that many women discontinue to use dilators before the recommended time, or never start or use less frequently than prescribed due to discomfort with, or dislike of, the dilators, other methods to maintain vaginal patency should be explored.

It has been postulated that the application of local estrogen or benzydamine to treat acute radiation-related changes may prevent the development of later vaginal complications such as VS via the promotion of epithelial regeneration and anti-inflammatory effects. There have been a small number of studies assessing such topical therapies. One study showed outcome improvement with the use of vaginal estrogen applications in acute and late toxicity. In particular, the vaginal estrogen-treated patients (in comparison with the controls) had significantly less dyspareunia and few alterations in the vaginal epithelium and vaginal narrowing. However, these conclusions have limitations in trial design (method of allocation concealment not stated, no quality of life assessment and outcome reporting (no duration of response reported), emphasizing the need for more contemporary studies to be conducted with improved designs to evaluate the efficacy of these topical treatments.
Preliminary analysis of another study\textsuperscript{46} showed that vaginal application of \( \alpha \)-tocopherol reduces vaginal toxicity and pain, although it does not seem to affect the fibrosis secondary to the effects of long-term RT.

**Technical factor**

In cervical cancer management, a pilot study\textsuperscript{47} has shown that by reducing dwell times in vaginal sources (ring and ovoids) and increasing them in tandem/or needles, the dose to vagina and ICRU rectal point can be decreased while maintaining the same dose to the high-risk clinical target volume. Application of this method of vaginal dose deduction is expected to reduce the development of VS and hence contribute toward the prevention of sexual dysfunction in women with cervical cancer.

In endometrial cancer, the use of brachytherapy alone after hysterectomy has increased over time in all women with Stage 1 and in those with high–intermediate-risk disease.\textsuperscript{48} However, given the high rate of successful salvage for patients who develop vaginal recurrence, and the high risk of morbidity from adjuvant radiotherapy, questions arise as to the alternative strategy of observation after surgery in the low- and high–intermediate-risk patients, who are the majority affected with endometrial cancer.\textsuperscript{49}

**Follow-up and treatment**

**Patient education**

- Patients should be advised at the outset of treatment about the risk of VS and its consequences with regard to sexual function and posttreatment surveillance.
- Practical advice about using vaginal dilator should be provided by a trained member of treatment team.
- Psychosocial support and education should be provided if RT-induced VS occurs.

**Clinical assessment**

Vaginal morbidity should be assessed at baseline, 3 monthly for first 2 years and then 6 monthly for subsequent 3 years until discharge from ongoing surveillance. As discussed previously, various grading systems exist for reporting purposes. We note that the recent EMBRACE study used CTCAE v3.0 for the purpose of monitoring VS.

In an ideal world, baseline sexual function should be established pretreatment and reassessed in the posttreatment follow-up period. However, resources and patient interest in this aspect of their care may be lacking as they come to terms with a recent diagnosis of cancer. Nevertheless, patient education regarding VS is part of the care that should be provided by radiation oncologists who treat women with gynecological, anal and rectal cancers.

**Conclusion**

Radiation-induced VS is a commonly observed side effect following treatment with pelvic RT for uterine, cervical, vaginal and anorectal cancers. Survivorship care should prioritize and recognize the potential negative impact of VS on the physical and psychological well-being of patients. However, there is a paucity of high-level evidence of the prevention and management strategies for VS, and more up-to-date empirical data are required. In clinical practice, vaginal dilatation remains an internationally accepted prevention strategy for radiation-induced VS. However, no single approach to using vaginal dilator is uniformly recognized, and expert consensus about this issue remains an area of continued need. Nevertheless, it has been strongly recommended that patients receive specialist education about VS at the outset of treatment. Importantly, ongoing psychosocial support and practical advice about VS and regular assessment of vaginal morbidity should be provided in the posttreatment surveillance period.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


RAINBOW BABIES

Sue Heath1*, Kathleen Summers2
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**Background:** Regardless of risk status, pregnant women can access midwifery continuity of care/ r across the childbirth continuum, within an interdisciplinary framework, including woman pregnant with Rainbow Babies, after recent late pregnancy loss. Recent UK longitudinal study reported that negative psychological impacts, including the fathers, of perinatal loss persisted far beyond the next pregnancy and despite the birth of a healthy child. Maternity care focuses on increased surveillance to minimise the risk of recurrence, but emotional and psychological support may be lacking.

**Methods:** Using the Essentials of Care Maternity Domains and Picker Dimensions of Care Valued by Patients, in addition to current high risk pregnancy continuity of midwifery care, a care pathway was initiated, commencing from perinatal mortality review of women (n = 17) with late pregnancy loss with potentially preventable stillbirths in future pregnancies. Women and their carer’s were interviewed, postnatally regarding their patient journey using EOC framework and consent. Themes identified and evaluated against the Dimensions of Care.

**Results:** Themes identified in these patient stories, confirmed the carepathway encompassed the eight dimensions of care. Women described “didn’t have to tell my story over and over again or get any conflicting advice” and “a positive experience with trust, respect, and good communication at your own level of understanding” and “committed to my best care and best outcome, even if it is a negative one”, but were “too pushy offering the social work service so often”.

**Conclusion:** Rainbow baby patient stories confirm that conti-onic Lung Disease (CLD).
INTRODUCTION

Caesarean section (CS) is one of the most common surgical procedures performed and the rates of CS deliveries are continuing to increase.\(^1,2\) Surgical site infections (SSIs) affect between 5–12% of CS deliveries.\(^2–6\) This is concerning because SSIs are a potentially preventable complication in a population of generally healthy women which can cause mortality and significant morbidity through physical pain, psychological stress and impairing mother–infant bonding, while also being a financial burden to the health system.\(^2–6\)

The rate of CS SSIs in Australia has been reported as <2% to 6.9% with 0.6–1.7% of patients requiring readmission.\(^7–10\) Some risk factors for post-CS SSIs have been identified in previous studies, such as emergency surgery, elevated body mass index (BMI) and diabetes mellitus.\(^5,6,11–14\) Therefore, the purpose of this study was to investigate the frequency and characteristics of readmissions for SSI post-CS in a Sydney tertiary hospital. We hypothesised that the rates of readmission for SSI following CS would be 1% (similar to published figures), and would be higher following emergency compared to elective CS.

MATERIALS AND METHODS

A retrospective study was conducted of patients who were readmitted to Westmead Hospital for treatment of SSI following CS. Westmead Hospital is a specialised tertiary referral hospital in western Sydney and has over 5000 deliveries per year. All CSs were performed using a modified Joel–Cohen method and lower segment transverse uterine incision. Local protocol included a single dose of pre-incisional intravenous (IV) cephazolin 1–2 g and surgical skin preparation using povidone-iodine. The skin was closed with Monocryl and covered with an occlusive dressing.

Patients who had suspected intra-amniotic infection (temperature ≥38°C or 37.5–37.9°C, with offensive liquor and/or uterine tenderness) were treated with ampicillin 2 g every 6 h, gentamicin 5 mg/kg IV daily and metronidazole 500 mg IV twice daily for a minimum of 24 h.
Cases were identified from the ‘Health Round Table for Obstetric and Gynaecology’ database, searching for patients readmitted between 1 January, 2012 and 31 December, 2015 with ‘Readmission Principal Diagnosis’ (IDC code) listed as puerperal or unspecified sepsis/fever (O85, A419, R509), maternal care due to uterine scar from previous surgery (O342), infection of obstetric surgical wound (O860), wound infection following a procedure (T8141) and disruption or haematoma of obstetric wound (O901,O902). Physical and electronic patient records were examined to confirm the diagnosis of SSI and obtain clinical details. Cases were classified as having SSI in the presence of at least one of the following at the surgical site: purulent discharge, pain/tenderness, swelling and/or erythema with or without fever (defined at temperature ≥38°C) within 28 days of CS.9

Details of patient demographics included age, BMI, nationality, diagnosis of hypertension or diabetes mellitus, smoking status and parity. Characteristics of the CS included length of stay, days between discharge and readmission, gestation, induction, duration of labour and rupture of membranes, reason for CS, liquor, febrile illness and wound culture results. Emergency CS was defined as surgery performed according to priority (Category 1 <15 min with an immediately life-threatening condition; Category 2 <1 h due to maternal or fetal compromise but not immediately life-threatening; Category 3 <4 h, needing earlier than planned delivery without current evidence of maternal or fetal compromise). Elective CS was defined as surgery that had been scheduled in advance at a time suitable for the patient and staff, including Category 4 CS. Data were analysed using descriptive statistics. Comparisons were analysed using χ² test for categorical data. Statistical significance was defined as P-value <0.05. The research was conducted as a quality improvement project, approved by Western Sydney Local Health District Human Research Ethics Committee.

RESULTS

A total of 6334 patients underwent CS from 2012–2015 at Westmead Hospital, representing 29.6% of all deliveries. Emergency CS was performed in 54.1% of cases while 45.9% had an elective CS. Readmission was required for 165 patients (2.6%) following CS. The most common reason for readmission was SSI, accounting for 25.5% of readmissions (n = 42). Other common reasons for readmission included infections of the genital tract, puerperal infections or pyrexia of unknown origin (17.0%), bleeding-related (9.1%) and migraine/headache (8.5%), hypertension (3.6%) or mastitis (3.0%).

Of the women readmitted with SSI after CS, 88% (37/42) had undergone emergency CS and 12% (5/42) elective CS, hence the absolute relative risk is 1.009 (95% CI: 1.005–1.013). The mean age of women readmitted for SSI following CS was 29.2 years (SD 2.7) (Table 2) with an average 5.9 days (SD 4.0) between initial discharge and readmission. Seventy-four percent of women readmitted with SSI post-CS underwent CS with ruptured membranes; 14% had prolonged rupture of membranes (<18 h). Nine women (21%) had CS at full dilatation. Category 1 surgery was required for 10 patients (24%). Ten patients (24%) had suspected intra-amniotic infection treated with antibiotics during labour and seven patients (17%) had a fever post-partum during their initial admission which was not wound-related. All patients received prophylactic pre-operative antibiotics, although the timing and rationale for dosages was not clearly documented. Wound culture results included 17% Streptococcus species, 14% Staphylococcus species, 14% Coliform species, 5% Gardnerella vaginalis, 2% Pseudomonas aeruginosa and 2% mixed anaerobes. Normal skin flora was cultured in 14%, while 29% had a negative culture.

DISCUSSION

Surgical site infection was the most common reason for readmission following CS, representing 25.5% of all readmissions. The overall rate of readmission for SSI was 0.7% which is consistent with published rates of 0.6–1.7%. Further, 88% of those readmitted for SSI were following an emergency CS, compared to 12%...
following an elective CS; this represents a seven-fold difference that is statistically significant ($P < 0.001$). One reason why rates of SSI may be higher following emergency CS is thought to be the rupture of membranes as the amniotic fluid is no longer sterile and may allow bacteria to colonise the uterus and incision.\textsuperscript{11,14} In our study, 74% had ruptured membranes and 14% of patients had prolonged rupture of membranes.

Another explanation for the high rate of SSI following emergency CS is the possible shorter duration of skin contact of surgical skin preparation, which was not controlled in this study. Further, the type of surgical skin preparation may also be important.\textsuperscript{3,5} In Darwin, post-CS SSI rates were halved by using alcoholic 2% chlorhexidine and adding gentamicin to pre-incisional cephalosporin.\textsuperscript{9} A Cochrane review also found that chlorhexidine gluconate was associated with lower rates of bacterial growth when compared to iodine alone.\textsuperscript{15} A recent paper demonstrated that chlorhexidine-alcohol reduces wound infection rates compared to iodine-alcohol.\textsuperscript{2} Therefore, as new evidence becomes available, local centres could consider making changes to their skin preparation in an attempt to reduce SSI.

There is strong evidence to support the use of pre-operative prophylactic IV antibiotics, which was received by all our patients. A recent randomised controlled trial supports the addition of azithromycin to reduce the rate of SSI following emergency CS.\textsuperscript{16} However, since most patients in our study with a positive wound culture grew a Streptococcus or Staphylococcus species, it is unlikely this would benefit our study population. In addition, widespread use of azithromycin may increase the risk of antibiotic resistance.

Apart from being in labour and the rupture of membranes, other risk factors for SSI following CS have previously been identified, including diabetes mellitus.\textsuperscript{5,12} It is believed that hyperglycaemia decreases vascular circulation resulting in tissue hypoxia and impairs cellular immunity.\textsuperscript{17} Our findings are consistent with this trend as 14.3% of patients readmitted with SSI had diabetes compared to the background rate of diabetes of 12.5% at our obstetric population;\textsuperscript{18} however, this was not statistically significant ($P = 0.7$). Similarly, obesity is an independent risk factor for SSI, perhaps due to an insufficient antibiotic dose or poor wound healing.\textsuperscript{13} This was reflected in our results as 69% were overweight or obese, compared to the background rate of 34–43%.\textsuperscript{19,20} This is an important issue since obesity is a rapidly growing problem worldwide.

This study is unique in terms of its focus on patients who required readmission for management of SSI. We considered readmission as an important outcome due to the increased severity of infection, psychological stress to patients and financial burden to the healthcare system.\textsuperscript{3,5} However, our study was limited by small sample size, retrospective design and lack of a control group. Furthermore, patients who were readmitted to other hospitals were not detected and the socio-economic and ethnic composition of this community may not reflect the general obstetric population.

Our study found that SSIs were the most common reasons for readmissions following CS, a potentially preventable complication in a population of generally healthy women. Furthermore,
the rate of SSIs following emergency CS was statistically greater compared to elective CS. Our study reinforces the need to identify and target strategies to reduce SSI in women who have a higher risk of infection, such as women having an emergency CS with underlying comorbidities.

ACKNOWLEDGEMENTS

Kind acknowledgements to EG for assistance with data analysis, and MH and DH for assistance with data acquisition. Emma Gibbs, NHMRC Clinical Trials Centre, University of Sydney. Monica Hook, Midwifery Educator, Obstetric Data Custodian, Westmead Hospital. Diane Healy, Manager Clinical Documentation Specialists, Health Information and Records Service, Westmead Hospital.

REFERENCES


Reduced angiogenic factor expression in intrauterine fetal growth restriction using semiquantitative immunohistochemistry and digital image analysis

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Abstract

Aim: To localize, quantify and compare angiogenic factors, vascular endothelial growth factor (VEGF), placental growth factor (PlGF), as well as their receptors fms-like tyrosine kinase receptor (Flt-1) and kinase insert domain receptor (KDR) in the placentas of normal pregnancy and complications of preeclampsia (PE), intrauterine fetal growth restriction (IUGR) and PE + IUGR.

Methods: In a prospective cross-sectional case-control study, 30 pregnant women between 24–40 weeks of gestation, were recruited into four clinical groups. Representative placental samples were stained for VEGF, PlGF, Flt-1 and KDR. Analysis was performed using semiquantitative methods and digital image analysis.

Results: The overall VEGF and Flt-1 were strongly expressed and did not show any conclusive difference in the expression between study groups. PlGF and KDR were significantly reduced in expression in the placentas from pregnancies complicated by IUGR compared with normal and preeclamptic pregnancies.

Conclusion: The lack of PlGF and KDR may be a cause for the development of IUGR and may explain the loss of vasculature and villous architecture in IUGR. Automated digital image analysis software is a viable alternative method to the manual reading of placental immunohistochemical staining.

Key words: Fms-like tyrosine kinase receptor-1, intrauterine fetal growth restriction, kinase insert domain receptor, preeclampsia, placental growth factor, vascular endothelial growth factor.

Introduction

Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) as well as their receptors fms-like tyrosine kinase receptor (Flt-1) and kinase insert domain receptor (KDR) are thought to be important for placental angiogenesis. These factors are expressed in the placental trophoblast throughout gestation. VEGF protein has been identified in villous trophoblast in the first trimester and in the cytotrophoblast and syncytiotrophoblast as well as extra-villous trophoblast at term, suggesting a role in the regulation of cytotrophoblast growth and differentiation. Studies have localized Flt-1 protein and mRNA to extra villous trophoblast, syncytiotrophoblast, and villous cytotrophoblast in normal pregnancy. Flt-1 is a transmembrane receptor and binds VEGF and PlGF with high affinity. Alternative splicing of the Flt-1 pre-mRNA results in the production of sFlt-1, a soluble form comprising the ligand-binding domain of Flt-1 but lacking the membrane-spanning and intracellular domains. Soluble Flt-1 has been shown to be secreted by endothelial cells, monocytes and placental tissues. sFlt-1 has potent antagonistic action of VEGF and PlGF, by inhibiting their binding to cell surface receptors as well as...
by forming heterodimers with the other VEGF receptor, KDR. Immunostaining of PIGF protein has been localized to the vascular endothelium and syncytiotrophoblast membrane and in the media of large blood vessels of the placental villi. PIGF mRNA has been predominantly expressed by the villous trophoblast. These results suggest that PIGF may be an important paracrine factor for vascular endothelial cells in placental angiogenesis and an autocrine mediator of trophoblast function. KDR is a transmembrane receptor which binds VEGF and regulates placental vasculogenesis and angiogenesis. The pro-angiogenic biological activities of VEGF and PIGF appear to be mediated exclusively by the KDR/Flt-1 receptors and include the mitogenic, angiogenic and permeability-enhancing effects of VEGF on the endothelium. KDR expression has been demonstrated in the placenta and is known to be mainly localized to the vascular endothelium.

Most studies to date on angiogenic factors in the placenta have focused on maternal hypertensive disorders. Several research groups including the current authors have demonstrated an increase in the maternal circulating sFlt-1 and a decrease in PIGF with these changes postulated to contribute to the pathophysiology in preeclampsia (PE) by leading to endothelial dysfunction. Studies suggest the altered placental sFlt/PIGF ratio is associated with vascular lesions and placenta hypoxia, and it is the source of anti-angiogenic factors. Studies that assess VEGF expression in placental trophoblast in PE are inconsistent with data suggesting both reduced as well as increased VEGF protein expression. These studies included a mix of patients with early and late-onset of PE as well as intrauterine fetal growth restriction (IUGR) complicating PE. Not surprisingly, discrepant findings have also been published on placental VEGF mRNA levels in PE as compared with normal pregnancy. Similar inconsistent data exist regarding the expression of other angiogenic factors such as sEng, sFlt and PIGF. Importantly, the selection criteria for IUGR or small for gestation age in the published studies have not included any physiological parameters such as umbilical artery or uterine artery Doppler studies – such flow assessments distinguish placental cause of IUGR rather than constitutionally small fetuses.

Manual reading of immunohistochemistry staining with semiquantitative scoring systems and analysis has been used to compare staining characteristics between normal and pathological pregnancies in studies of angiogenic factors. While quantitative immunohistochemistry techniques have been used in studies to evaluate placental morphological characteristics in PE and IUGR, no studies utilizing digital image techniques for the analysis of placental angiogenic factor expression have been published. The main aim of this study was to identify any differences in the expression of angiogenic factors VEGF and PIGF as well as their receptors Flt-1 and KDR between normal pregnancy and pregnancies complicated by PE and/or IUGR, using both quantitative and semiquantitative image analysis techniques.

Methods

The research was conducted with the approval of the Human Research Ethics Committee of Western Sydney Area Health Service, Australia. All women provided written informed consent before the collection of samples. In a cross-sectional study, pregnant women between 24–40 weeks of gestation were recruited into four groups: (i) normal, (ii) PE, (iii) IUGR and (iv) PE and IUGR.

All patients classified as PE in this study satisfied the ISSHP/International Society for the Study of Hypertension in Pregnancy 2001 criteria for preeclampsia. IUGR was defined as birth weight less than 10th centile with elevated umbilical artery Doppler systolic/diastolic ratio or Resistance Index >95th centile for gestation. All patients with PE, PE + IUGR or IUGR underwent antenatal ultrasound examination after 24 weeks of gestation and within 7 days of delivery. Ultrasound assessments were performed using General Electric Voluson 730 or E8 ultrasound equipment.

Patients with pre-existing hypertension, renal disease (including pre-existing proteinuria), pre-existing diabetes, gestational diabetes and multiple pregnancies were excluded from the study.

Placental sample collection, processing and immunohistochemistry

Four representative 1 cm × 1 cm placental blocks were selected from each placenta, 2 cm away from the placental margin. Areas of obvious infarction were avoided. The tissues were fixed in 10% neutral buffered paraformaldehyde for 18 h prior to embedding in paraffin. Five micron sections were cut from formalin fixed tissue embedded in paraffin blocks and mounted on silane coated slides for immunohistochemistry. An
automated immunostainer (Discovery XT, Ventana Medical Systems) was used with standard staining techniques. Immunoreactivity was localized with 3,3'-diaminobenzide (DAB) map kit with an incubation time of 30 min. All sections were stained in batches to minimize variations. Hematoxylin and Eosin (H&E) staining was performed.

Placental morphologic criteria and number of villi
The H&E stained slides were reviewed and scored by an independent blinded perinatal pathologist. The placental morphological characteristics were defined using accepted pathological features of PE and IUGR such as increased syncytiotrophoblastic knots, villous hypercapillarization, increased perivillous fibrin deposition, villous infarction, shrinkage of villi, vascular obliteration and villous fibrosis compared with normal pregnancy. The number of villi per high power field (magnification ×400) was recorded for five randomly and blindly selected fields from each placental sample.

Placental immunohistochemical staining for angiogenic factors and their receptors
Vascular endothelial growth factor, PlGF, Flt-1 and KDR were studied using commercially available polyclonal antibodies and the rabbit ImmunoCruz staining system sc-2051. The antibodies and the dilutions used are listed in Table 1.

Optimization and staining method
Primary antibody dilutions were optimized using manual immunohistochemical staining methods (Santa Cruza Biotechnology Immunocruz staining systems). Manually optimized primary antibody dilutions were then used to assess the localization and expression of VEGF (anti-VEGF 1:100), PlGF (anti-PlGF 1:50), Flt-1 (anti-Flt-1 1:100) and KDR (anti-KDR 1:50). The samples were incubated with blocking serum to reduce nonspecific reactions and incubated with primary antibody at 37°C. The slides were incubated with secondary antibody for 20 min at 37°C. The sections were counterstained with Mayer’s Hematoxylin.

Semi-quantitative (manual) and digital image analysis of immunohistochemical staining
Semi-quantification of immunoreactivity was accomplished using a scoring system.

Five randomly selected high power fields (magnification ×400) from each placental sample were examined by two independent blinded observers for VEGF and Flt-1 staining and scored for localization, tissue types and intensity in color. Staining intensity was rated on a scale of 0–3, with 0 = negative; 1 = weak staining; 2 = moderate staining; and 3 = strong staining (Table 2). The mean of the five fields was taken as the staining intensity score for each sample. Localization of staining was recorded for trophoblast, vascular endothelium, stromal cells and Hofbauer cells. The slides stained with PlGF and KDR were not assessed with the semi-quantitative method due to the low overall staining intensity levels. Interobserver variability was assessed by comparing the VEGF immunostaining score for 120 slides for the two observers (see statistical analysis).

Digital image analysis of placental angiogenic factor expression was performed on a total of 120 individual slides for each of the biomarkers. Slides were digitized using the Aperio Scanscope CS microscope (Aperio Technologies, Version 6.25) with a ×20 objective magnification and a digital image generated. Quantitation of immunohistochemical staining intensity and percentage of cells that were immunopositive (DAB, brown color) was accomplished by using Aperio Image scope reader software v11.2.0.780.

Table 1 Summary of primary antibodies used for immunostaining

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Host</th>
<th>Source</th>
<th>Dilution</th>
<th>Incubation time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF antibody (sc-152)</td>
<td>Rabbit polyclonal</td>
<td>Santa Cruz Biotechnology, California, USA</td>
<td>1:100</td>
<td>2</td>
</tr>
<tr>
<td>Anti-PlGF antibody (sc-1880)</td>
<td>Goat polyclonal</td>
<td>Santa Cruz Biotechnology, California, USA</td>
<td>1:50</td>
<td>2</td>
</tr>
<tr>
<td>Anti-Flt-1 antibody (sc-316)</td>
<td>Rabbit polyclonal</td>
<td>Santa Cruz Biotechnology, California, USA</td>
<td>1:100</td>
<td>2</td>
</tr>
<tr>
<td>Anti-KDR antibody (sc-19530)</td>
<td>Goat polyclonal</td>
<td>Santa Cruz Biotechnology, California, USA</td>
<td>1:50</td>
<td>2</td>
</tr>
</tbody>
</table>
The digitized images were read using the Positive Pixel Count Algorithm (PPCA) for quantitative analysis of the amount of brown (DAB) stain present in the scanned slide images. In this algorithm, the region of interest on each of the virtual slides was set as the whole tissue sample to minimize any selection bias in choosing more or less stained sections for analysis. A color markup image for each slide was obtained based on membrane staining intensity (Fig. 1). The output was viewed as determinations of staining intensity ranging from 0 to 3 to correlate with conventional manual scoring methods (0, negative; 3, strong staining) and statistical analysis was performed using the mean of these values. Intensity is the brightness of the pixel and ranged from 0 (black) to 255 (bright white). Using this PPCA, the stronger staining pixels (darker) will have a lower value due to lower intensity of the pixel while the higher numbers indicate weaker staining pixels. The algorithm’s pre-configured set of default input threshold parameters for brown color quantification in the three intensity ranges were used for the quantification of the current slides. The pseudo color markup image generated by the program corresponded to the desired color and intensity ranges observed with the naked eye using a light microscope (Fig. 1). The thresholds used to define each intensity category are listed in Table 2. Pixels which stained, but did not fall into the positive color specification, were considered negative stained pixels. These pixels were also counted by the algorithm, so that the fraction of positive to total stained pixels could be determined.

### Table 2. Intensity thresholds and colour as assigned by the positive pixel algorithm

<table>
<thead>
<tr>
<th>Intensity range</th>
<th>Intensity range</th>
<th>Color on mark-up image</th>
<th>Semiquantitative levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tissue</td>
<td>NA</td>
<td>White</td>
<td>NA</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt;220</td>
<td>Blue</td>
<td>Negative</td>
</tr>
<tr>
<td>Weak-positive intensity</td>
<td>175–220</td>
<td>Yellow</td>
<td>1</td>
</tr>
<tr>
<td>Moderate-positive intensity</td>
<td>100–175</td>
<td>Orange</td>
<td>2</td>
</tr>
<tr>
<td>Strong-positive intensity</td>
<td>&lt;100</td>
<td>Red</td>
<td>3</td>
</tr>
</tbody>
</table>

Statistical analysis

The statistical software packages SPSS for windows version 21 and SPLUS version 8 were used to analyze the data. Two-tailed tests with a 5% significance level were used throughout.

For statistical analysis of semiquantitative methods, the mean immunostaining data categorized into three levels of 1, 2 and 3 for each variable were used in repeated measures analysis of variance to investigate the effects of the intensity of VEGF staining characteristics and the clinical group. In digital image analysis, the median and interquartile ranges were used to describe the representative results of four samples from each placenta. Kruskal Wallis nonparametric analysis of variance was used to test for homogeneity across the four clinical groups for each of the variables VEGF, PIGF, FIt-1 and KDR. One way analysis of variance or Kruskal–Wallis nonparametric equivalent was used to investigate

![Image 1](image.png)

Figure 1 The image scope markup image showing the correlation between the manual read of intensity (a) and the automatic analysis using the Positive Pixel Count Algorithm set thresholds (b). Higher intensity staining in (a) is marked by red staining in (b) magnification ×200. Color coding of the three intensities were used to ensure that the three thresholds correlated with the color intensity as viewed through the light microscope. Different colors indicate the intensity level of positive pixels (red = strong, orange = moderate, yellow = low). (→), syncytiotrophoblast, (→→), vascular endothelium.
used to test for differences between the clinical groups. Where statistically significant different heterogeneity was detected, multiple pairwise comparisons using Mann–Whitney tests were used to examine differences between particular clinical groups. Bonferroni correction was applied to these multiple pairwise comparisons for analyses of expression of placental angiogenic factors in this study.

Bland–Altman plots were used to investigate the interobserver variation in semiquantitative analysis of staining intensity. The Spearman rank correlation and kappa correlation coefficient were used to quantify the extent of the association between the manual semiquantitative reading and digital image analysis.

Results

The baseline characteristics of the four study groups are shown in Table 3. Results are presented for 120 placental samples from 30 pregnancies. The study subjects from the PE and IUGR delivered earlier and had lower birth weights as compared with term normal controls. All neonates delivered to the IUGR or PE + IUGR groups were <10th centile for gestation, while all subjects in the normal pregnancy and PE-only groups delivered a neonate with birth weight ≥10th centile for gestation.

Morphological characteristics of the placenta

Approximately, 50% of the placental biopsies in the three pathological PE, IUGR and PE + IUGR groups had areas of villous infarction as well as widespread syncytial knots, loss of villi and fibrin deposition (Table 4). The morphological changes associated with PE and IUGR are demonstrated in Figure 2.

Density of terminal villi

Placentae from the PE and IUGR groups had significantly less number of villi than normal placenta. The combination of PE and IUGR was associated with significant reductions in the number of villi compared with PE and IUGR alone (Table 4).

Angiogenic factors and their receptors: Manual semiquantitative analysis of immunostaining intensity

The immunolocalization of the angiogenic factor staining in different tissue types was similar in all clinical groups. VEGF was detected in syncytiotrophoblast,

<table>
<thead>
<tr>
<th>Table 3 Maternal and fetal demographic data and clinical characteristics of the study population</th>
</tr>
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<tbody>
<tr>
<td>Clinical groups</td>
</tr>
<tr>
<td>Maternal age (years)</td>
</tr>
<tr>
<td>Gestation at delivery (weeks)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Primigravidae (n)</td>
</tr>
<tr>
<td>Current smokers (n)</td>
</tr>
<tr>
<td>Caesarean sections (n)</td>
</tr>
<tr>
<td>Maternal corticosteroid treatment prior to delivery</td>
</tr>
<tr>
<td>Results are presented as median (from lower quartile 25% to upper quartile 75%) for each continuous variable unless otherwise specified. and IUGR, intraterine fetal growth restriction; PE, preeclampsia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4 Placental morphological characteristics by clinical group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental morphology</td>
</tr>
<tr>
<td>No of placental biopsies</td>
</tr>
<tr>
<td>Mean number of villi per high power field (×400) ± SD</td>
</tr>
<tr>
<td>Placental biopsies with loss of villi</td>
</tr>
<tr>
<td>Loss of villi</td>
</tr>
<tr>
<td>Hypovascular villi</td>
</tr>
<tr>
<td>Syncytial knots</td>
</tr>
<tr>
<td>Intervillositis</td>
</tr>
<tr>
<td>Perivillous fibrin</td>
</tr>
<tr>
<td>Large infarcts</td>
</tr>
</tbody>
</table>
*Compared to normal pregnancies, P < 0.05. IUGR, intrauterine fetal growth restriction; PE, preeclampsia.
cytotrophoblast, extra villous trophoblast, endothelium and Hofbauer cells (Fig. 3), while the Flt-1 was mainly localized to syncytiotrophoblast, cytotrophoblast and Hofbauer cells (Fig. 4). Increased staining for KDR was demonstrated in the endothelial cells. Strong PlGF immunoreactivity was localized to the syncytiotrophoblast and endothelium with minor staining of the villous stroma. A feature in all three pathological groups was the prominence of extra-villous trophoblast in the stem villi with infiltration into the areas of villous infarctions (Table 4). These cells demonstrated intense immunoreactivity for VEGF as well as its Flt-1 receptor.

**Angiogenic factors and their receptors: Quantitative image analysis of immunohistochemical staining**

Staining intensity and positive pixel counts for VEGF, PlGF, Flt-1 and KDR are presented in Table 5 and Figure 5a–d.

The PlGF intensity and area stained in placenta were lower in pregnancies complicated by IUGR and...
PE + IUGR compared with normal and PE pregnancies (Table 5 and Fig. 5a). The PlGF staining was in the moderate range for normal pregnancy and PE, while IUGR and PE + IUGR staining was weak. Statistically significant differences were seen in the percentage of area positive for PlGF between normal pregnancy and IUGR as well as PE + IUGR with IUGR also showing a lower percentage of positive cells. A significant difference was also seen between PE and IUGR as well as PE and PE + IUGR. No difference was seen between normal pregnancy and PE for level of staining or area positively stained (Fig. 5a). Over 65% of tissue stained positive for VEGF in all clinical groups (Table 5). All the clinical groups demonstrated VEGF staining in the moderate range (100–175) (Fig. 5b). VEGF was found significantly less in placenta of pregnancies with PE ($P < 0.05$) and PE + IUGR ($P < 0.01$). No significant difference in VEGF was noted between the pathological groups (i.e. PE, PE + IUGR and IUGR groups) (Fig. 5b).

For Flt-1 staining, all clinical groups displayed a high percentage area of positive pixels averaging over 75% of total area, median ranging from 78 to 85% (Table 5). Flt-1 is noted to be more widely expressed in pathological group placentas, but at a lesser intensity (Fig. 5c). For KDR staining, the majority of placental tissue was positively stained in all clinical groups. Normal pregnancy placentas had higher intensity of KDR staining compared with the pathological pregnancies with significant difference seen between normal and PE ($P < 0.01$), normal and IUGR ($P < 0.05$) as well as normal and PE + IUGR ($P < 0.01$). No difference in staining intensity was seen between the pathological groups (Fig. 5d). The majority of KDR positively stained tissue in normal pregnancy was moderate while the pathological groups PE, IUGR and PE + IUGR demonstrated mainly weak staining (Table 5).

**Inter- and intraobserver variability**

The results showed a significant correlation between the scoring of the two observers (kappa correlation coefficient 0.469, $P < 0.01$). The correlation coefficient for grading of VEGF immunostaining scores between two independent observers using Bland–Altman limits of agreement was 88% ($P < 0.001$). There was a significant tendency for observer 2 to score slightly higher than observer 1, mean difference 0.12 (SD 0.03, $P < 0.001$).

**Comparison between semiquantitative and digital image analysis of VEGF staining**

A moderate correlation was seen between the average score for manual reading and the score generated by the automated digital image analysis, across all study subjects in the moderate to strong VEGF intensity levels (correlation coefficient 0.51, $P < 0.01$). The

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**Figure 4** Immunolocalization of fms-like tyrosine kinase receptor in the placenta. (a) Normal term placenta ×200, (b) preeclampsia ×200, (c) isolated intrauterine fetal growth restriction (IUGR) ×400, (d) endothelial staining isolated IUGR ×400. (→), intense staining of Hofbauer cells; (→), staining of endothelial cells.
correlation was weaker and did not reach significance in the weak intensity levels.

**Discussion**

This study has correlated the angiogenic effects of VEGF, PIGF and the anti-angiogenic response of Flt-1 and KDR in the placenta to histopathological changes as well as the clinical features of PE and IUGR which were defined on the basis of umbilical artery Doppler waveforms.

The results from our study have demonstrated that PE and IUGR are associated with loss of villous architecture, vascularity and tissue. The description of placental morphology in our study is comparable with previous findings of syncytiotrophoblast knotting, villous infarcts, avascular villi and uteroplacental fibrinoid necrosis as characteristic placental morphological features of PE and intrauterine growth restriction. The features were similar in PE and IUGR. The cumulative effect of PE and IUGR appear to lead to a more significant loss of villous architecture than either condition alone. The decreased number of villi in the IUGR and PE + IUGR is also consistent with prior histopathological studies documenting loss of terminal villi with IUGR.

The localization of VEGF, PIGF, Flt-1 and KDR in the placental tissue types was similar across the four clinical groups and comparable to previous work, in which positive staining for VEGF, PIGF and Flt were mainly localized to syncytiotrophoblast, while KDR was detected in endothelium.

In an objective assessment of angiogenic factor expression using automated digital analysis, we showed that while no major differences in placental VEGF and Flt-1 were noted between clinical groups, placental expression of PIGF and KDR were significantly reduced in pregnancies complicated by IUGR as compared with normal and PE-only pregnancies.

These results on the overall VEGF distribution and the level of VEGF in the placentas demonstrated that while a higher number of cells were positive for VEGF in the pathological placentas, the intensity of staining was in the moderate staining range in all the clinical groups. These findings are consistent with data from previous studies showing increased as well as reduced VEGF levels in PE. The variation in staining may be explained by the fact that placental pathology is often patchy within the disc of the placenta and an overall assessment may not be able to demonstrate a difference. Recent study showed the concentrations of sFlt/PIGF in placental homogenates were significantly increased in early-onset PE compared with normotensive, but no difference was noted between late-onset PE and normotensive patients. This finding suggests late-onset PE and early-onset PE could have different etiology. Differences in the

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**Table 5** The percentage of immune-reactive cells and the intensity as evaluated by automatic Aperio digital image analysis software for each of the antibodies staining for VEGF, PIGF, Flt-1 and KDR

<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Clinical group</th>
<th>Average area (mm²) analyzed</th>
<th>Average % of positive cells</th>
<th>Distribution of intensity of positive cells %</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>Normal</td>
<td>17.82</td>
<td>69.76</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>34.45</td>
<td>74.52</td>
<td>21.72</td>
</tr>
<tr>
<td></td>
<td>IUGR</td>
<td>25.46</td>
<td>75.2</td>
<td>30.57</td>
</tr>
<tr>
<td></td>
<td>PE + IUGR</td>
<td>25.33</td>
<td>71.34</td>
<td>27.91</td>
</tr>
<tr>
<td>PIGF</td>
<td>Normal</td>
<td>23.38</td>
<td>57.11</td>
<td>25.46</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>31.42</td>
<td>68.70</td>
<td>23.38</td>
</tr>
<tr>
<td></td>
<td>IUGR</td>
<td>10.49</td>
<td>15.76</td>
<td>31.42</td>
</tr>
<tr>
<td></td>
<td>PE + IUGR</td>
<td>12.00</td>
<td>20.07</td>
<td>10.49</td>
</tr>
<tr>
<td>Flt-1</td>
<td>Normal</td>
<td>22.01</td>
<td>76.52</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>40.10</td>
<td>77.66</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>IUGR</td>
<td>30.52</td>
<td>82.23</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>PE + IUGR</td>
<td>31.18</td>
<td>80.24</td>
<td>33.06</td>
</tr>
<tr>
<td>KDR</td>
<td>Normal</td>
<td>18.68</td>
<td>13.77</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>31.08</td>
<td>6.06</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>IUGR</td>
<td>18.58</td>
<td>8.11</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>PE + IUGR</td>
<td>22.2</td>
<td>11.85</td>
<td>7.93</td>
</tr>
</tbody>
</table>

Flt-1, fms-like tyrosine kinase receptor; IUGR, intrauterine fetal growth restriction; KDR, kinase insert domain receptor; PE, preeclampsia; PIGF, placental growth factor; VEGF, vascular endothelial growth factor.
Placental pathological findings between early and late-onset PE were confirmed in a small cohort study showing higher rates of placental lesions in early-onset than late-onset.\textsuperscript{41}

In our study, PIGF was significantly reduced in IUGR and PE + IUGR as compared with normal pregnancy and PE, both in the area positive as well as in level of staining. Consistent with previous descriptions, the PIGF expression was not significantly different in the PE-only group.\textsuperscript{35} A recent longitudinal and cross-sectional study into plasma PIGF levels\textsuperscript{62} suggested that low maternal PIGF throughout pregnancy identifies a subset of PE patients that develop early and severe disease. That study did not include IUGR and it is not clear whether the described group of patients had significant IUGR as a result of low PIGF. Our results on reduced PIGF correlate with published literature showing that PIGF expression is

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{(a–d) Average staining intensity of PIGF, vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor and kinase insert domain receptor (KDR) for all positively stained pixels. (a) PIGF staining intensity was in the moderate range (intensity 100–175) for normal pregnancy and preeclampsia (PE), while intrauterine fetal growth restriction (IUGR) and PE + IUGR staining intensity was weak (>175). No difference was seen between normal pregnancy and PE. (b) All the clinical groups demonstrated an average VEGF staining intensity in the moderate range (100–175) with some variation in the levels in the intensity between the groups. Normal pregnancy placentas had lower intensity (higher staining) compared to PE (P = 0.007). No significant difference between normal versus IUGR (P = 0.055) and normal versus PE + IUGR (P = 0.052). No difference was seen between the pathological groups. (c) The staining intensity of Flt for normal pregnancy was in the moderate range (100–175) with a small reduction in the staining in the pregnancies complicated by IUGR/PE + IUGR. (d) Normal pregnancy placenta had higher intensity of KDR staining compared to the pathological pregnancies with significant difference seen between normal and PE (P = 0.002), normal and IUGR (P = 0.013) as well as Normal and PE + IUGR (P = 0.004). No difference in staining intensity was seen between the pathological groups. Arrow indicates that higher intensity = lower staining.}
\end{figure}
reduced in the presence of placental hypoxic/ischemic morphological changes and provides further evidence that hypoxic/ischemic changes occur in IUGR placentas.\textsuperscript{59}

The results on Flt-1 parallels previously published results documenting moderate to strong immune staining of syncytiotrophoblast and extra villous trophoblast in normal pregnancy and PE.\textsuperscript{63} Immunolocalization of KDR in the current study has demonstrated a lower membrane bound intensity and area positive for KDR expression in pathological placentas with PE and IUGR compared with normal pregnancy. The findings raise the possibility that changes in VEGF and Flt-1 expression may be a consequence rather than the cause of placental vascular disease and PE and that lack of PI GF and KDR may be a main cause for the development of IUGR. A compromised expression of KDR may play a significant part in the pathogenesis of PE and IUGR.

The published literature to date on angiogenic factors and their receptor expression using immunohistochemical methods has used semiquantitative methods of interpreting and scoring the staining intensity.\textsuperscript{64,65} The current study adds to the existing literature as the first description of digital image analysis techniques in the assessment of angiogenic factor expression in the placenta.

Several studies have published comparisons between semiquantitative scoring systems and digital analysis techniques for immunohistochemical staining.\textsuperscript{66–69} The accuracy of digital techniques including Aperio computer-assisted analysis of immunohistochemical staining techniques has been assessed and validated in multiple tissue types including brain, breast and kidney.\textsuperscript{66–68} In published literature, Aperio PPCA is comparable with the pathologist’s scoring and could add benefits of automated and reproducible measurement.\textsuperscript{69} This study has also shown that automated digital image analysis using software such as Aperio PPCA can be successfully used as an alternative method to the manual reading of placental immunohistochemical staining and may provide a more reproducible, standardized, less time consuming method of analysis that can be applied in clinical as well as research methodology. However, automated digital image analysis does not distinguish which placental cells express these proteins.

A strength of this study was the classification of the clinical groups according to the umbilical artery Doppler flow velocity waveforms as well as maternal hypertensive disease ensuring that the samples were collected from pregnancies affected by placental vascular disease.

This study was limited by small patient numbers, and the cross-sectional design, although comparable with previously published studies using similar techniques.\textsuperscript{50} The use of the digital image analysis of the whole placental biopsy has increased the area of placenta analyzed for staining as compared with a limited number of high power fields usually analyzed by the manual assessment of staining.

The results of this study showing major changes in placental expression of PI GF and KDR, but not in VEGF or Flt-1 raise the possibility that changes in VEGF and Flt-1 expression may be a consequence rather than the cause of placental vascular disease and PE and that lack of PI GF and KDR may be a main cause for the development of IUGR. The factors controlling these pro-angiogenic factors need further study in understanding the pathogenesis of IUGR.

Acknowledgments
The authors gratefully acknowledge the contributions from Aysen Yuksel in immunohistochemistry staining, Wei Li in reviewing stained slides and Karen Byth for the assistance with the statistical analysis of data. Financial support was provided by Ella Macnight Research Scholarship, Royal Australian and New Zealand College of Obstetrics and Gynecology (RANZCOG) Research Foundation.

Disclosure
None declared.

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RESOLUTION OF SEVERE HYDROPS ASSOCIATED WITH A LARGE CPAM: MIRACLE OR MEANT TO BE?

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Background: Congenital pulmonary airway malformation of the lung (CPAM) has a varied antenatal course, however most lesions regress or remain stable. The CPAM Volume Ratio (CVR)[1] helps when counselling patients regarding the likelihood of regression, development of hydrops and, by association, of foetal demise. The presence of early onset fetal hydrops has been associated with a poor prognosis[2].

Methods: Case report of an antenatally diagnosed, large CPAM associated with non-immune hydrops and elevated CVR (2.93). The pregnancy was managed expectantly in keeping with parental wishes.

Results: The initial diagnosis of a large CPAM with polyhydramnios and ascites was made at morphology ultrasound. From 30 weeks gestation, resolution of the ascites and polyhydramnios occurred, whilst the mediastinal shift and diaphragmatic eversion reduced. A live female infant was delivered following induction at 40 weeks. Following a very difficult neonatal stabilisation and pulmonary embolization the lesion was surgically removed with a bilobectomy. The baby was extubated to CPAP after one week and was discharged with no respiratory support.

Conclusions: The association of a large CPAM with ascites, elevated CVR, diaphragmatic eversion and mediastinal shift indicates a poor postnatal prognosis. We present the ultrasonographic findings that demonstrate natural resolution of these features, as well as the clinical course of a child that many would have expected to not survive into neonatal life let alone discharge home early in the neonatal period.

Letter to the Editor

Response to: Cervical cancer in women under 25 years of age in Queensland, Australia: To what extent is the diagnosis made by screening cytology?

Amy Jamieson, Alison Brand
Australian and New Zealand Journal of Obstetrics and Gynaecology, 2018; 58(3), E5-E6


Dear Editor,

With the Australian National Cervical Screening Program changing in December 2017, this article by Morgan et al. addresses the topical issue of increasing the commencement of cervical screening to age 25 years. Despite there being considerable evidence to support the safety of increasing the commencement screening age to 25 years, there are concerns by some this will delay the diagnosis of cervical cancer in this age group with adverse effects.

In the article by Morgan et al., they found the commonest reason for the diagnosis of cervical cancer in women under 25 years of age was the investigation of abnormal symptoms rather than routine Pap smear. However, in 34% of the total cases reviewed it was unknown how these patients presented.

Recently, we reviewed cases of cervical cancer diagnosed at age 25 years or younger and treated at Westmead Hospital from 1994 until 2017, using the Westmead Gynaecologic Oncology Database. Only 14 cases were identified during this 23 year time period, which is consistent with the known very low incidence of cervical cancer in this age group. The histologies were as follows: eight squamous cell carcinomas, two adenocarcinomas, one adenosquamous carcinoma, two undifferentiated high-grade carcinomas and one serous carcinoma. The stage and presentation are shown in Table 1.

Table 1. Stage and presentation of cervical cancer age 25 years and younger

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. patients</th>
<th>Abnormal routine Pap</th>
<th>Abnormal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>1B</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2B</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3B</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Half of the women presented with an abnormal routine Pap smear. Four out of seven of these women with an abnormal routine Pap were age 25 years and would therefore have human papilloma virus (HPV) testing with the new screening guidelines. Half the women presented with abnormal symptoms and would be investigated. Therefore 11/14 of the cases would have been picked up with the new National Cervical Screening Program. The three remaining cases included one patient who had early sexual debut and had not received the HPV vaccine. Such a patient would be eligible for a single HPV test between the ages of 20–24 years with the new screening guidelines. The second patient was eligible for, but did not receive, the HPV vaccine, which would have lowered her risk. The third patient had a very unusual disease course. She presented at age 22 with a routine Pap smear suggestive of low-grade change and a biopsy which showed HPV change only. Despite this, she had a large-loop excision of the transformation zone procedure at six weeks gestation. The final pathology showed cervical intraepithelial neoplasia grades 1/2 with an area of atypical squamous cells, favouring early invasive squamous cell carcinoma (0.3 mm). She subsequently had no further treatment and no further abnormalities. It is unknown how rapidly such a tumour would grow.

No population-based screening tests are 100% sensitive. We agree with Morgan et al. that Australian women and health professionals should be reassured by the effectiveness of the new cervical screening program, and the age at which screening should commence.
Response to: Confounding factors in readmissions due to surgical site infections after caesarean section

Dear Editor,

We would like to thank the author of this letter for their interest in readmissions for surgical site infections following caesarean section surgery and their comments on our paper.

Firstly, regarding readmissions of patients to other hospitals, we agree that this information would have given us a more complete dataset; however, we do not believe that significant numbers were missed. Most patients (90%) are public and the majority live very close to the hospital with birthing restricted to those in nominated local government areas. Tracking readmissions in the small number of high-risk out-of-area women, including those from the country, who presented to other hospitals rather than coming back to Westmead would have been difficult due to the large catchment area. Ideally, a state-wide database would allow the identification of all patients for future studies.

Secondly, readmissions for acute pain were uncommon – they were detected as International Classification of Diseases – 10 categories of ‘Other and unspecified abdominal pain’ or ‘Pain localised to other parts of lower abdomen’ which accounted for <3% of readmissions. Of course, many of the women being readmitted with pyrexia, endometritis, secondary postpartum haemorrhage, migraine, severe hypertension or mastitis may have had pain, but the diagnostic category allocated to each case is the underlying cause, rather than the pain itself. From the time of caesarean section, women are given regular paracetamol and a nonsteroidal anti-inflammatory drug supplemented with oxycodone as required. They are strongly encouraged to continue with adequate analgesia at home. This, together with an active midwifery discharge program, probably contributes to low rates of readmission for acute abdominal pain as a diagnosis in itself.

Finally, previous studies have identified emergency surgery as a risk factor for surgical site infections post-caesarean section.\textsuperscript{1,2} Our study was an observational study, which was not designed or powered to determine risk factors. Therefore, we could not conclude that emergency surgery was a risk factor for wound infection, rather that surgical site infections were the most common reasons for readmissions following caesarean section.

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DOI: 10.1111/ajo.12845

Re: Gastric decompression before laparoscopic entry via Palmer’s point

To the editor,

We read the letter by Cook and Land with great interest.\textsuperscript{1} They describe the utilisation of Palmer’s entry point\textsuperscript{2} and the need for pre-emptive gastric decompression. Despite their meticulous citation data collection, several important issues need further consideration.

Gastric injury during gynaecological laparoscopy is a rare complication encountered in 0.2% of all laparoscopy-associated gastrointestinal injuries which occur in about 2% of these procedures.\textsuperscript{3}

As stated by the authors,\textsuperscript{1} entry within the abdominal left upper quadrant or Palmer’s point should be considered in patients suspected to have periumbilical adhesions or following several failed attempts at periumbilical entry. We would like to elaborate on this issue and advise that this approach should be also utilised among patients with morbid obesity or a prior history of laparotomy, and those with extremely low weight due to the higher risk of major blood vessel injury associated with periumbilical entry. It is worth noting that this approach should not be performed in those with previous gastric surgery, portal hypertension and masses involving the upper abdomen.

It should be emphasised that the normal empty stomach is located remote from trocar entry points, including the Palmer’s point. Yet the inflated stomach, such as in a case of a difficult airway management and inadvertent oesophageal intubation, can fill the upper abdomen leaving the stomach vulnerable for penetrating trauma.\textsuperscript{4} Therefore, patients at particular risk are those with difficult airways (eg those with respiratory comorbidities, obesity) that necessitate long bag-and-mask.
Risk and prognostic factors for endometrial carcinoma after diagnosis of breast or Lynch-associated cancers—A population-based analysis

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Funding information
Cancer Council Tasmania, Grant/Award Number: 403031 and 457636; Cancer Australia, Grant/Award Number: 1010859; Cancer Council Queensland, Grant/Award Number: 4196615; National Health and Medical Research Council, Grant/Award Number: 339435

Abstract
We hypothesized that endometrial carcinoma (EC) patients with a prior cancer diagnosis, after accounting for EC arising after tamoxifen-treated prior breast carcinoma, are more likely to have an underlying genetic basis. We used information from a population-based study to compare measured risk factors, tumor characteristics, survival, and known mismatch repair (MMR) pathogenic variant status for EC subgroups according to prior diagnosis of cancer (none, breast cancer tamoxifen-treated or not, Lynch Syndrome (LS)-associated cancer). Family history of any cancer was increased for EC cases with prior breast cancer, both tamoxifen treated (P = 0.005) and untreated (P = 0.01). EC cases with prior LS-associated cancer more often reported family history of LS-associated cancer (P = 0.04) and breast cancer (P = 0.05). EC patients with a germline pathogenic MMR gene variant were more likely to report a prior cancer than cases with a MMR proficient tumor (P = 0.0001), but more than half (54.5%) of MMR carriers reported no prior cancer. Women developing EC after tamoxifen treatment for breast cancer were significantly more likely to develop EC of malignant mixed mullerian tumor subtype (13.2% vs 2.6%, P = 1.3 × 10⁻⁶),
present with stage IV disease (8.8% vs 1.2%, \( P = 1.6 \times 10^{-6} \)), and have poorer survival (HR\(_{\text{adj}}\) 1.96; \( P = 0.001 \)). While report of prior cancer is an indicator of MMR pathogenic variant status, molecular analysis of all ECs at diagnosis is warranted to detect all patients with LS. Results also indicate the importance of longer-term monitoring of women treated with tamoxifen for symptoms of EC, and the need for studies assessing the biological mechanism underlying the poorer prognosis of this subset of EC patients.

**KEYWORDS**
endometrial cancer, MMR status, prior cancer, prognosis, risk

## 1 | INTRODUCTION

Endometrial carcinoma (EC) is the fifth most common cancer in women in developed countries, accounting for 4.8% of new cancers and 2.1% of cancer deaths. The highest incidence rates in 2012 were estimated to be 19.1 and 15.6 per 100,000 in North America and Western Europe, respectively, attributed to the greater overall prevalence of obesity and metabolic syndromes in these regions.³

Established nongenetic risk factors for EC include age and exposure to exogenous estrogens, or endogenous hyperestrogenic status associated with nulliparity, early age at menarche, late-onset menopause and obesity.⁴ In addition, tamoxifen use for treatment of invasive breast cancer is associated with an increased risk of developing EC,⁵ with several reports indicating that EC arising after tamoxifen-treated breast cancer may have poorer prognostic features.⁶,⁷ Genetic risk factors for EC have been supported by the fact that there is at least a twofold increased risk of EC among women with at least one first- or second-degree relative with EC.¹²,¹³ Such genetic factors include high-risk pathogenic variants in the DNA mismatch repair (MMR) genes causing Lynch Syndrome, and very rarely, germline loss-of-function variants in the PTEN tumor suppressor gene causing Cowden Syndrome.¹⁴ We have recently shown that carriage of a pathogenic variant in an MMR gene only partly accounts for risk of EC associated with reported family history,¹² indicating that additional genetic risk factors remain to be identified. It is clear that common genetic variants identified through large-scale genomewide association studies and candidate gene studies also contribute to EC risk, with currently identified risk variants accounting for ~6.8% of the familial relative risk of EC, and modeling studies suggesting an upper estimate of 28% of familial relative risk may be due to common variants.¹⁵,¹⁶

There is evidence that individuals with moderate-high-risk pathogenic variants in cancer predisposition genes are more likely to develop multiple cancers in their lifetime. The cumulative risk of metachronous colorectal carcinoma was reported to be up to 69% among carriers of pathogenic germline MMR gene variants.²³ Members of Li Fraumeni families (due to TP53 pathogenic variants) were shown to have a fivefold increased risk of developing a second primary cancer compared to the general population.²⁴ Further, studies evaluating BRCA1/2 pathogenic variant carriers have reported that women with a first diagnosis of breast carcinoma had a significantly higher risk of developing a pathologically similar contralateral breast carcinoma²⁵ or ovarian carcinoma compared to noncarriers.²⁶

We thus hypothesized that report of a prior cancer, after accounting for EC arising after tamoxifen-treated breast carcinoma, might identify women with EC more likely to have an underlying genetic basis. We anticipated that EC patients with a prior cancer diagnosis might be more likely to report a family history of cancer than EC cases with no prior cancer diagnosis. In addition, we considered the possibility that classical epidemiological risk factors for EC (such as obesity) may be less important for EC patients with prior cancer report (and suspected genetic basis). To investigate these questions, we detailed prior cancer report and tamoxifen use for women with EC and controls participating in the population-based Australian National Endometrial Cancer Study (ANECS). We compared epidemiological risk factors, reported family history, tumor characteristics, survival, and known MMR gene pathogenic variant status for EC subgroups according to cancer types diagnosed prior to recruitment, and for women without EC and no reported personal history of cancer.

## 2 | METHODS

### 2.1 | Study sample sets

All ANECS participants provided informed written consent, and approval was obtained from the QIMR Berghofer Medical Research Institute Human Research Ethics Committee, participating hospitals and cancer registries. Details of participant ascertainment, eligibility criteria, questionnaires, and
data collection, including blood samples for genetic testing, and assessment of family history have been previously reported.\textsuperscript{12,27} Clinicopathological data including histological subtype, grade, tumor stage, and lymphovascular space invasion (LVSI) were abstracted from medical/pathology records. Cases were re-staged using the International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria. Following convention regarding grading of “non-endometrioid” tumors, and knowledge of prognostic features of tumors of mixed histology,\textsuperscript{28} tumor histology and grade were combined in a single variable with the following categories: endometrioid grade 1, endometrioid grade 2, endometrioid grade 3, serous (≥5%), clear cell (≥10%, and no serous ≥5%), carcinosarcoma (malignant mixed mullerian tumor, MMMT), and other epithelial. Vital status was determined from medical records and using probabilistic record data linkage to the Australian National Death Index. Survival time was calculated from date of primary treatment for EC to date of death (overall, EC-specific) or censored at 31 December 2013.

The dataset used for this analysis was based on information for 1399 EC cases and 740 controls who were eligible to participate. Information about report of prior cancer was extracted from questionnaires (cases and controls), and supplemented by information from medical reports ascertained by clinical follow-up studies, and from information about prior cancer noted in endometrial cancer pathology reports (cases only). Tamoxifen use for individuals with prior breast cancer was verified where possible from breast or EC pathology reports, and/or from clinical records.

The detailed breakdown of all prior cancers in controls and EC cases is reported in Table S1. After in-depth reviews from all available data sources, we identified 86 controls and 184 EC cases with a prior cancer diagnosis. The most commonly reported prior cancer diagnosis was breast cancer; 41 controls and 101 EC cases (97 self-reported and four identified from medical records). Among the 101 EC cases with prior breast cancer, 68 had been treated with tamoxifen (47 self-reported, and another 21 identified from clinical follow-up studies or pathology reports), and 33 self-reported no tamoxifen use with no contradictory information from all available clinical records.

We also analyzed a subset of EC cases with at least one diagnosis of a cancer type falling into the Lynch Syndrome (LS) spectrum (termed LS-associated) prior to EC diagnosis. Cancers considered to be LS-associated included cancer of the bile duct, bladder, brain, colon/rectum, duodenum, endometrium, gastrointestinal tract, ovary, pancreas, renal pelvis, and stomach. Of 15 women self-reporting prior ovarian cancer, only two were determined to be true prior cancers, based on age at diagnosis and information from clinical follow-up or pathology reports; for 11 women, their ovarian cancer diagnosis was actually concurrent with EC, and EC pathology reports for another two women indicated that their ovaries were normal and intact at hysterectomy for EC. For the purposes of this analysis, women who had ovarian cancer that was concurrent with EC were included among those with no prior cancer unless they had been diagnosed with another cancer prior to their EC diagnosis. A total of 27 EC cases had been diagnosed with at least one prior LS-associated cancer.

In addition to breast and LS-associated cancers, there were 68 EC patients and 38 controls with reports of other cancer types, with some individuals reporting multiple prior cancer types (Table S1). The remaining 1215 EC patients and 653 controls reported no prior cancer at enrollment in ANECS. An additional control had insufficient data to determine her prior cancer status.

### 2.2 Statistical analysis

The risk of EC associated with known epidemiologic risk factors was evaluated using age-adjusted logistic regression models. Using controls reporting no prior cancer at interview (n = 653) as reference, risk estimates were evaluated for: (a) cases with no history of cancer prior to EC diagnosis (n = 1215); (b) cases diagnosed with breast cancer prior to EC who were treated with tamoxifen (n = 68); (c) cases diagnosed with breast cancer prior to EC with no known tamoxifen use (n = 33); and (d) cases who had been diagnosed with at least one LS-associated cancer prior to EC (n = 27). Age (at diagnosis for women with EC, at enrollment for controls) was entered into regression models as a continuous variable.

Body mass index (BMI) was analyzed as a categorical variable comparing women with a BMI 25-29, and ≥30 to those with BMI <25 kg/m\(^2\). Parity, defined as the number of pregnancies ≥6 months, was analyzed as 1 or ≥2 vs 0. Age at menarche was analyzed as 12-13 or ≥14 vs ≤11. Risk factors for EC, for example, oral contraceptive use, smoking, and ≥3 months use of systemic menopausal hormone therapy (postmenopausal women only) were entered into models as ever vs never use. We also evaluated all patient subgroups for EC risk associated with family cancer history comparing any vs no first- or second-degree relative (FDR or SDR) reporting any invasive cancer, any LS cancer, and breast or ovarian cancer. For patient characteristics analyzed as ordinal variables, we assessed the trend across ordered groups using the nonparametric Cuzick’s test for trend.

We used Cox regression models to evaluate overall and EC-specific survival of cases with a prior breast cancer diagnosis and tamoxifen use, prior breast cancer and no known tamoxifen use, and cases diagnosed with at least one LS-associated cancer prior to EC, compared to those with no history of cancer prior to EC diagnosis. Cox models were adjusted for the following: age at EC diagnosis as a continuous variable; tumor stage in three categories (FIGO stages I, II, and III & IV); tumor histology in seven categories (endometrioid Grade 1, 2, or 3, serous, clear cell, carcinosarcoma/MMMT,
other epithelial); presence/absence of LVI. Survival time was defined as the interval from date of first treatment for EC to date of death from any cause or due to EC, or censored at 31 December 2013.

In addition, we evaluated the relationship between prior cancer and tumor/germline MMR status as previously determined for 722 of the 1399 cases included in this study; 558 were classified as IHC proficient and did not undergo germline genetic testing on the assumption they were very unlikely to carry a pathogenic MMR gene variant, 142 were IHC deficient with no pathogenic variant identified by germline DNA testing, and 22 were IHC deficient and carriers of a pathogenic MMR gene variant. Differences in the frequency of IHC proficient and deficient tumors were evaluated for patients with prior breast cancer according to tamoxifen treatment, and patients with prior LS-associated cancer compared to patients with no prior cancer.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Association of epidemiological risk factors with endometrial cancer risk, according to report of prior breast or Lynch syndrome cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Controls with no prior cancer (n = 653)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>60.6 (9.9)</td>
</tr>
<tr>
<td>Age Range</td>
<td>31.5-80.1</td>
</tr>
<tr>
<td>&lt;50</td>
<td>94 (14.4)</td>
</tr>
<tr>
<td>≥50</td>
<td>559 (85.6)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>315 (49.5)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>189 (29.7)</td>
</tr>
<tr>
<td>≥30</td>
<td>133 (20.9)</td>
</tr>
<tr>
<td>Test for Trend</td>
<td>1.14E−39</td>
</tr>
<tr>
<td>OC use</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>106 (16.3)</td>
</tr>
<tr>
<td>Ever</td>
<td>546 (83.7)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46 (7.0)</td>
</tr>
<tr>
<td>1</td>
<td>59 (9.0)</td>
</tr>
<tr>
<td>≥2</td>
<td>548</td>
</tr>
<tr>
<td>Test for Trend</td>
<td>1.36E−10</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>384 (58.9)</td>
</tr>
<tr>
<td>Ever</td>
<td>268 (41.1)</td>
</tr>
<tr>
<td>Age at menarche</td>
<td></td>
</tr>
<tr>
<td>≤11</td>
<td>96 (15.9)</td>
</tr>
<tr>
<td>12-13</td>
<td>328 (50.9)</td>
</tr>
<tr>
<td>14+</td>
<td>221 (34.3)</td>
</tr>
<tr>
<td>Test for Trend</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hormone use in postmenopausal women</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>298 (57.6)</td>
</tr>
<tr>
<td>Ever</td>
<td>219 (42.4)</td>
</tr>
</tbody>
</table>

*a*Age at diagnosis for patients, at interview for controls; SD, standard deviation; BMI, body mass index; OC, oral contraceptive use.

*b*Ns may not sum to the total because of missing or unknown data; proportions (%) sum to 100% of observations where data available and excludes missing/unknowns.

*c*Risk estimates (Odds Ratios and 95% confidence intervals) are adjusted for age as a continuous variable (at diagnosis for patients, at interview for controls).

*d*P-values for Mean age variables represent pairwise comparisons of means between Controls no prior cancer and Case subgroups.
All tests for association were two-tailed, and performed using STATA SE v. 13 (Stata Corp., USA), and the R project for Statistical Computing version 3.2.2 (http://www.r-project.org/).

3 | RESULTS

As detailed in Table S1, there was no indication that report of prior cancer was elevated in patients compared to controls, overall (13.2% vs 11.8%, \( P = 0.4 \)), or considering individual cancer types. The proportion with reported tamoxifen-treated breast cancer was nonsignificantly higher in cases compared to controls (3.4% vs 2.8% based on self-reported data only, \( P = 0.5 \); additional exploration of tamoxifen usage for cases only (from pathology reports or clinical follow-up) increased the proportion of tamoxifen-treated prior breast cancer among cases to 4.9%). There was no difference between cases and controls for report of prior LS-associated

<table>
<thead>
<tr>
<th>Patients with prior breast cancer and no tamoxifen use (n = 33)</th>
<th>Patients with prior LS-associated cancers (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}^b ) (%)</td>
<td>( \text{OR}^c \ (95% \text{ CI}) )</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>66.0 (7.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>51.2-78.4</td>
<td>33.3-78.4</td>
</tr>
<tr>
<td>0 (0.0)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>33 (100.0)</td>
<td>25 (92.6)</td>
</tr>
<tr>
<td>12 (36.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>9 (27.3)</td>
<td>1.14 (0.47-2.78)</td>
</tr>
<tr>
<td>12 (36.4)</td>
<td>2.47 (1.07-5.70)</td>
</tr>
<tr>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>14 (42.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>19 (57.6)</td>
<td>0.36 (0.16-0.78)</td>
</tr>
<tr>
<td>6 (18.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>4 (12.1)</td>
<td>0.51 (0.13-1.97)</td>
</tr>
<tr>
<td>23 (69.7)</td>
<td>0.26 (0.10-0.69)</td>
</tr>
<tr>
<td>0.03</td>
<td>0.18</td>
</tr>
<tr>
<td>25 (78.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>7 (21.9)</td>
<td>0.46 (0.20-1.09)</td>
</tr>
<tr>
<td>4 (12.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>19 (59.4)</td>
<td>1.44 (0.47-4.37)</td>
</tr>
<tr>
<td>9 (28.1)</td>
<td>0.99 (0.29-3.31)</td>
</tr>
<tr>
<td>0.70</td>
<td>0.47</td>
</tr>
<tr>
<td>20 (60.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>13 (39.4)</td>
<td>0.89 (0.43-1.83)</td>
</tr>
<tr>
<td>Family Cancer History</td>
<td>Controls with no prior cancer (n = 653)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td></td>
<td>N^a (%)</td>
</tr>
<tr>
<td>Family history any cancer (FDR &amp;/or SDR)^c</td>
<td>297 (45.5) 447 (36.8) 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>356 (54.5) 768 (63.2) 1.43 (1.18-1.74) 2.52E-04</td>
</tr>
<tr>
<td>FDR &amp;/or SDR with any Lynch- associated cancer^d</td>
<td>376 (57.6) 593 (48.8) 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>277 (42.4) 622 (51.2) 1.43 (1.18-1.73) 2.73E-04</td>
</tr>
<tr>
<td>FDR &amp;/or SDR with breast cancer</td>
<td>477 (73.0) 859 (70.8) 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>176 (27.0) 355 (29.2) 1.12 (0.90-1.38) 0.31</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
</tr>
<tr>
<td>FDR &amp;/SDR with ovarian cancer</td>
<td>627 (96.0) 1164 (95.9) 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (4.0) 50 (4.1) 1.03 (0.64-1.68) 0.89</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
</tbody>
</table>

^aNs may not sum to the total because of missing or unknown data; proportions (%) sum to 100% of observations where data available and excludes missing/unknowns.
^bORs are adjusted for age as a continuous variable (at diagnosis for patients and at interview for controls).
^cFamily history of cancer reported in at least one first- or second-degree relative.
^dReport of at least one first- or second-degree relative with bile duct, bladder, brain, colon/rectum, duodenal, endometrial, gastrointestinal/GI, ovary/FT, pancreas, renal pelvis, stomach cancers.
TABLE 3  Endometrial tumor pathology prognostic characteristics according to report of prior breast or Lynch Syndrome-associated cancer

<table>
<thead>
<tr>
<th>Tumor characteristic</th>
<th>Patients with no prior Cancer (n = 1215)</th>
<th>Patients with prior breast cancer and tamoxifen use (n = 68)</th>
<th>Patients with prior breast cancer and no tamoxifen use (n = 33)</th>
<th>Patients with prior LS-associated cancers (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
</tr>
<tr>
<td>Tumor histology and grade</td>
<td></td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
</tr>
<tr>
<td>Endometrioid grade 1</td>
<td>637 (52.4)</td>
<td>31 (45.6) 0.76 (0.45-1.28) 0.27</td>
<td>17 (51.5) 0.96 (0.45-2.06) 0.92</td>
<td>11 (40.7) 0.62 (0.26-1.45) 0.23</td>
</tr>
<tr>
<td>Endometrioid grade 2</td>
<td>315 (25.9)</td>
<td>8 (11.8) 0.38 (0.16-0.81) 0.0088</td>
<td>7 (21.2) 0.77 (0.28-1.84) 0.54</td>
<td>5 (18.5) 0.65 (0.19-1.78) 0.38</td>
</tr>
<tr>
<td>Endometrioid grade 3</td>
<td>100 (8.2)</td>
<td>7 (10.3) 1.28 (0.48-2.90) 0.55</td>
<td>3 (9.1) 1.12 (0.21-3.68) 0.86</td>
<td>3 (11.1) 1.39 (0.26-4.71) 0.59</td>
</tr>
<tr>
<td>Serous (&gt;5%)</td>
<td>89 (7.3)</td>
<td>9 (13.2) 1.93 (0.81-4.08) 0.07</td>
<td>4 (12.1) 1.75 (0.44-5.13) 0.30</td>
<td>5 (18.5) 2.88 (0.83-8.02) 0.03</td>
</tr>
<tr>
<td>Clear cell (&gt;10%), no serous</td>
<td>29 (2.4)</td>
<td>2 (2.9) 1.23 (0.14-5.08) 0.80</td>
<td>2 (6.1) 2.64 (0.29-11.24) 0.18</td>
<td>1 (3.7) 1.57 (0.04-10.28) 0.66</td>
</tr>
<tr>
<td>Carcinosarcoma (MMMT)</td>
<td>32 (2.6)</td>
<td>9 (13.2) 5.64 (2.26-12.77) 1.30E-06</td>
<td>0 (0.0) na</td>
<td>2 (7.4) 2.96 (0.33-12.73) 0.13</td>
</tr>
<tr>
<td>Other epithelial&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 (1.2)</td>
<td>2 (2.9) 2.60 (0.28-11.68) 0.20</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
</tr>
<tr>
<td>I</td>
<td>1011 (83.2)</td>
<td>53 (77.9) 0.72 (0.39-1.41) 0.28</td>
<td>24 (72.7) 0.54 (0.24-1.34) 0.11</td>
<td>22 (81.5) 0.89 (0.32-3.04) 0.81</td>
</tr>
<tr>
<td>II</td>
<td>88 (7.2)</td>
<td>2 (2.9) 0.39 (0.05-1.50) 0.18</td>
<td>4 (12.1) 1.77 (0.44-5.19) 0.29</td>
<td>2 (7.4) 1.02 (0.12-4.22) 0.97</td>
</tr>
<tr>
<td>III</td>
<td>95 (7.8)</td>
<td>7 (10.3) 1.35 (0.51-3.07) 0.46</td>
<td>3 (9.1) 1.18 (0.23-3.90) 0.79</td>
<td>2 (7.4) 0.94 (0.11-3.88) 0.94</td>
</tr>
<tr>
<td>IV</td>
<td>15 (1.2)</td>
<td>6 (8.8) 7.74 (2.37-21.95) 1.59E-06</td>
<td>1 (3.0) 2.50 (0.06-17.23) 0.37</td>
<td>1 (3.7) 3.08 (0.07-21.49) 0.26</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (0.5)</td>
<td>0 (0.0) 1 (3.0) 1.39 (0.07-21.49) 0.26</td>
<td>0 (0.0) na</td>
<td>na</td>
</tr>
<tr>
<td>Lymphovascular space involvement</td>
<td></td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
<td>P&lt;sub&gt;chi-sq&lt;/sub&gt;</td>
</tr>
<tr>
<td>No/unknown</td>
<td>964 (79.3)</td>
<td>49 (72.1) 1.00</td>
<td>24 (72.7) 1.00</td>
<td>20 (74.1) 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>251 (20.7)</td>
<td>19 (27.9) 1.49 (0.81-2.63) 0.15</td>
<td>9 (27.3) 1.44 (0.58-3.26) 0.36</td>
<td>7 (25.9) 1.34 (0.47-3.35) 0.40</td>
</tr>
</tbody>
</table>

<sup>a</sup>Case-case comparisons using 2x2 tables as described in the Methods using cases with no prior cancer are the reference group.

<sup>b</sup>Other Epithelial includes mixed subtypes where serous or clear cell component does not reach % noted, or where histology was unknown (2 individuals diagnosed by curette).
cancers overall (1.9% vs 2.0%). There was some suggestion that cases were more likely to report two or more prior cancer types compared to controls (1.5% vs 0.7%), but this difference was not statistically significant ($P = 0.1$).

## 3.1 Association with epidemiological risk factors

Results are detailed in Table 1. Comparison of age at endometrial cancer diagnosis in patient subgroups shows that patients with prior breast cancer were diagnosed with EC at somewhat older age than those with no prior cancer (mean age 67 and 66 years among tamoxifen users and nonusers, respectively, vs 61 years among those with no prior cancers; $P \leq 0.002$). There was no evidence that endometrial cancer was diagnosed at an earlier age for patients with prior LS-associated cancers (62 years, $P = 0.4$).

Endometrial carcinoma risk in women with no cancer prior to EC diagnosis was associated with known epidemiologic risk factors for this disease.\(^4\) Compared to controls with no prior history of cancer, BMI $\geq 30$ was associated with an almost fivefold increased risk of EC for women with no prior cancer history. There was a highly significant trend in increased risk associated with BMI categories of $\geq 25$ to $<30$ and $\geq 30$ ($P = 1.4 \times 10^{-30}$). Oral contraceptive use, older age at menarche, parity, and use of systemic hormone therapy (mostly combination therapy in postmenopausal women) were inversely associated with EC risk in women with no prior cancers ($P \leq 0.001$), and there was a significant trend toward a lower risk of EC associated with older age at menarche ($P = 0.0002$) and higher numbers of full-term births ($P = 1.4 \times 10^{-10}$; Table 1). In addition, there was evidence to support the previously reported inverse association of EC risk with smoking ($P = 0.02$). The risk estimates for EC following a prior breast or LS-associated cancer associated with the risk factors highlighted above were necessarily imprecise given the smaller sample sizes. Nevertheless, they were generally in the same direction as those reported for EC with no prior cancer, with elevated risk associated with increasing BMI, and decreased risk associated with OC use, increasing parity, later age at menarche, and postmenopausal HRT use. Possible exceptions were ever-smoking, which did not appear to be inversely associated with EC among women with prior breast cancer and tamoxifen use, while age at menarche did not appear to be inversely associated with EC among women with prior breast cancer and no tamoxifen use.

## 3.2 Association with reported family history of cancer

As shown in Table 2, women with no prior cancer had a 43% increased risk of EC if at least one FDR or SDR was reported to have any cancer diagnosis ($P = 2.5 \times 10^{-5}$) or any LS cancer ($P = 2.7 \times 10^{-4}$), but no significant increased EC risk associated with having an FDR or SDR with breast cancer ($P = 0.3$) or ovarian cancer ($P = 0.9$). Despite small sample sizes, there was marginal evidence that women with prior breast cancer had increased risk of EC if they reported a family history of cancer in close relatives, be that family history of any cancer type (OR 2.23, $P = 0.005$ for tamoxifen users; OR 2.80, $P = 0.01$ for nonusers), family history of breast cancer (OR 1.98, $P = 0.01$ for tamoxifen users; OR 1.95, $P = 0.07$ for nonusers), or family history of LS-associated cancers (OR 1.78, $P = 0.03$ for tamoxifen users). All cases with prior LS-associated cancer reported a family history of cancer, and for this subgroup, there was evidence for increased risk associated with reported family history of LS-associated cancer (OR 2.34, $P = 0.04$) or family history of breast cancer (OR 2.15, $P = 0.05$).

### Table 4 Overall and EC-specific survival in patients reporting a prior cancer

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Overall survival$^a$</th>
<th>EC-specific survival$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Died (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Patients with no prior cancer (n = 1215)</td>
<td>153 (12.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Patients with prior breast cancer and tamoxifen use (n = 68)</td>
<td>23 (33.8)</td>
<td>1.96 (1.24-3.11)</td>
</tr>
<tr>
<td>Patients with prior breast cancer and no tamoxifen use (n = 33)</td>
<td>7 (21.2)</td>
<td>1.14 (0.46-2.78)</td>
</tr>
<tr>
<td>Patients with prior LS-associated cancers (n = 27)</td>
<td>3 (11.1)</td>
<td>0.72 (0.23-2.28)</td>
</tr>
</tbody>
</table>

$^a$Survival time estimated from date of primary treatment for EC to date of death from any cause censored.

$^b$Survival time estimated from date of primary treatment for EC to date of death due to EC.

$^c$Effect estimates are based on Cox models adjusted for age at EC diagnosis, FIGO stage, tumor subtype, and LVSI.
3.3 Differences in EC tumor pathology prognostic variables and survival according to prior cancer

Cases with prior breast cancer (irrespective of tamoxifen treatment) or prior LS-associated cancer were less likely to present with a grade 1 or 2 endometrioid adenocarcinoma than the reference group of EC cases with no prior cancer (Table 3). In particular, women with tamoxifen-treated breast cancer were significantly more likely to develop an endometrial carcinosarcoma (MMMT; 13.2% vs 2.6%, $P = 1.3 \times 10^{-6}$), and present with stage IV disease (8.8% vs 1.2%, $P = 1.6 \times 10^{-6}$). In accordance with this observation, women with tamoxifen-treated breast cancer had poorer overall survival (HR$_{adj}$ 1.96; $P = 0.001$) and EC-specific survival (HR$_{adj}$ 1.91; $P = 0.02$) compared to women with no prior cancer. Women with prior breast cancer and no tamoxifen use or prior LS-associated cancer exhibited similar survival to those with no prior cancer ($P \geq 0.27$; Table 4 & Figure S1). The minimum follow-up time was 7.8 years post-treatment.

3.4 Differences in EC tumor and germline MMR status

The relationship between MMR status and prior cancer is summarized in Table 5. EC patients with a proven germline pathogenic MMR gene variant were significantly more likely to report a prior cancer than cases whose cancers were MMR proficient (45.5% vs 14.3%, $P = 0.0001$). Prior cancers reported by pathogenic MMR gene variant carriers included breast cancer with tamoxifen use (9.1% vs 6.1% in the reference group, $P = 0.6$), prior LS-associated cancer (18% vs 2%, $P < 0.0001$), and other prior cancer (18.2% vs 4.7%, $P = 0.005$). Patients with MMR tumor deficiency but no MMR germline pathogenic variant identified were slightly more likely to report no prior cancer compared to the reference group of MMR proficient cases, but this difference was not statistically significant (91.5% vs 85.7%, $P = 0.07$).
have similar directions of effect for EC cases with no prior cancer compared to those with prior breast cancer or LS-associated cancer. We considered explanations for the possible exceptions to anticipated associations with epidemiological risk factors for women with prior cancer, noting that in all instances the relevant risk estimates included unity. Smoking is thought to reduce circulating endogenous estrogen and so result in a reduced risk of EC, as observed for EC after prior LS-associated cancer or prior breast cancer in the absence of tamoxifen use. The observation that smoking was not associated with EC among women with prior breast cancer and tamoxifen use might be explained by the fact that exposure to tamoxifen and not endogenous estrogen is the major mechanism for risk in this subset of women. There is no obvious explanation for the observation that women with prior breast cancer and no tamoxifen use did not show an inverse association with increasing age at menarche, especially since this subgroup of women did show a statistically significant inverse EC risk associated with increasing parity. It thus seems reasonable to discount the observation as spurious, reflecting the small sample size for this group.

All subgroups of individuals with prior cancer showed an increased proportion of reported family history of cancer (FDR and/or SDR) compared to EC cases with no prior cancer or controls with no prior cancer, even those with tamoxifen-treated breast cancer (Table 2). EC risk associated with reported family history of breast cancer did not differ according to tamoxifen usage for prior breast cancer (OR 1.98 for prior breast cancer with tamoxifen use vs OR 1.95 for prior breast cancer no tamoxifen use). Interestingly, for patients with prior LS-associated cancer, the elevation in EC risk for reported family history of LS-associated cancer (OR 2.34; 95% CI 1.05-5.09) was similar to that for reported family history of breast cancer (OR 2.15; 95% CI 0.99-4.69). These observations are consistent with the expectation that individuals with genetic factors underlying their disease might present with prior cancer and/or family history of cancer. Indeed, all patients with a prior LS-associated cancer reported a family history of cancer, and the cancer type in relative/s was designated as LS-associated for 17/27 (63%) of these patients (Table 2).

Report of prior LS-associated cancer is considered an indicator of MMR pathogenic variant carrier status. Patients identified as carriers of a pathogenic MMR gene variant were overall more likely to report a prior cancer. Recognizing that these observations were based on a small sample set of 22 carriers, it was surprising to note that less than half of the prior cancers reported (4/10 total) were LS-associated cancers, with the remainder comprising tamoxifen-treated breast carcinoma (n = 2), melanoma (n = 2), and cervical and thyroid carcinomas. Nonetheless, when considering MMR status within groups defined by prior cancer, 4/17 (23.5%) individuals with prior LS-associated cancer were identified to be a pathogenic variant carrier, compared to 12/620 (1.9%) of individuals with no prior cancer. This observation emphasizes that diagnosis of a first primary LS-associated cancer is an important clinical indicator to prioritize MMR gene testing and could enable timely identification of MMR gene pathogenic variant carriers for implementation of appropriate cancer risk reduction strategies to prevent second primary cancers. However, it is also important to note that more than half (54.5%) of MMR pathogenic variant carriers did not report any prior cancer, indicating that history of prior LS-associated cancer alone has poor sensitivity to delineate patients with EC due to a germline MMR gene defect.

Although tamoxifen has clearly been shown to be beneficial for treatment of breast cancer, it is associated with a two- to threefold increased risk of EC compared to age-matched women in the general population. There is evidence that this subgroup of EC patients are enriched for poor-prognosis pathological features and/or have poor survival, of interest since tamoxifen users might be expected to be under greater scrutiny for symptoms of EC. A brief review summarizing the main findings of selected studies is presented in Table S2. As detailed in Table 3, our findings support previous reports that EC after tamoxifen use for breast cancer has adverse prognostic features. In our study, the proportion of MMMTs after tamoxifen treatment for breast cancer was increased (13% vs <3% in cases with no prior cancer), equating to a 5.6-fold increase. Patients were more likely to present with stage IV EC after tamoxifen treatment for breast cancer (9% vs 3% for tamoxifen nonusers). Interestingly, these correlations appear to be independent; only two of the nine individuals with MMT (22.2%) were Stage IV and another 3 (33.3%) were stage III. Our study did not collect information on duration of tamoxifen use, so we were not able to assess if MMMT are more likely to arise after long-term tamoxifen use (as previously reported). Compared to EC patients with no prior cancer, women diagnosed with EC after tamoxifen-treated breast cancer had significantly worse survival outcomes (HR 1.96; P = 0.004 any cause, HR 1.91; P = 0.02 EC-specific). In stark contrast, there was no evidence for a survival difference for women reporting prior breast cancer without tamoxifen treatment or prior LS-associated cancers (P ≥ 0.3). Notably, although women with prior tamoxifen-treated breast cancer had a higher prevalence of MMT tumors compared to those with prior breast cancer and no tamoxifen use, this survival difference was not totally accounted for by poorer prognostic features of EC subtypes (Table 4).

A limitation of our study was that information on prior cancers was based on patient self-report, although where possible these were confirmed using data from clinical follow-up, and pathology reports. Information appeared to be reasonably accurate with the exception of self-reported
prior ovarian cancer, most of which were determined to be concurrent with EC. ANECS participants had to have an intact uterus at the time of EC diagnosis to participate, so it is not surprising that there were so few prior ovarian cancers among EC cases since standard surgical management for ovarian carcinoma, which accounts for the great majority of ovarian cancers, includes hysterectomy. Clinical follow-up was undertaken for cases but not controls, allowing us to verify self-reported data for EC cases only. Since we restricted the reference group to controls with no prior cancer for case-control analysis, failure to identify over-report of prior cancers in this group (estimated to be only 2/740 controls based on observations for cases) would have minimally biased our overall results toward the null. Further, any bias in data quality should not have impacted case-case analysis.

This study has confirmed the relationship between EC risk and prior tamoxifen-treated breast cancer, and also previous reports that tamoxifen-treated breast cancers are more likely to lead to poorer prognosis EC. However, considering all possible sources of information regarding tamoxifen treatment, we also estimate that one-third of all EC after breast cancer did not appear to be tamoxifen related. Epidemiological risk factors were similarly large across subgroups according to prior cancer report. Supporting our hypothesis that cancer-causing genetic factors will be enriched in individuals with prior cancer, a family history of cancer was increased for all patient subgroups reporting prior cancer. Surprisingly, this included family history of LS-associated cancers for EC cases with tamoxifen-treated prior breast cancer, and family history of breast cancer for individuals with prior LS-associated cancer. Further, while prior LS-associated cancer is clearly an indicator of MMR pathogenic variant status, so is report of other prior cancer types. However, 55% of established carriers did not report prior cancer, supporting the increasingly accepted role of universal immunohistochemical or molecular analysis of all ECs at diagnosis to detect patients with LS.

An important finding arising from this study is that women developing EC after tamoxifen treatment for breast cancer exhibited poorer survival—even after adjustment for known EC-related prognostic features. We suggest that it is important to ensure longer-term monitoring of women treated with tamoxifen for symptoms of EC. We also believe there is scope for studies assessing the biological mechanism underlying the poorer prognosis of this subset of EC patients.

ACKNOWLEDGMENTS

The authors wish to thank all clinical and scientific staff, as well as the women who participated in the Australian National Endometrial Cancer Study (ANECS). ANECS was supported by project grants from the National Health and Medical Research Council (NHMRC) of Australia (Grant No. 339435); The Cancer Council Queensland (Grant No. 4196615); Cancer Council Tasmania (Grant No. 403031 and Grant No. 457636); the Cancer Australia Priority-driven Collaborative Cancer Research Scheme (#552468), Cancer Australia (Grant No. 1010859). A.B.S. and P.W. are supported by NHMRC Senior Research Fellowships.

CONFLICT OF INTEREST

None declared.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Johnatty SE, Stewart CJR, Smith D, et al. Risk and prognostic factors for endometrial carcinoma after diagnosis of breast or Lynch-associated cancers—A population-based analysis. *Cancer Med*. 2018;00:1–12. [https://doi.org/10.1002/cam4.1890](https://doi.org/10.1002/cam4.1890)
The association between diabetes, comorbidities, body mass index and all-cause and cause-specific mortality among women with endometrial cancer

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HIGHLIGHTS
• Diabetes and co-morbidity were associated with higher EC-specific mortality.
• Diabetes and obesity have a negative impact on non-cancer related mortality.
• Understanding the impact of these factors can help inform women and clinicians.

ARTICLE INFO
Article history:
Received 1 February 2018
Received in revised form 4 April 2018
Accepted 6 April 2018
Available online 26 April 2018

Keywords:
Endometrial cancer
Survival
Diabetes
Body mass index
Co-morbidities
Cause-specific survival

ABSTRACT
Objective. Although endometrial cancer (EC) is associated with relatively good survival rates overall, women diagnosed with high-risk subtypes have poor outcomes. We examined the relationship between lifestyle factors and subsequent all-cause, cancer-specific and non-cancer related survival.

Methods. In a cohort of 1359 Australian women diagnosed with incident EC between 2005 and 2007 pre-diagnostic information was collected by interview at recruitment. Clinical and survival information was abstracted from women’s medical records, supplemented by linkage to the Australian National Death Index. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific survival (EC death vs. non-EC death) associated with each exposure, overall and by risk group (low-grade endometrioid vs. high-grade endometrioid and non-endometrioid).

Results. After a median follow-up of 7.1 years, 179 (13%) women had died, with 123 (69%) deaths from EC. As expected, elevated body mass index (BMI), diabetes and the presence of other co-morbidities were associated with a significantly increased risk of all-cause and non-cancer related death. Women with diabetes had higher cancer-specific mortality rates (HR 2.09, 95% CI 1.31–3.35), particularly those who had not been obese (HR 4.13, 95% CI 2.20–7.76). The presence of ≥2 other co-morbidities (excluding diabetes) was also associated with increased risk of cancer-specific mortality (HR 3.09, 95% CI 1.21–7.89). The patterns were generally similar for women with low-grade and high-grade endometrioid/non-endometrioid EC.

Conclusion. Our findings demonstrate the importance of diabetes, other co-morbidities and obesity as negative predictors of mortality among women with EC but that the risks differ for cancer-specific and non-cancer related mortality.

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1. Introduction

Endometrial cancer (EC) is the fourth most commonly diagnosed cancer among women in highly developed countries [1]. EC incidence rates exceed those of other gynaecological cancers and have increased rapidly over the last decade [2]. Overall 5-year survival is 82% [3] but survival varies substantially by tumour cell type and grade. In particular, high grade ECs, predominately serous and clear cell carcinomas, augur a worse outcome than the more commonly occurring low-grade, endometrioid ECs [4]. Furthermore, while endometrial cancer-specific deaths are frequent in the subset of women with high-grade, poor prognosis ECs [5], many women with low-grade endometrioid EC do not die from their cancer but from cardiovascular or cerebrovascular disease.

Obesity is one of the strongest risk factors for the development of EC, particularly the low-grade endometrioid subtype, but has been inconsistently associated with survival following a diagnosis of EC. Some previous studies report no association between a higher body mass index (BMI) and all-cause mortality in women with EC [6,7], whereas others report an increased risk [8,9]. Similarly, a higher BMI has been associated with endometrial cancer-specific mortality in some studies [8,10,11], while others have reported no association [12,13]. Diabetes is common among women with EC and may contribute to their higher all-cause mortality [12,14,15]; however few studies have assessed the association between diabetes and risk of dying from EC and the results are conflicting [11,16–19]. Other factors including smoking [20] and the use of common nonsteroidal anti-inflammatory drugs like aspirin [21–24] and also statins [23,25] have been investigated in relation to risk of dying from EC, however findings have been inconclusive. Furthermore, the given low prevalence of the more aggressive subtypes of EC, few studies have been able to examine these associations separately by tumour subtype. Since obesity and diabetes are strongly associated with low-grade endometrioid ECs, which have inherently better survival than high risk histological subtypes, failure to control for tumour subgroup introduces substantial confounding.

The aim of this study was to describe the association between lifestyle factors and survival following a diagnosis of EC. We considered women with different risk groups (low-grade endometrioid vs. high-grade endometrioid/non-endometrioid) separately and examined deaths from all-causes, cancer-specific and deaths due to non-cancer causes.

2. Methods

2.1. Study population

This study included women with EC who participated in a population-based case-control study: the Australian National Endometrial Cancer Study. The full details of the study have been reported elsewhere [26]. Briefly, 2231 women aged 18–79 years, newly diagnosed with EC between 2005 and 2007, identified through major treatment centres and state-based cancer registries across Australia were invited to participate and, of these, 1497 (67%) agreed to take part. Women were eligible for the current analyses if they had completed the baseline study questionnaire (N = 1399). We excluded thirty women with synchronous endometrial and ovarian cancers, seven women with cancers of unknown stage, and three women who did not have any primary treatment; the remaining 1359 women were included in this analysis. The study was approved by the Human Research Ethics Committees at the QIMR Berghofer Institute of Medical Research and all participating institutions, and all women provided informed consent.

2.2. Exposure assessment

Detailed pre-diagnostic sociodemographic and lifestyle information was collected using a standard questionnaire that was administered by telephone interview when women were recruited into the study.
de Glas et al., that suggests in etiological research competing risks models are less preferable to Cox proportional hazard models [28].

We first examined the association between known prognostic factors and cause-specific mortality (all-cause, cancer-specific, non-cancer related). We then examined the association between selected exposure variables (BMI, diabetes, other major co-morbidities, smoking status, physical activity, use of aspirin, and use of NSAIDs), all-cause and cause-specific mortality. We present HRs and 95% Cs from models including known prognostic factors that were significant predictors in minimally adjusted models for cancer-specific death (age [continuous], stage [1; 2; 3; 4] and tumour cell type/grade [low-grade endometrioid; high-grade endometrioid/non-endometrioid]). Additional adjustment for adjuvant treatment in the cancer-specific models did not appreciably alter estimates and hence was not included in final models. For all-cause mortality models included age, stage, tumour cell type/grade and BMI (18.5–24.9; 25–29.9; 30–34.9; ≥35 kg/m²). For non-cancer related mortality, models included age and BMI, but not stage and tumour cell type/grade because these were not significant predictors in minimally adjusted models. We also examined relationships between selected exposure variables, all-cause and cause-specific mortality, stratified by EC risk group (low- grade endometrioid EC [endometrioid grade 1 or grade 2, n = 1043] and high-grade endometrioid/non-endometrioid EC [endometrioid grade 3, endometrioid with serous or clear cell, serous, clear cell and carcinosarcoma, n = 316]). We also conducted subgroup analyses to examine if the associations between diabet- es and mortality were modified by obesity (BMI <30; BMI ≥30). Proportional-hazards assumptions were confirmed by testing whether the inclusion of time-varying covariates altered the magnitude of the associations. Stage was the only factor where the association appeared to vary over time. When we re-ran models including stage × time interactions the estimates were virtually unchanged, therefore final models did not include these interactions. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

Among the 1359 women included in this analysis, median follow-up time was 7.1 years after start of primary treatment for EC (range: 0.05 to 8.5 years). Of the 179 (13%) deaths that occurred during the full follow-up period, 68% of women died from EC and 32% from non-cancer related causes. Of the 148 deaths that occurred during the first 5 years after diagnosis, 109 (74%) were due to EC. In the multivariable analysis of known prognostic factors, an increased risk of all-cause mortality was associated with increasing age, higher stage and high-grade endometrioid and non-endometrioid subtypes of EC. Likewise an increased risk of cancer-specific mortality was associated with increasing age at diagnosis (HR 1.06, 95% CI 1.04–1.09 per year) and stage of disease (HR stage 4 vs. stage 1 (HR 6.69, 95% CI 5.22–18.0), as well as tumour cell type (Table 1). Relative to women with low-grade endometrioid EC, cancer-specific HRs were elevated among women with high-grade endometrioid (HR 6.69, 95% CI 4.03–11.1), serous, clear cell, mixed endometrioid and serous/clear cell (HR 4.00, 95% CI 2.40–6.65), and carcinosarcoma (HR 10.2, 95% CI 5.88–18.6). Increased risk of death from non-cancer related causes was associated with increasing age at diagnosis (HR per year 1.05, 95% CI 1.02–1.08), but not tumour cell type/stage or grade of disease.

Table 2 presents the adjusted all-cause and cause-specific HRs and 95% CI for the association between selected exposures and survival for all women with EC. Although in crude analyses obese women appeared to have better cancer-specific survival, this association was attenuated and non-significant after adjustment for tumour cell type/stage and grade. However obese women did have a significantly increased risk of death from all-causes (HR per 5-unit increase in BMI 1.11, 95% CI 1.01–1.22) and non-cancer related causes (HR per 5-unit increase in BMI 1.28, 95% CI 1.16–1.46). Women with diabetes had significantly increased risk of all-cause, cancer-specific (HR 2.09, 95% CI 1.31–3.35) and non-cancer related mortality (HR 2.23, 95% CI 2.2–4.07). Additional adjustment for BMI did not substantially alter the HR for cancer-specific mortality (HR 2.65, 95% CI 1.60–4.40). The HR for cancer-specific mortality among women with ≥2 major co-morbidities (including diabetes) was 2.55 (95% CI 1.39–4.66) and 4.42 (1.86–10.46) for non-cancer related mortality (results not shown). When we excluded diabetes, women with ≥2 other major co-morbidities also had significantly increased risk of all-cause (HR 3.21, 95% CI 1.95–5.27) and cancer-specific mortality (HR 3.09, 95% CI 1.21–7.89) but non-cancer related death. Use of low-dose aspirin was associated with a significantly increased risk of non-cancer related mortality but not cancer-specific mortality: however this association was attenuated when we further adjusted for all co-morbidities (HR 1.70, 95% CI 0.81–3.60). Smoking, physical activity and use of aspirin or NSAIDs were not associated with cancer-specific or non-cancer related death.

Of the 79 deaths that occurred among the 1043 women with low-grade endometrioid EC, 33 were due to EC and 46 from non-cancer related causes. There were no significant associations between the
variables of interest and cancer-specific death among women with low-grade endometrioid tumours (Supplementary Table 1). A significant increased risk of death from all-causes and non-cancer related causes among women with low-grade endometrioid EC was evident among women who were obese, those with a history of diabetes and other major co-morbidities.

Among the 316 women with high-grade endometrioid and non-endometrioid carcinomas, 90 died from EC and 10 from non-cancer related causes. In this group of women diabetes was associated with a significantly increased risk of cancer-specific mortality (HR = 2.13, 95% CI 1.20–3.80) and additional adjustment for BMI did not substantially alter this association (Supplementary Table 2). Physical inactivity was also associated with a significantly increased risk of cancer-specific mortality (HR = 1.69, 95% CI 1.00–2.86), however additional adjustment for BMI slightly weakened this association (HR 1.54, 95% CI 0.88–2.67). A history of diabetes was associated with significantly higher mortality risk from all-causes and non-cancer related causes among women with high-grade endometrioid/non-endometrioid EC. There was a suggestion that users of low-dose aspirin had a significantly increased risk of all-cause and non-cancer related mortality. The presence of other co-morbidities (excluding diabetes) was also associated with increased risk of all-cause mortality.

The risk estimates for diabetes were not materially affected by adjusting for BMI and vice versa, however in analyses of the association between diabetes and mortality stratified by obesity (BMI <30, ≥30) we found that women who were lean and diabetic did worst in terms of all cause, cancer-specific and non-cancer related mortality (Table 3). Similar patterns were seen for the low-grade endometrioid tumours and high-grade endometrioid/non-endometrioid tumours (data not shown).

4. Discussion

Consistent with previous reports, our study confirms the finding that obesity and diabetes are associated with an increased risk of all-cause and non-cancer related mortality in women treated for EC. We additionally found an association between diabetes and other major co-morbidities (excluding diabetes) and cancer-specific mortality; this association was strongest in non-obese women with high risk EC - high-grade endometrioid/non-endometrioid EC.

Although diabetes has consistently been associated with higher all-cause mortality in women in the general population [29] and among women with EC [7,12,15,18,19], less is known about the association between diabetes and cancer-specific death among women with EC. Our
findings are generally in accord with those of Folsom et al., who, in a follow-up of 415 women with EC found a two-fold increased risk of EC-specific death among diabetic women with EC. Using SEER-Medicare data, Olson et al. also reported that diabetes was associated with poorer EC-specific survival in older white (n = 11,610) but not black women [30] and similarly, Lindemann et al., reported that diabetes increased the risk of EC specific death among women with EC [19]. By contrast, Chai and colleagues found no association between diabetes and EC specific survival in a study of 745 women with EC, nor did Felix et al. in their follow-up of 4609 women with EC [11,12]. The contrasting results of previous studies, particularly the study by Felix et al. [11] the largest study to date, could reflect differences in study methodology (different study design, inclusion criteria and analytic modelling techniques), as well as different adjustment for confounders and length of follow-up times.

Diabetes may impact the growth and progression of EC through a number of mechanisms. Insulin is known to drive endometrial tumour growth through several pathways and insulin and insulin-like growth factors act directly on endometrial cancer cells to drive proliferation [31]. Insulin also decreases the levels of circulating sex hormone binding globulin, which increases the bioavailability of oestradiol, itself a potent stimulator of cell growth. Several groups have shown diabetes is associated with aggressive tumour phenotypes and poor prognosis in other cancer types, including colorectal [32] and pancreatic cancer [33]. Our finding that the increased risk of dying from EC associated with diabetes was more pronounced in non-obese, compared to obese women, is in line with one previous report [19]. Lindermann et al., found a four-fold higher risk of dying from EC in women with diabetes and BMI ≥25 kg/m² compared to women BMI ≥25 kg/m². Although results were not presented separately for subtypes, adjustment was made for age, histological subtype and stage and competing risks were accounted for. The authors postulated that low BMI could be an indicator of the severity of diabetes, the type of diabetes or presence of co-morbidity [19].

Most previous studies have shown that medical comorbidity/higher comorbidity scores significantly and negatively impact overall survival in women with EC [30,34–37]. Fewer studies have considered EC-specific mortality. Like us, Cook et al., reported co-morbidity score ≥2 was associated with a modest elevation in risk of death from EC [35] and Binder and colleagues reported reduced recurrence-free survival among women with EC who had a higher Adult Comorbidity Evaluation 27 score (which included diabetes) [34]. In contrast, Robbins et al., in a study of women with early stage EC, found higher comorbidity score (which included diabetes) was not a significant predictor of disease-specific survival [36] and Olson et al., found that a higher Charlson comorbidity score (excluding diabetes) was not related to EC-specific survival, however this analysis was restricted to older women (66+ years) [30]. Previous work has shown that women with multiple comorbidities tend to have more advanced EC at presentation and lower utilisation of surgery and adjuvant therapies [30,36,38,39], thus it is plausible that they might experience worse cancer-specific outcomes.

It has been well documented that the most common causes of death among women with EC are cardiovascular events [5,40]. It was therefore not surprising that elevated BMI and diabetes were associated with a significantly increased risk of all-cause and non-cancer related death in our cohort. Similarly elevated BMI and diabetes were associated with non-cancer related death in women with low-grade endometrioid EC, and diabetes with an increased risk of non-cancer related death among women with high-grade endometrioid/non-endometrioid EC.

Strengths of our analysis include the large population-based sample, long duration and essentially complete follow-up, and detailed information on pre-diagnostic exposures and known prognostic factors such as stage of disease, tumour grade and histologic subtype. Cause of death was based on information from the medical records and is likely to be accurate. We were able to examine associations separately for low and high risk EC (tumour cell type/grade), a major advantage over most other studies which have considered only overall estimates. A limitation of our study is that we lacked information on women’s post-diagnostic behaviours. However conditions like diabetes and comorbidities are unlikely to resolve and research suggests that most women with EC do not make sustained, positive lifestyle changes after diagnosis [41]. The study relied on exposure information that was self-reported, however previous validation studies have shown high correlations between self-report and measured BMI [42] and diabetes [43]. Information regarding diabetic treatment was unfortunately not available in our study. Future studies need to consider the fact that associations might vary by anti-diabetic medications which may attenuate or enhance the risks. Another limitation of our study was that we had relatively few non-cancer deaths in our cohort, resulting in imprecise estimates. Finally, type 1 ECs are typically low-grade endometrioid whereas type 2 ECs are high-grade non-endometrioid, so we chose to group high-grade endometrioid ECs with other high-grade cancers for the subtype specific analyses because of their poor survival. This limits our understanding of these potentially distinct subtypes and factors that might influence mortality.

In summary, diabetes adversely impacts both cancer-specific mortality, as well as mortality from non-cancer related causes among women with EC. Interestingly obesity, one of the strongest risk factors for the development of EC, was only associated with higher risk of death from non-cancer related causes. The presence of other comorbidities (excluding diabetes) was associated with worse cancer-specific mortality. Smoking, physical activity and use of aspirin, NSAIDs were not associated with cancer-specific or non-cancer related death. Understanding the impact of these factors in women with EC may help maximise both medical and cancer management.

Conflict of interest statement
C.M.N., E.J.C., A.B., M.O., M.Q., Y.L., A.B.S., and P.M.W. have no relevant conflicts to declare. A.O. reports the following relevant financial activities outside the submitted work - CEO of surgical performance (a surgical audit software), travel grants from the O.R. Company (formerly Tyco Healthcare) and non-financial support from Covidien, NSW, Australia.

Funding
The Australian National Endometrial Cancer Study was supported by project grants from the National Health and Medical Research Council (NHMRC) of Australia (#393435); Cancer Council Tasmania (#403031 and #457636) and the Cancer Australia Priority-driven Collaborative Cancer Research Scheme (#552468). C.M.N. is supported by NHMRC Program Grant #1073898, E.J.C. is supported by a National Institute for


The effect of caffeine loading on cerebral autoregulation in preterm infants

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ABSTRACT

Aim: To evaluate cerebral autoregulation changes in preterm infants receiving a loading dose of caffeine base.

Methods: In a cohort of 30 preterm infants, we extracted measures of cerebral autoregulation utilizing time and frequency domain techniques to determine the correlation between mean arterial pressure (MAP) and tissue oxygenation index (TOI) signals. These measures included the cerebral oximetry index (COx), cross-correlation and coherence measures, and were extracted prior to caffeine loading and in the 2 hours following administration of 10 mg/kg caffeine base.

Results: We observed acute reductions in time domain correlation measures, including the cerebral oximetry index (linear mixed model coefficient /C0 0.093, standard error 0.04; \( p = 0.028 \)) and the detrended cross-correlation coefficient (\( \rho_{q} \) coefficient /C0 0.13, standard error 0.055; \( p = 0.025 \)). These reductions suggested an acute improvement in cerebral autoregulation. Features from detrended cross-correlation analysis also showed greater discriminative value than other methods in identifying changes prior to and following caffeine administration.

Conclusion: We observed a reduced correlation between MAP and TOI from near-infrared spectroscopy following caffeine administration. These findings suggest an acute enhanced capacity for cerebral autoregulation following a loading dose of caffeine in preterm infants, contributing to our understanding of the physiological impact of caffeine therapy.

INTRODUCTION

Cerebral autoregulation is a mechanism by which cerebral blood flow is maintained relatively constant over a range of perfusion pressures. Impaired cerebral autoregulation is common in very preterm infants (1) and is considered a risk factor for brain injury including intraventricular haemorrhage (IVH) (2). Early work in this area advanced umbilical artery catheters to collect cerebral blood flow data (3), whereas recent studies have focused on applying analysis techniques to quantify the relationship between arterial blood pressure and the tissue oxygenation index (TOI) signal as an indirect measure of autoregulatory function (1, 4–7). The applied techniques include time domain correlation (1,4), frequency domain coherence (5) and transfer function analyses (6,7). Most of these studies have been cross-sectional, with consistent findings of impaired cerebral autoregulation in the more preterm, low birthweight and distressed preterm infant. There has been limited work

Key notes

- Following caffeine base administration, preterm infants exhibit falls in tissue oxygenation index (TOI) and cerebral blood flow velocity.
- Preterm infants exhibited reduced correlation between arterial blood pressure and cerebral oxygenation, suggestive of enhanced cerebral autoregulation which may counter the direct effects of vasoconstriction.
- Detrended cross-correlation analysis may be used to describe cerebral autoregulation in preterm infants.
Cerebrovascular effect of caffeine in preterm infants

Huvanandana et al.

Evaluating the effect of treatments or procedures common to neonatal intensive care on the cerebral autoregulation.

Caffeine therapy is commonly administered to preterm infants, many of which are extremely premature, to reduce apnoea of prematurity and prevent the need for intubation. Caffeine is a non-specific inhibitor of adenosine receptors (8) and among the most frequently used medication in neonatal intensive care (9). Evaluation of long-term outcomes from the Caffeine for Apnoea of Prematurity (CAP) trial has shown improved neurodevelopmental outcomes at 18–21 months corrected age (10), though differences were attenuated and no longer significant at 5 years follow-up (11). At 11 years follow-up however, caffeine therapy was associated with reduced risk of motor impairment (12), though little is known on its underlying mechanisms.

Following a loading dose of caffeine, our group previously showed reduced cerebral perfusion using Doppler blood flow velocity and TOI (13), and increased pulse pressure variability from continuous arterial blood pressure data (14). The potential effect of these acute changes on cerebral autoregulation required further evaluation. A study in adults examining the effects of caffeine in 12 healthy adult subjects found an acute increase in an index of cerebral autoregulation (15). Given its capacity to attenuate adenosine-induced vasodilation (16), we hypothesise that caffeine therapy in preterm infants may have acute effects on cerebral autoregulation. The aim of this study was to evaluate these effects in a published cohort of preterm infants (13), using a range of correlation analyses, including the cerebral oximetry index (COx) proposed by Brady et al. (4), the regression coefficient (reg) and measures of mean coherence at the very low and low frequency ranges (cohVLF and cohLF, respectively). These techniques have previously been evaluated and compared by Eriksen et al. (17) in a cohort of preterm infants. We also sought to extend this evaluation to cross-correlation and detrended cross-correlation analyses, two additional time domain measures that may reflect changes in cerebral autoregulation.

PATIENTS AND METHODS

Data collection

Physiological data were collected as part of a study approved by the Western Sydney Area Health Service Human Research and Ethics and conducted according to the World Medical Association Declaration of Helsinki. Informed parental consent was obtained in all cases. The examined cohort comprised of infants with gestational age <34 weeks who required caffeine therapy for any of the following reasons: weaning from mechanical ventilation, reducing risk of extubation failure, and treatment of apnoea of prematurity. Infants with significant congenital anomalies and high-grade peri-intraventricular haemorrhage at time of study were excluded.

Thirty infants had concurrently available MAP and TOI data. Arterial blood pressure data were collected via an umbilical or peripheral arterial catheter via the Phillips CMS modular system (Phillip Healthcare, North Ryde, Australia). Cerebral near-infrared spectroscopy (NIRS) data were collected simultaneously via the NIRO-300 system (Hamamatsu Photonics, Hamamatsu City, Japan), with smoothed mean values acquired at 6 Hz. Both signals were recorded by an analogue data acquisition system (ADInstruments, Sydney, Australia), with 6 Hz sampling for NIRS data and 1 kHz for MAP data.

NIRS offers a measure of cerebral oxygenation by emitting and receiving NIR light at specific wavelengths (775, 825, 850 and 904 nm) to determine a range of variables: oxygenated haemoglobin (HbO₂) and deoxygenated haemoglobin (HHb). TOI is defined as:

\[
\text{TOI} = \frac{\text{HbO}_2}{\text{HbO}_2 + \text{HHb}}
\]

Physiological data acquisition commenced in the 20–30 minutes prior to caffeine administration. MAP and TOI data were extracted from two timepoints relative to intravenous administration of 10 mg/kg of caffeine base: (i) prior to start of dose (precaffeine) and (ii) up to 2 hours following dose completion (postcaffeine).

Signal processing

All signal processing and feature extraction were completed in Python v2.7 (Python Software Foundation, https://www.python.org/). We downsampled the arterial blood pressure signal to 100 Hz and completed beat-to-beat extraction of MAP. We then applied a running 10-minute window shifted in increments of 5 minutes and extracted a range of correlation features to those that satisfied the quality criteria (pulse rate of 40–250 beats per minute). The techniques applied to the aligned time series of MAP and TOI are described in the following sections.

Coherence analysis

Magnitude-squared coherence (MSC) is defined as:

\[
\text{MSC}(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)}
\]

where \(S_{xx}\) is the autospectrum of changes in mean arterial pressure, \(S_{yy}\) is the autospectrum of changes in cerebral oxygenation and \(S_{xy}\) the cross-spectrum between the two signals. Magnitude-squared coherence approaching 1 suggests an increasing linear relationship while coherence approaching 0 suggests a loss of this relationship or a potentially non-linear relationship between the given input (MAP) and output (TOI).

MAP and TOI signals were first resampled to 2 Hz in the Fourier domain. Each 10-minute running window was further divided into three five-minute windows with 50% overlap (5). We applied a Hanning window and mean-centred both signals prior to power spectral density calculations. The coherence was then determined in the very low frequency domain using a magnitude-squared coherence approach.
frequency (coh\textsubscript{VLF}; <0.003 Hz) and low frequency (coh\textsubscript{LF}; 0.003–0.004 Hz) ranges.

**Time domain correlation analysis**

The COx index is defined as the moving linear correlation coefficient between cerebral perfusion pressure and cerebral oximeter waveforms. They defined a sliding window of 5 minutes in length and shifted it in increments of 1 minute to obtain 6 correlation coefficient values for a 10-minute epoch, with the mean of these being the calculated COx value for the given epoch (4).

The MAP and TOI signals were resampled to 0.1 Hz in the Fourier domain, and we determined the corresponding COx and corresponding regression coefficient (reg, slope of the fitted line) for each qualifying 10-minute window.

**Cross-correlation analysis**

Cross-correlation analysis involves incrementally shifting one signal relative to another and determining the linear correlation between them. For a positively correlated signal, the corresponding coefficient is the maximum value that this function takes, and the time delay represents shift (or lag) at which this occurs. Like in linear correlation, potential coefficient values range from −1 to 1, denoting perfectly negative and positive correlation, respectively.

As in the COx evaluation, the MAP and TOI time series were downsampled to 0.1 Hz in the Fourier domain. We then determined the cross-correlation coefficient \( r \) and time delay \( \tau \) within ±30 seconds, sufficient to account for the reported <10-second time lag associated with normal autoregulation (18).

**Detrended cross-correlation analysis**

Detrended cross-correlation analysis is a generalisation of the detrended fluctuation analysis method (19, 20) which has been applied widely to physiological data. The corresponding coefficient \( \rho_{\text{DCCA}} \) has been proposed by Zebende et al. (19) to quantify the degree of cross-correlation between fluctuations in detrended time series at a given time scale. Like the linear correlation coefficient, it is bound by −1 and 1, however, may be better-suited data where nonstationarities are present (21).

It is calculated as follows: the two series \( y_1(k) \) and \( y_2(k) \) with same length \( N \) are first mean-centred and integrated to obtain \( R_1(k) \) and \( R_2(k) \), respectively, where \( k = 1, \ldots, N \). For a given box size \( n \), the time series are divided into \( N-n \) overlapping boxes and the covariance of the residuals is determined:

\[
\rho^2_{\text{DCCA}}(n,i) = 1/(n+1) \sum_{k=i}^{n} (R_1(k) - \bar{R}_1(k))(R_2(k) - \bar{R}_2(k))
\]

where \( \bar{R}_{1,i}(k) \) and \( \bar{R}_{2,i}(k) \) are the local linear trend in each box beginning at \( i \). The covariance of residuals across all boxes is averaged to determine \( \rho^2_{\text{DCCA}}(n) \). The coefficient \( \rho_{\text{DCCA}} \) is then expressed as:

\[
\rho_{\text{DCCA}} = \frac{\rho^2_{\text{DCCA}}(n)}{\rho^2_{\text{DFA1}}(n)\rho^2_{\text{DFA2}}(n)}
\]

where \( \rho^2_{\text{DCCA}}(n) \) is the detrended covariance function, and \( \rho^2_{\text{DFA1}}(n) \) and \( \rho^2_{\text{DFA2}}(n) \) are the detrended variance functions for \( y_1(i) \) and \( y_2(i) \), respectively. Figure 1 shows two sets of raw MAP and TOI traces corresponding to a low and high absolute value of \( \rho \).

To maintain consistency between the time domain analyses, we downsampled the MAP and TOI signals to 0.1 Hz in the Fourier domain. We extracted detrended cross-correlation coefficient at the following three-time scales: 1 minute (\( \rho_1 \)), 2 minutes (\( \rho_2 \)) and 5 minutes (\( \rho_3 \)).

**Statistical analysis**

R version 3.4 (R Core Team, 2012) and lme4 (Bates, Maechler & Bolker, 2012) were used for statistical analysis. Statistical significance for all models was defined as \( p < 0.05 \). To determine the mean weighted feature for a single subject, features were weighted according to the variability (SD) of the MAP time series (5,17). Using univariate linear regression modelling, we first determined

![Figure 1](image-url) Examples of mean arterial pressure (MAP) and tissue oxygenation (TOI) traces corresponding to a lesser \( \rho \) (panels A and C) and greater \( \rho \) (panels B and D). Closed and open circles denote MAP and TOI time series, respectively.
the relationship between weighted features and the corresponding gestational age and birthweight z scores from Fenton growth charts (22). We also determined the Spearman rank correlation between the weighted features of cerebral autoregulation.

All qualifying windows were taken into consideration via linear mixed modelling. We evaluated the effect of caffeine on the extracted features, adjusting for gestational age and birthweight z scores and including a random intercept for each subject. Statistical significance of independent variables was evaluated using likelihood ratio tests of the model with and without the variable in question (23). As part of a sensitivity analysis, we independently adjusted for IVH and low Apgar score (5-minute Apgar score < 7) in addition to the above covariates.

RESULTS
The cohort characteristics (n = 30) are summarised in Table 1. Infants had a mean (SD) gestational age of 27 (2.3) weeks, with birthweight 1080 (400) g and postnatal age at evaluation of 2.6 (2.2) days. A median (interquartile range; IQR) of 5 (2.8) and 24 (17.8) 10-minute windows were extracted for each patient at the pre- and postcaffeine timepoints were extracted. This corresponded to a median (IQR) duration of 30 (10) and 125 (31.2) minutes, respectively.

Effect of caffeine therapy
Figure 2 provides examples of the change in weighted mean for (i) a coherence feature (coh_{VLF}), (ii) time domain correlation analysis (COx) and (iii) a detrended cross-correlation feature (\rho_s). From mixed model analysis (Table 2), coherence features did not change significantly between timepoints (coh_{VLF}; p = 0.915 and coh_{LF}; p = 0.479). In contrast, caffeine base administration contributed significantly to the reduction in time domain correlation metrics: COx (p = 0.028), \rho_1 (p = 0.046), \rho_2 (p = 0.006) and \rho_5 (p = 0.025). Following adjustments of IVH and low Apgar score in two separate models, the effect of caffeine and statistical significance remained consistent.

Relationship between extracted features, gestational age and birthweight
Univariate linear regression modelling showed that coh_{LF} was mildly and inversely correlated with gestational age (linear coefficient –0.0073, standard error 0.0053; p = 0.037, Table S1). In this dataset, COx and \rho_1 exhibited a negative linear relationship with birthweight, independent of sex and gestational age. Examples of these relationships are also presented in Figure S1.

Associations between cerebral autoregulation features
We identified significant associations between the time domain features (Table S2). Mean coherence at very low frequencies (coh_{VLF}) was mildly correlated with COx and \rho_5, whereas coh_{LF} was not correlated with any of time domain features, nor coh_{VLF}. COx was strongly and linearly correlated with \rho_5. The coefficient from cross-correlation was correlated with both COx and \rho_5, though the time delay was not correlated with any of the other metrics.

DISCUSSION
In this study, we evaluated various time and frequency domain features to describe cerebral autoregulation in preterm infants following a loading dose of caffeine base. To our best knowledge, this is the first paper to examine these changes in preterm infants, and the first to apply detrended cross-correlation analysis to describe cerebral autoregulation. We observed a reduction in time domain correlation as characterised by COx, \rho_1, \rho_2 and \rho_5 in order of increasing sensitivity. Coherence in the low frequency range similarly trended towards a reduction, though was not statistically significant. This reduced correlation between changes in TOI and those in MAP is congruent with an improved capacity to autoregulate and may offer insight into the CAP trial findings (10,12). The findings are also in agreement with a recent study in adults (15) examining the effect of 200 mg caffeine which reported reduced cerebral blood flow with concurrent improved cerebral autoregulation, quantified by rate of regulation (24). A possible explanation for these observations may be the caffeine-induced inhibition of the adenosine receptors: adenosine induces dilation of cerebral vessels (25), and may thus play a role in cerebral autoregulation (15,26). The resulting cerebral vasconstriction may then alter the dynamic autoregulation. Further work is required to understand if the observed effects are consistent in other cohorts and persist through maintenance dose administration, especially given the tolerance effect observed in adults (27).

Our original study with the same cohort showed significant reduction in two different parameters of cerebral blood flow: doppler cerebral blood velocity and reduced TOI (15), which had suggested some cause for caution. However, in the context with the potentially improved

<table>
<thead>
<tr>
<th>Variable</th>
<th>Summary (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27 (2.3)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>1080 (400)</td>
</tr>
<tr>
<td>Male sex</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Postnatal age caffeine loading (days)</td>
<td>2.6 (2.2)</td>
</tr>
<tr>
<td>Continuous positive airway pressure</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Ventilated (%)</td>
<td>29 (96.7%)</td>
</tr>
<tr>
<td>Respiratory distress syndrome (%)</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>IVH (%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Grade I IVH</td>
<td>2 (6.6%)</td>
</tr>
<tr>
<td>Grade II IVH</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Grade III IVH</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Low 5 minutes Apgar Score (&lt;7)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Surfactant administered (%)</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>Died (%) NEC at 4 wks</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis.
measures of cerebral autoregulation observed in this analysis, these findings suggest there may be benefits that accrue acutely following loading dose of caffeine in preterm infants at risk of impaired cerebral autoregulation.

We observed significant associations between the time domain features (Table S2), especially between COx and $q^5$, which may have been due to similar window sizes (5 minutes) over which these correlations were evaluated. The $coh_{\text{VLF}}$ feature was associated with COx, reg and $q^5$, though in contrast, $coh_{\text{VLF}}$ was not significantly associated with any of the extracted features. This lack of association may reflect differences in sensitivity to phase shifts between the methods. For example, a phase delay between the TOI and MAP signals may alter correlations in the time domain, while mean coherence measures may be less affected. This also suggests that time domain measures may be more sensitive in detecting changes in autoregulation. Eriksen et al. (17) also noted that decreases in cerebral oxygenation as blood pressure increased at low frequency may lead to spuriously high coherence measures.

Frequency domain metrics were showed relatively poor discriminative value in this analysis. A contributing factor may have been the quantity of data available, where the infants in our cohort had median collection times of 30 and 125 minutes at pre- and postcaffeine timepoints, respectively. Previous evaluation of coherence measurements by Hahn et al. (5) found a minimum of 1.3–3.7 hours required to discriminate between patients. This approach may be better suited to long-term monitoring of cerebral autoregulation, rather than the detection of acute changes as in this study.

Despite earlier speculation that the time delay may hold autoregulatory information (28), this feature was not particularly discriminative, nor related to other measures of autoregulation. The cross-correlation coefficient similarly remained unaltered by caffeine. The sampling frequency (0.1 Hz) may not have been sufficiently high to capture changes in both metrics.

The detrended cross-correlation coefficient was proposed by Zebende et al. (19) as a means of quantifying the level of cross-correlation between two nonstationary time series. In this analysis, this coefficient demonstrated strong discriminative power in identifying changes following caffeine administration, which may have been due in part to the local linear detrending inherent to its application. It is also possible that detrending or preprocessing of the signals to mitigate nonstationarities may improve the discriminative

**Table 2** Linear mixed model coefficients (standard error) and statistical significance for characterising the impact of caffeine on multivariable features, adjusted for gestational age and birthweight $z$ scores from Fenton charts

<table>
<thead>
<tr>
<th></th>
<th>Caffeine (p)</th>
<th>Gestational age (p)</th>
<th>BW z scores (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$coh_{\text{VLF}}$</td>
<td>-0.0035 (0.033)</td>
<td>0.915</td>
<td>-0.0016 (0.0047)</td>
</tr>
<tr>
<td>$coh_{\text{LF}}$</td>
<td>-0.0057 (0.0081)</td>
<td>0.479</td>
<td>-0.0029 (0.0021)</td>
</tr>
<tr>
<td>COx</td>
<td>-0.093 (0.04)</td>
<td>0.028</td>
<td>0.0029 (0.0089)</td>
</tr>
<tr>
<td>reg</td>
<td>-0.05 (0.047)</td>
<td>0.287</td>
<td>-0.0089 (0.01)</td>
</tr>
<tr>
<td>CC r</td>
<td>0.017 (0.021)</td>
<td>0.414</td>
<td>-0.0044 (0.0056)</td>
</tr>
<tr>
<td>CC $\tau$</td>
<td>0.024 (0.22)</td>
<td>0.913</td>
<td>0.035 (0.039)</td>
</tr>
<tr>
<td>$p_1$</td>
<td>-0.061 (0.029)</td>
<td>0.046</td>
<td>0.0013 (0.0066)</td>
</tr>
<tr>
<td>$p_2$</td>
<td>-0.12 (0.04)</td>
<td>0.006</td>
<td>-0.0015 (0.01)</td>
</tr>
<tr>
<td>$p_5$</td>
<td>-0.13 (0.055)</td>
<td>0.025</td>
<td>0.003 (0.015)</td>
</tr>
</tbody>
</table>

BW, birthweight; CC, cross-correlation.
power of other methods such as the COx index, however, these methods have been applied as they were originally validated and published, and validation over longer monitoring periods incorporating detrending is required.

Limitations
Data quality and the concurrent availability of MAP and TOI signals limited the available data for analysis; not all subjects had arterial blood pressure lines and of those that did (n = 50), the presence of artefact necessitated the exclusion of certain pre- or postcaffeine timepoints. The total evaluation time at each timepoint may also have been insufficient to discriminate between infants, with total evaluation time at each timepoint may also have exclusion of certain pre- or postcaffeine timepoints. Hahn et al. (5) reporting a minimum time of 1.3–3.7 hours required for coherence analysis. There may also have been other influencing factors which were not accounted for in statistical analysis: for example, the partial pressure of CO2 (5) is an important regulator of cerebral blood flow and can thus affect the TOI signal. We also cannot attribute the observed effect to entirely caffeine base administration, given the absence of a control group not receiving caffeine.

CONCLUSION
We applied a range of time and frequency domain techniques to characterise cerebral autoregulation in preterm infants. We observed a reduction in COx and detrended cross-correlation coefficients over a range of time windows (p1, p2 and p3), suggestive of an improved capacity of cerebral autoregulation following a loading dose of caffeine therapy. These observations help to clarify the underlying mechanisms and serve as a first step towards understanding the findings of the Caffeine for Apnoea of prematurity trial. These further observations of the caffeine cohort reported in this journal (13) help to clarify the underlying cerebrovascular physiological changes and potential mechanisms of harm and benefit. The discriminative value of the detrended cross-correlation coefficient also supports its potential for cerebral autoregulation monitoring in preterm infants, an important step in understanding commonly used treatments and risk stratification.

FUNDING
The authors have no funding to report.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

References


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article:

**Figure S1** Scatter plots of linear relationship with gestational age and birthweight for cohLF (panels A, B), COx (C, D) and p1 (E, F), respectively.

**Table S1** Relationship between cerebral autoregulation features and gestational age and birthweight. Model coefficients (standard error) from univariate linear regression are presented, with statistical significance denoted by *p < 0.05*. BW: birthweight, CC: cross-correlation.

**Table S2** Summary of Spearman correlation coefficients between extracted features. Statistical significance denoted by *p < 0.05, **p < 0.01, ***p < 0.001*. CC: cross-correlation.
The effectiveness of Ambu neonatal self-inflating bag to provide consistent positive end-expiratory pressure

Mark Tracy,1,2 Dharmesh Shah,1,3 Archana Priyadarshi,1,3 Murray Hinder1,3

ABSTRACT

Background The self-inflating bag (SIB) is the most common device used to resuscitate newborn infants worldwide. Delivering positive end-expiratory pressure (PEEP) may be important in infant resuscitation and limited research using one brand (Laerdal) SIB has led to international guidelines stating SIBs ‘often deliver inconsistent positive end-expiratory pressure’.

Aim To measure delivered PEEP using disposable and reusable Ambu SIBs fitted with Ambu PEEP valve and manometer comparing different rates of 20, 40 and 60 inflations per minute (IPM) and test lung compliance.

Design Three experienced neonatal medical staff provided positive pressure ventilation each using different disposable and reusable Ambu SIBs, targeting peak inflation pressure of 30–35 cm H2O at three different set PEEP levels of 5, 7.5 and 10 cm H2O on test lungs of compliance of 0.5 and 3.0 mL/cm H2O. Inflation data were captured with Florian Monitor and analysed by analysis of variance for repeated measures.

Results A total of 3265 inflations were analysed. The delivered PEEP was rate and lung compliance dependent. At set PEEP of 5 cm H2O the adjusted measured PEEP was 3.6, 4.4 and 4.8 cm H2O at rates 20, 40 and 60 IPM, respectively, while at set PEEP of 10 cm H2O, the adjusted measured PEEP was 7.0, 8.8 and 9.8 cm H2O. The delivered PEEP was statistically higher with more compliant test lungs.

Conclusions The Ambu SIB with Ambu PEEP valve can deliver consistent mean levels of PEEP close to the operator set PEEP. The performance of SIB with PEEP valves is likely brand specific and requires further evaluation.

BACKGROUND

Globally, approximately 10% of all newborn infants require stabilisation immediately following birth, with 5 to 8% requiring positive pressure ventilation to establish adequate respiration.1 2 A recent systematic review of neonatal resuscitation has estimated that there is a potential for 30% reduction in the rates of neonatal death due to prematurity worldwide with improved facility-based resuscitation.3 Establishing an adequate functional residual capacity (FRC) is an essential component of postpartum adaptation, which can be delayed in states of surfactant deficiency.4 Although positive end-expiratory pressure (PEEP) has been shown to be of benefit in the care of preterm infants with surfactant deficiency, the role of PEEP during resuscitation, particularly for term infants remains to be established.1 Birthing environments in high-resource countries have access to a variety of resuscitation methods (T-piece resuscitators (TPR), self-inflating bags (SIBs) and anaesthetic bags) and commonly access to blended air/oxygen medical gases. TPR have been shown to provide the most reliable PEEP5 6 yet these systems are not available to most infants at need globally.

There is an urgent need for SIB devices with functional PEEP valve systems for newborn resuscitation in low-resource settings. However, the 2010 International Liaison Committee for Resuscitation (ILCOR) recommendations for newborn resuscitation suggests SIBs with PEEP valves ‘often deliver inconsistent end-expiratory pressures’.1 This is based on findings from two small studies examining the ability of one brand of SIB (Laerdal) fitted with a PEEP valve.7 8

The Laerdal SIB is unusual in comparison with most SIBs, in that to provide PEEP a clip-on adaptor is placed over the head section of the SIB to allow the PEEP valve to be attached. Morley and colleagues examined one disposable and one reusable Laerdal 240 mL SIB and examined manual inflations at rates of 20, 40 and 60/min at peak

What is known on this topic

▸ Previous studies on only one brand of self-inflating bag (SIB) (Laerdal) show inconsistent positive end-expiratory pressure (PEEP) delivery with PEEP valve.
▸ There is a need for a cheap effective device to deliver PEEP during newborn resuscitation in resource-poor countries.
▸ International Liaison Committee for Resuscitation (ILCOR) guidelines recommend provision of PEEP during resuscitation if suitable equipment is available.

What this study adds

▸ Ambu SIB (reusable and disposable) with Ambu PEEP valve can provide consistent levels of PEEP.
▸ Ambu SIB with Ambu manometer fitted can provide adequate peak inflation pressure.
▸ Delivery of PEEP via SIB may vary between brands depending on PEEP valve attachment design.


Original article

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Received 23 March 2015
Revised 21 December 2015
Accepted 22 December 2015
Published Online First 19 January 2016
inflation pressures (PIPs) of 30–35 cm H₂O and differing PEEP levels of 5, 7 and 10 cm H₂O. Morley et al.⁸ concluded the Laerdal SIB with a PEEP valve cannot provide continuous positive airway pressure (CPAP) and PEEP rapidly falls from the set values. Kelm and colleagues examined one resuscitator using 11 Ambu PEEP valves sequentially attached to one new Laerdal SIB aiming to deliver 5 cm H₂O. They found six Ambu valves delivered PEEP <3 cm H₂O.⁹ Kelm and colleagues reported in detail their findings of the lack of consistent PEEP and followed up with an alert to the German regulator.⁹

Most other SIB manufacturers have either SIBs that are designed with an integrated PEEP valve connector in the SIB moulding or have a design that precludes fitting a PEEP valve and so cannot deliver PEEP. They may perform differently. The ability of SIBs to provide PEEP particularly in resource-poor countries with limited resuscitation facilities requires further evaluation.

The aim of this study was to assess the delivered end-expiratory pressures from the Ambu disposable PEEP valve attached to Ambu neonatal SIBs across a range of set PEEP values. The test structure was designed to examine if there were differences between two test lungs with differing compliance, three inflation rates and two device types (Ambu SIB disposable compared with reusable). We used the Ambu Mark IV Baby (reusable) and Ambu SPUR-II (disposable) SIBs fitted with the Ambu single-use disposable PEEP valve 0–20 cm H₂O (Part Number 199 102 001).⁹

METHODS

Our sample included the Ambu reusable and single-use disposable SIB models both fitted with a moulded expiratory diverter (figure 1). Both were fitted with Ambu disposable manometer and PEEP valves. The Ambu PEEP valve is spring loaded with scales marked in 5 cm major ticks. The PEEP dial is screwed inwards towards the centre of the SIB to increase the set PEEP. One revolution of the valve knob produced a PEEP increase of approximately 5 cm H₂O. The user checks delivered PEEP with the attached manometer, as instructed in the manufacturer’s product insert.⁹

Three operators each tested two different devices (disposable and reusable) at combinations of three different inflations per minute (IPM) (20, 40 and 60 IPM); three PEEP valve settings (5, 7.5 and 10 cm H₂O) and two lung compliances (0.5 and 3 mL/cm H₂O). Approximately 30 inflations were recorded for each combination totalling 3265 inflations.

The two different leak-free test lungs used were (1) a 50 mL Dräger test lung (Dräger, Lubeck, Germany) with measured compliance of 0.5 mL/cm H₂O and (2) a 200 mL IMT newborn test lung (Smart Lung Infant, IMT medical, Buchs, Switzerland) with measured compliance of 3.0 mL/cm H₂O. A Florian Respiratory Function Monitor (Accutronics, Medical Systems AG, Zug, Switzerland) was connected via the hot wire pneumotach and pressure sensor line sited between the SIB and the test lung (figure 1). The Florian Monitor was calibrated with an external syringe of known volume and pressure/flow via a ventilator calibration analyser with pressure resolution of 0.1 cm H₂O with pressure accuracy of ±0.5% and flow calibration with resolution of 0.1 L/min with accuracy of ±1% (RT-200; Timeter Instrument, Allied Healthcare Products, St Louis, Missouri, USA). The analogue signals output from the Florian Monitor were collected and digitised at 200 Hz with analysis software (Grove Medical, London, UK). The test lungs and monitoring system were pressurised to static pressure of 50 cm H₂O and over 60 s there was no fall in pressure indicating the system was leak free.

The testing sequence involved each operator squeezing the SIB aiming to achieve a PIP between 30 and 35 cm H₂O using the Ambu disposable manometer. For each sequence, the PEEP valve was adjusted to one of the three predefined PEEP levels (5, 7.5 and 10 cm H₂O) using the Ambu manometer. Each operator was asked to provide 2 min bagging at rates of 20, 40 and 60 IPM, which were randomly sequenced. The first five inflations were discarded and the following 30 inflations were analysed. A 2 min rest period occurred between each sequence. This was repeated for the two different compliance test lungs. Morley et al.⁸ demonstrated no difference with or without gas inflow into SIBs testing PEEP and thus no gas inflow was used in this study. Operator inflation rates were timed with audible metronome.

DATA ANALYSIS

Analysis was conducted using Stata (V12 MP, StataCorp, College Station, Texas, USA). The measured parameters included the mean, minimum and maximum PIP and PEEP at end expiration. ANOVA for repeated measures was used to determine differences between rates, device types and test lung compliance at different set PEEP levels. Differences between means determined by ANOVA were reported with p values adjusted F test using Box’s conservative epsilon. p Values of <0.05 were considered significant. The ANOVA for repeated measures allows a valid statistical comparison between different rates, devices and lung compliance delivered by the same individual when the repeat measurements between individuals are not independent. Table 1 details the measured mean PEEP values with IQR and SD for each parameter with p values calculated with ANOVA for repeated measures. Predicted mean PEEP levels were reported graphically in figures 2–4 with 95% CI adjusted for explanatory variables in the model.

RESULTS

Six Ambu devices were tested of which three were disposable single-use devices and three reusable systems. A total of 3265 inflations were analysed; 1636 with disposable and 1629 with reusable Ambu SIBs. Operators were able to accurately deliver the desired PIP over the range of set PEEPs with a mean (SD) PIP at set PEEP 5 cm H₂O of 33.8 (1.04) cm H₂O and at set PEEP 7.5 cm H₂O of 34.4 (1.5) cm H₂O and 33.7 (1.1) cm H₂O. These PIPs were not statistically different. Figure 5 shows representative airway pressure waveforms for one subject.
for each set PEEP level (5, 7.5 and 10 cm H$_2$O) at 20 IPM (figure 5A–C) and at 60 IPM (figure 5D–F) to demonstrate the decay in pressure between inflations.

**Rate**
The measured PEEP as a percentage of set PEEP ranged from 70% to 72% at a rate of 20 IPM, 88–89% at 40 IPM and 96–98% at 60 IPM (table 1 and figure 2). These differences were statistically different ($p<0.001$).

**Device type**
Disposable Ambu SIB with PEEP valve had statistically higher measured PEEP at set PEEP valves adjusted for covariates at 7.5 and 10 cm H$_2$O ($p<0.01$) (table 1 and figure 3). There was no statistical difference at set PEEP of 5 cm H$_2$O. At 7.5 cm H$_2$O, the mean measured PEEP was 15% higher with disposable compared with reusable. There was a smaller difference at set PEEP of 10 cm H$_2$O (8% measured to set PEEP).

**Lung compliance**
The measured PEEP as a percentage of set PEEP ranged from 79% to 84% with test lung compliance of 0.5 mL/cm H$_2$O and from 90% to 93% with test lung compliance of 3.0 mL/cm H$_2$O ($p<0.005$) (table 1 and figure 4).

**DISCUSSION**
Our study shows Ambu SIBs fitted with Ambu disposable manometers and PEEP valves provide consistent mean delivered PEEP close to set PEEP at all rates tested. Our results indicate delivered PEEP is significantly closer to set PEEP at higher rates. An interesting finding not previously examined is the impact of

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Table 1  Measured positive end-expiratory pressure (PEEP) values with differing rates, device types and test lung compliance

<table>
<thead>
<tr>
<th>Rate</th>
<th>Set PEEP cm H$_2$O</th>
<th>20 IPM</th>
<th>40 IPM</th>
<th>60 IPM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>IQR (SD)</td>
<td>Mean</td>
<td>IQR (SD)</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3.6</td>
<td>3.5–4.2 (0.8)</td>
<td>4.4</td>
<td>4.2–4.7 (0.5)</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>5.3</td>
<td>4.7–6.2 (1.3)</td>
<td>6.7</td>
<td>6.1–7.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7.0</td>
<td>6.4–7.9 (1.5)</td>
<td>8.7</td>
<td>8.6–9.3 (0.8)</td>
</tr>
</tbody>
</table>

**Device type**

<table>
<thead>
<tr>
<th>Reusable</th>
<th>Mean</th>
<th>IQR (SD)</th>
<th>Disposable</th>
<th>Mean</th>
<th>IQR (SD)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Set PEEP cm H$_2$O</td>
<td>5</td>
<td>4.2</td>
<td>3.6–4.8 (1.0)</td>
<td>4.3</td>
<td>4.1–4.6 (1.0)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>5.9</td>
<td>5.0–6.8 (1.4)</td>
<td>7.0</td>
<td>6.3–7.4 (0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8.1</td>
<td>7.5–9.6 (1.8)</td>
<td>8.9</td>
<td>8.3–9.8 (0.9)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Test lung compliance**

<table>
<thead>
<tr>
<th>0.5 mL/cm H$_2$O</th>
<th>Mean</th>
<th>IQR (SD)</th>
<th>3 mL/cm H$_2$O</th>
<th>Mean</th>
<th>IQR (SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set PEEP cm H$_2$O</td>
<td>5</td>
<td>4.0</td>
<td>3.6–4.6 (0.8)</td>
<td>4.6</td>
<td>4.2–4.8 (0.5)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>5.9</td>
<td>5.0–6.8 (1.3)</td>
<td>7.0</td>
<td>6.4–7.5 (0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8.1</td>
<td>7.4–9.4 (1.7)</td>
<td>9.0</td>
<td>8.3–9.9 (1.0)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*p Values are reported with ANOVA.
IPM, inflations per minute.

---

Figure 2  Rates, predicted mean positive end-expiratory pressure (PEEP) with 95% CI adjusted for self-inflating bag type and test lung compliance.

Figure 3  Device types, predicted mean positive end-expiratory pressure (PEEP) with 95% CI adjusted for inflation rate and test lung compliance.

compliance of the test lung. The delivered PEEP was statistically higher in the compliance lung model of similar values to a normal term lung (4.5 cm H$_2$O compared with 4.0 cm H$_2$O adjusted for covariates p=0.002). PEEP delivered during resuscitation has defined benefits of improved FRC and oxygenation in preterm animal models with surfactant deficiency. CPAP in non-intubated infants and end-expiratory pressure in intubated infants are routine and well-evidenced methods in the treatment of respiratory distress. However, a recent randomised trial comparing T-piece resuscitators and SIB in resuscitation of preterm newborns in delivery suite failed to demonstrate any difference in the primary outcome of oxygenation at 5 min after birth. Our study differs from Morley et al who examined two Laerdal SIBs, one reusable and the other disposable and found much lower PEEP values (36% of set PEEP value at 5 cm H$_2$O and rate of 20 IPM) at each rate examined. The Laerdal SIB system has a separate flow diverter which needs to be positioned over the patient valve assembly (Part Number 851250) on the SIB to allow a PEEP valve to be connected. Other brands we have examined provide a SIB either for use with PEEP valve where an integrated moulded port in the patient valve assembly allows connection to the PEEP valve or not. Unpublished research from our group indicates a significant leak from the Laerdal disposable flow diverter packaged with the disposable PEEP valve (Part Number 845040) and the reusable flow diverter (Part Number 843080) that is independent of the PEEP valve. If the flow diverter is installed incorrectly (not completely clipped on) or is moved during use, further loss of PEEP will occur and will be undetected if a manometer is not connected. We believe this may account for most of the differences found between our results and those of Morley et al and Kelm et al. The Cochrane review on the resuscitation at term stated there were no trials meeting the defined search criteria to examine the effect of PEEP in this group. Although there are not sufficient research data to currently recommend the use of PEEP in term resuscitation, a recent resuscitation practice survey in 2011 of UK’s lead paediatricians (n=180) at 212 hospitals with newborn units showed that between 65.9% and 82.8% target PEEP (4–6 cm H$_2$O) during resuscitation of term babies and between 4.9% and 7.2% of practitioners use SIB with PEEP valves. These survey data would suggest that our study

Figure 4 Compliance, predicted mean with 95% CI adjusted for self-inflating bag type and inflation rate.

Figure 5 Recordings of airway pressure waveforms for each set positive end-expiratory pressure level (5, 7.5 and 10 cm H$_2$O) at 20 inflations per minute (IPM) (A–C) and 60 IPM (D–F).
findings of Ambu SIB fitted with PEEP valve can consistently provide delivered mean PEEP in the range of PEEP commonly targeted by clinicians in the UK for rates 40 and 60 IPM. This is in contrast to the findings of Morley et al8 and Klem et al9 using the Laerdal SIB with clip on PEEP adaptor. Our results also indicate it is possible to consistently deliver a required PIP using an Ambu disposable manometer.

CONCLUSION
Disposable and reusable Ambu SIB with Ambu PEEP valve attached can provide and maintain consistent mean delivered PEEP at inflation rates examined (20, 40 and 60 IPM). Our study indicated that the Ambu SIB used with the Ambu manometer allows accurate targeting of desired PIP which is in contrast to the findings of others examining Laerdal SIB.10–12 Delivered PEEP is closer to set value with normal compliance test lung suggesting establishing an FRC in a term baby resuscitation using an Ambu SIB with PEEP valve is in line with current clinician’s practice.13 Further research is warranted to examine other brands of SIB that offer PEEP valves to determine their effectiveness in delivering PEEP.

Acknowledgements We thank Professor Sally Tracy and Dr Jan Klimk for their helpful comments and suggestions. We also acknowledge and thank Ambu Australia for supply of devices to examine in this study.

Contributors MT is primary researcher responsible for conceiving, designing, analysing and writing manuscript. MH contributed by assisting design, data collection, analysis, manuscript writing and review. AP, DS contributed data collection, analysis, interpretation, manuscript construction.

Funding This study was researcher generated and conducted with no external funding required.

Competing interests None declared.

Ethics approval This study was approved by the Western Sydney Local Health District human research ethics committee approval number SAC2014/5/6.8 (3998).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Raw data waveforms for each data collection collected from Florian Respiratory Monitor to Grove Spectra.

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The effect of medical and operative birth interventions on child health outcomes in the first 28 days and up to 5 years of age: A linked data population-based cohort study

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Abstract

Background: Spontaneous vaginal birth rates are decreasing worldwide, while cesarean delivery, instrumental births, and medical birth interventions are increasing. Emerging evidence suggests that birth interventions may have an effect on children’s health. Therefore, the aim of our study was to examine the association between operative and medical birth interventions on the child’s health during the first 28 days and up to 5 years of age.

Methods: In New South Wales (Australia), population-linked data sets were analyzed, including data on maternal characteristics, child characteristics, mode of birth, interventions during labor and birth, and adverse health outcomes of the children (ie, jaundice, feeding problems, hypothermia, asthma, respiratory infections, gastrointestinal disorders, other infections, metabolic disorder, and eczema) registered with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification codes. Logistic regression analyses were performed for each adverse health outcome.

Results: Our analyses included 491 590 women and their children; of those 38% experienced a spontaneous vaginal birth. Infants who experienced an instrumental
1 | INTRODUCTION

Worldwide cesarean delivery rates are increasing, while spontaneous vaginal birth rates are decreasing. The rate of cesarean delivery has risen steadily in Europe to 25%, in Australia to 33%, and the highest rates are reported in Latin America and the Caribbean (41%). Instrumental birth (ie, forceps or vacuum) and medical birth interventions (ie, including the use of exogenous oxytocin for labor induction and/or augmentation) are increasing globally as well.

There is emerging evidence that operative birth (ie, instrumental vaginal birth or cesarean) may have an effect on children’s physical health and cognitive development in the longer term. The Extended Hygiene Hypothesis (EHH) hypothesizes that infants born by cesarean delivery have different colonization of the gut flora compared with infants born by vaginal birth. This may potentially affect the neonatal immune response. The EPIgenetic Impact of Childbirth (EPIIC) hypothesis raises concern over the effects of stress (too high and too low) caused by medical and operative birth interventions to the epigenetic regulation of gene expression in the immune system.

Studies have demonstrated that children born vaginally at term have different short- and longer-term physical health outcomes than those born by cesarean, particularly when there has been no exposure. Epidemiological studies that analyzed population-based registry data, reported conflicting associations between operative birth interventions, and the increased risk of several immune-related diseases, including asthma, type 1 diabetes, obesity, and inflammatory bowel disease. These conflicting findings may be due to different statistical methods used, differences in study population characteristics (eg, maternal age, morbidity, smoking, and gestational age), and failure to differentiate between mode of birth and medical birth interventions.

The aim of this study was to examine the associations between operative and/or medical birth interventions on children’s health outcomes in the first 28 days and up to 5 years of age, in a large population of healthy pregnant women and their children.

2 | METHODS

The study cohort consisted of women and their children born in New South Wales (NSW), Australia, between January 1, 2000 and August 31, 2008. Children’s health was followed until August 31, 2013. The NSW Centre for Health Record Linkage utilized probabilistic data linkage techniques to merge data of the following data sets: Record Linkage from the Perinatal Data Collection (PDC), Admitted Patient Data Collection, Register of Congenital Conditions, NSW Registry of Birth Deaths and Marriages, the Australian Bureau of Statistics—Socio-Economic Indexes for Areas. Probabilistic record linkage software assigns a “linkage weight” to pairs of records. For example, records that match perfectly or nearly perfectly on first name, surname, date of birth, and address have a high linkage weight and records that match only on date of birth have a low-linkage weight. If the linkage weight is high, it is likely that the records truly match, and if the linkage weight is low it is likely that the records are not truly a match. This technique has been shown to have a false-positive rate of 0.3% of records. Several studies have evaluated the validity of the NSW linkage data and reported a tendency toward underreporting of maternal medical conditions during pregnancy. However, by comparing PDC and Admitted Patient Data Collection data with women’s individual medical records, it showed that conditions and procedures regarding delivery and discharge status had high specificity, indicating that false positives were uncommon.

The study was approved by the Ethics Committee of the NSW Population and Health Services Research Committee (HREC/10/CIPHS/96). The ethics privacy statement outlines that consent is waived due to the size of the data set, retrospective nature of the data, and the inherent difficulties in obtaining consent.
2.1 | Data

Data were routinely collected from women who gave birth or had subsequent births in either a public or private hospital in NSW, Australia. Data of nulliparous and multiparous women were selected if they were low-risk pregnant women according to the guideline of the National Institute for Health and Care Excellence on intrapartum care and in alignment with methodology previously utilized on this and other linked data sets.20,25,26 This resulted in a cohort of “healthy pregnant women” who had no preexisting or pregnancy-related hypertension or diabetes, did not smoke or take drugs, were within the age range of 20-35 years, and gave birth at 37-41 weeks of gestation to a singleton baby in cephalic presentation with a birthweight of ≥2500 g. In addition, children with minor or major congenital conditions were excluded based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification codes (ICD-10-AM, Q0.0-Q99.9).25 Minor malformations could be related to more major malformations, which could be caused by genetic factors, for example, and which may become apparent some time after birth. Moreover, women and their children were excluded from the analyses if stillbirth or death had occurred during the 5-year follow-up period. By making this selection, we aimed to include a population of healthy pregnant women and their healthy born children, to reduce confounding and to increase the likelihood of finding the true association between exposure (birth interventions) and outcomes (child’s health short and longer term).

Women or children with missing data on either mode of birth, maternal age, parity, gestational age, or birthweight were also excluded from the analyses since these variables have a potential effect on children’s health. If missing data on other variables occurred, that is, country of birth, socioeconomic status, and infant gender, these variables were indicated as system missing in the linked data file and subsequently excluded from the logistic regression models.

2.2 | Variables

Mode of birth and birth interventions were collected from the PDC file and included: spontaneous vaginal birth, instrumental birth, elective cesarean delivery, and an emergency cesarean (either with or without medical birth interventions). Medical birth interventions included induction or augmentation of labor with oxytocin, prostaglandin, and/or artificial rupture of membranes.

The short-term follow-up data of infants during the first 5 years of age included admissions to public and private hospitals located in NSW (Admitted Patient Data Collection file). The children were followed from the date of birth until their fifth birthday to identify any adverse health outcomes which occurred during this time period. The classifying diagnoses and reasons with accompanying hospital visit dates were registered with ICD-10-AM-codes. Short-term adverse health outcomes included jaundice, feeding problems, and hypothermia and often are part of the adaptation of the infant to being outside the uterus.7,27,28 The longer-term adverse health outcomes included asthma, respiratory infections (eg, common cold, pneumonia, bronchitis), gastrointestinal disorders, other infections (eg, sepsis, streptococcus, cystitis), metabolic disorder (eg, hypoglycemia, neonatal diabetes mellitus, diabetes mellitus type 1 or 2, localized adiposity), and eczema, based on the potential effect that mode of birth has on immune-related diseases.5,7,12-18 An overview of all adverse health outcomes and other covariates with corresponding ICD-10-AM codes are presented in the Supporting Information.

Potential confounders of either women or children characteristics were selected from several data files. Women’s characteristics were extracted from the PDC and NSW Registry of Birth Deaths and Marriages files and included, for example, age and country of birth. From the Socio-Economic Indexes for Areas file, the socioeconomic status of women were collected and were based on area indices of income and education using women’s postal codes and defined as low (10-30 percentiles), medium (40-60 percentiles) or high (≥70 percentiles). Pharmacological pain medication during labor and birth (ie, nitrous oxide, systematic opioid, local administered to perineum, pudendal, morphine, and pethidine), and anesthesia (ie, epidural, caudal, and spinal) were extracted from the PDC file. Children’s characteristics were extracted from the PDC and Admitted Patient Data Collection files and included gender, gestational age, birthweight, small-for-gestational age, large-for-gestational age, and birth trauma (appendix).

2.3 | Data analyses

A retrospective analysis of prospectively collected linked data was performed. Baseline characteristics of the women and children were reported using descriptive statistics. Statistical differences in baseline characteristics in women and children in the different mode of birth and birth interventions groupings (ie, spontaneous vaginal birth, vaginal birth with induction or augmentation, instrumental birth, instrumental birth with induction or augmentation, elective cesarean delivery, emergency cesarean, and an emergency cesarean delivery after induction) were calculated with chi-square tests.

Univariate and multivariate logistic regression analyses were performed to examine the association between the exposure variable and each child outcome. Univariate logistic regression analysis was performed to compare spontaneous vaginal birth without induction or augmentation of labor with oxytocin, prostaglandin, and/or artificial rupture of membranes. The univariate regression models were adjusted for maternal characteristics (maternal age, country of birth, socioeconomic status, parity), birth characteristics (pain medication during birth), and child characteristics (gender, gestational age, birthweight, small-for-gestational age, large-for-gestational age, birth trauma). Crude and adjusted odds ratios (OR) with corresponding 95% confidence
### TABLE 1 Maternal, mode of birth, and child characteristics by type of birth interventions, New South Wales, Australia, 2000-2008

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Spontaneous vaginal birth</th>
<th>Vaginal birth with induction or augmentation</th>
<th>Instrumental birth with induction or augmentation</th>
<th>Cesarean elective</th>
<th>Cesarean emergency</th>
<th>Cesarean emergency after induction or augmentation</th>
<th>Statistical differences among groups that differed on mode of birth</th>
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<tbody>
<tr>
<td></td>
<td>N = 491,590</td>
<td>n = 185,883</td>
<td>n = 136,651</td>
<td>n = 19,865</td>
<td>n = 41,631</td>
<td>n = 55,499</td>
<td>n = 17,216</td>
<td>n = 34,845</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>37.8%</td>
<td>27.8%</td>
<td>4.0%</td>
<td>8.5%</td>
<td>11.3%</td>
<td>3.5%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Maternal age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>20-24</td>
<td>82,638 (16.8)</td>
<td>360,51 (19.4)</td>
<td>25,482 (18.6)</td>
<td>29,01 (14.6)</td>
<td>6063 (14.6)</td>
<td>4612 (8.3)</td>
<td>2175 (12.6)</td>
<td>5354 (15.4)</td>
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<td>25-29</td>
<td>185,308 (37.7)</td>
<td>71,439 (38.4)</td>
<td>53,382 (38.3)</td>
<td>77,49 (39.0)</td>
<td>16,514 (39.7)</td>
<td>17,391 (31.3)</td>
<td>6175 (35.9)</td>
<td>13,658 (39.2)</td>
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<td>30-35</td>
<td>223,644 (45.5)</td>
<td>78,393 (42.2)</td>
<td>58,787 (43.0)</td>
<td>92,15 (46.4)</td>
<td>19,054 (45.8)</td>
<td>33,496 (60.4)</td>
<td>8866 (51.5)</td>
<td>15,833 (45.4)</td>
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<td>Country of birth</td>
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<tr>
<td>Australia</td>
<td>339,072 (69.0)</td>
<td>122,577 (65.9)</td>
<td>99,432 (72.8)</td>
<td>13,096 (65.9)</td>
<td>27,620 (66.3)</td>
<td>41,191 (74.2)</td>
<td>11,653 (67.7)</td>
<td>23,503 (67.5)</td>
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<td>Not Australia</td>
<td>151,335 (30.8)</td>
<td>62,915 (33.8)</td>
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<td>67,30 (33.9)</td>
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<td>14,124 (25.5)</td>
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<td>293 (0.2)</td>
<td>39 (0.2)</td>
<td>127 (0.3)</td>
<td>184 (0.3)</td>
<td>55 (0.3)</td>
<td>94 (0.3)</td>
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<td></td>
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<tr>
<td>Low</td>
<td>123,311 (25.1)</td>
<td>52,186 (28.1)</td>
<td>35,710 (26.1)</td>
<td>37,62 (18.9)</td>
<td>7876 (18.9)</td>
<td>12,449 (22.4)</td>
<td>40,000 (23.2)</td>
<td>7328 (21.0)</td>
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<td>Middle</td>
<td>169,198 (34.4)</td>
<td>65,892 (35.4)</td>
<td>47,549 (34.8)</td>
<td>65,05 (32.7)</td>
<td>13,325 (32.0)</td>
<td>18,121 (32.7)</td>
<td>57,41 (33.3)</td>
<td>12,065 (34.6)</td>
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<td>High</td>
<td>197,712 (40.2)</td>
<td>67,344 (36.2)</td>
<td>53,037 (38.8)</td>
<td>95,35 (48.0)</td>
<td>20,222 (48.6)</td>
<td>24,816 (44.7)</td>
<td>74,33 (43.2)</td>
<td>15,325 (44.0)</td>
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<tr>
<td>Missing</td>
<td>1369 (0.3)</td>
<td>461 (0.2)</td>
<td>355 (0.3)</td>
<td>63 (0.3)</td>
<td>208 (0.5)</td>
<td>113 (0.2)</td>
<td>42 (0.2)</td>
<td>127 (0.4)</td>
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<tr>
<td>Nulliparous</td>
<td>219,951 (44.7)</td>
<td>63,906 (34.4)</td>
<td>56,547 (41.4)</td>
<td>15,163 (76.3)</td>
<td>34,574 (83.0)</td>
<td>11,560 (20.8)</td>
<td>87,88 (51.0)</td>
<td>29,413 (84.4)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>271,639 (55.3)</td>
<td>121,977 (65.6)</td>
<td>80,104 (58.6)</td>
<td>47,02 (23.7)</td>
<td>70,57 (17.0)</td>
<td>43,93 (79.2)</td>
<td>84,28 (49.0)</td>
<td>5432 (15.6)</td>
</tr>
<tr>
<td>Mode of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pain medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>57,214 (11.6)</td>
<td>42,889 (23.1)</td>
<td>13,602 (10.0)</td>
<td>418 (2.1)</td>
<td>305 (0.7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pharmacological pain medicationc</td>
<td>231,106 (47.0)</td>
<td>12,601 (67.8)</td>
<td>82,384 (60.3)</td>
<td>10,080 (50.7)</td>
<td>12,631 (30.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Epidural, caudal, spinal or general anesthesia</td>
<td>200,942 (40.9)</td>
<td>15,427 (8.3)</td>
<td>40,017 (29.3)</td>
<td>93,26 (46.9)</td>
<td>28,666 (68.9)</td>
<td>55,461 (99.9)</td>
<td>17,208 (100)</td>
<td>34,837 (100)</td>
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<tr>
<td>Missing</td>
<td>2328 (0.5)</td>
<td>1556 (0.8)</td>
<td>648 (0.5)</td>
<td>41 (0.2)</td>
<td>29 (0.1)</td>
<td>38 (0.1)</td>
<td>8 (0)</td>
<td>8 (0)</td>
</tr>
<tr>
<td>TABLE 1  (Continued)</td>
<td></td>
<td></td>
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<tr>
<td>------------------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>Spontaneous vaginal birth</td>
<td>Vaginal birth with induction or augmentation</td>
<td>Instrumental birth</td>
<td>Cesarean elective</td>
<td>Cesarean emergency after induction or augmentation</td>
<td>Cesarean emergency</td>
<td>Statistical differences among groups that differed on mode of birth</td>
<td></td>
</tr>
<tr>
<td>N = 491 590</td>
<td>n = 185 883</td>
<td>n = 136 651</td>
<td>n = 19 865</td>
<td>n = 41 631</td>
<td>n = 55 499</td>
<td>n = 17 216</td>
<td>n = 34 845</td>
<td></td>
</tr>
<tr>
<td>100% N (%)</td>
<td>37.8% n (%)</td>
<td>27.8% n (%)</td>
<td>4.0% n (%)</td>
<td>8.5% n (%)</td>
<td>11.3% n (%)</td>
<td>3.5% n (%)</td>
<td>7.1% n (%)</td>
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</tr>
</tbody>
</table>

Child characteristics

Gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total population</th>
<th>Spontaneous vaginal birth</th>
<th>Vaginal birth with induction or augmentation</th>
<th>Instrumental birth</th>
<th>Cesarean elective</th>
<th>Cesarean emergency after induction or augmentation</th>
<th>Cesarean emergency</th>
<th>Statistical differences among groups that differed on mode of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>242 168 (49.3)</td>
<td>94 616 (50.9)</td>
<td>69 096 (50.6)</td>
<td>8993 (45.3)</td>
<td>19 367 (46.5)</td>
<td>26 988 (48.6)</td>
<td>7650 (44.4)</td>
<td>14 458 (44.4)</td>
</tr>
<tr>
<td>Male</td>
<td>249 242 (50.7)</td>
<td>91 237 (49.1)</td>
<td>67 517 (49.4)</td>
<td>10 864 (54.7)</td>
<td>22 246 (53.4)</td>
<td>28 449 (51.3)</td>
<td>9554 (55.5)</td>
<td>19 375 (55.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>180 (0)</td>
<td>30 (0)</td>
<td>38 (0)</td>
<td>8 (0)</td>
<td>18 (0)</td>
<td>62 (0)</td>
<td>12 (0)</td>
<td>12 (0)</td>
</tr>
</tbody>
</table>

Gestational age

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Total population</th>
<th>Spontaneous vaginal birth</th>
<th>Vaginal birth with induction or augmentation</th>
<th>Instrumental birth</th>
<th>Cesarean elective</th>
<th>Cesarean emergency after induction or augmentation</th>
<th>Cesarean emergency</th>
<th>Statistical differences among groups that differed on mode of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>37-37 + 6</td>
<td>21 800 (4.4)</td>
<td>8503 (4.6)</td>
<td>5646 (4.1)</td>
<td>885 (4.4)</td>
<td>1251 (3.0)</td>
<td>3303 (6.0)</td>
<td>1358 (7.9)</td>
<td>854 (2.5)</td>
</tr>
<tr>
<td>38-40 + 6</td>
<td>367 792 (74.8)</td>
<td>149 685 (80.5)</td>
<td>92 235 (67.5)</td>
<td>15 646 (78.8)</td>
<td>28 202 (67.7)</td>
<td>49 328 (88.9)</td>
<td>13 016 (75.6)</td>
<td>19 680 (56.5)</td>
</tr>
<tr>
<td>41-41 + 6</td>
<td>101 998 (20.7)</td>
<td>27 695 (14.9)</td>
<td>38 770 (28.4)</td>
<td>3334 (16.8)</td>
<td>12 178 (29.3)</td>
<td>2868 (5.1)</td>
<td>2842 (16.5)</td>
<td>14 311 (41.1)</td>
</tr>
</tbody>
</table>

Birthweight

<table>
<thead>
<tr>
<th>Birthweight</th>
<th>Total population</th>
<th>Spontaneous vaginal birth</th>
<th>Vaginal birth with induction or augmentation</th>
<th>Instrumental birth</th>
<th>Cesarean elective</th>
<th>Cesarean emergency after induction or augmentation</th>
<th>Cesarean emergency</th>
<th>Statistical differences among groups that differed on mode of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2500 g</td>
<td>4993 (1.0)</td>
<td>1618 (0.8)</td>
<td>1496 (1.1)</td>
<td>174 (0.9)</td>
<td>362 (0.9)</td>
<td>729 (1.3)</td>
<td>218 (1.3)</td>
<td>396 (1.1)</td>
</tr>
<tr>
<td>2500-3499 g</td>
<td>240 896 (49.0)</td>
<td>97 316 (52.4)</td>
<td>63 789 (46.6)</td>
<td>10 629 (53.5)</td>
<td>19 811 (47.6)</td>
<td>28 020 (50.5)</td>
<td>8195 (47.6)</td>
<td>13 136 (37.7)</td>
</tr>
<tr>
<td>3500-3999 g</td>
<td>176 014 (35.8)</td>
<td>64 872 (34.9)</td>
<td>50 361 (36.9)</td>
<td>6947 (35.0)</td>
<td>15 558 (37.4)</td>
<td>19 029 (34.3)</td>
<td>5692 (34.6)</td>
<td>13 285 (38.1)</td>
</tr>
<tr>
<td>≥4000 g</td>
<td>69 687 (14.2)</td>
<td>22 077 (11.9)</td>
<td>21 005 (15.4)</td>
<td>2115 (10.6)</td>
<td>5900 (14.2)</td>
<td>7721 (13.9)</td>
<td>2841 (16.5)</td>
<td>8028 (23.0)</td>
</tr>
</tbody>
</table>

Small-for-gestational age

<table>
<thead>
<tr>
<th>Small-for-gestational age</th>
<th>Total population</th>
<th>Spontaneous vaginal birth</th>
<th>Vaginal birth with induction or augmentation</th>
<th>Instrumental birth</th>
<th>Cesarean elective</th>
<th>Cesarean emergency after induction or augmentation</th>
<th>Cesarean emergency</th>
<th>Statistical differences among groups that differed on mode of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>2151 (0.4)</td>
<td>720 (0.4)</td>
<td>594 (0.4)</td>
<td>88 (0.4)</td>
<td>170 (0.4)</td>
<td>327 (0.6)</td>
<td>177 (0.7)</td>
<td>135 (0.4)</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

Birth trauma child

<table>
<thead>
<tr>
<th>Birth trauma child</th>
<th>Total population</th>
<th>Spontaneous vaginal birth</th>
<th>Vaginal birth with induction or augmentation</th>
<th>Instrumental birth</th>
<th>Cesarean elective</th>
<th>Cesarean emergency after induction or augmentation</th>
<th>Cesarean emergency</th>
<th>Statistical differences among groups that differed on mode of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 460 (3.3)</td>
<td>2954 (1.6)</td>
<td>1990 (1.5)</td>
<td>151 (0.8)</td>
<td>626 (1.5)</td>
<td>871 (1.6)</td>
<td>324 (1.9)</td>
<td>994 (2.9)</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

**Induction or augmentation with oxytocin, prostaglandin, and/or artificial rupture of membranes.**

**Socioeconomic status are index data of relative socioeconomic advantage and disadvantage, low (deciles 0-3), middle (deciles 4-6), high (7-10 deciles).**

**Pharmacological pain medication (ie, nitrous oxide, systematic opioid, local administered to perineum, pudendal, morphine, and pethidine).**

**Birth trauma refers to birth trauma to central or peripheral nervous system, birth trauma to scalp, birth trauma to skeleton, intracranial laceration, and hemorrhage due to birth trauma.**
intervals (CI) were reported. For all analyses, a *P*-value of .01 was defined as significant and all statistical analyses were performed with SPSS Statistics 23.0 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

The total population linked data set contained the antenatal, birth, and postnatal details of 669 880 women and 1 097 762 births which occurred in public or private hospitals during the study period 2000-2008 with a follow-up until age 5 years. A total 548 815 births (50%) were excluded due to medical or obstetric risk factors (eg, maternal morbidity, preterm birth) or substance abuse in pregnancy (eg, smoking or drug abuse). We excluded 54 254 (4.9%) children with congenital abnormalities. After applying all other exclusion criteria, mortality was recorded for 1638 (0.1%) children during the study period. There were 653 stillbirths, 353 cases of neonatal mortality, and 632 of childhood mortality. The risk of neonatal mortality was similar across the different mode of births. Finally, 1465 cases were excluded due to missing data on either maternal characteristics (ie, age, mode of birth, parity) or child characteristics (ie, gestational age, birthweight). The final study cohort consisted of 491 590 healthy pregnant women and their children.

The majority of the women were Australian born (69%) and had a mean age of 29 (SD 4) years. Fifty-five percent of the women were nulliparous. About 38% had a spontaneous vaginal birth, 28% had a vaginal birth with induction or augmentation, 4% had an instrumental birth without induction or augmentation, and 8% had an instrumental birth with induction or augmentation. Eleven percent of these women had an elective cesarean delivery, 4% had an emergency cesarean, and 7% had an emergency cesarean delivery after induction or augmentation of labor (Table 1). Overall, 43% of the women included were induced before labor, or received augmentation during labor. The majority (88%) of women received pain medication and infant’s birth trauma was experienced in 3% of the births. Maternal (eg, socioeconomic status), birth (eg, pain medication), and child characteristics (eg, gestational age) showed statistically significant differences across seven modes of the birth group (*P* ≤ .001, Table 1). Missing values ranged from 0.04% (ie, infant gender) to 0.3% (ie, socioeconomic status) in the final linked data set.

3.1 | Outcomes at short-term follow-up (first 28 days)

The prevalence of jaundice, feeding problems, and hypothermia were, respectively, 4%, 3%, and 2%. Compared with infants who were born by spontaneous vaginal birth, all other infants born with either medical or operative birth interventions had significantly higher odds of jaundice and feeding problems, except for an elective cesarean delivery which was not associated with the risk of jaundice (*P* = .07). Infants born by instrumental vaginal birth after induction or augmentation showed the highest association of jaundice (crude OR 3.26 [95% CI 3.12-3.41], adjusted OR [aOR] 2.75 [95% CI 2.61-2.91]). Significantly higher odds of hypothermia were observed for infants born by all the specified cesarean groups compared with those born by spontaneous vaginal delivery (Table 2).

3.2 | Outcomes at longer-term follow-up (up to 5 years of age)

Diagnosed respiratory infections had the highest prevalence of any of the medical conditions during the 5-year follow-up period, 14%. The lowest prevalence was observed for gastrointestinal disorders, 0.5%. Other bacterial infections, sepsis, otitis, cystitis, or urethritis, were reported in 8% of the children in the study. There was no evidence to suggest an association between mode of birth and the odds of asthma. Metabolic disorder was reported in 1% of children and 3% were diagnosed with eczema. Compared with children born after spontaneous vaginal birth without induction or augmentation, all other groups had higher odds of respiratory infections, metabolic disorder, and eczema (Table 3). Odds of gastrointestinal disorders were higher among children born after vaginal birth with induction or augmentation and after elective cesarean delivery. Other infections were more prevalent among all exposure groups compared with those born after spontaneous vaginal birth without induction or augmentation. No statistical significant associations between other infections and groups born after instrumental birth either without or with induction or augmentation were observed (*P*-values .07 and .02, respectively). Compared with children born by spontaneous vaginal birth, children born by cesarean delivery had higher odds of longer-term adverse health outcomes. Birth by elective cesarean delivery aOR 2.49 (95% CI 2.19-2.82), an emergency cesarean aOR 2.63 (95% CI 2.26-3.07), and emergency cesarean delivery after induction aOR 2.41 (95% CI 2.11-2.76) was associated with increased odds of metabolic disorder.

4 | DISCUSSION

The aim of this study was to examine the association between medical birth interventions and/or operative birth interventions on short- and longer-term child health outcomes in healthy women and their children by analyzing population-based linked data. Our results showed that newborns born by instrumental birth after induction or augmentation were more likely to experience jaundice. Children born by cesarean delivery were particularly at increased risk for adverse health outcomes in the longer term, that is, respiratory infection, other infection, and metabolic disorder.
There is emerging evidence that some birth interventions may have an effect on the neonatal immune response and the child’s health in the longer term.\textsuperscript{7,29} There is evidence of short-term health impacts for the infant after a cesarean delivery, such as hypothermia, impaired lung function, altered metabolism, altered blood pressure, and altered feeding, which is consistent with our results.\textsuperscript{7,27,28} Some of these changes might be due to a lack of labor stress, associated with physiological maladaptation after birth. Some epidemiological studies have linked the mode of birth (particularly cesarean delivery) to increasing rates of asthma and gastrointestinal disorders.\textsuperscript{15,17} However, other epidemiological studies did not report higher rates of asthma, diabetes type 1, obesity, and inflammatory bowel disease for children born with birth interventions.\textsuperscript{12,16} Several studies that included meta-analyses reported that children born by cesarean delivery were at higher risk of developing obesity, diabetes, or asthma in childhood.\textsuperscript{5,6,30,31}

The EPIIC hypothesis postulated by some of the authors in this paper, proposes that nonphysiological interventions during the intrapartum period, and specifically the use of synthetic oxytocin, epidural analgesia, and cesarean delivery, may interrupt the normal stress of being born.\textsuperscript{10,11} This could have an epigenetic effect on specific genes, such as those that program immune responses, including weight regulation and metabolism. In support of an epigenetic hypothesis in this area, an association between mode of birth and DNA methylation has previously been reported.\textsuperscript{32,33} Schlinzig et al examined 37 term babies born by elective cesarean delivery (n = 16) or vaginal birth (n = 21) and found a higher global measure of DNA methylation if the infant was born by cesarean delivery. While there was a nonsignificant difference between vaginal birth and cesarean delivery at 3-5 days postpartum, the pattern did not alter in the infants born vaginally but significantly

### Table 2

Prevalence and associations between birth interventions and short-term child health outcomes, New South Wales, Australia, 2000-2013

<table>
<thead>
<tr>
<th>Short-term adverse health outcomes</th>
<th>Total population</th>
<th>No. of events</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted\textsuperscript{a} OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jaundice</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal birth</td>
<td>5299 (2.9)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaginal birth with induction or augmentation</td>
<td>4986 (3.6)</td>
<td>1.28 (1.23-1.33)\textsuperscript{b}</td>
<td>1.36 (1.31-1.42)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal birth without induction or augmentation</td>
<td>1615 (8.1)</td>
<td>3.01 (2.84-3.19)</td>
<td>2.34 (2.20-2.49)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal birth with induction or augmentation</td>
<td>3662 (8.8)</td>
<td>3.26 (3.12-3.41)</td>
<td>2.75 (2.61-2.91)</td>
<td></td>
</tr>
<tr>
<td>Elective cesarean</td>
<td>1638 (3.0)</td>
<td>1.02 (0.96-1.07)</td>
<td>1.07 (1.00-1.14)</td>
<td></td>
</tr>
<tr>
<td>Emergency cesarean without induction or augmentation</td>
<td>686 (4.0)</td>
<td>1.39 (1.29-1.51)</td>
<td>1.24 (1.14-1.36)</td>
<td></td>
</tr>
<tr>
<td>Emergency cesarean after induction or augmentation</td>
<td>1375 (3.9)</td>
<td>1.38 (1.30-1.46)</td>
<td>1.31 (1.22-1.41)</td>
<td></td>
</tr>
<tr>
<td><strong>Feeding problems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal birth</td>
<td>1886 (1.0)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaginal birth with induction or augmentation</td>
<td>1907 (1.4)</td>
<td>1.37 (1.28-1.46)</td>
<td>1.23 (1.15-1.32)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal birth without induction or augmentation</td>
<td>513 (2.6)</td>
<td>2.58 (2.34-2.85)</td>
<td>1.44 (1.30-1.60)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal birth with induction or augmentation</td>
<td>1344 (3.2)</td>
<td>3.22 (3.00-3.46)</td>
<td>1.73 (1.59-1.89)</td>
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<tr>
<td>Elective cesarean</td>
<td>1095 (2.0)</td>
<td>1.93 (1.79-2.08)</td>
<td>1.81 (1.64-1.99)</td>
<td></td>
</tr>
<tr>
<td>Emergency cesarean without induction or augmentation</td>
<td>450 (2.6)</td>
<td>2.58 (2.33-2.87)</td>
<td>1.82 (1.61-2.05)</td>
<td></td>
</tr>
<tr>
<td>Emergency cesarean after induction or augmentation</td>
<td>1090 (3.1)</td>
<td>3.10 (2.87-3.34)</td>
<td>1.85 (1.67-2.04)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypothermia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal birth</td>
<td>5537 (3.0)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaginal birth with induction or augmentation</td>
<td>4484 (3.3)</td>
<td>1.09 (1.05-1.14)</td>
<td>1.04 (1.00-1.08)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal birth without induction or augmentation</td>
<td>687 (3.5)</td>
<td>1.16 (1.07-1.26)</td>
<td>0.96 (0.88-1.04)</td>
<td></td>
</tr>
<tr>
<td>Instrumental vaginal birth with induction or augmentation</td>
<td>1542 (3.7)</td>
<td>1.24 (1.17-1.31)</td>
<td>1.01 (0.94-1.08)</td>
<td></td>
</tr>
<tr>
<td>Elective cesarean</td>
<td>2104 (3.8)</td>
<td>1.26 (1.20-1.32)</td>
<td>1.16 (1.08-1.24)</td>
<td></td>
</tr>
<tr>
<td>Emergency cesarean without induction or augmentation</td>
<td>742 (4.3)</td>
<td>1.45 (1.34-1.56)</td>
<td>1.24 (1.13-1.36)</td>
<td></td>
</tr>
<tr>
<td>Emergency cesarean after induction or augmentation</td>
<td>1775 (5.1)</td>
<td>1.72 (1.63-1.82)</td>
<td>1.43 (1.33-1.54)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted for maternal characteristics (ie, maternal age, country of birth, socioeconomic status, parity), birth characteristics (ie, pharmacological pain medication or anesthesia), and child characteristics (ie, gender, gestational age, birthweight, small-for-gestational age, large-for-gestational age, birth trauma).

\textsuperscript{b}Associations reported in bold reflect a statistical significant association (P ≤ .01).
### TABLE 3 Prevalence and associations between birth interventions and longer-term child health outcomes, New South Wales, Australia, 2000-2013

<table>
<thead>
<tr>
<th>Longer-term adverse health outcomes</th>
<th>Total population</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events N (%)</td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted(^a) OR (95% CI)</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal birth</td>
<td>5738 (3.1)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Vaginal birth with induction or augmentation</td>
<td>4294 (3.1)</td>
<td>1.01 (0.97-1.05)</td>
<td>1.01 (0.96-1.05)</td>
</tr>
<tr>
<td>Instrumental vaginal birth without induction or augmentation</td>
<td>640 (3.2)</td>
<td>1.04 (0.96-1.13)</td>
<td>1.07 (0.98-1.17)</td>
</tr>
<tr>
<td>Instrumental vaginal birth with induction or augmentation</td>
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<td>0.92 (0.87-0.98)</td>
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<tr>
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<td>1.04 (0.97-1.11)</td>
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<tr>
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<td>1.12 (1.03-1.23)(^b)</td>
<td>1.09 (0.99-1.20)</td>
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<tr>
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<td>1.03 (0.95-1.12)</td>
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<td>665 (0.4)</td>
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<tr>
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<td>1630 (9.5)</td>
<td>1.32 (1.25-1.39)</td>
<td>1.10 (1.04-1.17)</td>
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<tr>
<td>Emergency cesarean after induction or augmentation</td>
<td>3218 (9.2)</td>
<td>1.28 (1.23-1.33)</td>
<td>1.10 (1.05-1.16)</td>
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<td>Reference</td>
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<td>1.35 (1.23-1.48)</td>
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<td>1.28 (1.08-1.52)</td>
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<td>Elective cesarean</td>
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<td>653 (1.9)</td>
<td>3.34 (3.02-3.68)</td>
<td>2.41 (2.11-2.76)</td>
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(Continues)
TABLE 3 (Continued)

<table>
<thead>
<tr>
<th>Longer-term adverse health outcomes</th>
<th>Total population</th>
<th>No. of events</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
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<td>Eczema</td>
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<tr>
<td>Vaginal birth with induction or augmentation</td>
<td>3529 (2.6)</td>
<td>1.34 (1.28-1.41)</td>
<td>1.16 (1.10-1.22)</td>
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<tr>
<td>Instrumental vaginal birth without induction or augmentation</td>
<td>1171 (5.9)</td>
<td>3.20 (2.99-3.42)</td>
<td>2.18 (2.03-2.35)</td>
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<tr>
<td>Instrumental vaginal birth with induction or augmentation</td>
<td>2817 (6.8)</td>
<td>3.68 (3.50-3.87)</td>
<td>2.30 (2.16-2.45)</td>
<td></td>
</tr>
<tr>
<td>Elective cesarean</td>
<td>1541 (2.8)</td>
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<td>2.54 (2.35-2.75)</td>
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</tr>
<tr>
<td>Emergency cesarean after induction or augmentation</td>
<td>2476 (7.1)</td>
<td>3.85 (3.65-4.06)</td>
<td>2.38 (2.22-2.55)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for maternal characteristics (ie, maternal age, country of birth, socioeconomic status, parity), birth characteristics (ie, pharmacological pain medication or anesthesia), and child characteristics (ie, gender, gestational age, birthweight, small-for-gestational age, large-for-gestational age, birth trauma).

A decreased in infants born by cesarean delivery.33 Almgren et al32 undertook a more precise analysis, looking at DNA from hematopoietic stem cells (CD34+). Those in specific gene sites that programmed for immune-mediated disease showed different methylation patterns in infants born by cesarean delivery than those born vaginally.32 Furthermore, those infants born after shorter labor showed similar DNA methylation patterns to those born by cesarean, suggesting that physiological labor stress over a certain period of time is required to program certain autoimmune responses in the neonate.

An alternative theory, the Extended Hygiene Hypothesis suggests that in utero, during a vaginal birth, and following skin-to-skin contact and breastfeeding, the infant needs to gather a community of microbes that come from the mother and the surrounding environment.8,9 Establishing the gut microbiota may be important in protecting the child, and later the adult, against atopic and immunological diseases.10,34 Disturbances in this process could be linked to developing infectious, inflammatory, and allergic diseases later in life.10,34 However, some studies associate the mode of birth with differences in the child’s microbiota, other conflicting results showed that there was no effect of cesarean delivery on the early microbiota beyond the immediate neonatal period.35

Despite this, there is a global awareness that cesarean delivery rates are too high. Currently, the emphasis is on labor induction to address this issue, as in, for example, a recently reported randomized controlled trial on routine induction of labor at 39 weeks in nulliparous women.36 Although this study showed a reduced cesarean delivery, our population level analysis shows that replacing one technical intervention with another might not improve longer-term outcomes. We suggest that those looking to reduce unnecessary intervention could consider results of systematic reviews that show that relationship-based interventions, such as continuous support in labor, or continuity of midwifery care, are associated with decreased interventions, improved rates of physiological birth, and higher levels of maternal reports of well being, without adversely affecting mortality and morbidity, and at reduced cost for women and health systems.37,38

Our study had several strengths and limitations. To our knowledge, this is the first study that has provided an overview of associations between all possible birth interventions and a wide range of adverse child health outcomes within a large population of healthy pregnant women and their children. In our analyses, we adjusted for a range of confounders, including maternal characteristics, birth characteristics, and child characteristics. However, our associations could still be affected by unmeasured confounding, such as maternal body mass index, antibiotic use during pregnancy or administered during childhood until the age of 5, breast or artificial feeding, paternal characteristics, and familial environmental and genetic factors. Moreover, we were unable to control for confounding by indication since the underlying reasons for the provided medical and operative birth interventions were unknown.39 All of these factors may independently be associated with some of the health outcomes seen in children and therefore our findings must be interpreted with caution. It is possible that the routine use of intrapartum antibiotics also plays a role in the disturbance of the microbiome. As a consequence, the infant may experience adverse outcomes. Furthermore, experimental and laboratory-based studies are needed to determine the precise mechanism and contribution of the different factors to the outcome. While we included country of birth, we could not include ethnicity and this may also affect outcomes and associations. We were only able to examine admissions of the child to a hospital while visits to general practitioners were not incorporated, suggesting an underreporting of adverse outcomes. Unfortunately, population-based linked data are restricted to the selection of variables and limited ability to verify the accuracy of the data, but do
provide a cost-effective way of establishing incidence and association of (rare) health outcomes and can direct future research.

Further research is required to confirm or refute the findings from this study. Research ideally would include other population-based data registries, including a longer follow-up period for a wider range of adverse child health outcomes, particularly those that are found more commonly beyond 5 years of age (eg, asthma). More research is also needed to explain some of the potential mechanisms at play, including epigenetic and microbiome research.

By analyzing linked population data, we obtained insight into the association of medical and operative birth interventions and short- and longer-term child health outcomes. These results support the “Too little too late, too much too soon debate” in maternal care, in which Miller et al argued that unnecessary use of nonevidence-based interventions can be harmful for healthy women and infants, as much as a lack of lifesaving interventions is damaging for those that need them. Our results should make consumers and maternal health care professionals aware of the potential harm that birth interventions may have in the longer term, encouraging a “precautionary principle” approach that weighs the possible benefits of the intervention against its potential detrimental effects for each mother and child. The aim should always be to provide the right amount of care at the right time in the right way to childbearing women, with a clear assessment of the potential consequences of just-in-case interventions.

4.1 Conclusion

Children born by spontaneous vaginal birth had fewer short- and longer-term health problems, compared with those born after birth interventions. This suggests that when examining labor interventions, researchers need to pay attention to use of exogenous oxytocin and to instrumental and operative birth, and that follow-up should be continued into the longer term.

ACKNOWLEDGMENT

We are grateful to the Centre for Health Data Linkage NSW Health (CHeReL) for their assistance in providing linked population data sets.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Peters LL, Thornton C, de Jonge A, et al. The effect of medical and operative birth interventions on child health outcomes in the first 28 days and up to 5 years of age: A linked data population-based cohort study. *Birth*. 2018;45:347-357. [https://doi.org/10.1111/birt.12348](https://doi.org/10.1111/birt.12348)
INTRODUCTION

Obstetric anal sphincter injuries (OASIS) can complicate up to 6% of births\(^1\text{--}^8\) and are a major contributor to preventable maternal morbidity.\(^9\) OASIS have been linked with a number of long-term complications such as faecal incontinence, urinary incontinence, perineal pain, dyspareunia, embarrassment and low self-esteem.\(^10\) Instrumental delivery, increasing birthweight and prolonged second stage are all recognised risk factors for OASIS;\(^6,8,11\text{--}^14\) however, the role of ethnicity remains uncertain.

Women of different ethnic groups exhibit diverse profiles of maternal morbidity, with their individual risk of postpartum haemorrhage, peripartum infection and OASIS influenced by their background.\(^15\text{--}18\) A number of studies have looked at ethnicity as a risk factor for OASIS\(^11,17,19\text{--}24\) and found that Asian women have a risk of third and fourth degree perineal tears up to four times greater than women of other ethnicities in the same community, but the lack of differentiation of Asian women into regional groups has limited insight into the reasons behind their increased risk.
times greater than women of other ethnicities in the same community.25,26 This is of particular importance because Asian women also have a greater burden of maternal morbidity in general, including worse perineal pain after delivery and lower rates of sexual intercourse 6-12 weeks following birth.27 Prevention of OASIS in this population will make a significant contribution to improving their postnatal quality of life and long-term bowel function.

A number of explanations for this phenomenon have been proposed. One suggestion is the difference in practice between Western and Eastern countries,28 however, it has been shown that migrants of Asian ethnicity in Western countries have higher risk than comparable women in their country of origin.29 Meanwhile, hospitals who serve different patient ethnic compositions within the same country, report discrepant rates of OASIS.30 It has also been suggested that Asian women may have a variation in perineal anatomy that makes them vulnerable to OASIS; however, studies have not shown any significant difference in this regard.26,31

In previous studies of OASIS country of birth has been used as an indirect marker of ethnic background and analysis has been based on regional groups. In the previous studies, the lack of differentiation of Asian women into regional groups has limited insight into the reasons behind their increased risk – particularly in light of evidence that Indian or South-East Asian women are at a higher risk of OASIS even among Asian women.32,33 Given the broad range of socioeconomic, anatomical and cultural differences within the large population of Asia, it is critical that the increased risk of OASIS is more specifically stratified.29

Westmead Hospital in the western suburbs of Sydney, Australia, represents a large tertiary referral centre that delivers up to 5600 babies each year from mothers born primarily overseas (62.1%). The majority of women (42.7%) seen at Westmead Hospital were born in Asia, making it an ideal sample group to examine the risk of OASIS in specific Asian ethnicities, in particular South-East Asian and South Asian women.

Making use of this population, the aim of this study was to explore the risk of OASIS in women of Asian ethnicity based on the country of birth when stratified by region. In turn, policy may be better directed at preventing OASIS in women most at risk.

MATERIALS AND METHODS

Study population

This was a retrospective cohort study of all women with a singleton, nulliparous pregnancy who delivered vaginally by spontaneous vaginal birth (SVB) or an instrumental delivery at Westmead Hospital, New South Wales, Australia, between 1 January 2009 and 31 December 2015. The demographics of women who experienced third or fourth degree perineal tears (the OASIS group) were compared with those women who had either no perineal trauma, minor perineal trauma, episiotomies, first or second degree perineal tears.

Data collection

Data were obtained from the ObstetriX database of the Western Sydney Local Health District. Demographic information included: maternal age, body mass index (BMI), country of birth, gravidity, parity and smoking status. Intrapartum details included perineal trauma, mode of birth, fetal position, episiotomy, birthweight, head circumference, gestational age and augmentation/induction of labour.

Definitions

OASIS were classified using the criteria defined by Sultan and endorsed by the International Consultation on Incontinence and the Royal College of Obstetricians and Gynaecologists. Grade 3 through Grade 4 tears were classified as OASIS. The diagnosis of OASIS in our centre is always confirmed by an experienced medical officer.

Country of birth (COB) was grouped into the following regional groups on the basis of the WHO regional classification, with additional divisions isolating South Asia and Australia and New Zealand (NZ) as distinct groups given their concentration in our study population:

- ‘Australia and New Zealand’, including Australia and NZ
- ‘South Asia’, including Afghanistan, Bangladesh, India, Nepal, Pakistan and Sri Lanka
- ‘South-East Asia’, including Brunei, Myanmar, Cambodia, East Timor, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand and Vietnam
- ‘Other Asia’, including China, Hong Kong, Japan, Kazakhstan, South Korea, Kyrgyz Republic, Macau, Mongolia, Taiwan and Uzbekistan
- ‘Middle East’ including Armenia, Bahrain, Cyprus, Gaza Strip, Georgia, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Qatar, Saudia Arabia, Syria, Turkey and United Arab Emirates
- ‘Other’ including all other countries.

Data analysis

Data analysis was performed using SPSS v22 software (IBM, Armonk, NY, USA). Student’s t-test and the χ² test were used to compare differences between continuous and categorical demographic variables between the groups, respectively. Logistic regression analysis was used to identify prognostic variables for the prediction of OASIS. Variables for which the P-value was <0.3 in the univariate analysis of those who are likely to be associated with OASIS on clinical grounds were included in a multivariate logistic regression analysis to identify factors that are independently associated with OASIS. A variable was considered to be a significant predictor if the P-value was less than 0.05. All statistics produced in the analysis were reviewed and validated by our centre’s on-site statistician.
Ethics

This study was approved by the Western Sydney Local Health District Human Research Ethics Committee, with the approval number SAC2016/7/6.12 (4770) QA.

RESULTS

From January 2009 to December 2015 there were 10 750 singleton, nulliparous and natural vaginal births (NVB), forceps or vacuum deliveries. Of these deliveries, 581 (5.4%) had third degree tears and 36 (0.3%) fourth degree tears. The demographic and obstetric characteristics of the women in the OASIS and control groups are presented in Table 1. Almost half of all women included were born in Asia (49.6%), while only 35.2% of women were born in Australia. There was no statistically significant increase in third or fourth degree tears over the years studied, odds ratio (OR) 1.03 (95% CI: 0.99–1.07; P = 0.15).

The overall rate of OASIS for the nulliparous, singleton vaginal or instrumental deliveries was 5.7% (N = 617) (Table 1). Women born in South Asia were at a much higher risk of OASIS than other groups, including women of other Asian descent, compared to the Australian/NZ cohort. One in every 10 South Asian women, compared to Australian/NZ, nulliparous women having a singleton vaginal or instrumental delivery will sustain an OASIS (P < 0.001). The next highest risk group, South-east Asia, have a rate almost half that (5.5%). Subsequently, South Asian women account for over half (54.6%) of all OASIS despite representing 31.2% of the study population.

Further investigation reveals a number of significant differences between South Asian and the rest of the study population. South Asian women have more forceps deliveries and less normal vaginal deliveries than any other group (Table 1), which may also account for their higher rate of episiotomy (our facility introduced a policy mandating episiotomy in all forceps deliveries during the study period from 1 July 2014).

Univariable analysis shows that Asian women are at a much higher risk of OASIS than women born domestically, South Asian women in particular are over three times more likely to have OASIS than women born in Australia (Table 2), which includes women of similar ethnicity who were born domestically. This also revealed a number of other risk factors associated with OASIS, including head circumference, lower BMI, increased birthweight, augmentation, induction, episiotomy and instrumental delivery. Unfortunately, BMI and head circumference were unknown for certain deliveries, thus some of the models in the analysis include smaller sample sizes. Postdate pregnancies (gestational age ≥ 42 weeks) accounted for 25 deliveries of the total cohort analysed and given the small numbers this cohort was not separately analysed.

A further multivariable analysis was conducted with the significant variables for OASIS. Asian COB remained a significant risk factor for OASIS following multivariable analysis with an OR of 3.62 for South Asian women compared to women born in Australia (Table 2). In particular, despite the higher instrumental rates observed in women born in Asia, COB remained a significant risk factor after adjusting for this in the multivariable analysis.

DISCUSSION

As noted in previous studies, Asian women are at an increased risk of OASIS with both normal and instrumental deliveries compared to women from other continents. South Asian women in particular, are at a dramatically increased risk. They are over four times more likely to sustain an OASIS than Australian-born women, while other Asian women are only twice as likely compared to domestically born women. This equates to one in every 10 South Asian nulliparous women having a singleton vaginal or instrumental delivery sustaining an OASIS, a rate previously found in a study by Davies-Tuck et al. This association is independent of expected confounders, and despite South Asian women having higher frequencies of historically protective factors, such as lower birthweight and more episiotomies. Also, this study further confirms that South Asian women have higher rates of birth intervention in general compared to the background population, with higher rates of induction/augmentation, a higher prevalence of episiotomies, and more frequent instrumental delivery.

It is unclear why this association is so strong in South Asian women compared to other Asian women, particularly when the literature notes that South Asian countries have among the lowest rates of OASIS. Accepting limitations such as routine episiotomy for nulliparous women in South Asian countries and variability of reporting internationally, the wide discrepancy between South Asian women giving birth in their home country versus a developed country like Australia warrants further investigation.

Anatomy has been suggested as one factor, with studies revealing South Asian women have a smaller pelvic inclination than other women, resulting in a more horizontal pelvis. This anatomical pattern ‘may alter the direction of expulsive forces normally directed anteriorly, towards a more posterior aspect, thereby increasing the risk for perineal damage’. More broadly, race and ethnicity play an important role in the effectiveness of patient and doctor communication. Australian midwives have noted that Asian women experienced more perineal injury due to communication problems during the birth – with difficulty in understanding the shift from pushing to breathing as the baby crowns. This observation is supported by Davies-Tuck’s finding that the need for an interpreter was significantly associated with OASIS in nulliparous women in univariate analyses.

It is clear that the consistent growth in the Australian immigrant population, and the concentration of women born overseas in communities such as western Sydney, necessitates culturally and ethnically tailored approaches to preventing OASIS. In our
Birth country as a risk factor for OASIS

TABLE 1 Demographics for all singleton vaginal deliveries of nulliparous women by country of birth (N = 10 750)

Total
(N = 10 750)

Aus/NZ,
N = 3780
(35.2%)

South Asia,
N = 3357
(31.2%)

South-East
Asia, N = 602
(5.6%)

Other Asia,
N = 1376
(12.8%)

Middle East,
N = 788
(7.3%)

Other,
N = 847
(7.9%)

10 133 (94.3%)

3669 (97.1%)

3020 (90.0%)

569 (94.5%)

1296 (94.2%)

760 (96.4%)

819 (96.7%)

581 (5.4%)

104 (2.8%)

315 (9.4%)

32 (5.3%)

75 (5.5%)

27 (3.4%)

28 (3.3%)

36 (0.3%)

7 (0.1%)

22 (0.7%)

1 (0.2%)

5 (0.4%)

1 (0.1%)

0 (0.0%)

365 (3.4%)

324 (8.6%)

6 (0.2%)

5 (0.8%)

3 (0.2%)

10 (1.3%)

17 (2.0%)

<0.001

<25

2638 (24.5%)

1366 (36.1%)

564 (16.8%)

76 (12.6%)

153 (11.1%)

295 (37.4%)

184 (21.7%)

<0.001

25–35

7584 (70.5%)

2217 (58.7%)

2750 (81.9%)

463 (76.9%)

1123 (81.6%)

441 (56.0%)

590 (69.7%)

528 (4.9%)

197 (5.2%)

43 (1.3%)

63 (10.5%)

100 (7.3%)

52 (6.6%)

73 (8.6%)

27.54 (4.63)

26.56 (5.25)

27.52 (3.29)

29.74 (4.75)

29.17 (3.99)

26.71 (5.24)

28.52 (5.02)

<0.001

34.15 (2.13)

33.75 (1.97)

33.57 (2.04)

33.95 (1.86)

34.24 (1.95)

34.14 (2.10)

<0.001

136 (3.6%)

58 (1.7%)

18 (3.0%)

15 (1.1%)

14 (1.8%)

21 (2.5%)

<0.001

P-value

Perineal trauma
No or minor
trauma
Third degree
tear
Fourth degree
tear

<0.001

Smoking
Yes
Maternal age

>35
Mean (SD)

Head circumference (cm)
Mean (SD)

33.97 (2.04)

Gestational age (weeks)
<34 weeks
34–37 weeks

262 (2.4%)
488 (4.5%)

177 (4.7%)

151 (4.5%)

36 (6.0%)

51 (3.7%)

38 (4.8%)

35 (4.1%)

>37 weeks

9998 (93.0%)

3465 (91.7%)

3148 (93.8%)

548 (91.0%)

1310 (95.3%)

736 (93.4%)

791 (93.4%)

Mean (SD)

39.21 (2.21)

39.20 (2.48)

39.18 (2.07)

38.82 (2.40)

39.41 (1.81)

39.35 (1.92)

39.29 (2.10)

<0.001

<0.001

Body mass index
<18.5

916 (8.5%)

183 (5.0%)

312 (9.4%)

84 (14.3%)

234 (17.2%)

50 (6.4%)

53 (6.4%)

18.5–24.99

6655 (61.9%)

2025 (55.6%)

2205 (66.7%)

401 (68.3%)

1017 (74.6%)

486 (62.4%)

521 (62.7%)

25–29.99

2022 (18.8%)

842 (23.1%)

649 (19.6%)

86 (14.7%)

98 (7.2%)

174 (22.3%)

173 (20.8%)

30–34.99

633 (5.9%)

378 (10.4%)

116 (3.5%)

11 (1.9%)

10 (0.7%)

59 (7.6%)

59 (7.1%)

35–39.99

190 (1.8%)

141 (3.9%)

219 (0.6%)

2 (0.3%)

3 (0.2%)

7 (0.9%)

18 (2.2%)

87 (0.8%)

70 (1.9%)

3 (0.1%)

3 (0.5%)

1 (0.1%)

3 (0.4%)

7 (0.8%)

23.42 (4.69)

24.98 (5.58)

22.85 (3.66)

21.96 (3.71)

20.92 (2.94)

23.63 (4.22)

23.88 (2.89)

<0.001

<0.001

>40
Mean (SD)
Birth weight (kg)
<2.5

690 (6.4%)

251 (6.6%)

256 (7.6%)

39 (6.5%)

62 (4.5%)

42 (5.3%)

40 (4.7%)

2.5–4

9545 (88.8%)

3243 (85.9%)

3021 (90.0%)

551 (91.5%)

1271 (92.4%)

699 (88.9%)

760 (89.7%)

>4

508 (4.7%)

283 (7.5%)

78 (2.3%)

12 (2.0%)

43 (3.1%)

45 (5.7%)

47 (5.5%)

Mean (SD)

3.21 (5.38)

3.29 (5.87)

3.11 (4.95)

3.11 (5.23)

3.22 (4.63)

3.26 (5.06)

3.27 (5.40)

<0.001

<0.001

Augment, induction or none
Induction of
labour

3742 (34.8%)

1337 (35.4%)

1248 (37.2%)

175 (29.1%)

425 (30.9%)

264 (33.5%)

293 (34.6%)

Augmentation
of labour

3807 (35.4%)

1251 (33.1%)

1235 (36.8%)

216 (35.9%

547 (39.8%)

266 (33.8%)

292 (34.5%)

None

3201 (29.8%)

1192 (31.5%)

874 (26.0%)

221 (35.0%)

404 (29.4%)

258 (32.7%)

262 (30.9%)

Not
performed

5517 (51.3%)

2427 (64.2%)

1330 (39.6%)

287 (47.7%)

568 (41.3%)

405 (51.4%)

500 (59.0%)

Medio-lateral

Episiotomy†

5008 (46.6%)

1285 (34.0%)

1928 (57.4%)

304 (50.5%)

779 (56.6%)

371 (47.1%)

341 (40.3%)

Lateral

140 (1.3%)

35 (0.9%)

69 (2.1%)

5 (0.8%)

21 (1.5%)

6 (0.8%)

4 (0.5%)

Midline

85 (0.8%)

33 (0.9%)

30 (0.9%)

6 (1.0%)

8 (0.6%)

6 (0.8%)

2 (0.2%)

4712 (43.8%)

1768 (46.8%)

1434 (42.7%)

229 (38.0%)

570 (41.4%)

348 (44.2%)

363 (42.9%)

<0.001

Epidural
Yes

<0.001

(Continues)

521


TABLE 2  Analysis of risk factors for obstetric anal sphincter injuries in singleton vaginal or instrumental deliveries of nulliparous women

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>County of birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asia vs Aust/NZ</td>
<td>10 750</td>
<td>3.69 (2.96, 4.60)</td>
<td>3.62 (2.87, 4.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>South-East Asia vs Aust/NZ</td>
<td>386 (64.1%)</td>
<td>1.92 (1.29, 2.86)</td>
<td>1.84 (1.23, 2.76)</td>
<td></td>
</tr>
<tr>
<td>Other Asia vs Aust/NZ</td>
<td>922 (67.0%)</td>
<td>2.04 (1.52, 2.74)</td>
<td>1.98 (1.46, 2.68)</td>
<td></td>
</tr>
<tr>
<td>Middle East vs Aust/NZ</td>
<td>549 (69.7%)</td>
<td>1.22 (0.80, 1.86)</td>
<td>1.25 (0.82, 1.92)</td>
<td></td>
</tr>
<tr>
<td>Other vs Aust/NZ</td>
<td>593 (70.0%)</td>
<td>1.13 (0.74, 1.72)</td>
<td>1.08 (0.71, 1.65)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 750</td>
<td>0.31 (0.15, 0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 vs 25–35</td>
<td>10 750</td>
<td>0.46 (0.36, 0.58)</td>
<td>0.61 (0.48, 0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;35 vs 25–35</td>
<td>63 (0.63, 0.97)</td>
<td>0.63 (0.41, 0.97)</td>
<td>0.84 (0.54, 1.31)</td>
<td></td>
</tr>
<tr>
<td><strong>Head circumference (increasing in size)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34 vs &gt;37</td>
<td>10 748</td>
<td>0.06 (0.01, 0.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34–37 vs &gt;37</td>
<td>0.32 (0.17, 0.61)</td>
<td>0.32 (0.17, 0.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 vs 18.5–24.99</td>
<td>10 750</td>
<td>1.10 (0.83, 1.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29.99 vs 18.5–24.99</td>
<td>1.00 (0.81, 1.23)</td>
<td>1.00 (0.81, 1.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–34.99 vs 18.5–24.99</td>
<td>0.62 (0.41, 0.94)</td>
<td>0.62 (0.41, 0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–39.99 vs 18.5–24.99</td>
<td>0.43 (0.17, 1.04)</td>
<td>0.43 (0.17, 1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40 vs 18.5–24.99</td>
<td>0.96 (0.39, 2.38)</td>
<td>0.96 (0.39, 2.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5 vs 2.5–4</td>
<td>10 743</td>
<td>0.21 (0.11, 0.41)</td>
<td>0.21 (0.11, 0.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;4 vs 2.5–4</td>
<td>1.76 (1.30, 2.38)</td>
<td>1.76 (1.30, 2.38)</td>
<td>2.31 (1.68, 3.17)</td>
<td></td>
</tr>
<tr>
<td><strong>Augment, induction or spontaneous labour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augment vs spontaneous labour</td>
<td>10 750</td>
<td>1.18 (0.96, 1.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction vs spontaneous labour</td>
<td>1.23 (1.00, 1.51)</td>
<td>1.23 (1.00, 1.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Episiotomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medio-lateral vs not performed</td>
<td>10 750</td>
<td>1.50 (1.27, 1.77)</td>
<td>0.70 (0.56, 0.87)</td>
<td>0.011</td>
</tr>
<tr>
<td>Lateral vs not performed</td>
<td>1.92 (1.05, 3.51)</td>
<td>1.92 (1.05, 3.51)</td>
<td>1.04 (0.56, 1.94)</td>
<td></td>
</tr>
<tr>
<td>Midline vs not performed</td>
<td>1.84 (0.84, 4.02)</td>
<td>1.84 (0.84, 4.02)</td>
<td>0.81 (0.36, 1.83)</td>
<td></td>
</tr>
</tbody>
</table>

†Our hospital’s policy is to prioritise mediolateral episiotomies, and it is likely that those recorded as lateral or midline were incorrectly categorised.
analysis, South Asian ethnicity was the single strongest independent predictor of OASIS, even when compared to well-accepted risk factors for OASIS, such as head circumference, lower BMI, increased birthweight, augmentation, induction, episiotomy and instrumented delivery. Ethnicity must now be considered as a risk factor of at least equivalent importance when counselling patients and developing policy in these populations.

Limitations

Our study has a number of limitations, most importantly that country of birth was used as a surrogate marker of ethnicity. Many second and third generation women of Asian descent were included in the Australian-born study group and therefore the analyses are not strictly ethnographic. Even so, this would act to lessen the effect size given that there would have been more ethnic groups to examine. Moreover, as cross-ethnic reproduction occurs more frequently, it will become even more difficult to separate and as such only surrogate markers will have to be used.

Furthermore, it is known that communication plays a role in preventing OASIS and this study was unable to include data on whether women were English-speaking or if an interpreter was used during labour. Also, the large number of analyses may have also increased the risk of finding significant results by chance; however, no adjustment for multiple testing was performed.

Some important variables, which are predictors of OASIS, were not recorded in the database, including length of second stage. It is therefore possible that these results are confounded by an unexamined variable.

CONCLUSION

Our study further confirms the role of country of birth in the risk of OASIS, and is the second to confirm that South Asian women are at a dramatically increased risk even when adjusted for confounding. Further resources need to be allocated into the antenatal and intrapartum management of these women in attempt to reduce the likelihood of an OASIS in this cohort. Further investigation into the source of this risk is warranted, particularly with the magnitude of the effect compared to other well-accepted risk factors and the expansion of the Australian migrant population accessing the healthcare system for obstetric care.

REFERENCES


The motivation and capacity to go ‘above and beyond’: Qualitative analysis of free-text survey responses in the M@NGO randomised controlled trial of caseload midwifery

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ARTICLE INFO

Keywords:
Midwifery
Continuity of care
Patient empowerment
Psychophysiology
Qualitative research
Randomised controlled trial

ABSTRACT

Objective: to explore whether women allocated to caseload care characterise their midwife differently to those allocated to standard care.

Design: multi-site unblinded, randomised, controlled, parallel-group trial.

Setting: the study was conducted in two metropolitan teaching hospitals across two Australian cities.

Population: women of all obstetric risk were eligible to participate. Inclusion criteria were: 18 years or older, less than 24 weeks gestation with a singleton pregnancy. Women already booked with a care provider or planning to have an elective caesarean section were excluded.

Interventions: participants were randomised to caseload midwifery or standard care. The caseload model provided antenatal, intrapartum and postnatal care from a primary midwife or ‘back-up’ midwife; as well as consultation with obstetric or medical physicians as indicated by national guidelines. The standard model included care from a general practitioner and/or midwives and obstetric doctors.

Measurements and findings: participants’ responses to open-ended questions were collected through a 6-week postnatal survey and analysed thematically. A total of 1748 women were randomised between December 2008 – May 2011; 871 to caseload midwifery and 877 to standard care. The response rate to the 6-week survey including free text items was 52% (n=901). Respondents from both groups characterised midwives as Informative, Competent and Kind. Participants in the caseload group perceived midwives with additional qualities conceptualised as Empowering and ‘Endorphic’. These concepts highlight some of the active ingredients that moderated or mediated the effects of the midwifery care within the M@NGO trial.

Key conclusion: caseload midwifery attracts, motivates and enables midwives to go Above and Beyond such that women feel empowered, nurtured and safe during pregnancy, labour and birth.

Implications for practice: the concept of an Endorphic midwife makes a useful contribution to midwifery theory as it enhances our understanding of how the complex intervention of caseload midwifery influences normal birth rates and experiences. Defining personal midwife attributes which are important for caseload models has potential implications for graduate attributes in degree programs leading to registration as a midwife and selection criteria for caseload midwife positions.

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http://dx.doi.org/10.1016/j.midw.2017.03.012
Received 3 November 2016; Received in revised form 7 March 2017; Accepted 24 March 2017
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Introduction

Few interventions in maternity have been found to have as many benefits as midwifery-led models of care (caseload and team midwifery) which deliver beneficial clinical outcomes for mothers and babies including a lower risk of preterm birth, regional anaesthesia in labour, episiotomy, instrumental birth, fetal loss during the pregnancy and neonatal death (Sandall et al., 2016). Furthermore, randomised trials have demonstrated that caseload midwifery is cost-effective (Tracy et al., 2013) and increases the likelihood of maternal satisfaction across the spectrum of maternity care (McLachlan et al., 2016).

Caseload midwifery provides high-level relational continuity whereby childbearing women receive antenatal, intrapartum and postnatal care from a primary midwife and her/his back-up midwives (Beake et al., 2013). Consultation with and referral to other services and health professionals is foundational to midwifery practice (Skala and Newburn, 2014); within caseload models it occurs as clinically indicated (Australian College of Midwives, 2014). Caseload midwifery is a complex intervention with a number of interacting components that take different forms in different contexts. However, any complex intervention must conform to specific, theory driven processes, which underlie contextual differences (Hawe et al., 2004). While it is unclear how the intervention exerts its effects, the benefits appear to derive from a ‘therapeutic relationship’ (Sandall et al., 2016) or are ‘relationally mediated’ (Walsh and Devane, 2012). In this paper, the term ‘caseload midwifery’ will be used interchangeably with Midwifery Group Practice (MGP); and the terms ‘attributes’, ‘qualities’ and ‘characteristics’ will be used synonymously.

Therapeutic relationships

Rogers (1965) first described the core conditions under which a therapeutic relationship could occur: 1) a genuine and authentic professional who uses appropriate levels of self-disclosure, 2) unconditional respect for the client regardless of their thoughts or actions, and 3) empathy. The concept of therapeutic relationship is explicitly and frequently used in the nursing literature (Milton, 2008; Welch, 2005). Muetzel’s model of therapeutic nurse-patient relationships includes the concepts of partnership, intimacy and reciprocity (Richardson et al., 2015). Several authors suggest that nurses require specific personal attributes to engage therapeutically with patients including being caring, compassionate, sensitive and empathetic (Richardson et al., 2015: Shields, 2014; Attree, 2001). In midwifery, instead of a therapeutic relationship the widely adopted ‘Partnership Model’ characterises the relationship as one of “trust, shared control and responsibility and shared meaning through mutual understanding” (Guilliland and Pairman, 1995, p.7); a ‘professional friendship’ (Pairman, 2000; Walsh, 1999). The personal characteristics midwives need to work effectively in partnership relationships have not been articulated (Pairman and Mc Ara-Couper, 2015).

Personal attributes

Qualities including being intelligent, friendly, honest and trustworthy, a good listener and communicator, patient and tactful, sensitive and compassionate, positive and tolerant (Waugh et al., 2014; Nicholls and Webb, 2006; Powell Kennedy, 2000) are as important to childbearing women as the midwives’ clinical knowledge and competence (Borreli, 2014; Butler et al., 2008). A phenomenological study in the United Kingdom developed the concept of ‘emotional capability’ as an attribute, which includes empathy and the ability to connect with women (Byrom and Downe, 2008). A Delphi study conducted in the United States identified that the qualities of ‘exemplary midwives’ included philosophical commitments to: normal birth, family-centred care, women’s empowerment, and the midwifery profession (Powell Kennedy, 2000). A systematic review of women’s satisfaction with childbirth reported that feeling supported by caregivers, having a high quality caregiver-patient relationship, and feeling involved in decision-making were factors so important to women that they overrode differences in age, ethnicity and socioeconomic status (Hodnett, 2002).

The midwife’s personal characteristics and philosophical commitments affect the nature and quality of the partnership in caseload midwifery models (Allen et al., 2016). In the largest trial of caseload midwifery (n=2314), participants allocated to the intervention: “felt more in control during labour, were more proud of themselves, less anxious, and more likely to have a positive experience of pain” compared to participants in standard care (McLachlan et al., 2016, p.465). Although caseload midwifery is a ‘package of care’, researchers have hypothesised that midwives drawn to work in caseload models might have different personal attributes or philosophies of care compared to midwives who elect to work standard shifts (Newton et al., 2016). The purpose of this paper is to explore whether women allocated to caseload care characterise their midwife differently from women allocated to standard care.

Methods

Aim

The aim of this study was to address one of the secondary outcomes of the M@NGO randomised controlled trial (RCT) of caseload midwifery: women’s satisfaction with care. The research question which drove the analysis was: How do the midwife’s personal attributes affect women’s satisfaction with care? The objective was to analyse participants’ responses to open-ended questions about their maternity care experiences according to allocated model of care.

Design/Methodology

The methodological orientation that underpinned the study was Pragmatism (Creswell and Plano Clark, 2007) whereby researchers pose and attempt to answer specific research questions “in a way that offers the best chance to obtain useful answers” (Johnson and Onwuegbuzie, 2004, pp.17).

The study methods and primary outcomes are described in detail elsewhere (Tracy et al., 2013). Briefly, we conducted a multi-site unblinded, randomised, controlled, parallel-group trial: Midwives @ New Group practice Options (M@NGO: Trials Registry, number ACTRN12609000349246) at two metropolitan teaching hospitals in Australia. Pregnant women booking-in to give birth at one of the two sites during the recruitment period were given written information about the M@NGO study by the booking midwife. Women of all obstetric risk were eligible to participate in the study. Inclusion criteria were: 18 years or older, less than 24 week's gestation with a singleton pregnancy. Women were excluded if they were already booked with a care provider or planned to have an elective caesarean section. Interested potential participants were referred to a research midwife who obtained written informed consent before participants were randomly allocated to receive caseload midwifery or standard care. In both the intervention and control groups care was provided according to the same hospital guidelines and protocols. During the study period, the intervention of caseload midwifery did not deviate from how it was described in the research protocol.

Data collection

Participants’ baseline demographic characteristics and birth outcomes data were extracted from medical electronic records. Women’s experiences of antenatal, intrapartum and postnatal care were collected via email (with link to the survey URL) or postal hard-copy surveys, sent to women approximately six weeks after birth. One week later, a
reminder survey was sent to non-responders. Women who had withdrawn from the trial or experienced fetal loss/stillbirth were not sent a questionnaire.

The survey allowed the collection and analysis of both quantitative and qualitative data. Women's experiences of childbirth and maternity care were measured using 7-point scales; the results of the quantitative analysis will be published separately. In this paper, we report on the analysis of participants' free text comments which provided rich and valuable information and are considered a data source in their own right (Tavener et al., 2016). While the survey included eight statements that allowed free text responses, this paper focuses only on the following statements:

1) Please describe any things about your pregnancy that you were particularly happy with;
2) Please describe any things about your pregnancy that you were particularly unhappy with;
3) Feel free to make comments (labour and birth);
4) Please describe any things about your labour and birth that you were particularly happy with; and
5) Please describe any things about your labour and birth that you were particularly unhappy with.

Women’s experiences of postnatal care have been analysed and will be submitted for publication separately. Ethical approval for this multi-site trial was granted through two hospital Human Research Ethics Committees (HRECs)(Site 1: 0805-072 M; Site 2: 1526 M) and three university HRECs (Site 1: 12068, 2008-53; Site 2: Q2011-51).

Data analysis

The data analysis was led by the first author who is a Postdoctoral Researcher in a midwifery research unit and conducted mixed methods
research during her doctoral studies. The second author, who is a Professor of Midwifery, independently verified the themes. The researchers used qualitative software, NVIVO version 10, to code and organise the data using a five-step deductive approach (Pope et al., 2000). The steps included: 1) immersion in the raw data (reading all the free text responses), 2) identification of key attributes (thematic framework), 3) applying the thematic framework systematically to the data, modifying the framework as new themes emerged, 4) abstraction and synthesis of the themes into higher level categories, and 5) developing associations between categories with a view to explanation of findings (Pope et al., 2000). Participants did not provide feedback on the findings.

Findings

Participant flow

Fig. 1 reports the flow of participants through the trial. The 6-week survey response rate was 58%, the survey response rate from participants who answered one or more free text questions was 52%. At least 50% of respondents from each allocated group responded to each open-ended question. The majority of trial participants (76%, n=1328) derived from Site 1 with 24% (n=420) located at Site 2. The response rate to the free text questions on the 6-week survey reflected similar representation from both sites; 79% (n=707) and 22% (n=194) respectively.

Table 1 presents the characteristics of the free text respondents compared to all trial participants. Participants who were aged 20–35 years (p<0.001), those living in the most highly advantaged socio-economic areas (p=0.027), and those who had a vaginal birth (p=0.028) were more likely to respond to the free text questions compared to other trial participants.

Key findings

Both participant groups reported midwife attributes which were categorised as Informative, Competent and Kind. Through thematic analysis the first author identified additional attributes, which were commonly reported by respondents from the caseload group but rarely reported by participants allocated to standard care. These additional attribute categories were conceptualised as: Empowering and ‘Endorhic’ (defined below). Fig. 2 provides the thematic map which includes the over-arching theme with a view to explaining the association between the five categories.

Illustrative quotes to support the findings are provided along with diverse cases and minor themes. Quotes are identified by the study number and allocated model of care: Standard (S) or Caseload (C). Participants from Site 1 and Site 2 have study numbers that begin with the corresponding numeral. Italicised verbatim quotes have been corrected for spelling and typographic errors, deleted words are indicated by ... whereas word changes for grammatical fluency or to maintain anonymity are indicated within [square brackets]. Midwives names have been replaced with pseudonyms*.

Overarching theme: Above and Beyond

Caseload participants uniquely commented that their midwives put in “extra effort” and went beyond their expectations of midwifery care:

“The seemed to go out of her way to make things as easy for me as possible.” (P11232, C)
“During the birth of my baby I felt the midwives looking after me - Rita* and Susan* - went above and beyond the call of duty to help me to have a really healthy, joyful birth.” (P20208, C).

The capacity to go Above and Beyond was predicated on an intimate and trusting midwife-woman relationship. Participants in the caseload group were effusive about how much they enjoyed having their own midwife:

“This was my second labour and I didn’t believe how amazing everything went. Helped massively by having a dedicated midwife that I knew and trusted.” (P10556, C)
“I thought my caseload midwives were sensational. They always made us feel like we were top priority.” (P10608, C)
“I had a fantastic midwife Sam* who was always there to give support. She made me feel very special and important each time I saw her.” (P20186, C).

Respondents often referred to having a “bond” with their primary midwife and compared their relationship with the caseload midwives to other significant relationships in their life like friends or family:

“My family lives overseas and the support and care I have received throughout the pregnancy and after the birth made me feel safe and loved.” (P10715, C)
“My midwife Leanne* was absolutely amazing! She is a lovely person, who genuinely cared about us...I will actually miss not seeing her...” (P11326, C).

Particularly significant was having the midwife’s time and attention such that the woman felt known and understood:

“My family lives overseas and the support and care I have received throughout the pregnancy and after the birth made me feel safe and loved.” (P10715, C)
“My midwife Leanne* was absolutely amazing! She is a lovely person, who genuinely cared about us...I will actually miss not seeing her...” (P11326, C).

“The support of the midwives was amazing...I was ever grateful for how much effort and attention they gave me” (P11267, C).
"...you end up developing a relationship with them and they know everything about your pregnancy and what is important to you and your partner" (P20415, C).

Some respondents perceived that caseload midwives researching their concerns between appointments, or accommodating their birth preferences during labour, was connected to loving midwifery:

"I felt as though they really cared about their jobs and loved what they did." (P10836, C).

While respondents from the standard group often commented positively on the informative, kind competence of their midwife; none asserted the midwife went Above and Beyond. Indeed several participants in the standard group interpreted that midwives were "desensitised...just doing their job" (P10790, S).

Theme 1: Informative

Respondents from both standard and caseload groups described their midwife in terms conceptualised as Informative. Women in both groups referred positively to receiving accurate, timely and consistent information:

“(During) my check-ups with my midwife I was always given thorough information and always made to feel comfortable.” (P10844, S)

“I couldn’t have got through this pregnancy and birth without [the midwifes’] professional knowledge...” (P20164, C)

Respondents from both groups appreciated having their concerns validated and their questions comprehensively answered:

“My midwife Jane* was...incredibly knowledgeable, supportive and always answered my questions confidently.” (P10992, C)

“Midwives were all very friendly and helpful. My partner was welcomed [and] included...no question seemed too trivial or silly" (P10565, S).
However, because women in the standard group frequently saw a different clinician at each antenatal visit, the information could be perceived as repetitive rather than individualised:

“A lot of time went in to providing the same information at every visit. If I had any questions I often got the feeling that they were keen on getting me out in order to see the next person…” (P10389, S).

Participants commented on the constraints of midwives in the standard model that affected the time they had available to provide information. Conversely, in caseload care the information may have been more readily accepted because of the relationship between the woman and her midwife:

“I knew about [the midwives] as people and we shared experiences, this made me more comfortable and trusting of them and their information” (P20414, C).

Theme 2: Empowering

Respondents from the caseload group described their midwife in terms conceptualised as Empowering more commonly than those in the standard group. Empowering midwifery clients is predicated on the midwife’s professional knowledge and the development of a trusting relationship; it requires a dynamic use of complex communication skills that enable women to make informed decisions (Hermansson and Martensson, 2011). There were many examples of empowering interactions for women in the caseload group:

“The time the midwives took with their care, and ensuring I understood everything they said, empowered me to make my own decisions.” (P10139, C)

“…all of my personal decisions about what kind of birth I wanted were discussed and the pros and cons were explained.” (P10661, C)

“My decisions were respected and supported and my midwife explained every step of the process including each conceivable outcome…” (P11216, C).

Feeling empowered was also connected to feeling involved and in control during labour and birth:

“My midwife really made my husband and I feel like [birth] was just our moment and I thank her for that.” (P11146, C)

“Very thankful to the personal one on one care received [which] made us feel like it was our experience that we were in control of…” (P10849, C)

“The midwife supported me in every decision I made regarding the way I wanted to give birth. She made me feel like I was in total control…” (P11026, C).

While many respondents from the standard group perceived their midwife as Informative, there were scant examples of empowerment:

“She truly listened to me, understood my situation, and empowered me and assisted me obtain my ideal birth.” (P20384, S).

For some caseload respondents, feeling empowered was associated with their desire to avoid unnecessary medical intervention and experience a normal birth:

“My strong beliefs and wishes against a high degree of intervention in birth were respected.” (P10365, C)

“[I particularly liked] feeling like decisions were up to me and that I could have a pregnancy and birth that I wanted (active and as natural as possible).” (P11080, C).

Women from the caseload group uniquely commented that their midwife “believed in me” which was associated with believing in the woman’s ability to give birth normally:

“The strength and encouragement from Natasha* a fantastic midwife who believed in me.” (P10654, C)

“The midwives were excellent and they made me believe I could deliver naturally even though the doctors were doubtful.” (P10916, C).

For some women, the midwife’s confidence in their ability to birth normally affected their self-belief:

“I was in strong pain. But as soon as I saw my midwife’s face, I knew I could cope with this pain and could give birth…” (P111239, C).

Other respondents interpreted that caseload midwives pushed a normal birth “agenda” that was not consistent with their own approach:

“…midwifery group practice is a great system of care only if …the midwife does not have an agenda of her own she wishes to enforce on her patient.” (P10038, C)

 “[The midwives were] clearly pushing us towards certain points of view on things like breastfeeding, natural labour etc. While they were careful to say afterwards it was our choice to make…I was expecting more obvious support for individual choices.” (P20075, C).

In an ‘all-risk’ setting, caseload midwives were ideally placed to facilitate the woman to feel empowered during complex decision-making:

“When complications arose, the midwives assisted me in seeing doctors and in asking the right questions and helping in finding my way around the administrative processes at the hospital.” (P11097, C).

Women appreciated it when their caseload midwives attended medical appointments such that the consultation included all parties and focused on the woman’s choices:

“Loved the way the midwife and doctors interacted and included us in their conversations” (P10508, C).

However, there were rare instances when participants reported they felt excluded from the decision-making process:

“The decision [to plan a caesarean] was discussed between the doctor and midwives. I felt I didn’t get a say in the decision made.” (P20230, C).

Women in both groups wanted to be central to the decisions made regarding their maternity care.

Theme 3: Competent

Respondents from both groups described their midwife in terms conceptualised as Competent with similar frequency. Participants in both groups valued midwives who were clinically-skilled and experienced:

“I loved my midwife; she was professional, competent and a joy to have with me during one of the most important moments of my life!” (P10145, S)

“The midwives and the care they provide is so reassuring and competent. What a joy it was to have my baby…” (P10418, C).

Respondents commented positively on the midwives’ clinical skills in promoting normal birth:

“The midwives helped me change positions for active birth. Our birth plan was respected and used. The midwives were very encouraging and kind. A mirror was positioned so I could see the birth. My husband received the baby then placed him onto me. It was beautiful.” (P10157, C)

“I could not have achieved a natural birth without [the midwives] great encouragement, support, advice, positive energy, humanity, understanding, kindness, psychology. I did not feel it was a shame not to know the midwife before the labour.” (P10863, S).
These skills extended into keeping birth as normal as possible for women experiencing medical intervention:

“I was able to have a very empowering, wonderful and otherwise natural birth despite having to be induced before my due date with the Syntocinon drip due to the support and encouragement I received from the midwives…” (P20208, C)

“My labour was induced... I [delivered my daughter naturally, in a squatting position, without any form of pain relief throughout the labour and birth... The midwife] was fantastic, and met each of my needs perfectly.” (P20384, S)

Occasionally respondents from both groups described their midwife as lacking passion or skill in normal birth promotion:

“The [back-up] midwife kept disappearing during my labour to "write notes" so I did not feel I had any support or guidance from her...she pushed for me to use gas and later pethidine rather than offering other active birth strategies.” (P10612, C)

“My first midwife offered little help or strategies to ease the back pain from the posterior position of my baby. She seemed a little disinterested in what was happening.” (P20174, S).

The woman’s perception of the midwife’s competence was often linked with her perceived kindness and associated personal attributes: "competent and a joy".

Theme 4: Kind

Respondents from the standard group described their midwife in terms categorised as Kind more frequently than those in the caseload group. In the caseload group, midwives were often characterised in more effusive, friendship, or ‘endorphic’ terms (see Theme 5); all of which are Above and Beyond the attribute of Kind.

Respondents from both groups enjoyed feeling that the midwives cared about them, their baby and their pregnancy and making sure they received appropriate support and assistance:

“I believe the positive support and encouragement I received from [the midwives] enhanced the success of my pregnancy and birth.” (P10388, C)

“I always felt that my concerns were taken seriously and the midwives were very genuine. Sarah* and Leanne* were especially caring and I always felt supported.” (P10977, C)

“The midwife who welcomed us and brought my baby into the world was amazing...was kind and strong.” (P10656, S)

“Most of the other midwives I saw throughout the pregnancy and also after the birth were caring, patient, compassionate and very helpful.” (P11295, S).

In rare instances women in both groups reported uncaring behaviours from the midwife:

“All midwife and hospital appointments were very impersonal (as it was a different person each time) and NO-ONE spoke to or really even acknowledged my husband...” (P20393, S)

“Pregnancy is a very personal, sensitive experience and I felt like just another number. There wasn’t a huge amount of sensitivity with the midwife care, my check-ups where just another medical procedure.” (P10365, C).

No matter how technically competent, a lack of kindness affected women’s experience of midwifery care.

Theme 5: Endorphic

Respondents from the caseload group described their midwife in terms conceptualised as Endorphic more often than those in the standard group. Women in caseload care frequently commented that the midwife “makes me feel: relaxed, reassured, loved, nurtured, safe and/or comfortable”. We could find no English word to describe this ability or attribute. Endorphins are hormones that are released in the brain during normal labour that help alleviate pain and stress as well as facilitate feelings of relaxation and energy (Buckley, 2015). We conceptualised the term ‘Endorphic’ to describe the midwife’s ability to elicit these feelings (and associated hormones like endorphins and oxytocin) in pregnant and birthing women. The Latin suffix ‘-ic’ forms an adjective from other parts of speech (Dictionary, 2016); i.e. endorphin becomes ‘endorphic’.

During pregnancy women from the caseload group described how their midwives had a relaxing effect on them by being reassuring and helping alleviate their concerns:

“Our midwife Andrea* was exceptional in every way. I was always reassured that everything was good, and never felt worried or concerned for the wellbeing of myself or my child” (P10830, C)

“My midwife was very helpful, caring and put my mind at ease time and time again!” (P20119, C).

A significant component of helping women feel relaxed was the quality of preparation for labour and birth the midwives provided:

“My midwife...made me feel relaxed about the process of pregnancy and giving birth.” (P10468, C)

“All the midwives were wonderful...[they] relieved any anxieties I had, and I went into the labour feeling quite relaxed and unafraid...” (P10877, C)

“I was very anxious prior to the birth...the midwives in the midwifery group made me feel much more relaxed and prepared for the birth.” (P20204, C).

Women in the caseload group frequently associated the continuous supportive presence of their midwife to having a positive birth experience:

“I had an amazing birth, it was everything I could have hoped for and she was there every minute of it, not like in private where I had my first baby and didn’t feel like I received much support at all.” (P10294, C)

“My midwife was excellent. She let the natural course of labour take place without much intervention and she never left my side and was a positive strong presence...because of her it was the best birth I have had” (P10418, C)

“The midwife that delivered my baby was extremely considerate of my needs and provided the support and reassurance that I needed. I think my birthing experience would have been considerably harder had she not been there” (P11216, C).

This positivity was particularly pronounced for multiparous women who were able to compare their experiences with previous birth experiences in different models of care.

Confidence in the midwife enabled women to “feel totally safe in her hands” during labour and birth:

“I felt like my midwife had everything under control and that I could relax and do what I needed to do” (P10401, C).

“I thought the midwives were wonderful and felt confident they could deliver my baby safely...I felt safe in their care.” (P11313, C)

“Midwife mainly observed through the labour, allowed my husband and I to feel like it was our journey not a medical condition. Felt very safe, AND I knew my baby was in good hands, she was safe also.” (P20380, C).

However there was one example from the caseload group of a woman who felt she did not get the supportive presence she needed:

“I felt I was left alone and it was my partner and I alone, with the midwife just doing the checks and giving of options. There was no guidance and support or encouragement...” (P10720, C).

Feeling safe was reported on occasion by standard group participants “during labour, I had the best support from the [midwives]. They were fantastic and made me feel safe.” (P10501, S).

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Discussion

Main findings

Regardless of model of care, participants generally perceived their midwives as Informative, Competent and Kind which is consistent with the integrative review of what makes a ‘good’ midwife (Nicholls and Webb, 2006) and Australian midwifery competency standards (Nursing and Midwifery Board of Australia NMBA, 2006). We interpret the caseload model provided midwives with the motivation and capacity to go Above and Beyond; to be Empowering and Endorphic. These concepts highlight some of the active ingredients that moderated or mediated the effects of the midwifery care within the M@NGO trial.

Strengths

The M@NGO trial is the largest trial of caseload midwifery to include women of any risk status. To our knowledge, we have now conducted the largest qualitative study of women’s experiences of caseload midwifery; which includes women of all risk. The open-ended nature of the questions ensured participants were able to focus on the elements of maternity care that were significant to them. The credibility of the findings is supported by the randomisation of participants; which means differences in their experiences of midwifery are credibly associated with model of care rather than baseline characteristics. The large sample size drawn from two hospitals in different cities strengthens transferability of the findings to the wider population of midwives and childbearing women in similar maternity care contexts. Confirmitrability is strengthened through the analytic approach that ensured that themes were derived from that data; combined with a description of diverse cases and discussion of minor themes. A second researcher independently verified the themes.

Limitations

The survey was based on participant’s recall, six weeks after birth, of antenatal and intrapartum midwifery care. While there is a potential for recall bias to affect their perceptions of care; one study has found that women still remember their childbirth experience clearly after five years (Takehara et al., 2014). Whether this applies to women’s experiences of antenatal care is unclear and therefore recall bias is a potential limitation.

The response rates could limit the generalisability of the findings with 60% of caseload participants and 44% of standard participants providing free text comments on the survey. There is limited academic agreement on significant or meaningful response rates for surveys and a general consensus that at least half of a sample should have completed the survey instrument.

There remains the possibility of non-response bias for both caseload care and standard care survey data (Draugalis et al., 2008). Participants were less likely to respond to the free text survey if they were younger than 20 years or older than 35 years, were socio-economically disadvantaged or had experienced a caesarean section. Women with these characteristics may have perceived their midwifery care, and the attributes of their midwife, differently than those women who did respond. Therefore the generalisability of the findings may be limited.

The analysis of free text survey data is limited because unlike interviews, there is no capacity for researchers to clarify participants’ meaning or invite feedback on the findings.

Interpretation

The caseload model motivates and enables midwives to go Above and Beyond in their provision of maternity care.
Sandall, 2009) as well as feeling more able to manage fear of pain in labour (Leap et al., 2010). A critical review reported that feeling safe with the continuous support of the midwife was fundamental to managing feelings of fear during labour (Van der Gucht and Lewis, 2015). When the midwife is perceived as a friend or family member, like they were by caseload respondents in this study, it helps women feel relaxed and comfortable, and safe enough to ‘let go’ (Anderson, 2000). Our findings suggested caseload midwives reduced women’s anxiety and fear (adrenaline) and supported them to feel safe and loved (oxytocin, endorphin). There is a significant correlation between women’s anxiety state and degree of pain during labour (Floris and Irion, 2015). Therefore, lower levels of anxiety-pain may be associated with the clinical outcome that reported a higher proportion of women in the caseload group used no pharmacological analgesia during labour (OR 1.74, 95% CI 1.37–2.20; < .00001) (Tracy et al., 2013). The Endorphic midwife is important not only in terms of maternal satisfaction but significant in terms of facilitating physiological birth (Buckley, 2015) by optimising psychophysiology (Fahy and Parratt, 2006).

Conclusion
Caseload midwifery attracts, motivates and enables midwives to go Above and Beyond such that women feel empowered, nurtured and safe during pregnancy, labour and birth.

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Irion, 2015. 'Endorphic midwife is important not only in terms of facilitating physiological birth (Buckley, 2015) by optimising psychophysiology (Fahy and Parratt, 2006).
The presence of vaginal *Lactobacillus* species does not contribute to a measureable difference in amniotic fluid lactate levels collected from the vaginal tract of laboring women

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Key words
Amniotic fluid lactate, dystocia, labor, lactate, Lactobacillus

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Conflicts of interest
All authors have stated explicitly that there are no competing interests in connection with this article.

Please cite this article as: Hall B, Wong D, Healy C, Tracy MB, Tracy SK, Rawlinson WD. The presence of vaginal *Lactobacillus* species does not contribute to a measureable difference in amniotic fluid lactate levels collected from the vaginal tract of laboring women. Acta Obstet Gynecol Scand 2017; 96:487–495.

Received: 14 May 2016
Accepted: 20 December 2016
DOI: 10.1111/aogs.13089

Abstract
Introduction. Amniotic fluid lactate research is based on the hypothesis that a relationship exists between fatigued uterine muscles and raised concentrations of the metabolite lactate, which is excreted into the amniotic fluid during labor. To assess potentially confounding effects of lactate-producing organisms on amniotic fluid lactate measurements, we aimed to determine if the presence of vaginal *Lactobacillus* species was associated with elevated levels of amniotic fluid lactate, measured from the vaginal tract of women in labor. Material and methods. Results from this study contribute to a large prospective longitudinal study of amniotic fluid lactate at a teaching hospital in Sydney, Australia. Amniotic fluid lactate measurement was assessed at the time of routine vaginal examination, after membranes had ruptured, using a hand-held lactate meter StatStripXPRESS (Nova Biomedical). Vaginal swab samples were collected at the time of the first amniotic fluid lactate measurement and stored for later detection and quantification of *Lactobacillus* species using a TaqMan real-time PCR assay. Swab sample and amniotic fluid lactate results were paired and analyzed. Results. The PCR assay detected *Lactobacillus* species in 48 of 388 (12%) vaginal swab specimens (8% positive, 4% low positive) collected from women in labor after membranes had ruptured. There was no significant difference in median and mean (respectively) amniotic fluid lactate levels with (8.35 mmol/L; 8.95 mmol/L) or without (8.5 mmol/L; 9.08 mmol/L) *Lactobacillus* species detected. Conclusion. There was no association between the presence or level of vaginal *Lactobacillus* species and the measurement of amniotic fluid lactate collected from the vaginal tract of women during labor.

Abbreviations: C₇, threshold cycle; Spp., species; VMM, viral maintenance media.

Introduction
Recent clinical studies of amniotic fluid lactate suggest that high amniotic fluid levels are associated with both labor dystocia (1–3) and adverse fetal outcomes (4–6). In studies of amniotic fluid lactate, the authors hypothesize that irregular and long-standing myometrial contractions lead to myometrial tissue hypoxia with a decreased placental blood flow over time, resulting in an increase in the risk of hypoxia for the fetus (5). Given that the myometrium is shown to be a producer of lactate during the...
first stage of labor (7) and that human myometrial cells deliver lactate to the extracellular medium under both anaerobic and aerobic conditions, it is proposed that lactate produced by the myometrium has a potential role in the underlying pathology of dysfunctional labor (8). Although the fetus is recognized as a producer of lactate, and fetal scalp lactate is a useful indicator of intrapartum fetal distress, there is minimal evidence to show what proportion of lactate in amniotic fluid is of fetal or myometrial origin, or that lactate in fetal scalp blood is associated with high amniotic fluid lactate levels (5).

At present, conclusions about the clinical utility of amniotic fluid lactate as a biomarker in labor are partly limited by the methods of sampling and analysis, and lack of knowledge of potential confounders. For example, researchers in the early studies of amniotic fluid lactate have collected samples using intraterine catheters (3). More recent studies have applied less invasive methods, collecting samples of freely flowing amniotic fluid from the glove of the examining clinician during vaginal examination (1). There has been limited information published on the potential confounders of lactate measurement in amniotic fluid lactate (2,5,9,10). We hypothesized that Lactobacillus spp., the facultative, anaerobic and microaerophilic bacterium that convert lactose to lactic acid, have the potential to confound amniotic fluid lactate measurements, when collected from the vaginal tract during labor.

The aim of this study was to determine if among women in labor, naturally occurring vaginal Lactobacillus spp. produced sufficient lactate to confound amniotic fluid lactate results collected from the vaginal tract during labor. The results from this experiment contribute to a large prospective longitudinal study measuring the concentration of amniotic fluid lactate in the vaginal tract of women in labor (The Amniotic Fluid Lactate Project).

**Material and methods**

The study protocol for the Amniotic Fluid Lactate Project was approved by the New South Wales Northern Network Human Research Ethics Committee 11/140 through the National Ethics Application Submission AU/19E1A08.

Women eligible to be recruited to the Amniotic Fluid Lactate Research Project were nulliparous, with a singleton term pregnancy (>37 weeks) in a cephalic presentation and planning a vaginal birth at the study site, the Royal Hospital for Women, Sydney, Australia (Table 1). A study database contained consenting participant’s demographic, clinical and obstetric information, as well as details of amniotic fluid lactate results and vaginal swab collection. Women were included in the current study (The Lactobacillus Study) if they had a vaginal swab result recorded at the time of swab collection, after rupture of membranes.

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Amniotic fluid lactate and swab sample collection

Between June 2013 and October 2015, on admission to the labor ward, eligible women were invited to participate in the study by the attending midwife, doctor or research midwife. Vaginal amniotic fluid lactate samples were collected: on admission if membranes had already ruptured, or at the time of spontaneous rupture, or when artificial rupture of membranes was performed for the purpose of induction or augmentation of labor. Amniotic fluid lactate was measured at the bedside using a handheld lactate meter (StatStripXPress; Nova Biomedical, Runcorn, UK), validated to measure lactate in amniotic fluid (10). Further vaginal amniotic fluid lactate samples were collected at the time of routine vaginal examinations during the course of labor.

Vaginal swabs (Transystem Sterile Transport Swab; Copan, Murrieta, CA, USA) were collected from the mid vaginal cavity after membranes had ruptured either by

**Key Message**

A hypothesis that vaginal Lactobacillus may confound measurement of amniotic fluid lactate was not supported by experimental results. PCR detected Lactobacillus in an unexpected 12% of vaginal swabs collected from women during labor. This novel study and findings require further investigation.
the examining clinician at the time of vaginal examination, or self-collected by the woman in labor, according to the woman’s preference. Swabs were placed in a refrigerator for up to 24 h before being stored at −80°C.

Swabs (n = 388) with a valid corresponding vaginal amniotic fluid lactate result, recorded at the first vaginal examination in labor after membrane rupture, were selected and removed from the −80°C freezer for analysis. Total nucleic acid was extracted in batch sizes ranging from 30 to 55 swabs per Kingfisher run during July 2014 to November 2015. All samples were tested to show they were positive for the human housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (11).

Nucleic acid extraction

Total nucleic acid was extracted by the MagNA Pure LC total nucleic isolation kit (03 038 505 001; Roche Diagnostics Australia, North Ryde, NSW, Australia) and King-Fisher Flex Magnetic Particle Processor (Thermo Scientific, Waltham, MA, USA) as per the manufacturers’ protocols. Swabs were thawed from −80°C to room temperature and the cotton tips were transferred into 2-mL sterile tubes containing 500 μL of viral maintenance media (VMM). The VMM consisted of medium 199 (11150-059; Gibco, ThermoFisher Scientific Pty Ltd, Scorby, Vic, Australia) supplemented with 10% fetal bovine serum, 1.4% NaHCO₃ and gentamicin (40 mg/L/mL). Each tube containing the cotton tip and VMM was vortexed for 30 sec and 200 μL was immediately used for automated magnetic separation to a final volume of 100 μL in elution buffer; the remaining VMM mixture was stored at −80°C for future use. One negative process control using 200 μL of VMM only was included during each extraction run. Freeze–thawing of total nucleic acid was minimized by preparing each sample in three separate aliquots and storing them at −80°C until use.

Real-time TaqMan assay

The sequences for the PCR primers and probe for the TaqMan assay were selected from a published study targeting a 92-bp region of the 16S-23S intergenic spacer rRNA gene of 22 different Lactobacillus spp. (12). The probe was synthesized by Applied BioSystems (Life Technologies, Pleasanton, CA, USA) with a VIC reporter molecule attached to the 5’ end and an MGB-nonfluorescent quencher linked at the 3’ end. The primers were synthesized by Sigma-Aldrich (Castle Hill, NSW, Australia). The PCR amplification was performed in a 25-μL volume containing 2× SensiMix™ II Probe reagent, which includes MgCl₂ (3 mmol/L final concentration) (BIO-91005, Bioline, Eveleigh, Australia), optimized concentrations of primers (200 nmol/L final concentration) and probe (75 nmol/L final concentration) and 5 μL of template. After preparation of the reaction plate, the whole plate was centrifuged at 1400 g for 1 min at room temperature in a swingout rotor (Microcentrifuge 5416, Eppendorf®) to remove small air bubbles. The amplification and detection were performed in a Stratagene Mx3000P qPCR System (Agilent Technologies, Santa Clara, CA, USA) with the following conditions: (i) hot start 10 min at 95°C, (ii) amplification with 45 cycles of 95°C for 10 sec, and 60°C for 60 sec with acquisition of fluorescence at the end of each cycle. The threshold cycle (Cₜ) value for each sample was calculated by the MxPro qPCR software (Agilent Technologies), with the machine programmed to automatically determine the threshold at each run using its “Amplification-based threshold determination algorithm”. Each reaction plate contained several negative controls (no template and negative process control), a calibration curve consisting of plasmid DNA containing the target PCR sequence (see below) in experimental triplicates, and clinical samples in singlet reactions. The standard curve was created automatically with the MxPro qPCR software (Agilent Technologies) plotting Cₜ values against each standard of known concentration. This Cₜ value was also used for calculation of the intra- and inter-assay co-efficients of variation for this technique.

Preparation of standard

The gene copy number was standardized using a plasmid construct containing the partial sequence for Lactobacillus rhamnosus 16S-23S ribosomal RNA (rRNA) intergenic spacer region and its flanking 23S rRNA. This particular sequence was used because it bears 100% sequence match to the published primers and probe used for the real-time PCR assay. Briefly, “multiplex PCR-G” primers (13) were used to amplify a 400-bp PCR product directly from a bacterial culture of L. rhamnosus. The PCR amplicon was gel-purified (A9282; Promega, Madison, WI, USA) and cloned into pGEM®-T Easy Vector (A1360; Promega) according to the manufacturer’s instructions. The plasmid was transformed in JM109 competent cells (P9751; Promega) and streaked to obtain a single bacterial colony that was picked and grown in 5 mL of Luria–Bertani broth containing 100 μg/mL ampicillin. Plasmid was extracted using an Aurum plasmid miniprep kit (732-6400, Promega) and the inserted 400-bp sequence identity was verified against an L. rhamnosus intergenic spacer region sequence obtained from GenBank (Accession number AF182730) by standard Sanger sequencing (Ramaciotti Centre, UNSW). Plasmid was quantified by Nanodrop spectrometer (ND1000, Thermo Scientific) and diluted with nuclease-free water to obtain 0.2 × 10⁸ copies/μL. This stock standard was
frozen at −80°C in multiple aliquots. For preparation of the standard curve, stock standard was thawed to room temperature and diluted at each PCR run using the same pipettes and dilution method. Serial ten-fold and two-fold dilutions were performed on this standard to obtain 0.2 × 10^7 to 0.5 × 10^1 copies/µL. Five microliters of each diluted standard was used to characterize the linearity, precision, specificity and sensitivity of the TaqMan assay over the reporter range of 1 × 10^7 to 2.5 × 10^1 copies/reaction.

**StatStripXPress detection of Lactobacillus from cultures**

The capacity of the handheld StatStripXPress meter and strips to detect lactate produced by *Lactobacillus* spp. was unknown, therefore the meter and strips were studied by measuring the lactate produced from three different strains of *Lactobacillus* spp. (see Supplementary material, Table S3). The three species, known to exist in the human vagina and intestine, were obtained from the Department of Microbiology, South Eastern Area Laboratory Services at the Prince of Wales Hospital. Briefly, 500 µL of a 2.0 MacFarland density solution of a single species of *Lactobacillus* was inoculated to 5 mL of broth and incubated aerobically at 37°C on a shaking platform with the orbital speed set at 240 rpm. Lactate concentration (StatStripXPress), pH (Sigma pH test strips 0–14 pH, resolution 1.0 pH unit) and optical density (Biowave S2100 diode array spectrophotometer WPA) of the bacterial cultures were determined at 8, 17 and 24 h post-inoculation.

**Statistical analyses**

Statistical analysis of hand-held lactate (StatStripXPress) results and *Lactobacillus* spp. detected by PCR was conducted using Stata (version 13 MP; Statacorp, College Station, TX, USA). The amniotic fluid lactate value was treated as a continuous variable in mmol/L (range 0–24 mmol/L). A logarithmic (base 10) transformation was applied to the PCR count. Paired samples were coded for detection or nondetection of *Lactobacillus* spp. as a dichotomous variable. Specimens with values above the detection limit of 25 copies per reaction but below 100 copies per reaction could not be accurately quantified but were coded as positive for dichotomous outcome. Parametric (paired *t*-test), nonparametric (Kruskal–Wallis, *P* = 0.60), (Table 2, Figure 2). Bootstrapped interquartile regression showed regression co-efficient 0.16, 95% CI −0.8 to 1.1 (*p* = 0.60) (Figure 3). *Lactobacillus* measurement on PCR was not normally distributed with significant right skewing. Mode of labor onset and intrapartum use of antibiotics were not associated with differences in *Lactobacillus* spp. detection rates (Tables 3 and 4).

**Discussion**

The study found no correlation between amniotic fluid lactate collected from the vaginal tract of women in labor and detection of *Lactobacillus* spp. However, a detection rate of *Lactobacillus* in 48 of 388 (12%) samples was lower than expected given that the literature describes a
Figure 1. Lactobacillus real-time PCR assay characteristics: positive control plasmid was prepared in 10-fold serial dilutions, followed by twofold dilutions to obtain 25 copies. (a) The linearity of the assay spans six logs. (b) The standard curve shows the efficiency of over 90%, with the slope of $-3.534$ and $R^2$ value of 0.998. [Color figure can be viewed at wileyonlinelibrary.com]
The *Lactobacillus* study

predominance of *Lactobacillus* spp. as a hallmark of health in the female reproductive tract (14–16). Consensus on the predominance of *Lactobacillus* in the vagina has been founded on culture and culture-independent methods of analysis, although there are contradictory data regarding prevalence rates, and specific factors that impact rates of detection such as contraception, catametrical products and physiological elements, due in part to differences in the variety of study methods applied (15). Nonetheless, studies of pregnant and nonpregnant women have found a prevalence rate of *Lactobacillus* spp. in the vagina ranging from 71 to 100% although early studies applied culture methods before the application of DNA techniques (14,17–20). Recent vaginal ecological studies using culture-independent methods do not clearly report the prevalence rate of *Lactobacillus* spp. among women but focus on analyzing microbial colonizing distribution patterns, and report on microbial community states and associations between low levels of *Lactobacillus* spp., bacterial vaginosis and preterm labor (20–24). One study, the first longitudinal study of the human vaginal microbiota in pregnancy, compared vaginal community states between 22 pregnant and 32 nonpregnant women using culture-independent methods and found that 61% of pregnant women (who all gave birth to term infants) had a vaginal bacterial microbiome dominated by *Lactobacillus* spp. (20). Another study, using standardized sampling protocols, provided robust evidence that the vaginal bacterial microbiome is uniquely different in pregnancy, with variance of molecular phylogeny (species richness and diversity) across both subsite (mid vagina, posterior fornix and vaginal introitus) and according to gestational age (21). However, it was not the aim of the *Lactobacillus* study to identify or determine distribution patterns of

Table 2. Mean, median and interquartile range of amniotic fluid lactate results, grouped by the detection and nondetection of *Lactobacillus* species by PCR from vaginal swabs, collected after membranes ruptured during labor.

<table>
<thead>
<tr>
<th>Lactobacillus</th>
<th>n</th>
<th>%</th>
<th>Mean mmoL (SD)</th>
<th>Median mmoL</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>48</td>
<td>12.3</td>
<td>9.0 (4.2)</td>
<td>8.4</td>
<td>6.4–11.1</td>
</tr>
<tr>
<td>Not detected</td>
<td>340</td>
<td>8.7</td>
<td>9.1 (3.3)</td>
<td>8.5</td>
<td>7.1–11.0</td>
</tr>
</tbody>
</table>

*p* = 0.8

Table 3. Detection of *Lactobacillus* species by PCR in swab samples collected from the vaginal tract of women in labor after rupture of membranes, grouped by mode of labor onset.

<table>
<thead>
<tr>
<th>Lactobacillus</th>
<th>Spontaneous onset of labor</th>
<th>Induction of labor</th>
<th>Total (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>15</td>
<td>10.8</td>
<td>33</td>
</tr>
<tr>
<td>Not detected</td>
<td>124</td>
<td>89.2</td>
<td>216</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>249</td>
<td>388 (0.48)</td>
</tr>
</tbody>
</table>

Table 4. Detection of *Lactobacillus* species by PCR in swab samples collected from the vaginal tract of women in labor after rupture of membranes, grouped by use of intrapartum antibiotics during labor.

<table>
<thead>
<tr>
<th>Lactobacillus</th>
<th>Antibiotics</th>
<th>No antibiotics</th>
<th>Total (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>35</td>
<td>12.2</td>
<td>13</td>
</tr>
<tr>
<td>Not detected</td>
<td>251</td>
<td>87.8</td>
<td>89</td>
</tr>
<tr>
<td>Total</td>
<td>286</td>
<td>102</td>
<td>388 (0.89)</td>
</tr>
</tbody>
</table>

Figure 2. Box plot showing the amniotic fluid lactate grouped by the detection or nondetection of vaginal tract *Lactobacillus* species.

Figure 3. The association between amniotic lactate level and log (PCR) value with paired samples of vaginal tract *Lactobacillus* species with counts >0; *p* = 0.6.
different Lactobacillus species, or to measure the effect of different species’ capacity for lactate production. We performed a simple pragmatic study, to determine whether lactate-producing organisms in the vagina might confound lactate measurement. We chose Lactobacillus as our target organism, as before this experiment we considered that Lactobacillus would be the most likely lactate-producing organism present in the vagina. The primers and probe for this study were chosen on the basis of being the most comprehensive (covering 22 different species of Lactobacillus) probe-based, quantitative, real-time PCR method published at the time we initiated this experiment.

The Lactobacillus detection rate in this study contrasts significantly with previous research findings, although the method used to detect Lactobacillus spp. through quantitative PCR was found to be sensitive and specific in detecting DNA with a limit of detection of ≥25 copies. A major strength of our study is the relatively large sample size. However, technical and clinical factors may have contributed to the low detection rate of Lactobacillus spp. in swabs. The first technical limitation of the assay may have been that specimens tested were not the same quality as a highly purified target plasmid construct. Second, as we were interested in quantifying the amount of Lactobacillus spp. present in the vagina at the time of the lactate collection, specimens were not subject to culture enrichment or selectivity procedures before DNA extraction. Third, it may be that DNA-based PCR was not the best strategy for a study of this kind, which is focused on the production of a metabolite. A different approach may have been to use culture (non-enrichment), cell-membrane impermeable dye treatment before DNA extraction (such as propidium monoazide) and/or real-time RT-PCR. However, although kinetic measures of Lactobacillus assist in interpreting dynamic change in lactate levels, we believe that quantitative assessment of Lactobacillus at a single time point of lactate sampling represents an appropriate surrogate marker for contaminating Lactobacillus.

Several clinical factors may have contributed to low rates of Lactobacillus spp. detection in this study. Inconsistencies in swab sampling techniques between women and clinicians may have contributed to the low detection rate of Lactobacillus spp. However, we think it unlikely that self-collection vs. clinician collection is a major contributing factor to our low detection rate, as self-sampling is known to show no significant difference in specimen quality and to be as efficient as physician-based sampling in culture-based and molecular testing studies (4,25–28). Women who were induced with prostaglandins were also included in the study cohort. As hormonal regulation of vaginal glycogen content and ability of bacteria to adhere to vaginal epithelium are known factors controlling microbial types and population levels within the vagina (15,16), we examined the clinical data to investigate whether induction of labor with prostaglandins affected our rate of detection. We also assessed whether antibiotic use in labor was associated with an altered rate of detection as there is evidence to suggest that antibiotic therapy alters vaginal microflora levels (29,30). There is also evidence for the antibacterial properties of amniotic fluid (29,30), and that smoking reduces the vaginal Lactobacillus count due to cell lysis from lytic phages (31). However, analysis of the clinical data revealed that rates of detection were not associated with either mode of labor onset, antibiotic use or smoking, although in this study only five women reported that they smoked during pregnancy.

The unique clinical factor common to samples in this study was that swabs were collected from women in labor, after membranes ruptured. Although there was no difference between groups, the estimated average time between rupture of membranes and the time of first lactate sample and swab collection for women having artificial rupture of membranes was 73 min (SD ±38 min, range 0–15 h) and for women having spontaneous rupture, 16 h (SD ±6 h 55 min, range 0–56 h). We speculated on the lavage-like effect of the amniotic fluid, as there is evidence to show that buffering abolishes vaginal acidity attributable to Lactobacillus spp. (32). We also noted the findings from a study of persistent unbalanced microbial ecology (dysbiosis), which detected a loss of Lactobacillus and low rates of microbial DNA in samples collected from women with preterm premature rupture of membranes when compared with control women with uncomplicated pregnancies at 29 weeks of gestation. The authors suggested that the depletion of Lactobacillus may be due to the constant leakage of amniotic fluid (33). However, this comparison may be unfair given that low levels of Lactobacillus are associated with dysbiosis.

Lastly, sampling of lactate from free-flowing amniotic fluid in the vagina, as opposed to intra-uterine sampling using an intrauterine catheter, may have contributed to inconsistent lactate results due to the presence of confounding substances that may be found in the reproductive tract of women in labor. The potential for confounding agents has previously been noted in some publications (2,3,9). Aware of the potential limitations of hand-held lactate meters to measure lactate in amniotic fluid, the StatXPress meter has been formally validated to measure lactate in amniotic fluid (10). The StatXPress validation study found minimal variation between laboratory and point of care methods to measure lactate in amniotic fluid. A small study to assess common labor contaminants (blood, meconium, lubricating jelly and
obstetric cream) found lactate levels increased in the presence of whole blood and decreased in the presence of other contaminants as the ratio of contaminant to amniotic fluid increased (9). However, we believe any inconsistencies in lactate results are an unlikely source of error in this study and find that it is the low rate of Lactobacillus detection that is unexpected. The results of our study are novel and require further investigation.

Conclusion

This study demonstrated no association between either the presence or level of vaginal Lactobacillus spp. and the measurement of amniotic fluid lactate collected from the vaginal tract of women in labor. Our study is the first study to measure the presence of Lactobacillus spp. using molecular techniques, in a cohort of women in labor, after membranes ruptured. The results are an important finding for amniotic fluid lactate research in the development of a noninvasive diagnostic method to assess amniotic fluid lactate levels in the vaginal tract of women during labor.

Acknowledgments

Ms Joanna Cheng from the Department of Microbiology, SEALS Prince of Wales Hospital, is thanked for her professional advice and technical assistance in providing the Lactobacillus species. Dr Kiran Kaur from Human Genetic Signatures, Randwick, is thanked for her professional advice in real-time PCR techniques and analysis. All midwives at the Royal Hospital for Women, Randwick are thanked for their professional assistance recruiting women to the study and collecting clinical specimens, in particular, Ms Janet Hill, Ms Veronica Hegedus and Mrs Natalie Short.

Funding statement

Funding was received from an Australian National Health and Medical Research Council Grant, Project ID 00352 (2012).

References


Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Estimates of intra-assay precision by coefficient of variation (CV %) calculation – within one plate (n = 3).
Table S2. Estimates of inter-assay precision by coefficient of variation (CV%) calculation between plates (n = 4).
Table S3. Cell density, lactate and pH as a function of time among three strains of Lactobacillus species.
The relationship between intimate partner violence reported at the first antenatal booking visit and obstetric and perinatal outcomes in an ethnically diverse group of Australian pregnant women: a population-based study over 10 years

Hannah Grace Dahlen,¹,² Ana Maria Munoz,³ Virginia Schmied,¹ Charlene Thornton⁴

ABSTRACT

Objectives Intimate partner violence (IPV) is a global health issue affecting mainly women and is known to escalate during pregnancy and impact negatively on obstetric and perinatal outcomes. The aim of this study is to determine the incidence of IPV in a pregnant multicultural population and to determine the relationship between IPV reported at booking interview and maternal and perinatal outcomes.

Design This is a retrospective population-based data study. We analysed routinely collected data (2006–2016) from the ObstetriX system on a cohort of pregnant women.

Setting and participants 33,542 women giving birth in a major health facility in Western Sydney.

Primary outcomes Incidence of IPV, association with IPV and other psychosocial variables and maternal and perinatal outcomes.

Result 4.3% of pregnant women reported a history of IPV when asked during the routine psychosocial assessment. Fifty-four per cent were not born in Australia, and this had increased significantly over the decade. Women born in New Zealand (7.2%) and Sudan (9.1%) were most likely to report IPV at the antenatal booking visit, with women from China and India least likely to report IPV. Women who reported IPV were more likely to report additional psychosocial concerns including Edinburgh Postnatal Depression Scale scores ≥13 (7.6%), thoughts of self-harm (2.4%), childhood abuse (23.6%), and a history of anxiety and depression (34.2%). Women who reported IPV were more likely to be Australian born, smoke and be multiparous and to have been admitted for threatened preterm labour (Adjusted Odds Ratio (AOR) 1.8, 95% CI 1.28 to 2.39).

Conclusions A report of IPV at the first antenatal booking visit is associated with a higher level of reporting on all psychosocial risks, higher antenatal admissions, especially for threatened preterm labour. More research is needed regarding the effectiveness of current IPV screening for women from other countries.

Strengths and limitations of this study

- This was an ethnically diverse population that included all women in one hospital over a 10-year period.
- Detailed psychosocial and other important variables were available.
- We are unable to differentiate between immigrant and refugees.
- It is likely there is under-reporting of intimate partner violence by pregnant women, particularly in some cultural groups.

BACKGROUND

Intimate partner violence (IPV; physical, sexual or emotional) is a global health issue that affects mostly women (and some men) from different backgrounds and social groups. In 2016, the WHO released a global plan of action to address interpersonal violence, in particular against women, girls and against children.¹ WHO stated that all forms of interpersonal violence lead to negative health outcomes and should be addressed by the health system. WHO identified health services as an appropriate entry point for addressing this.¹ The Australian Personal Safety Survey estimated 186,000 women had experienced violence by a current cohabiting partner. Of those who had been pregnant, one in five (21.7%) reported that violence occurred during the pregnancy and for almost two-thirds of women (61.4%) this had been their first experience of violence in their relationship.² The prevalence of violence
during pregnancy is estimated to be between 4% and 8% of pregnant women. 

Global estimates of the prevalence of IPV range from 16.3% of ever-partnered women experiencing violence in their lifetime in East Asia to 50% of women suffering violence in Sub-Saharan Africa. However, these figures may be higher as the stigma and shame associated with IPV means disclosure remains low and in some cultural groups taboos about discussing what are considered to be family problems remain.

Pregnant women exposed to IPV face many challenges; however, migrant women who are pregnant and living in a different sociocultural environment experience additional stresses in their lives, such as conflicting cultural values, social isolation, language barriers, limited economic resources, discrimination and racism. In many cultures, IPV is socially accepted, abuse is not always considered criminal or even incorrect, and the woman is seen as subservient to their male partner. A lack of knowledge about the law regarding IPV and immigration represents a challenge for migrant women as they may fear losing custody of their child/children and their immigration status.

A meta-analysis of risk factors for domestic violence during pregnancy found across 92 studies that the average prevalence of emotional abuse was 28.4%, physical abuse was 13.8% and sexual abuse was 8%. The authors found that abuse before pregnancy and lower education level were strong predictors of abuse during pregnancy. A systematic review of domestic violence and perinatal mental health disorders including 67 papers found a three-fold increase in the odds of high-level depressive symptoms in the postnatal period after having experienced domestic violence during pregnancy. Post-traumatic stress disorder (PTSD) symptoms were also associated with a history of IPV. No studies identified a link between puerperal psychosis or eating disorders and IPV.

The Australian government places a strong emphasis on supporting women who are pregnant with mental health and other psychosocial issues, with particular focus on early intervention, social inclusion, and recovery and service access, coordination and continuity of care. The increased recognition that social and emotional problems in the perinatal period can impact negatively on outcomes for women and their babies has led a number of Australian states and territories to introduce psychosocial assessment which includes depression screening as well as questions on IPV. This process has been supported by beyondblue and the National Perinatal Depression Initiative which has led to the production of perinatal clinical practice guidelines for healthcare professionals. In addition, in New South Wales (NSW) the Supporting Families Early Policy has integrated psychosocial risk assessment into routine care (Integrated Perinatal Care) during pregnancy and after the birth. The aim of this approach is to provide a coordinated network of support for mothers and their babies. All women who they book in for their pregnancy care in public hospitals (this is not routine in the private healthcare sector) receive a psychosocial assessment from midwives and then again from the child and family health nurse (CFHN) following birth and again at the 6–8-weeks' postnatal check. The psychosocial screening tool includes the Edinburgh Postnatal Depression Scale (EPDS) and a series of questions that encompass seven key variables or areas of risk (table 1). This routine screening of pregnant women is not without its concerns regarding the specific skills required in understanding, interpreting and responding appropriately to women’s needs and the support provided to midwives to do this. This is an even more complex issue where migrant women are concerned and cultural understandings, taboos and language barriers could all have a significant influence.

The aim of this study was to determine the incidence of IPV in a pregnant multicultural population not born in Australia compared with Australian-born women and to determine the relationship between IPV reported at booking interview and obstetric and perinatal outcomes.

METHODS

Study design

This is a retrospective population-based data study. We analysed routinely collected data from the ObstetriX system on a cohort of all pregnant women giving birth in a major health facility in Western Sydney over a 10-year period (2006–2016; n=33 542).

Setting

Blacktown Hospital is located in Western Sydney, NSW, Australia and provides maternity services to over 3000 women per year. Blacktown is classified as a level 4 maternity unit, meaning it cares for women of low to moderate obstetric risk. Western Sydney is a rapidly growing area in NSW. It has a diverse population with a high proportion of young families, multiculturalism (57% not born in Australia) and significant socio-economic disadvantage. Routine antenatal psychosocial assessment, which includes depression screening and questions on domestic violence, has been conducted routinely at this site since 2006 when it was introduced at Blacktown Hospital.

Data sources

This study was a retrospective review of routinely collected data for a consecutive cohort of women who delivered babies at Blacktown Hospital between 1 January 2006 and 31 May 2016. Data were sourced from the Western Sydney Local Health District ObstetriX database, an information system that collects clinical data from first antenatal visit through to discharge of mother and baby from the hospital.

Variables

Variables of interest included (1) demographics (age, country of birth and private health insurance status); (2) baseline health, obstetric characteristics and medical risks

The booking midwife administered this screening tool in the privacy of the administration labour, antepartum haemorrhage; (3) psychosocial risks (evidence of IPV); (4) depressive and anxiety symptoms; (5) birth details (gestation at birth, birth type, perineal status) and (6) postnatal outcomes (Apgar scores, birth weight, admission to neonatal intensive care unit).

The relationship between IPV and above-listed health outcomes were examined independently. Pregnancy, labour and birth events were then analysed using contingency tables and χ² results were calculated. Logistic regression techniques were applied and reported as unadjusted and adjusted ORs and 95% CIs following adjustment for maternal age, gestation at birth, country of birth and smoking. Analysis was undertaken with IBM SPSS V.23. Due to the number of statistical tests undertaken, a p value <0.001 was set for significance.

Ethics approval was given by Western Sydney Local Health District (Protocol Number HREC2013/4/6.7 (3697) AU RED LNR/13/WMEAD/98) and an amended approval given in 2017. A waiver of individual consent was obtained due to the deidentified nature of the data.

### Analysis
Positive responses to the IPV questions, collected by clinical staff at the first antenatal visit, were grouped to form the dichotomous variable ‘IPV’ or ‘no IPV’ for all women. Women were grouped in non-Australian-born and Australian-born cohorts and for the non-Australian-born cohort the seven most commonly occurring countries of birth were examined independently. Pregnancy, labour and birth events were then analysed using contingency tables and χ² results were calculated. Logistic regression techniques were applied and reported as unadjusted and adjusted ORs and 95% CIs following adjustment for maternal age, gestation at birth, country of birth and smoking. Analysis was undertaken with IBM SPSS V.23. Due to the number of statistical tests undertaken, a p value <0.001 was set for significance.

### RESULTS
Over a 10-year period (2006–2016 inclusive), 33 542 women gave birth at the Western Sydney maternity unit.

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#### Table 1  Psychosocial risk variables I–IV, New South Wales Department of Health (2010)

<table>
<thead>
<tr>
<th>Variables (risk factors)</th>
<th>Suggested format for psychosocial assessment questions</th>
</tr>
</thead>
</table>
| I. Lack of support       | 1. Will you be able to get practical support with your baby?  
                          | 2. Do you have someone you are able to talk to about your feelings or worries? |
| II. Recent major stressors in the last 12 months | 3. Have you had any major stressors, changes or losses recently (ie, in the last 12 months) such as, financial problems, someone close to you dying or any other serious worries? |
| III. Low self-esteem (including lack of self-confidence, high anxiety and perfectionistic traits) | 4. Generally, do you consider yourself a confident person?  
                          | 5. Does it worry you a lot if things get messy or out of place? |
| IV. History of anxiety, depression or other mental health problems | 6. (a) Have you ever felt anxious, miserable, worried or depressed for more than a couple of weeks?  
                          | 6. (b) If so, did it seriously interfere with your work and your relationships with friends and family?  
                          | 7. Are you currently receiving, or have you in the past received, treatment for any emotional problems? |
| V. Couple’s relationship problems or dysfunction (if applicable) | 8. How would you describe your relationship with your partner?  
                                                                 | 9. (a) Antenatal: What do you think your relationship will be like after the birth?  
                                                                 | OR (b) Postnatal (in Community Health Setting): Has your relationship changed since having the baby? |
| VI. Adverse childhood experiences | 10. Now that you are having a child of your own, you may think more about your own childhood and what it was like. As a child were you hurt or abused in any way (physically, emotionally, sexually)? |
| VII. Domestic violence Questions must be asked only when the woman can be interviewed away from partner or family member over the age of 3 years. Staff must undergo training in screening for domestic violence before administering questions | 11. Within the last year, have you been hit, slapped or hurt in other ways by your partner or ex-partner?  
                                                                 | 12. Are you frightened of your partner or ex-partner?  
                                                                 | (If the response to questions 11 and 12 is ‘No’ then offer the Domestic Violence information card and omit questions 13–18)  
                                                                 | 13. Are you safe here at home/to go home when you leave here?  
                                                                 | 14. Has your child/children been hurt or witnessed violence?  
                                                                 | 15. Who is/are your children with now?  
                                                                 | 16. Are they safe?  
                                                                 | 17. Are you worried about your child/children’s safety?  
                                                                 | 18. Would you like assistance with this? ee |
| Opportunity to disclose further | 19. Are there any other issues or worries you would like to mention? |

(parity, body mass index (BMI), smoking, diagnosis of hypertension, diabetes, incidence of threatened premature labour, antepartum haemorrhage; (3) psychosocial risks (evidence of IPV); (4) depressive and anxiety symptoms; (5) birth details (gestation at birth, birth type, perineal status) and (6) postnatal outcomes (Apgar scores, birth weight, admission to neonatal intensive care unit). The relationship between IPV and above-listed health outcomes were also examined.

The psychosocial screening tool questions are based on a series of known risk factors and are administered alongside the EPDS (table 1). The booking midwife administers this screening tool in the privacy of the initial antenatal booking visit when women are around 12–20 weeks’ pregnant. Partners are asked not to be present or to leave when these questions are asked. If an NSW Health Interpreter was booked for the visit, the questions were asked verbally via the interpreter.
During this time, there was a decrease in the number of women giving birth who were born in Australia (figure 1). During the 10 years, the increase in women born in India was most notable (4.2%–25.7%) (figure 2). Overall, 4.3% of women reported a history of IPV. There were an additional 0.8% of women for whom screening was not undertaken due to refusal of their partner or other family member(s) to leave the interview room.

There were differences in demographics between Australian and non-Australian women, with Australian women being younger, more likely to be under 20 years of age and less likely to be over 35 years of age. Australian born women were more likely to have a BMI >30 (table 2).

During pregnancy, women born in Australia were more likely to smoke and have hypertensive disorders of pregnancy but they were less likely to have gestational diabetes and anaemia. In terms of birth outcomes, women born in Australia were more likely to have a normal vaginal birth, have an epidural and give birth in the birth centre. There was a significantly higher stillbirth rate observed in women not born in Australia (table 3).

Women who disclosed IPV at the first antenatal booking visit over this 10-year period weighed slightly less and smoked more than twice as much compared with those who did not disclose IPV. These women were also more likely to be having a subsequent baby. During pregnancy, they were more likely to have an admission with threatened premature labour (table 4).

Overall 4.3% of women reported a history (current partner 3.5%, previous partner 0.7%, other family member 0.1%) of IPV when asked during the routine psychosocial assessment at booking in for pregnancy care. Women born in New Zealand (7.2%) and Sudan (9.1%) were most likely to report IPV at the antenatal booking visit, with women from China and India least likely to report IPV. Missing data for variables relating to IPV equated to 8.7% (table 5).

Women who reported IPV were more likely to report concerns when psychosocial screening was attended,
including EPDS $\geq 13$ (7.63%), thoughts of self-harm (2.4%), childhood abuse (23.6%) and anxiety and depression (34.2%).

Women who reported IPV were more likely overall to be Australian born, smoke and be multiparous (table 6).

We examined women reporting IPV at booking and the incidence of pregnancy conditions and events compared with women with no report of IPV adjusting for smoking, parity and gestational age and found significant associations with IPV and being born in Australia, smoking, being multiparous and having threatened premature labour. Women reporting IPV were however less likely to have hypertensive disease of pregnancy (table 7).

**DISCUSSION**

In this study, we aimed to determine the incidence of IPV over 10 years in a pregnant multicultural population and to compare characteristics of those not born in Australia with those born in Australia. We also aimed to determine the relationship between IPV reported at the antenatal booking interview and selected obstetric and perinatal outcomes.

Australia has a large population of both economic and humanitarian migrant, and there has been a steady increase in new arrivals over the past decade in some metropolitan locations, including the study site. Understanding the specific healthcare needs of migrant women in pregnancy and following birth is important to inform health service design and delivery and ensure the best health outcomes for women and babies. We found a dramatic increase in the number of women born overseas (from 47% in 2006 to 62% in 2016) with the largest increase being in women born in India. We also found differences in demographics and obstetric outcomes between Australian-born and non-Australian-born women, with those not born in Australia tending to be older, less likely to have a BMI of $\geq 30$ compared with those born in Australia. They are also much less likely to smoke and much more likely to have gestational diabetes. These differences were identified previously in our analyses of the state-wide population.

Overall, a low proportion of women disclosed IPV (4.3%). This is comparable with, or a little lower than other Australian and international studies that also estimated IPV prevalence to be between 4% and 8% of pregnant women. However, this is very likely to reflect under-reporting by women, as demonstrated by James et al, the prevalence of IPV in pregnancy is close to 20%.

Furthermore, in NSW the IPV screening questions ask directly about physical abuse which was estimated to be around 13.8%.

The Maternal Health Study conducted in one Australian state (Victoria) reported that the prevalence of domestic violence across the first postnatal year was 17%.

At the 4-year follow-up, the authors found that 29% of women experienced IPV across the 4 years postbirth. This included women who were subjected to physical and or emotional and/or sexual abuse.

In our study, women who reported IPV were more likely overall to be Australian born. We found that of the non-Australian born cohort, women born in New Zealand and in Sudan were more likely to report IPV when asked. The New Zealand sample is likely to reflect the higher Maori and Pacific Islander population in this location (Western Sydney). New Zealand research has reported a higher prevalence of IPV among Maori women and in some locations, this is over 60%.

Studies also report that many Sudanese women experience IPV from their husbands prior to migration, and this represents a significant factor in these women’s premigration history.

In contrast, women born in India (the largest migrant group in the study location) and those born in China were the least likely to say they experienced IPV when asked.

We suggest that this reflects significant under-reporting by these women. Previous studies have reported rates of 4% in China and more recently James et al found a prevalence of 4.8% in China and a prevalence of 28% in India. This under-reporting is likely due to cultural concerns about sharing with strangers what is considered to be family business, something that is accepted in their country of origin.

Women who reported IPV were more likely to report a raised EPDS $\geq 13$ (7.63%), thoughts of self-harm (2.4%), and anxiety and depression (34.2%). These women were also more likely to worry, report stress and have a family history of mental illness. This means they are likely to have fewer social support systems in place that could buffer or protect them and their children from the effects of IPV.

A number of longitudinal studies of maternal well-being in Australia show a strong association between depressive symptoms in pregnancy and in the year after birth and poor partner relationship and IPV.

Another major concern reported when psychosocial screening was attended was childhood abuse (23.6%) which was significantly associated with IPV. Researchers have hypothesised that women with a history of childhood abuse may be at exceptionally high risk of revictimisation in adulthood, including rape and IPV.

In the Maternal Health Study, childhood abuse was reported by

**Table 2** Selected demographics of Australian-born and non-Australian-born women

<table>
<thead>
<tr>
<th>Feature</th>
<th>Australian born, n=15 459</th>
<th>Non-Australian born, n=18 083</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age*</td>
<td>27.7 (5.75)</td>
<td>29.8 (5.11)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Teenage pregnancy</td>
<td>7.9%</td>
<td>1.8%</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Pregnancy ≥35 years</td>
<td>13.0%</td>
<td>17.9%</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>25.0%</td>
<td>26.9%</td>
<td>$&lt;0.002$</td>
</tr>
<tr>
<td>Body mass index $\geq 30$</td>
<td>28.2%</td>
<td>17.7%</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Body mass index $\leq 18$</td>
<td>3.0%</td>
<td>3.0%</td>
<td>0.02</td>
</tr>
<tr>
<td>Private patient</td>
<td>3.7%</td>
<td>3.4%</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Mean and SD.
a high number of women (41%), and these women were more likely to experience IPV and poor mental health.  

As noted, women who reported IPV were more likely to be Australian born, they were more likely to smoke and be multiparous. During the pregnancy, they were less likely to have hypertensive disease of pregnancy and more likely to have been admitted for threatened preterm labour (AOR 1.8, 95%CI 1.28 to 2.39). Various studies have demonstrated a significant impact of IPV on women’s health behaviours during pregnancy, including higher rates of smoking, alcohol and substance use. Experiencing IPV is a significant life stress and higher rates of mental illness, seen in this study, also correlate with high smoking rates. One study found probable major depression and generalised anxiety disorder were associated with a 93% and 44% increased odds, respectively, of being a current smoker.

Likewise, the higher number of multiparous women reporting IPV would impact on the higher rates of normal birth seen in this group as well as the lower episiotomy rate and severe perineal trauma rate.

The impact of IPV on maternal mental health cannot be underestimated. During the pregnancy and the postpartum period, IPV is associated with depression, anxiety

---

**Table 3  Pregnancy events and outcomes of Australian-born and non-Australian-born women**

<table>
<thead>
<tr>
<th></th>
<th>Australian born, n=15 459</th>
<th>Non-Australian born, n=18 083</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>19.7%</td>
<td>4.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>2.6%</td>
<td>1.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>6.4%</td>
<td>13.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admitted for threatened premature labour</td>
<td>3.6%</td>
<td>2.8%</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Maternal anaemia</td>
<td>7.7%</td>
<td>10.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any antepartum haemorrhage</td>
<td>0.8%</td>
<td>0.9%</td>
<td>0.38</td>
</tr>
<tr>
<td>Gestation at birth*</td>
<td>39.2 (2.01)</td>
<td>39.1 (1.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestation grouped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28 weeks</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.12</td>
</tr>
<tr>
<td>29–32 weeks</td>
<td>0.4%</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>32–36 weeks</td>
<td>5.3%</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>37 weeks and greater</td>
<td>93.7%</td>
<td>94.0%</td>
<td></td>
</tr>
<tr>
<td>Normal vaginal birth</td>
<td>66.4%</td>
<td>60.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Instrumental birth</td>
<td>8.6%</td>
<td>11.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>25.0%</td>
<td>28.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syntocinon usage</td>
<td>46.1%</td>
<td>53.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth centre</td>
<td>9.2%</td>
<td>4.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Born before arrival</td>
<td>0.8%</td>
<td>0.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Operating theatre</td>
<td>25.0%</td>
<td>28.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delivery ward</td>
<td>65.0%</td>
<td>66.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amniotomy</td>
<td>51.9%</td>
<td>51.4%</td>
<td>0.36</td>
</tr>
<tr>
<td>Epidural usage†</td>
<td>19.8%</td>
<td>15.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Third-degree and fourth-degree tears†</td>
<td>0.5%</td>
<td>1.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Episiotomy†</td>
<td>14.4%</td>
<td>22.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postpartum haemorrhage &gt;1500 mL</td>
<td>1.2%</td>
<td>1.4%</td>
<td>0.38</td>
</tr>
<tr>
<td>Birth weight*</td>
<td>3414 (588.22)</td>
<td>3290 (563.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admitted to special care nursery/neonatal intensive care unit</td>
<td>7.5%</td>
<td>8.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stillbirth rate/1000 births</td>
<td>5.2</td>
<td>8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 min Apgar &lt;7</td>
<td>1.6%</td>
<td>1.6%</td>
<td>0.56</td>
</tr>
<tr>
<td>Fetal anomaly</td>
<td>0.8%</td>
<td>0.7%</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Median, IQR, Mann-Whitney U.
†As a % of vaginal births.
and PTSD. PTSD rates associated with IPV range from anywhere between 19% and 84%. Around 40% of women who experience IPV report symptoms of depression. The most serious reported outcomes of IPV during pregnancy are homicide and suicide, with maternal injury a leading cause of maternal mortality. It has been estimated that 38% of murders of women are by an intimate partner or ex-partner.1

### Table 4 Maternal characteristics and perinatal outcomes for women who disclosed IPV at the first booking visit compared with those who have not

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>IPV reported, n=1302</th>
<th>IPV not reported, n=29,026</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age*</td>
<td>28.7 (5.46)</td>
<td>28.6 (6.07)</td>
<td>0.29</td>
</tr>
<tr>
<td>Body mass index*</td>
<td>26.6 (6.54)</td>
<td>27.1 (7.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiparous</td>
<td>82.7%</td>
<td>68.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>26.8%</td>
<td>11.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension diagnosed in pregnancy</td>
<td>1.5%</td>
<td>2.4%</td>
<td>0.04</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>9.4%</td>
<td>8.6%</td>
<td>0.96</td>
</tr>
<tr>
<td>Threatened premature labour</td>
<td>5.5%</td>
<td>3.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Antepartum haemorrhage</td>
<td>2.22%</td>
<td>1.55%</td>
<td>0.08</td>
</tr>
<tr>
<td>Antenatal admission</td>
<td>10.8%</td>
<td>8.6%</td>
<td>0.006</td>
</tr>
<tr>
<td>Gestation at birth†</td>
<td>39.2 (1.96)</td>
<td>39.1 (1.90)</td>
<td>0.12</td>
</tr>
<tr>
<td>Birth type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vaginal birth</td>
<td>66.7%</td>
<td>61.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Instrumental birth</td>
<td>7.0%</td>
<td>10.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>26.3%</td>
<td>27.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epidural usage‡</td>
<td>29.7%</td>
<td>28.3%</td>
<td>0.36</td>
</tr>
<tr>
<td>Third-degree and fourth-degree tears‡</td>
<td>0.46%</td>
<td>1.3%</td>
<td>0.01</td>
</tr>
<tr>
<td>Episiotomy‡</td>
<td>18.8%</td>
<td>25.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Postpartum blood transfusion</td>
<td>1.08%</td>
<td>0.83%</td>
<td>0.94</td>
</tr>
<tr>
<td>Birth weight*</td>
<td>3349 (568.0)</td>
<td>3344 (573.6)</td>
<td>0.77</td>
</tr>
<tr>
<td>Admitted to special care nursery/neonatal intensive care unit</td>
<td>8.6%</td>
<td>8.5%</td>
<td>0.88</td>
</tr>
<tr>
<td>Stillbirth rate/1000 births</td>
<td>3.9%</td>
<td>5.4%</td>
<td>0.49</td>
</tr>
<tr>
<td>Feeding difficulty</td>
<td>38.6%</td>
<td>39.6%</td>
<td>0.49</td>
</tr>
<tr>
<td>Male gender</td>
<td>51.0%</td>
<td>51.3%</td>
<td>0.88</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>6.5%</td>
<td>4.8%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Mean, SD and t-test. †Median, IQR, Mann-Whitney U. ‡As a % of vaginal births.

IPV, intimate partner violence.

### Table 5 IPV expressed as a percentage of country of birth for the most commonly occurring countries of birth of all women assessed

<table>
<thead>
<tr>
<th>Country</th>
<th>IPV, domestic violence, current partner</th>
<th>IPV, domestic violence, other family member</th>
<th>IPV, domestic violence, previous partner</th>
<th>IPV, deferred questions due to partner or family members' presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3.9%</td>
<td>0.1%</td>
<td>1.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>India</td>
<td>1.6%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Philippines</td>
<td>3.3%</td>
<td>0.0%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>NZ</td>
<td>6.2%</td>
<td>0.4%</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Fiji</td>
<td>4.3%</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Sudan</td>
<td>8.2%</td>
<td>0.0%</td>
<td>0.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>2.5%</td>
<td>0.0%</td>
<td>0.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>China</td>
<td>1.4%</td>
<td>0.0%</td>
<td>0.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Other</td>
<td>2.7%</td>
<td>0.0%</td>
<td>0.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Total</td>
<td>3.5%</td>
<td>0.1%</td>
<td>0.8%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

IPV, intimate partner violence; NZ, New Zealand.
In this study, we found women who were multiparous were more likely to disclose IPV, and this has been reported previously. This is important to know as women may be more prepared to disclose with a subsequent pregnancy. This may be due to their realising the impact of IPV on the child but also they may be feeling more comfortable with and trusting of the service.

Another possibility for this higher rate of disclosure of IPV with multiparous women may be due to the fact that hopes that a coercive partner may reform once the baby has arrived are not realised. Perhaps also motherhood shifts loyalty from a non-supportive partner to a baby, and energy and affection is channelled more to the baby. This in turn may make reporting easier but may also lead to an escalation of IPV. It is really important more research is done to help understand this. It is also possible that relationship strains may be taking a toll with the presence of children and escalation of IPV. In a study undertaken in Nigeria where a much higher IPV was found in multiparous women, the authors suggest lower socioeconomic status could be a factor in this as well as this is associated with larger families.

A number of studies have reported that women who suffer IPV during pregnancy are twice as likely to miss antenatal visit appointments or initiate antenatal care early. Women with a history of IPV are more likely to miss three or more antenatal visits compared with their non-abused counterparts (45% vs 28%). In addition, there are increased numbers of hospitalisation reported for these women.

In our study, we found women were more likely to be hospitalised with threatened preterm birth if they had a history of IPV. Several studies have reported a link between insufficient antenatal care associated with IPV and adverse birth outcomes, including preterm birth and low birth weight (LBW) and small for gestational age. While we did not find an actual increase in preterm birth in this study, it is well known that preterm birth and LBW are the primary causes of neonatal morbidity and mortality.

### Table 6

<table>
<thead>
<tr>
<th>Associated psychosocial issues for pregnant women reporting intimate partner violence (IPV) compared with those who do not</th>
<th>IPV reported (%)</th>
<th>IPV not reported (%)</th>
<th>P values</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh Postnatal Depression Scale ≥13</td>
<td>7.6</td>
<td>2.1</td>
<td>&lt;0.001</td>
<td>3.57 (2.84–4.47)</td>
</tr>
<tr>
<td>Thoughts of self-harm</td>
<td>2.4</td>
<td>0.5</td>
<td>&lt;0.001</td>
<td>5.55 (3.73–8.25)</td>
</tr>
<tr>
<td>Illegal drug use risk</td>
<td>4.30</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td>6.11 (4.52–8.24)</td>
</tr>
<tr>
<td>Childhood abuse risk</td>
<td>23.6</td>
<td>7.6</td>
<td>&lt;0.001</td>
<td>3.74 (3.27–4.28)</td>
</tr>
<tr>
<td>Pregnancy-related anxiety risk</td>
<td>5.9</td>
<td>2.1</td>
<td>&lt;0.001</td>
<td>2.88 (2.26–3.67)</td>
</tr>
<tr>
<td>Work/relationship effect risk</td>
<td>23.0</td>
<td>7.4</td>
<td>&lt;0.001</td>
<td>3.76 (3.28–4.30)</td>
</tr>
<tr>
<td>Anxiety/depression risk</td>
<td>34.2</td>
<td>14.0</td>
<td>&lt;0.001</td>
<td>3.19 (2.84–3.60)</td>
</tr>
<tr>
<td>Worried about mess risk</td>
<td>34.3</td>
<td>25.0</td>
<td>&lt;0.001</td>
<td>1.57 (1.39–1.76)</td>
</tr>
<tr>
<td>Positive response to ‘are you generally confident?’ question</td>
<td>75.4</td>
<td>84.6</td>
<td>&lt;0.001</td>
<td>0.24 (0.21–0.27)</td>
</tr>
<tr>
<td>Recent worry/stress risk</td>
<td>47.2</td>
<td>22.2</td>
<td>&lt;0.001</td>
<td>3.20 (2.81–3.52)</td>
</tr>
<tr>
<td>Emotional support risk</td>
<td>8.6</td>
<td>4.4</td>
<td>&lt;0.001</td>
<td>2.04 (1.67–2.50)</td>
</tr>
<tr>
<td>Mental health disorder</td>
<td>7.07</td>
<td>1.72</td>
<td>&lt;0.001</td>
<td>4.36 (3.46–5.48)</td>
</tr>
<tr>
<td>Family history of mental health disorder</td>
<td>19.1</td>
<td>10.7</td>
<td>&lt;0.001</td>
<td>1.97 (1.71–2.28)</td>
</tr>
</tbody>
</table>

### Table 7

<table>
<thead>
<tr>
<th>OR calculations for women reporting intimate partner violence (IPV) at booking and pregnancy conditions and events when compared with women not reporting IPV (ref category is non-IPV)</th>
<th>OR</th>
<th>AOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian born</td>
<td>1.5 (1.31–1.64)</td>
<td>1.3 (1.09–1.46)</td>
</tr>
<tr>
<td>Smoking</td>
<td>3.0 (2.60–3.36)</td>
<td>2.7 (2.30–3.20)</td>
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<tr>
<td>Multiparous</td>
<td>2.3 (1.98–2.70)</td>
<td>2.0 (1.68–2.49)</td>
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<td>Gestational diabetes</td>
<td>1.0 (0.87–1.24)</td>
<td>1.1 (0.85–1.29)</td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td>0.6 (0.39–0.97)</td>
<td>0.5 (0.32–0.91)</td>
</tr>
<tr>
<td>Threatened premature labour</td>
<td>1.8 (1.44–2.36)</td>
<td>1.8 (1.28–2.39)</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>1.5 (1.04–2.11)</td>
<td>1.4 (0.95–2.19)</td>
</tr>
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<td>Normal vaginal birth</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Instrumental birth</td>
<td>0.6 (0.49 – 0.76)</td>
<td>1.1 (0.90 – 1.25)</td>
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<tr>
<td>Caesarean section</td>
<td>1.1 (0.94 – 1.20)</td>
<td></td>
</tr>
<tr>
<td>Born preterm</td>
<td>1.3 (1.04–1.60)</td>
<td>1.0 (0.71–1.33)</td>
</tr>
<tr>
<td>Special care nursery/ neonatal intensive care unit admission</td>
<td>1.0 (0.77–1.16)</td>
<td>1.0 (0.82–1.23)</td>
</tr>
<tr>
<td>Apgar 2 (less than 7)</td>
<td>1.5 (1.00–2.12)</td>
<td>1.1 (0.64–1.80)</td>
</tr>
<tr>
<td>Breastfed</td>
<td>0.8 (0.73–0.93)</td>
<td>1.0 (0.86–1.20)</td>
</tr>
</tbody>
</table>

Health services

The WHO has identified health services as an appropriate entry point for addressing IPV, in particular against...
women and girls who bear the vast burden of IPV. Women who experience IPV are more likely to use health services than those who do not even though they rarely explicitly disclose violence as the underlying reason. This is even more the case when they are pregnant, and midwives and doctors are the front-line healthcare providers in this case. Unfortunately, health and other services are slow to recognise and address this violence, either because they do not recognise the signs, do not have appropriate services in place or they are simply at capacity.

Currently, the Australian Government has a clear aim to reduce the incidence of IPV against women through public education and health promotion. However, more is required from health providers than simply asking the question. Spangaro et al found multiple pathways to disclosure with no single factor necessarily sufficient for a decision to disclose. While being asked the question was important in women disclosing IPV, the way the question was asked (with interest and being non-judgemental) were found to be key conditions. With the increasing use of computers to guide questions and document women’s responses to sensitive questions included in psychosocial screening, questions are raised as to how effective this will be if a trusting relationship is important in disclosure. A recent ethnographic study of psychosocial assessment and depression screening in pregnancy and following birth found that some midwives and CFHNs were reticent to ask questions related to IPV as well as childhood abuse, at times avoiding asking these questions, rewording the question or minimising women’s responses. Midwives and nurses also indicated that many women from non-English speaking backgrounds did not always understand the question being asked of them and interpreters were not always available. This suggests that we have less knowledge of how to screen for IPV among diverse cultural and linguistic groups. We also have limited information about how many women who report IPV are provided with appropriate referrals and whether they take up the referral. Our study also raises important questions around the need to have a higher level of awareness and vigilance regarding possible IPV when women report childhood abuse and other commonly gathered antenatal information.

There are current discussions among health workers and government services that screening women for IPV initially at booking and again during the third trimester could be advisable as IPV may escalate and/or women may feel more comfortable and trusting of their care provider initially at booking and again during the third trimester and government services that screening women for IPV is required from health providers than simply asking the question. Spangaro et al found multiple pathways to disclosure with no single factor necessarily sufficient for a decision to disclose. While being asked the question was important in women disclosing IPV, the way the question was asked (with interest and being non-judgemental) were found to be key conditions. With the increasing use of computers to guide questions and document women’s responses to sensitive questions included in psychosocial screening, questions are raised as to how effective this will be if a trusting relationship is important in disclosure. A recent ethnographic study of psychosocial assessment and depression screening in pregnancy and following birth found that some midwives and CFHNs were reticent to ask questions related to IPV as well as childhood abuse, at times avoiding asking these questions, rewording the question or minimising women’s responses. Midwives and nurses also indicated that many women from non-English speaking backgrounds did not always understand the question being asked of them and interpreters were not always available. This suggests that we have less knowledge of how to screen for IPV among diverse cultural and linguistic groups. We also have limited information about how many women who report IPV are provided with appropriate referrals and whether they take up the referral. Our study also raises important questions around the need to have a higher level of awareness and vigilance regarding possible IPV when women report childhood abuse and other commonly gathered antenatal information.

There are current discussions among health workers and government services that screening women for IPV initially at booking and again during the third trimester could be advisable as IPV may escalate and/or women may feel more comfortable and trusting of their care provider as the pregnancy advances. This may be even more useful in continuity of care models where women are cared for by a trusted midwife who they get to know and trust. Others suggest that questions about IPV should not be asked at the first visit as is currently done as no relationship has been developed. There is little evidence as to what might be the best approach. There is debate about both the effectiveness of IPV enquiry and the most appropriate time to conduct assessments in pregnancy and after birth. A number of authors report that when asked, women may choose not to disclose about the abuse at the initial time of asking, for fear of their own safety but asking signifies that she can disclose at a later contact. As a result of this debate, there is inconsistent and at times poor uptake of screening in antenatal services in Australia.

Strengths and limitations

There are several limitations with this study, and these include that it involves only one hospital in Western Sydney and so may not be generalisable to other areas with different populations. Also, we were unable to determine ethnicity as the variable provided is country of birth, and we could not distinguish between refugees and migrants. Other outcomes not reported here because of the nature of the dataset include urinary and faecal incontinence. The division of non-Australian-born women into the seven counties dilutes the data pool and limits conclusions about individual groups. There is missing data for the IPV variable as already reported, and this is more frequent in the first few years of the dataset when psychosocial screening was being introduced. The advantages of using the ObstetriX database are the large number of variables available compared with the other state-wide routine databases, such as the Perinatal Data Collection and Admitted Patient Data Collection. Socioeconomic factors which affect health such as BMI, psychosocial risk factors, marital status, education level and occupation are not collected in the latter, and adjustment for these variables cannot be undertaken when modelling statistical interactions with these databases and the use of ObstetriX provides this advantage.

CONCLUSION

There appears to be a relationship between psychosocial risks identified at the antenatal booking visit and a history of IPV; in particular, this is seen in women who have a history of anxiety and depression and childhood abuse. This provides maternity healthcare providers with more evidence for incorporating routine psychosocial screening during antenatal care and providing appropriate services. The fact that women with a history of IPV had more antenatal admissions, particularly for threatened preterm labour, could provide another potential warning sign for midwives and doctors. More research is needed regarding the effectiveness of current IPV screening for women from other countries.

Acknowledgements The authors are grateful to Blacktown hospitals and Western Sydney University for supporting AMM to have time working with academics to develop research skills under the Nurse/Midwives Consultant Research and Capacity Building Scheme.

Contributors HGD designed the study, assisted with analysis and wrote the paper. AMM undertook a review of the literature and helped access the data for analysis. VS consulted on the study and contributed to the writing of the paper. CT analysed the data and assisted in writing the paper.

Funding Funding for the project came from a Western Sydney University Research Partnership grant with NSW Health.

Competing interests None declared.
References


T-piece resuscitators: how do they compare?

Murray Hinder,1,2 Alistair McEwan,2 Thomas Drevhammer,3 Snorri Donaldson,3 Mark Brian Tracy1,4

Background The T-piece resuscitator (TPR) has seen increased use as a primary resuscitation device with newborns. Traditional TPR design uses a high resistance expiratory valve to produce positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) at resuscitation. A new TPR device that uses a dual flow ratio valve (fluidic flip) to produce PEEP/CPAP is now available (rPAP). We aimed to compare the measured ventilation performance of different TPR devices in a controlled bench test study.

Design/methods Single operator provided positive pressure ventilation to an incremental test lung compliance (Crs) model (0.5–5 mL/cmH2O) with five different brands of TPR device (Atom, Neopuff, rPAP, GE Panda warmer and Draeger Resuscitaire). At recommended peak inflation pressure (PIP) 20 cmH2O, PEEP of 5 cmH2O and rate of 60 inflations per minute. Results 1864 inflations were analysed. Four of the five devices tested demonstrated inadvertent elevations in mean PEEP (5.5–10.3 cmH2O, p<0.001) from set value as Crs was increased, while one device (rPAP) remained at the set value. Measured PEEP exceeded the set value in two infant warmer devices (GE and Draeger) with built-in TPR at Crs of 0.5 (24.5 and 23.5 cmH2O, p<0.001). Significant differences were seen in tidal volumes across devices particularly at higher Crs (p<0.001).

Conclusions Results show important variation in delivered ventilation from set values due to inherent TPR device design characteristics with a range of lung compliances expected at birth. Device-generated inadvertent PEEP and overdelivery of PIP may be clinically deleterious for term and preterm newborns or infants with larger Crs during resuscitation.

Background

The T-piece resuscitator (TPR) is used as a primary resuscitation device for newborns in the developed world. TPR research has centred on preterm infants, but its popularity has seen an increase in use with term birth in both tertiary and non-tertiary birthing units.1–4 This is due in part to the perceived ease of use and their ability to deliver a consistent preset peak inflation pressure (PIP) and positive-end expiratory pressure (PEEP) during resuscitation compared with other devices.5 Some local resuscitation guidelines recommend TPR use over self-inflating bag or flow inflating bag (FIB) (Australia and New Zealand).6 However, the 2015 International Consensus on Cardiopulmonary Resuscitation (ILCOR) states: ‘there is insufficient evidence to recommend one device over another’.7 The TPR and FIB (with expiratory flow control) are the most commonly used infant resuscitation devices that can provide either intermittent positive pressure ventilation (IPPV) with PEEP or deliver continuous positive airway pressure (CPAP). Initial use of CPAP is recommended for preterm infants with respiratory distress rather than intubation and IPPV has been extrapolated from its use in preterm newborn infants8–11 and preterm animal studies.12–15

Traditional TPRs are flow-dependent devices and require a constant gas inflow to enable provision of positive pressure ventilation (PPV); delivered PIP is adjustable via an airway pressure limit valve (APL), and PEEP/CPAP is adjustable via an adjustable expiratory flow resistor. We have previously detailed important physical characteristics and functionality of current TPR design.14–17

Use of a flow resistor to generate PEEP and CPAP in Neopuff (Fisher & Paykel Healthcare, Auckland, New Zealand) TPR design has been shown in in vitro studies to have high imposed work of breathing (WOB)16–20 and can produce inadvertent PEEP16 during PPV16 compared with alternate...
Changes in device performance during resuscitation due to dynamic physiological changes and inherent device limitations in the popular Infant Flow CPAP system produced by several companies (Electro Medical Equipment, Brighton, UK, and SiPAP Carefusion, California, USA). Clinical studies have shown that this method of providing CPAP has a more consistent delivery of pressure and increase in tidal volume, and more effective in the treatment of apnoea than other methods of providing CPAP treatment. Although the new rPAP system is essentially a flow occluding TPR, the use of the ‘fluidic flip’ method to produce either PEEP during PPV, mask CPAP or nasal CPAP with the one device at resuscitation differs from other TPR systems.

Establishment of a functional residual capacity and initiation of spontaneous breathing are the primary goals when stabilising a newborn infant. Transition from liquid to air-filled lungs is a dynamic and phasic process, often not detected or adjusted for by clinicians, in both manikins and human studies. Changes in device performance during resuscitation due to dynamic physiological changes and inherent device design characteristics are relatively unexplored across expected weight range (≈450 g to 10 kg). The effect of device-imposed flow resistance used to provide PEEP and CPAP, and APL valve performance limiting PIP of these devices may impose different ventilation responses across this range between device models.

We aimed to examine the dynamic biomechanical performance of the new rPAP device compared with a range of commonly used TPR devices in a leak-free lung model with fixed resistance (50 cmH₂O/L/sec), and increasing lung compliance (0.5–5 mL/cmH₂O), typical of preterm to term lung pulmonary function.

We used commonly recommended initial settings of: PEEP 5 cmH₂O, PIP 20 cmH₂O, device gas inflow rate of 10 LPM and inflation rate (60 per minute). Inspiratory time of 0.5 s was selected to reflect current international testing standards and previous studies indicating longer inspiratory times with TPR use. The outcome measures were the delivered respiratory mechanical data at the interface of the test lung. Our null hypothesis was that all TPR devices would perform adequately (±10% of set pressure values) and similarly across the compliance range, regardless of the type of device or method of providing PEEP (flow resistor or dual flow ratio).

All devices were tested with their respective manufacturers recommended patient delivery circuit.

Two different leak-free test lungs with measured static compliances were used: (1) a Schaller newborn test lung (Schaller-Mt, Dresden, Germany) Crs 0.5 mL/cmH₂O and (2) Michigan infant test lung Model 5600i (Michigan Instruments, Grand Rapids, USA) with Crs of 1, 2, 3, 4 and 5 mL/cmH₂O.

A calibrated 50 cmH₂O/L/sec airway resistor (Rp50, Michigan Instruments) was used with each test lung Crs. A Florian inspiratory function monitor (RFM) (Accutronics, Medical Systems AG, Zug, Switzerland) was connected via the hot wire pneumotach and pressure sensor line sited between the TPR device under test and the test lung where airway pressures and flows were measured. The Florian monitor was calibrated in air with an external syringe of known volume, and pressure/flow via a traceable reference ventilator analyser (PF300, IMT Medical, Buchs, Switzerland) with pressure resolution of 0.1 cmH₂O (accuracy of ±0.75%), and flow calibration with resolution of 0.05 L/min (accuracy of ±1.75%). Devices with air oxygen blenders were set to deliver 21% fractional inspired oxygen (FiO₂) and checked with reference ventilator analyser. The analogue signals output from the RFM were collected and digitised at 200 Hz with analysis software (Grove Medical, London, UK). The test lungs and monitoring system were pressurised to static pressure of 50 cmH₂O, and over 120s, there was no fall in pressure indicating the test system was leak free.

A single operator experienced in newborn resuscitation was asked to deliver 1 min of IPPV to each lung Crs starting at 0.5 mL/cmH₂O and incrementing to 5 mL/cmH₂O with each different TPR device. The operator was rested between each lung Crs and device change. At the start of each device test sequence, the RFM pneumotach was rezeroed; patient circuit gas flow rate of 10 LPM air, PIP of 20 cmH₂O, PEEP of 5 cmH₂O, overpressure (over pressure on some devices internally preset by manufacturer) of 40 cmH₂O were set as per manufacturer’s instructions and verified with reference ventilator analyser. Operator was guided by metronome to deliver an inflation rate of 60 inflations per minute at an inspiratory expiratory ratio (I:E) of 1:1 across all devices under test and test lung Crs combinations. Operator was also blinded to RFM display; only the manometer on device under test was visible. Detection of PEEP valve positional change and instruction on finger dwell distance above PEEP valve orifice was also carried out on each device and has been previously published.

DATA ANALYSIS
Analysis was conducted using Stata (V.15 MP). The measured parameters included the mean, minimum and maximum delivered PIP, PEEP and tidal volume (TV). Analysis of variance (ANOVA) for repeated measures was used to determine measured parameter differences between devices at different Crs settings. Differences between means determined by ANOVA were reported with p values adjusted F test using Box’s conservative epsilon; p values of <0.05 were considered significant. Bonferroni corrections of estimates were made to adjust for multiple comparisons.

RESULTS
A number of 1864 inflations were recorded and analysed. Three devices demonstrated delivered PIP values outside the prespecified acceptable range (±10% of set PIP 20 cmH₂O). The Panda and Draeger systems at Crs of 0.5 mL/cmH₂O showed significantly elevated mean (SD) PIPs over set value.
(24.5 (0.19) cmH₂O and 23.5 (0.1) cmH₂O, respectively), p<0.001 (table 1 and figure 1). The Atom system failed to reach lower acceptable limit at Crs >3 mL/cmH₂O (table 1 and figure 1).

All devices except the rPAP system showed significant elevations of measured mean PEEP above upper acceptable limit (5.5 cmH₂O) with Crs >2 mL/cmH₂O, p<0.001 (table 1 and figure 2).

**DISCUSSION**

The results of this study indicate significant biomechanical performance differences between the TPR brands tested across

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**Table 1** Measured respiratory parameters with differing test lung compliance and T-piece device

<table>
<thead>
<tr>
<th>Test lung compliance mL/cmH₂O</th>
<th>TPR device</th>
<th>rPAP mean (SD)</th>
<th>Neopuff mean (SD)</th>
<th>GE Panda mean (SD)</th>
<th>Draeger Resuscitaire mean (SD)</th>
<th>Atom mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>PIP</td>
<td>20.5 (0.07)</td>
<td>20.3 (0.09)</td>
<td>24.5 (0.19)</td>
<td>23.5 (0.10)</td>
<td>20.1 (0.07)</td>
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<td>PEEP</td>
<td>4.9 (0.08)</td>
<td>4.8 (0.07)</td>
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<td>5.2 (0.07)</td>
<td>4.9 (0.09)</td>
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<tr>
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<td>TV</td>
<td>9.4 (0.13)</td>
<td>8.9 (0.12)</td>
<td>11.3 (0.15)</td>
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<tr>
<td></td>
<td>IPM</td>
<td>60.0 (1.90)</td>
<td>60.0 (1.34)</td>
<td>60.0 (1.34)</td>
<td>60.0 (1.84)</td>
<td>60.0 (2.45)</td>
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<td>1.0</td>
<td>PIP</td>
<td>20.4 (0.07)</td>
<td>20.2 (0.06)</td>
<td>21.0 (0.12)</td>
<td>20.4 (0.09)</td>
<td>20.1 (0.10)</td>
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<tr>
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<td>PEEP</td>
<td>4.9 (0.09)</td>
<td>5.0 (0.09)</td>
<td>5.1 (0.09)</td>
<td>5.0 (0.09)</td>
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<td>TV</td>
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<td>17.5 (0.21)</td>
<td>16.0 (0.20)</td>
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<td></td>
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<td>60.0 (2.47)</td>
<td>60.0 (1.39)</td>
<td>60.0 (1.64)</td>
<td>59.9 (1.66)</td>
<td>60.0 (1.98)</td>
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<td>2.0</td>
<td>PIP</td>
<td>19.9 (0.10)</td>
<td>19.6 (0.23)</td>
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<td>19.9 (0.07)</td>
<td>19.2 (0.14)</td>
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<tr>
<td></td>
<td>PEEP</td>
<td>4.8 (0.09)</td>
<td>5.8 (0.33)</td>
<td>5.4 (0.12)</td>
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<td>37.4 (1.05)</td>
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<td>60.0 (1.45)</td>
<td>60.2 (1.70)</td>
<td>60.0 (1.34)</td>
<td>60.1 (1.42)</td>
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<td>PIP</td>
<td>18.7 (0.19)</td>
<td>18.7 (0.15)</td>
<td>19.9 (0.12)</td>
<td>19.4 (0.13)</td>
<td>17.2 (0.24)</td>
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<tr>
<td></td>
<td>PEEP</td>
<td>4.9 (0.10)</td>
<td>9.0 (0.16)</td>
<td>9.1 (0.20)</td>
<td>10.0 (0.21)</td>
<td>7.2 (0.16)</td>
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<tr>
<td></td>
<td>TV</td>
<td>48.8 (1.67)</td>
<td>35.3 (0.86)</td>
<td>37.9 (0.91)</td>
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<td>60.1 (2.74)</td>
<td>60.1 (1.58)</td>
<td>60.1 (1.65)</td>
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<td>60.1 (1.77)</td>
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<td>5.0</td>
<td>PIP</td>
<td>18.0 (0.16)</td>
<td>18.6 (0.16)</td>
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<tr>
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<td>5.0 (0.14)</td>
<td>9.5 (0.20)</td>
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<td>9.5 (0.16)</td>
<td>7.4 (0.19)</td>
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<tr>
<td></td>
<td>TV</td>
<td>54.7 (1.51)</td>
<td>35.7 (1.00)</td>
<td>38.9 (1.07)</td>
<td>38.6 (0.94)</td>
<td>35.6 (1.25)</td>
</tr>
<tr>
<td></td>
<td>IPM</td>
<td>60.1 (1.55)</td>
<td>60.0 (1.52)</td>
<td>60.1 (1.65)</td>
<td>60.0 (1.32)</td>
<td>60.1 (1.62)</td>
</tr>
</tbody>
</table>

IPM, inflations per minute; PEEP, positive end-expiratory pressure (cmH₂O); PIP, peak inspiratory pressure (cmH₂O); TPR, T-piece resuscitator; TV, tidal volume (mL).
compliance ranges expected in newborn infants, which may be clinically significant and potentially hazardous. Given the low level evidence cited in the latest ILCOR recommendations for the use of PEEP in both preterm and term resuscitation at birth, device-dependent performance characteristics are critical and require more clinical studies.

Dramatic differences in the two methods of PEEP generation and their contribution to device imposed inadvertent PEEP during IPPV can be seen between the new rPAP device and traditional TPR design. Only rPAP showed no inadvertent elevations in delivered PEEP over set value across the range of lung compliances tested (figure 2). At Crs of 5 mL/cmH\textsubscript{2}O, the other four brands of TPR demonstrated significant elevations of mean PEEP ranging from 7.4 cmH\textsubscript{2}O (Atom) to 10.3 cmH\textsubscript{2}O (GE Panda). These systems use a screw occlusion flow resistor that imposes substantial expiratory resistance, which is system inflow dependent. PEEP levels over 8 cmH\textsubscript{2}O in preterm animal resuscitation models without surfactant use have been associated with pneumothorax.

The specific behaviour of the warmer inbuilt TPR systems tested (GE Panda and Draeger) at low Crs of delivering elevated PIPs over the set value was unexpected. This characteristic was confirmed on six GE Panda systems and two Draeger Resuscitaire units. Investigation of the APL valves revealed a flow/pressure controlled diaphragm design that exhibited a slower pressure limiting response with low system compliance, compared with

Figure 2  Box plot of measured positive-end expiratory pressures (PEEP) cmH\textsubscript{2}O grouped by test lung compliance (Crs).

Figure 3  Box plot of measured tidal volume (TV) mL grouped by test lung compliance (Crs).
the spring relief design of the three other stand-alone models tested (figure 4). Excessive PIPs may injure fragile preterm lung and initiate chronic lung disease.\textsuperscript{36,37} This brief adverse PIP spike over set value was undetected by the operator. Preliminary investigations with another lung simulation model\textsuperscript{38} indicate the effect may be reflected in the alveolar and be greater in magnitude with shorter lung time constants and higher preset PIP values.

A recent review of newborn respiratory transition from fluid filled to air filled state by Hooper\textit{et al.}\textsuperscript{27} proposes a three-phase process characterised by rapid dramatic changes from high airways resistance and low compliance to a state of much lowered resistance and higher compliance several minutes later with established respiration. Existing data on healthy term infants less than 3 hours old showed measured mean compliance of 4.75±1.67 mL/cmH\textsubscript{2}O, which increased to a mean of 6.24±1.45 mL/cmH\textsubscript{2}O (2.0±0.4 mL/cmH\textsubscript{2}O/kg) after 24 hours of life.\textsuperscript{39} Recent work by McEvoy\textit{et al.}\textsuperscript{33} showed similar values with mean Crs in term infants examined at 3 days of life of 1.32±0.36 mL/cmH\textsubscript{2}O/kg. The TPR devices examined are rated for use by the manufacturers to 10 kg weight, which corresponds to infants between 6 and 12 months of age. In New South Wales, Australia, TPR devices are in common use for infant resuscitation in emergency departments. We have previously published the only study to date of a 10 kg infant model that assessed one brand of TPR.\textsuperscript{14} This study compared the Neopuff TPR to an Ambu SIB with PEEP and showed the TPR had elevations of PEEP above set value (5 cmH\textsubscript{2}O) to 10 cmH\textsubscript{2}O with slower inflation rates of 30 per minute. Finer and Rich\textsuperscript{40} detailed eight instances of inadvertent PEEP (7.1–15.5 cmH\textsubscript{2}O) above set value (5 cmH\textsubscript{2}O) in 120 recorded preterm (470–875 g) resuscitations using Neopuff TPR, which were attributed to possible accidental rotation of the PEEP knob. Although lung compliance in this population is generally low (<1 mL/cmH\textsubscript{2}O), other combined mitigating factors can increase the total system time constant, contributing to inadvertent PEEP when using TPR for IPPV. These may include: presence of ETT, use of surfactant, high initial set PIP, lower delivery circuit gas flowrate, finger distance above PEEP valve outflow during expiration, high airway resistance, increasing compliance and TPR PEEP valve expiratory resistance. Results in our study indicated device design influences only contributed to inadvertent PEEP with lung compliances >1 mL/cmH\textsubscript{2}O.

Interpretation of bench test and manikin model data is subject to the usual caveats of generalising results to actual human resuscitations and lung physiology. The model in this study is limited in the use of a fixed airway resistance, a single gas inflow rate and one level of PIP that may contribute to producing inadvertent PEEP.\textsuperscript{14–16} Results in this study provide a valuable insight into basic performance and safety characteristics in a no-leak model similar to the presence of endotracheal tube or good face mask seal in human resuscitation.

Increasing the PIP is a standard method of resuscitation escalation.\textsuperscript{10} The considerable performance differences seen between brands in this study with recommended starting pressures suggest further research is required to examine the impact of increasing PIP at different Crs.

There is an established clinical use of the fluidic flip design used in the rPAP device to provide CPAP for newborn respiratory distress providing less WOB; this may be advantageous compared with higher values reported with standard TPR and face mask at resuscitation. However, its use to produce PEEP during IPPV at newborn resuscitation is a new method with only one clinical feasibility trial to date.\textsuperscript{22} We have shown significant advantages of this design over a range of current TPR devices.

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**Figure 4** Examples of recorded pressure waveforms for each TPR device tested: 1: rPAP; 2: Neopuff; 3: GE Panda; 4: Draeger Resuscitaire; and 5: Atom at test lung compliances: A: 0.5 mL/cmH\textsubscript{2}O and B: 5.0 mL/cmH\textsubscript{2}O. Time scale 1 s per segment. PEEP, positive-end expiratory pressure; PIP, peak inflation pressure; TPR, T-piece resuscitator.
with regard to the production of device generated inadvertent PEEP.

CONCLUSION

The results of this study indicate important biomechanical differences in performance between differing brands of TPR across the range of lung compliance expected at birth that can have clinically relevant consequences. The overpressure spike of PIP demonstrated in the two inbuilt TPR systems at low compliance is of concern and requires further detailed examination. Clinicians need to be aware of the inherent potential of standard TPRs using mechanical screw occlusion that may result in significant levels of inadvertent PEEP with higher lung compliance.

Contributors

MKH: study design, data collection, data and statistical analysis and writing of manuscript. MBT: data collection, data and statistical analysis and writing of manuscript. AM and SD: data interpretation, manuscript writing, construction and review. TD: manuscript writing, construction and review.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

TD is one of the inventors of the rPAP system and was not expressly granted.

Patient consent

Not required.

Ethics approval

This study was approved by the Sydney West Area Health Service Review and Ethics Committee.

Provenance and peer review

Not commissioned; externally peer reviewed.

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REFERENCES

Transducin-Like Enhancer of Split 3 (TLE3) Expression Is Associated with Taxane Sensitivity in Nonserous Ovarian Carcinoma in a Three-Cohort Study

Brian Z. Ring, Rajmohan Murali, Robert A. Soslow, David D.L. Bowtell, Sian Fereday, Anna deFazio, Nadia Traficante on behalf of the Australian Ovarian Cancer Study; Catherine J. Kennedy, Alison Brand, Raghwa Sharma, Paul Harnett, and Gol Samimi

Abstract

Background: Chemoresistance is a major challenge in ovarian cancer treatment, resulting in poor survival rates. Identifying markers of treatment response is imperative for improving outcome while minimizing unnecessary side effects. We have previously demonstrated that expression of transducin-like enhancer of split 3 (TLE3) is associated with favorable progression-free survival in taxane-treated ovarian cancer patients with nonserous histology. The purpose of this study was to perform an independent evaluation of the association of TLE3 expression with response to taxane-based chemotherapy in nonserous ovarian cancer, to validate its role as a potential therapeutic response marker for taxane-based chemotherapy.

Methods: We performed immunohistochemical staining of TLE3 on ovarian cancer specimens from the Australian Ovarian Cancer Study, the Westmead Gynaecological Oncology Biobank, and Memorial Sloan Kettering Cancer Center. Progression-free survival and overall survival were assessed to validate an association between TLE3 expression and response to taxane therapy that we previously observed in a smaller study.

Results: Expression of TLE3 was associated with favorable outcome only in patients who had received paclitaxel as part of their treatment regimen for both 3-year progression-free survival (n = 160; HR, 0.56; P = 0.03) and 5-year overall survival (HR, 0.53; P = 0.04). Further analysis revealed that the predictive association between TLE3 expression and outcome was strongest in tumors with clear cell histology.

Conclusions: The association between high TLE3 expression and a favorable response to taxane-containing chemotherapy regimens was validated in patients with nonserous ovarian cancer.


Introduction

Epithelial ovarian carcinoma is the most lethal gynecologic cancer, with a 5-year survival rate of 30% to 50%. Epithelial ovarian cancers are generally classified according to their histology and molecular characteristics (1). Histologic and molecular characterization of ovarian carcinoma has revealed that the different histotypes of ovarian cancer represent distinct diseases with distinct sites of origin, pathogenesis, and responses to therapy. High-grade serous carcinomas are characterized by mutations in TP53, whereas endometrioid, clear cell, low-grade serous, and mucinous carcinomas are characterized by mutations in genes including KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A, and/or PPP2R1A (1, 2).

The poor survival rate in women with ovarian cancer reflects late diagnosis (due to lack of adequate screening options) and poor response to chemotherapy. The standard treatment regimen following debulking surgery includes a combination of platinum-based and taxane-based chemotherapy, which shows improved response rates, progression-free survival, and overall survival in ovarian cancer patients compared with platinum-based chemotherapy alone (3). Although a majority of women initially respond to treatment, up to 75% eventually relapse with chemoresistant disease (4). Chemoresistance in ovarian cancer develops in response to alterations in intracellular drug concentration (increased sequestration, increased efflux), DNA repair/cell-cycle regulation and/or intracellular signaling (5). In ovarian cancers are generally classified according to their histology and molecular characteristics (1). Histologic and molecular characterization of ovarian carcinoma has revealed that the different histotypes of ovarian cancer represent distinct diseases with distinct sites of origin, pathogenesis, and responses to therapy. High-grade serous carcinomas are characterized by mutations in TP53, whereas endometrioid, clear cell, low-grade serous, and mucinous carcinomas are characterized by mutations in genes including KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A, and/or PPP2R1A (1, 2).

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TLE3 is Associated with Taxane Sensitivity

Tissue microarrays, immunohistochemistry, and scoring

The AOCS cohort consisted of 15 tissue microarray (TMA) blocks containing one to eight 0.6-mm cores sampled from representative paraffin blocks from each patient. The three Westmead TMAs each contained one to three samples from representative paraffin blocks of each patient's tumor, whereas the three MSKCC TMAs each contained two to 15 samples from representative paraffin blocks of each patient's tumor. Staining methods and scoring criteria are as described earlier (17, 18). Briefly, slides were de-paraffinized by submerging in xylene 3 × 10 minutes and rehydrated by rinsing 3x in 100% ethanol and 2x in 95% ethanol. Antigen retrieval was performed by boiling in a microwave for 11 minutes in 10 μmol/L buffered citrate (pH 6.0). Slides were blocked in 0.03% hydrogen peroxide and stained using antibody diluted to appropriate titer in Dako Diluent (DakoCytomation, Glostrup, Denmark) for 1 hour at room temperature. Breast cancer cases and tumor-derived cell lines were tested as positive and negative controls. Secondary antibody was applied for 1 hour and staining was visualized using the DakoCytomation Envision staining kit according to the manufacturer's instructions. Cores were manually scored by a pathologist (R. Murali), and considered positive if greater than 30% of nuclei stained regardless of staining intensity. Composite scores for a single case were compressed by assuming the maximum score (for 1–3 replicate cores, or by using the rounded average score for ≥4 replicate cores).

Statistical considerations

The correlation between TLE3 expression (TLE3þ or TLE3−) and outcome was analyzed using S-plus software (Tibco Software Inc.). Kaplan–Meier and log-rank analyses were used to analyze the association between expression of TLE3 and progression-free survival or overall survival in invasive cases. χ2, Log-rank, and Kruskal–Wallis analyses were used to analyze differences between the cohorts (as indicated in Table 1). Cox proportional hazards analysis was performed to investigate the association between TLE3 expression and outcome grouped by grade or stage. Interactions between TLE3 expression and taxane treatment were examined by multivariate analysis in which TLE3 expression, taxane treatment, and the interaction term were assessed simultaneously by Cox proportional hazards analysis. All P values are two-sided.

Results

Patient characteristics and TMA staining for TLE3 expression

Table 1 describes the clinical characteristics for the patient cohorts analyzed in this study, which significantly differed between the AOCS, the MSKCC, and the Westmead cohorts. In the combined study (62.7%) of patients were treated with a regimen containing a taxane, ranging from 34% (MSKCC) to 65% (AOCS, Table 1). Across all cohorts, 465/886 (53%) of patients expressed TLE3 (58% AOCS, 49% MSKCC, 40% Westmead). Expression of TLE3 was slightly higher in the nonserous histotypes compared with serous cases (58.0% TLE3þ in nonserous, 50.3% serous, χ2 P = 0.04). Within patients of known treatment used for the analyses in this study, there was no significant difference in TLE3 expression (52.9% TLE3þ in nonserous, 51.2% serous, χ2 P = 0.75). Fig. 1 presents immunohistochemical expression of TLE3 in different tumors types.

Materials and Methods

Patient samples and assembly of clinical datasets

Ovarian cancer cohorts, including paraffin tissue blocks and anonymized clinical data (treatment and outcome data) from the Australian Ovarian Cancer Study (AOCS), Memorial Sloan Kettering Cancer Center (MSKCC) and the Gynecological Oncology Biobank at Westmead (Westmead) were used in this study. Institutional review board approval was obtained for the use of patient blocks and examination of clinical data at each respective institute (AOCS: HREC 01/56; MSKCC: protocol 06-107; Westmead: HREC/92/10/4.13). A total of 1,059 patients were analyzed, of whom 1,041 had invasive carcinoma. Of those patients with invasive carcinoma, 633 (496 AOCS, 29 MSKCC, and 108 Westmead) had undergone primary treatment with a taxane-containing regimen. Progression-free survival was determined by CA-125 criteria (19), imaging, and clinical assessment.
The association between TLE3 expression and outcome

Table 2 and Fig. 2 describe the associations between TLE3 expression (TLE3⁺ or TLE3⁻) and progression-free survival (3- and 5-year) in patient subsets defined by treatment (with or without taxane), institutional cohort and tumor histology. Our original study assessed 5-year progression-free survival (18); however, as the median recurrence rate was high, outcome was assessed at 3 and 5 years for the nonserous cases. Across all cohorts, TLE3 expression was significantly associated with reduced recurrence within 3 years in taxane-treated patients with nonserous tumors (n = 160; HR, 0.56; 95% CI, 0.33–0.95; P = 0.03), whereas there was no significant relationship with recurrence in patients not treated with a taxane (n = 40; HR, 0.94; 95% CI, 0.33–2.71; P = 0.91; Table 2; Fig. 2A and B). At 5 years, the association between TLE3 expression and recurrence in the taxane-treated nonserous cancer patients was no longer statistically significant (HR, 0.68; 95% CI, 0.42–1.1; P = 0.12). The association between TLE3 expression and outcome was independent of the contributing institution. Within the AOCS cohort, TLE3 expression was significantly associated with recurrence within 3 years in the nonserous cancers treated with taxane (n = 96; HR = 0.46; 95% CI, 0.23–0.91; P = 0.02). An interaction test to assess the apparent differential response to therapy based on TLE3 expression (TLE3:taxane) was not significant.

Similar results were found upon examination of associations between TLE3 expression and overall survival (Table 2). Across all cohorts, TLE3 expression was significantly associated with improved survival in taxane-treated patients with nonserous tumors (n = 160; HR, 0.53; 95% CI, 0.29–0.99; P = 0.04), whereas there was no significant relationship with overall survival at 5 years in patients not treated with taxane (n = 40; HR, 1.37; 95% CI, 0.44–4.25; P = 0.59; Table 2; Fig. 2C and D). We also performed Cox proportional hazards analysis in the taxane-treated, nonserous cases to investigate the association between TLE3 expression and outcome grouped by grade (low or high) or stage (early or late; Supplementary Tables S1 and S2). When broken down by stage or grade, TLE3 expression was only significantly associated with 3-year PFS in the high-grade group (P = 0.03), possibly due to the decreased size in the subsets. TLE3 was independent of grade when examined in the subsets. TLE3 was independent of grade when examined in the subsets. TLE3 was an independent variable in Cox model including stage (n = 110; HR, 0.52; 95% CI, 0.27–0.99; P = 0.05); however, TLE3 failed to remain significant when assessed in combination with stage.

Among the nonserous carcinomas, a significant association between TLE3 expression and outcome was found only in patients with clear cell carcinoma treated with a taxane, for both 3-year progression-free survival and 5-year overall survival (Table 3; Fig. 3A and B). In the other nonserous tumors, no significant association was observed (Fig. 3C and D). The interaction between
taxane and TLE3 was significant at 5-year overall survival \( (n = 79, \ P = 0.003) \) among clear cell carcinoma cases. The interaction between taxane and TLE3 at 3-year progression-free survival in clear cell carcinoma was stronger than in all nonserous tumors, but did not reach significance \( (P = 0.13) \). In all nonserous tumors, associations of TLE3 with survival were not independent of stage; when examined in a Cox model, including stage, the effect size in the clear cell carcinomas was larger and there was a trend toward significance for improved 5-year overall survival \( (n = 63; \text{HR}, 0.38; 95\% \text{ CI}, 0.14–1.07, \ P = 0.07) \).

Discussion

TLE3 is a member of the TLE family, and acts as a transcriptional repressor of β-catenin in the Wnt pathway. The Wnt pathway regulates cellular processes that promote tumor progression,
Table 2. Associations of TLE3 expression with survival

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<tr>
<td>MSKCC</td>
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<tr>
<td>Nonserous</td>
<td>0.78 (0.25–2.48)</td>
<td>0.86</td>
<td>139</td>
<td>97</td>
<td>236</td>
<td></td>
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<tr>
<td>Serous</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
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including differentiation, cell polarity, and cytoskeletal remodeling, the target of taxane agents (20, 21). Taxanes exert their mechanism of action by interacting with the microtubule structure within the cytoskeleton; thus, it is reasonable to hypothesize that TLE3, as a regulator of the Wnt pathway, may serve as a biomarker of response to agents that disrupt downstream processes of this pathway.

In a previous study, we found an association between TLE3 expression and favorable outcome in a small cohort of nonserous ovarian cancer cases after treatment with taxane (18). As our original study was underpowered to parse out differences between histologic subtypes, in this study we analyzed additional biospecimens to determine whether the association with response to taxane treatment was more prevalent in any specific nonserous subtype. Because nonserous subtypes make up a minority of overall ovarian cancer cases (~30%), we obtained TMAs from 3 different institutions in an effort to validate our previous finding and to strengthen our ability to examine associations of TLE3

### Table 3. TLE3 expression in clear cell (CC) and other nonserous (non-CC) ovarian tumors

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>N: TLE3−</th>
<th>N: TLE3+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>3 years</td>
<td></td>
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</tr>
<tr>
<td>Non-CC</td>
<td>0.59 (0.30–1.17)</td>
<td>0.12</td>
<td>46</td>
<td>51</td>
<td>97</td>
</tr>
<tr>
<td>Taxane+</td>
<td>0.49 (0.09–2.68)</td>
<td>0.40</td>
<td>12</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Taxane−</td>
<td>0.47 (0.21–1.07)</td>
<td>0.07</td>
<td>40</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>CC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxane+</td>
<td>1.94 (0.48–7.93)</td>
<td>0.36</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Taxane−</td>
<td>0.75 (0.41–1.38)</td>
<td>0.35</td>
<td>46</td>
<td>51</td>
<td>97</td>
</tr>
<tr>
<td>5 years</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Non-CC</td>
<td>0.75 (0.41–1.38)</td>
<td>0.35</td>
<td>46</td>
<td>51</td>
<td>97</td>
</tr>
<tr>
<td>Taxane+</td>
<td>0.48 (0.01–2.05)</td>
<td>0.31</td>
<td>12</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Taxane−</td>
<td>0.54 (0.25–1.17)</td>
<td>0.12</td>
<td>40</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>CC</td>
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</tr>
<tr>
<td>Taxane+</td>
<td>1.94 (0.48–7.93)</td>
<td>0.36</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Taxane−</td>
<td>0.71 (0.32–1.57)</td>
<td>0.40</td>
<td>46</td>
<td>51</td>
<td>97</td>
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<tr>
<td>Overall survival</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Non-CC</td>
<td>0.71 (0.32–1.57)</td>
<td>0.40</td>
<td>46</td>
<td>51</td>
<td>97</td>
</tr>
<tr>
<td>Taxane+</td>
<td>0.31 (0.03–3.03)</td>
<td>0.28</td>
<td>12</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Taxane−</td>
<td>0.30 (0.11–0.85)</td>
<td><strong>0.02</strong></td>
<td>40</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>CC</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Taxane+</td>
<td>5.23 (1.99–23.06)</td>
<td>0.03</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Taxane−</td>
<td>0.31 (0.03–3.03)</td>
<td>0.28</td>
<td>12</td>
<td>12</td>
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expression and taxane sensitivity in individual nonserous subtypes. We examined a total of 1,041 cases and found that TLE3 was expressed in 52% of tumors, compared with 30% in our previous study (Table 1). This difference in the proportion of cases expressing TLE3 could reflect the enrichment for nonserous histotypes used in our current study (in particular, mucinous cases are significantly over-represented in the group of TLE3+ tumors). Studies have demonstrated that mutations in the Wnt pathway are frequently present in nonserous histotypes of ovarian cancer (11, 22), suggesting that TLE3 expression may also be altered in this subset of tumors. In the combined cohorts, and in AOCS alone (the cohort with the largest sample size), expression of TLE3 was associated with improved progression-free survival at 3 years specifically in taxane-treated, nonserous cases (Table 2). Furthermore, TLE3 expression was associated with favorable overall survival only in taxane-treated, nonserous cases (Table 2). Additional analysis demonstrated that clear cell tumors specifically drive this association (Table 3), warranting additional molecular studies in this tumor type.

A number of studies have investigated TLE3 as a biomarker of taxane sensitivity in other cancer types, with conflicting results. Kulkarni and colleagues (17) first identified an association between TLE3 expression and reduced recurrence and improved disease-free interval in cancer patients treated with a taxane-based regimen. This finding was validated in a cohort of tumors from women with triple negative breast cancer who had been treated with a taxane-based regimen, suggesting that TLE3 does not merely serve as a surrogate biomarker for ER or HER2 expression. Although early studies have supported the role of TLE3 as a marker of taxane response, the findings of other studies are contradictory. In a study of TLE3 expression in angiosarcoma, TLE3 expression was not associated with taxane sensitivity (12). More recently, Bartlett and colleagues (23) prospectively examined TLE3 expression in a large NCIC Clinical Trial Group breast cancer cohort which had been randomized to two taxane-based treatment arms and a single non-taxane-based treatment arm. In this study, 83% of breast cancers expressed TLE3, compared with 58% in the original breast cancer study. The authors found no evidence that TLE3 expression was associated with taxane response in women diagnosed with breast cancer, contrary to earlier findings. These differences may be due to the heterogeneity of the breast cancer cohort used in this study (24).

These conflicting findings indicate that there is still a great need for identification and validation of biomarkers of chemotherapy response, particularly in cancers with poor outcomes and high rates of recurrence (such as ovarian cancer and triple negative breast cancer). The inability to validate response-associated biomarkers may be due to (i) insufficient sample numbers; (ii)
incomplete stratification of histologic subtypes, and (iii) variabil-
ity in biomarker staining and quantification.

In summary, we have demonstrated an association between high TLE3 expression and a favorable response to taxane-contain-
ning chemotherapy regimens in a large multi-institutional cohort of patients with nonserous (especially clear cell) ovarian carci-
noma. Further studies are needed to explore in detail the molec-
ular mechanisms underlying this apparent chemosensitiveness. In
patients with nonserous ovarian carcinoma being considered for
systemic therapy, TLE3 expression may serve as a simple and
useful method of identifying patients who are likely to benefit
from taxane-based regimens.

Disclosure of Potential Conflicts of Interest

A. deFazio reports receiving commercial research funding from AstraZeneca.
No potential conflicts of interest were disclosed by the other authors.

Disclaimer

This material should not be interpreted as representing the viewpoint of
the U.S. Department of Health and Human Services, the NIH, or the National
Cancer Institute.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.Z. Ring, R. Murali, S. Fereday, A. deFazio, R. Sharma, G. Samimi

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Writing, review, and/or revision of the manuscript: B.Z. Ring, R. Murali, R.A. Soslow, D.D.L. Bowtell, S. Fereday, A. deFazio, C.J. Kennedy, A. Brand, R. Sharma, Paul Harnett, G. Samimi

Acknowledgments

AOCS: The AOCS gratefully acknowledges the cooperation of the partic-
ipating institutions in Australia, and also acknowledges the contribution of the
study nurses, research assistants, and all clinical and scientific collabora-
tors. A complete list of the AOCS Study Group can be found at www.
aocs.org. AOCS was supported by the U.S. Army Medical Research and Materiel Command under DAMD17-01-1-0729, The Cancer Council
Victoria, Queensland Cancer Fund, The Cancer Council New South Wales, The Cancer Council South Australia, The Cancer Foundation of Western
Australia, The Cancer Council Tasmania and the National Health and Medical Research Council of Australia [NHMRC; ID 400413, ID 400281].
The AOCS gratefully acknowledges additional support from Ovarian
Cancer Australia and the Peter MacCallum Foundation. MSKCC: This
research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA08748. Westmead: We acknowledge the Cynecological Oncology Biobank at Westmead (Cynbiobank), a member of the Aus-
trasian Biospecimen Network Oncology group, which was funded by the
National Health and Medical Research Council Enabling Grants ID
310670 & ID 628903 and the Cancer Institute NSW Grant ID 12/RIG/1-
15 & RIG/1-16.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 27, 2017; revised January 25, 2018; accepted March 5, 2018, published first March 12, 2018.

www.aacjournals.org
Cancer Epidemiol Biomarkers Prev; 27(6) June 2018

567
Transvaginal evisceration of small bowel

Transvaginal evisceration of the small bowel is a rare event. It was first described by Hyernaux in 1864. In 1996, a review of the literature from 1901 onwards reported 60 cases.¹ By 2002, O’Brien et al. had updated this to 80 cases.² Transvaginal small bowel evisceration is an extremely unusual condition that most physicians and surgeons will never encounter.

In this case, we present a 66-year-old female who was transferred to our tertiary referral unit. She initially presented to a rural hospital with symptoms of nausea, vomiting, obstipation, per vaginal bleeding and lower back pain. She had a background history of cystectomy, radical hysterectomy and had an ileal conduit for bladder cancer, without adjuvant chemoradiotherapy. On examination, she was haemodynamically stable with evidence of small bowel herniation through the vagina which appeared grossly oedematous with no evidence of ischaemia (Fig. 1). Computed tomography confirmed the transvaginal evisceration of small bowel (Figs 2,3). Attempts for reduction were unsuccessful and she was then transferred to our unit with planned operative management by specialist colorectal surgeons and pelvic gynaecologist.

She was examined in the operating theatres in a lithotomy position under general anaesthesia. There was approximately 50 cm of small bowel prolapsing from an anterior vaginal wall defect extending from the vaginal vault to the pubic tubercle. The herniated single loop of mid small bowel was non-viable. Healthy proximal and distal ends of the bowel was successfully retracted down through the defect with enough length to perform a side-to-side stapled anastomosis with resection in continuity for the affected loop of small bowel using the EndoGIA 80 stapler and Ligasure for mesenteric ligation. The anastomosis was reinforced with 3-0 PolyDioxanone sutures along the staple line and cut edges of the mesentery, washed with saline and reduced through the vaginal wall defect. Following bowel resection and manual reduction, a pelvic repair was performed by gynaecologists. This included an anterior and posterior vaginal repair with Restorelle mesh and transvaginal sacrospinous ligament fixation with Aris transobturator tape. She had an unremarkable post-operative recovery with return

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Fig. 1. Perineal evisceration of small bowel.

Fig. 2. Computed tomography (sagittal section) of the abdomen and pelvis; P, pubic tubercle; C, coccyx; H, hernia.
of bowel function within 2 days, and no significant post-operative complications.

Small bowel evisceration has been most commonly described after abdominal hysterectomy or vaginal hysterectomy. It has also been reported to be associated with radical cystectomy, vaginal prolapse surgery, perineal proctectomy (Altemeier’s procedure) and trauma. Majority of patients described in case reports and series had associated enteroceles, stretching and thinning the vagina and increasing its susceptibility to rupture. In this case, the patient had both cystectomy and hysterectomy. Prior to this emergency presentation, the patient reported having multiple previous reoperations for transvaginal bowel herniation with primary repair and anterior vaginal wall repair. This was actually her third reoperation post cystectomy and hysterectomy.

Transvaginal evisceration of the small bowel is a surgical emergency. It often leads to strangulation of small bowel. Both repair by laparotomy and via the vaginal route have been described in the literature, and successful laparoscopic repair has also been described. Majority of cases with small bowel ischaemia reported in the literature required a laparotomy. In this case, even though the small bowel was ischaemic, we were able to successfully resect and anastomose the small bowel and repair the vaginal prolapse from a vaginal approach without a laparotomy.

References


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doi: 10.1111/ans.14290
Two Rare Cases of Antenatal Microphthalmia and Anophthalmia: Case Presentation and Review

Authors: Searle A, Shetty P, Melov S, Alahakoon TI.
Journal of paediatrics and child health (1034-4810), 54, p. 109

Background: Microphthalmia (Case A) and anophthalmia (Case B) are rare fetal abnormalities. These conditions refer to a small eye or the complete absence of ocular tissue. The combined incidence is estimated at 1/10,000 births. Pre-natal diagnosis is neither frequent nor easy and relies on precise high quality ultrasonography. MRI and amniocentesis with microarray testing provide useful information for counselling and diagnosis in microphthalmia or anophthalmia cases.

Methods: Patient consent and ethics approval for both cases studies were obtained. Patient file review was undertaken together with imaging, cytogenetic and pathology results.

Results: Case A was a 36 year old women with a history of a 35 week stillbirth of unknown aetiology. Left microphthalmia with a small biparietal diameter of <5th centile was diagnosed at 21 weeks. Postmortem demonstrated left sided microphthalmia with associated persistent hyperplastic primary vitreous, probable hypoplasia to the left side of the face and thin left optic nerve as compared to the right. Case B morphology scan at 20 weeks revealed an absent right globe with suspected brain anomaly. An MRI confirmed dysplastic ventricular system with the ophthalmic anomaly.

Post mortem revealed right sided anophthalmia and right optic nerve atrophy with mild bilateral ventriculomegaly. Both women had normal chromosome microarray on amniocentesis. Maternal fetal medicine and genetic counselling was provided and both women elected termination of pregnancy due to the uncertainty of outcome for these conditions.

Conclusions: Optimal care requires early diagnosis. Current Ultrasound protocols for imaging of the fetal eye are inconsistent and inadequate to screen for the spectrum of ocular malformations.
Validation of the accuracy of postpartum haemorrhage data in the ObstetriX database: A retrospective cohort study

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\textbf{ARTICLE INFO}

\textbf{Keywords:}
Australia
data collection
Electronic record
Medical record
ObstetriX
Postpartum
Postpartum haemorrhage

\textbf{ABSTRACT}

\textbf{Background:} Data related to postpartum haemorrhage (PPH) are important clinical parameters which can be applied to all places of birth, and their recording can be missed by busy clinicians providing critical care to women. We compared the accuracy of electronic ObstetriX records to the paper-based medical records of the women who sustained PPH.

\textbf{Methods:} In this retrospective cohort study over a period of one month, 363 electronic records were compared to the paper-based medical records. The volume of blood loss for each patient and interventions for PPH were compared across birth unit, operating theatre and postpartum ward. The kappa statistic for agreement between the two types of recording methods was calculated.

\textbf{Results:} There was substantial agreement between the ObstetriX records and medical records for the volume of blood loss at birth (kappa = 0.74), but poor agreement between records for the cumulative total volume of blood loss (kappa = 0.18). More women who experienced PPH and delivered in the operating theatre had errors in their ObstetriX records compared to women who had PPH with births in the birth unit (50% vs 16%; n = 73, P = 0.005). Interventions for PPH were found to be poorly recorded in ObstetriX, with 84% (n = 64/76) of women who experienced PPH having none of the interventions they received recorded.

\textbf{Conclusions:} The ObstetriX database was not a generally reliable source of data relating to PPH. However, some data were recorded reliably, in particular, the volume of blood loss at birth.

\section{1. Introduction}

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide and contributes to severe maternal morbidity in western countries \cite{1,2}. More than half of all maternal deaths happen due to PPH during the first day after birth. PPH can occur when there are risk factors, but it often happens without warning. It is estimated that PPH is the cause of 140,000 deaths across the world each year, indicating one death every four minutes \cite{3}. Women who do not die suffer serious morbidity after PPH, including conditions such as adult respiratory distress syndrome, coagulopathy, shock, loss of fertility and pituitary necrosis (Sheehan syndrome). Considering the critical impact that PPH can have on women’s lives, accurate recording of it in the women’s medical files is crucial so that the haemorrhage can be properly managed and any consequences can be prevented or treated \cite{4}.

Evidence from previous research indicates that data relating to PPH are not accurately recorded in hospital databases. A review of a stratified random sample of 4541 hospital medical records of women who gave birth in Washington state in the United States in 2000 showed that 6.7% (n = 305) of women had medical records of PPH. However, only

\textbf{Abbreviations:} EBL, estimated blood loss; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; NSW, New South Wales; PPH, postpartum haemorrhage

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https://doi.org/10.1016/j.ijmedinf.2018.09.020

Received 25 May 2018; Received in revised form 21 September 2018; Accepted 25 September 2018

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4.8% (n = 219) were recorded in the women’s hospital discharge data [5]. A retrospective study comparing medical records with coded hospital discharge data in California found that coding for PPH had a sensitivity of 59% (95% CI, 48%–69%) [6]. Similar research on French discharge data reveal that miscoding of postpartum interventions for PPH resulted in a high number of false negatives in the coded data [7].

Another prospective observational study in the United Kingdom showed that among 10,213 patient records, the error rate of reported estimated blood loss (EBL) in the electronic records was 14%, which was higher than error rates of maternal age (0.5%), maternal date of birth (0.2%), mode of birth (2.0%), baby date of birth (0%), time of birth (0.4%), sex (0.4%) and birth weight (0.2%) [8]. In a large-scale study in France [9], the blood transfusion data recorded in administrative databases was used to estimate the frequency of obstetric haemorrhage in pregnant women (n = 1,629,537). Results of that study showed that administrative data have a sensitivity of 66.3%. It was concluded that the data were sufficiently accurate to estimate the rates of obstetric haemorrhage.

Validation of New South Wales (NSW) hospital administrative data relating to PPH records has been performed several times. A sensitivity of 73.8% (95% CI, 63.1%–82.8%) for the diagnosis of PPH in hospital discharge data (with medical records as the gold standard) has been reported [10]. The same study also found a sensitivity of 50.3% when PPH was defined by reviewing medical records on EBL. Similar sensitivities have been reported for PPH in coded data in NSW (58.6%, 95% CI, 38.9–76.5) [11].

ObstetriX is an electronic database used across NSW that contains demographic data, obstetric history and details about the current pregnancy, birth and postpartum events. It is the database used by most obstetric hospitals in NSW. This prospective recording of birth demographics and events allows for an accurate record of birth data of women. ObstetriX has the potential to be an easily assessable, powerful database for monitoring and standardisation of obstetric data, and collection of relevant data for future research. The ObstetriX database has been used as a source of information for retrospective studies, for example the exploration of the effect of skin-to-skin contact and breastfeeding on the rates of PPH [12]. Research based on this database has assumed a high degree of data accuracy. Given its increasing popularity as a source of data for obstetrics research, we planned to investigate the accuracy of ObstetriX in women who sustained PPH.

Despite the wide application of digital database recording system like ObstetriX database, most hospitals still use paper record in conjunction with this electronic system. The paper records allow staff to give descriptive notes and provide more detailed picture of any event to complement the electronic recording system.

Digital data and paper-based records are used in combination of each other to form a comprehensive source of information. A major element of integrating these records is improving data quality and completeness and having important clinical data available when required. This is fundamental to promoting communication between healthcare professionals and enhancing patient safety [13]. Research has shown that digitising health records can introduce new risks, as missing or inaccurate data may disallow valid interpretation for health-related questions that can, in turn, endanger patient’s safety [14].

Data related to PPH are important clinical parameters which can be applied to all places of birth. However, their recording can be missed by busy clinicians providing critical care to women. There is the added complexity of transferring women between wards for appropriate care (e.g. the operating theatre, intensive care unit and postpartum care). Versatile systems and training methods that allow accurate recording of these important data in dynamic situations are crucial to the effectiveness of the electronic recording system.

The use of electronic health records has emerged to enhance patient’s care, improve safety and security, promote evidence based practice, ease the staff workload, decrease the use of paper charts and drop the cost [15,16]. Accurate register of electronic health records enables examination and development of effective treatments and facilitates the integration of patient health history for safe and appropriate care [17]. The current challenge is that few clinicians and healthcare professionals receive formal training in informatics, data entry or other increasingly relevant skills, hence increasing the risk of inaccurate data in electronic records [14].

So far, there has been no validation of the PPH data in the ObstetriX database, but validation of other data sets from ObstetriX has found low accuracy. For example, one study has shown that the accuracy of the ObstetriX database in collecting data on female genital mutilation increased from 14% to 90% over six years [18]. However, it was only 35% correct in identifying the type of female genital mutilation. Since the recording of accurate ObstetriX data on the prevalence of PPH is necessary to improve health care services and women’ outcomes, we conducted this study to validate the PPH data in the ObstetriX database and to determine whether the rates of discrepancies are similar to those in the literature for other key performance indicators. The ObstetriX database allows clinicians to record the volume and location of blood loss. We were also interested if the accuracy of data collected regarding PPH differed between locations of delivery within the same hospital.

2. Materials and methods

2.1. ObstetriX database

The ObstetriX database was first introduced to our hospital in 2004 and is currently being upgraded to a new version (eMaternity). Our hospital (Westmead Hospital) is a tertiary unit serving a multiethnic, low-middle income population in addition to referred high-risk pregnancies. It is the largest maternity hospital in the state of New South Wales, Australia with about 5500 births per year and 14 neonatal intensive care beds. In the majority of hospitals in the NSW that use electronic recording, ObstetriX database is used for record keeping. These hospitals range from tertiary hospitals like Westmead to smaller hospitals of just over a thousand births per year with only low risk patients and special care nursery. At the study hospital and NSW hospitals that use ObstetriX database, data relating to labour and birth are entered into the ObstetriX database by midwives when the patient is transferred from the birth unit to the postnatal ward. Subsequent data from the period spent in the postnatal ward are entered by midwives when the woman is discharged home. Midwifery staff have regular in-service training on the use of the database. Validation rules are built in to flag errors and inconsistencies in data entry. A data custodian at each hospital undertakes limited checking of the validity of the data daily to ensure accuracy of data entry. Any data errors or omissions are followed up with the appropriate clinical staff. To assess the validity of the ObstetriX data relating to PPH in a large tertiary referral hospital, the recorded data were compared to written medical records.

2.2. Medical records

Medical records are considered the conventional method of recording as the data are written on paper contemporaneously by staff member directly involved in the events recorded. Staff in our hospital use medical records to complement the ObstetriX recording, giving it a more detailed and descriptive approach in recording the events, which is still considered a gold standard practice.

2.3. Study design

Our study was a retrospective cohort study to assess the accuracy of the mother’s paper-based medical record compared to the information in the ObstetriX database. We included all patients’ data from booking into the hospital to the time of discharge after the birth of their babies. The relevant data from ObstetriX from booking-in to post-birth discharge were extracted for those who gave birth between 1 and 26
January 2016. Because our aim was to assess the accuracy of the mother’s medical record, we treated multiple births as a single.

2.4. Procedure

Two independent researchers who were not involved in the care for women compared women’ medical records to the ObstetriX records and noted discrepancies. The progress notes, partogram (graphed labour progress), state-wide standard maternity observation chart and operation reports were included in the assessment when applicable. Women were excluded from the analysis if records were incomplete (progress notes absent or partially absent, EBL from birth unit or operating theatre not recorded in written medical record, data absent from ObstetriX). Records were also excluded when the birth did not occur in the study hospital but women were transferred there after birth.

2.5. Outcomes

2.5.1. Calculating estimated blood loss

We compared EBL for each birth recorded in the written medical records to the data available in the ObstetriX database. ObstetriX allows the recording of EBL in categories of 500 mL, from 0 mL to a maximum of ‘more than 1500 mL’. PPH was defined as EBL of 500 mL or more, according to local practice. It is mandated hospital practice for all staff to measure blood loss rather than simply estimate it. Measurement is achieved by meticulous collection including the weighing of all blood-soaked pads, sponges and bed linen. All beds have a waterproof sheets to capture losses on the bed. Blood on the floor is also collected. All losses are entered into a dedicated blood loss progress table which is regularly updated.

2.5.2. Location and volume of blood loss

ObstetriX contains three data fields that allow clinicians to record the location in which blood loss has occurred and the volume of blood loss in each location. The first field records the EBL in the birth unit and the second field records on the postnatal ward. It is standard practice at the study hospital to record blood loss occurring in the operating theatre or in the birth unit in the first field, giving a record of EBL at the time of birth. The third field gives a cumulative total of EBL and presents the total blood loss in the birth unit, the postnatal ward, during transfer, and including blood loss in the operating theatre and recovery, if applicable. Within each location field, blood loss is recorded categorically, by groups of 500 mL. Since ObstetriX database was designed for large number of hospitals with large amount of data to be entered by different users, it was designed in such a way to avoid free-text entry and minimise the risk of erroneous entries and out of range data. Thus, in the case of estimated blood loss due to postpartum haemorrhage, there is there is no option to record the exact amount of blood loss. Instead, the only option is to choose the levels from a drop-down box.

2.5.3. Interventions

ObstetriX allows the recording of different types of medical and surgical intervention for the management of PPH. Multiple choices of interventions can be selected if applicable.

2.6. Data analysis

We recorded the characteristics of the sample population, and categorised continuous variables when appropriate. We compared the proportions of women with no discrepancy between their ObstetriX record and their medical record across the groups for each characteristic, using the Pearson chi-square test for discrete variables. The sensitivity and specificity of the data in ObstetriX were compared to the written medical records, with exact Clopper–Pearson confidence intervals. The positive predictive value and negative predictive value were also calculated, with the standard logit confidence intervals [19]. We also calculated the discrepancy rate.

Women in the study delivered in one of two locations, the birth unit or the operating theatre. Data relating to the location of blood loss were also compared between the group with incorrect ObstetriX records and those with correct records. Agreement between volume of EBL in ObstetriX and in the medical record were compared across each location by calculation of the kappa score. A kappa score of more than 0.8 was defined as excellent agreement, 0.60 to 0.80 as substantial agreement, 0.40 to 0.59 as moderate agreement and less than 0.40 as poor agreement [20]. We performed a Pearson chi-square test to explore an association between birth location and the recording of PPH in ObstetriX. Analyses were done using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and Excel 2016 (Microsoft). The recording of interventions after PPH in ObstetriX was compared to the medical record, and the error rate for each intervention was calculated.

2.7. Ethics approval

This study was approved by the Western Sydney Local Health District Human Research Ethics Committee, New South Wales, Australia (17/11/2017; 5418QA).

3. Results

3.1. Sample population

There were 387 women who gave birth in the study period, and 363 were included in the data analysis and 24 excluded (Fig. 1). Of the included women, 20.9% (n = 76) were found to have experienced PPH (> 500 mL EBL) based on entry in the medical record. We compared the proportion of women with discrepancies between their medical record and their ObstetriX record, comparing different subgroups of demographic and obstetric characteristics. There was no association between the demographic characteristics and presence of discrepancies (Table 1). However, there were significant differences between the groups for several obstetric characteristics (Table 2). The women pregnant with multiple fetuses were more likely to have had incorrect ObstetriX data recorded (21.2% with singletons, 60.0% with multiples, but this was not significant (P = 0.07) [using Fisher exact test]). Different modes of birth had significantly different proportions of incorrect ObstetriX data recorded, with 12.7% for vaginal birth compared to 40.7% of caesarean section (P < 0.001). Longer length of stay (three or more days) was also associated with a significantly greater proportion of errors (40.5%) than those with a shorter length of stay (18.0%) (P = 0.002) (Fig. 2).

3.2. Agreement between medical record and ObstetriX database

We found substantial agreement between the ObstetriX records and medical records for the volume of blood loss at birth, without considering accuracy at different locations, with kappa scores of 0.74 and 0.71, respectively (Table 3). However, there was poor agreement for the cumulative total EBL, with a kappa score of 0.18. We were unable to calculate the kappa score for comparison of the category of ‘primary blood loss on the postpartum ward,’ because no medical records reported any PPH occurring on the postpartum ward. The data field with the highest error rate in ObstetriX compared to the medical records was the cumulative total EBL (Table 3). The accuracy for this field was also notably lower than the accuracy for the location specific EBL, at 13% (95% CI, 6%–23%), compared to 62% (95% CI, 50%–73%) for EBL at birth. It was also observed that, although there were no episodes of blood loss ≥ 500 mL recorded in any woman’s medical record as having occurred in the postnatal ward, 20 ObstetriX entries recorded PPH ≥ 500 mL as occurring in the maternity ward, resulting in an error rate of
6% in ObstetriX when compared to the medical record.

3.3. Location of birth

For the women who experienced PPH based on the medical record, we found a significant association between the location of birth (birth unit or operating theatre, as per their medical record) and the correct recording of PPH in ObstetriX ($\chi^2 = 8.0$, $P = 0.005$, df = 1). Of the 76 women who experienced PPH, two experienced ongoing blood loss on the postpartum ward, which took them over the cumulative 500 mL threshold, and one woman had > 1500 mL EBL in the birth unit, and also 500 to < 1000 mL EBL in theatres. This left 73 women who had PPH in either the birth unit or operating theatre. Half of the 48 women who had PPH in the operating theatre had this recorded in ObstetriX (Fig. 3), but 84% of the 25 women who had PPH in the birth unit had this recorded.

3.4. Medical and surgical interventions to control bleeding in PPH

Of the 76 women who experienced PPH in the study period, only one had no medical or surgical interventions to control the haemorrhage and was correctly recorded in ObstetriX. This gave an error rate of 99%. Of the 75 women who had incorrect interventions listed in ObstetriX, 64 had none of the interventions they received recorded, seven had incomplete lists, and four had interventions listed in ObstetriX that were not mentioned in their medical record. The interventions most commonly not recorded in ObstetriX were urinary catheterisation, intravenous fluid therapy and use of therapeutic oxytocics (Table 4). Importantly, more serious interventions such as blood transfusions, insertion of Bakri balloons and curettage were also on the list of interventions that were not mentioned in ObstetriX. There were eight women of the 76 with PPH who required major interventions (10.5%). These eight women had a total of 17 major interventions between them, with 13 interventions (76.5%) not recorded in ObstetriX. Half of the women who received major intervention ($n = 4$) required multiple major interventions, and one woman required five.

4. Discussion

We found the percentage of women who experienced PPH to be higher than previously reported for the state-wide population (20.9%, compared to 7.2%), which may reflect that the sample site is a tertiary hospital which manages complex pregnancies [10]. This likely also reflects that PPH is defined in ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision) as $\geq$ 500 mL or post-Caesarean haemorrhage of $\geq$ 750 mL, so studies relying on coded hospital discharge data [10] may underestimate the rate of PPH compared to the ObstetriX database (which only records EBL categorically by 500 mL increments). Of the 76 women who experienced PPH, none had ObstetriX records which correctly recorded the details as in their medical records. We found that Caesarean section, multiple fetuses and longer hospital stays were associated with higher error rates in recording EBL in ObstetriX. This probably indicated that the accuracy of EBL recording is affected by the complexity of birth. This is an important finding, as accurate recording of these data is critically important in more complex obstetrics cases. It also highlights the importance of increased vigilance and more rigorous training of staff in relation to accurate recording.

There was substantial agreement between the medical records and ObstetriX records for the volume of blood loss at birth, but there was poor agreement for the cumulative total blood loss field when compared to the medical record (Table 3). From comparing the medical and ObstetriX records, it seems that many ObstetriX records have accurate blood loss at birth recorded, but inaccurate loss (often recorded as < 500 mL EBL) recorded as the cumulative total. This is likely because the total (cumulative) blood loss is usually recorded as the woman is being discharged from hospital, when all discharge documentation has to be ready within a short time and the woman is well. These factors might
prompt staff to be less careful in accurate recording of post-birth events. Another factor could be that staff in the postpartum ward may pay less attention to acute birth events, because they have other priorities in the care of mothers and infants after birth. Inaccurate recording poses a problem in recording of primary PPH, which is defined as occurring in the 24 h after birth, not confined to the time of birth [21]. We suggest that the ObstetriX system should have an automatic sum of all blood loss, rather than relying on users to enter this information.

The lack of documentation of PPH in medical records of twenty women who had their PPH recorded in ObstetriX (6% error rate) is concerning. This issue combined with the finding that no details of PPH were recorded in medical records of women who experienced PPH (6% error rate) is problematic in recording of primary PPH, which is defined as occurring in the 24 h after birth, not confined to the time of birth [21]. We suggest that the ObstetriX database should have an automatic sum of all blood loss, rather than relying on users to enter this information.

The sensitivity of the ObstetriX database for EBL at birth was 62% (95% CI, 50%–73%), which is comparable to the previously reported sensitivity of coded hospital discharge data for PPH, which was 73.8% (95% CI, 63.1%–82.8%) and 58.6% (95% CI, 38.9%–76.5%) [10,11]. The sensitivity of the cumulative total was significantly less, at 13% (95% CI, 6%–23%). Until more accurate recording can be achieved on ObstetriX, n/N (%)

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion of women with errors in ObstetriX, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>7/44 (15.9)</td>
</tr>
<tr>
<td>25-34</td>
<td>56/252 (22.2)</td>
</tr>
<tr>
<td>35+</td>
<td>16/67 (23.8)</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>26/117 (22.2)</td>
</tr>
<tr>
<td>Other</td>
<td>53/246 (21.5)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>4/16 (25.0)</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>29/176 (16.5)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>28/105 (26.7)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>18/66 (27.3)</td>
</tr>
<tr>
<td>Term pregnancies</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10/43 (23.3)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>34/166 (20.5)</td>
</tr>
<tr>
<td>3 or more</td>
<td>7/34 (20.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28/120 (23.3)</td>
</tr>
<tr>
<td>Pre-term pregnancies</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46/220 (20.9)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>5/23 (21.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28/120 (23.3)</td>
</tr>
<tr>
<td>Non-viable pregnancies</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24/109 (22.0)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>25/118 (21.2)</td>
</tr>
<tr>
<td>3 or more</td>
<td>2/16 (12.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28/120 (23.3)</td>
</tr>
<tr>
<td>Living children</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11/39 (28.2)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>33/170 (19.4)</td>
</tr>
<tr>
<td>3 or more</td>
<td>7/34 (20.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28/120 (23.3)</td>
</tr>
</tbody>
</table>

* There were no significant associations between any characteristic and the proportion of women with incorrect ObstetriX records.

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women with errors in ObstetriX by subgroups n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth (weeks)</td>
<td></td>
</tr>
<tr>
<td>&lt; 37</td>
<td>4/32 (12.5)</td>
</tr>
<tr>
<td>37-42</td>
<td>75/331 (22.7)</td>
</tr>
<tr>
<td>Number of fetuses this pregnancy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>76/358 (21.2)</td>
</tr>
<tr>
<td>2 or more</td>
<td>3/5 (60.0)</td>
</tr>
<tr>
<td>Oxytocics used in labour Yes</td>
<td>28/132 (21.2)</td>
</tr>
<tr>
<td>No</td>
<td>51/231 (22.1)</td>
</tr>
<tr>
<td>Complications in laboura</td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>67/327 (20.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2/5 (40.0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1/1 (100.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6/14 (42.9)</td>
</tr>
<tr>
<td>Intrapartum haemorrhage Yes</td>
<td>0/1 (0.0)</td>
</tr>
<tr>
<td>No</td>
<td>5/18 (27.8)</td>
</tr>
<tr>
<td>Third-stage management</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>79/361 (21.9)</td>
</tr>
<tr>
<td>Physiological</td>
<td>0/2 (0.0)</td>
</tr>
<tr>
<td>Mode of birth</td>
<td></td>
</tr>
</tbody>
</table>
| Spontaneous vertex (normal vaginal birth) | 25/201 (12.4) | < 0.001*
| Instrumental                    | 5/40 (12.5)                                         |
| Vaginal breech birth            | 1/4 (25.0)                                          |
| Caesarean section               | 48/118 (40.7)                                       |
| Sex of babyc                    |                                                     |
| Male                            | 42/193 (21.8)                                       |
| Female                          | 41/176 (23.3)                                       |
| Maternal length of stay (days)d  |                                                     |
| < 1                             | 1/42 (2.4)                                          |
| 1-2                            | 54/263 (20.5)                                       |
| 3 or more                       | 23/57 (40.5)                                        |
| Unknown                         | 1/1 (100.0)                                         |

* Denotes where Fisher exact test was used; otherwise analysis was done with Pearson chi-squared test.

b Collapsed into ‘none versus any’ for statistical analysis.

c Collapsed into ‘ < 3 versus ≥ 3′ for statistical analysis.

d N = 369 babies. *(Collapsed into ‘ < 3 versus ≥ 3′ for statistical analysis.*

birth, with more women who had PPH in the operating theatre having incorrect records than those who had PPH in the birth unit. This may reflect the increased number of distractions for clinicians when women are taken to theatre for birth, and also that once a baby is delivered in the operating theatre, the focus of the midwives (who record the data) shifts to provide care for the newborn infant during the procedure.

Although the main cause of higher error rate in data recorded outside of birth unit is arguable, we assume that rather than a lack of awareness and training of staff, the lack of accessibility of the system in operating theatre by different clinicians makes the contemporary data entry impossible reducing their accuracy. Further to this, the use of several complimentary systems, ie. ObstetriX, medical record and operating notes, might have contributed to inconsistent data. General expectations in the NSW hospitals that use ObstetriX database is for the midwives who record the data to submit a request for access. However, due to their busy schedule, they choose not to have an access and, instead, ask the midwives to record all the observations (such as estimated blood loss) around labour, birth and post-partum. The obstetricians and anaesthetists write their reports on operating notes. Midwifery staff on the other hand, are also given the flexibility of documentation in patients’ paper record in addition to recording into ObstetriX database. Mikkelsen and Aasly [22] found that “parallel use of electronic and paper-based patient records result in inconsistencies between the record
systems” and “…documentation missing in both.” In a study comparing paper recording note with electronic recording system, Jurgen Stausber [23] concluded that the paper-based patient record should not be taken as the gold standard over the electronic record when circumstances create two different and supplemental records. However, in our hospital, we use paper-based medical record as the gold standard as we expect that PPH is significant enough to prompt staff to write contemporaneous notes rather than routine daily report. The ObstetriX record entry is not designed to be completed at the end of each hospital shift. But, it is rather completed at designated points of care (ie. after giving birth in birth unit and before being discharged from the hospital). Since all discharge summaries are generated electronically from the data obtained from ObstetriX and become the main source of information for clinicians and researchers, effort should be made to improve the accuracy of electronic records.

The interventions that were recorded in the ObstetriX database were also not found to be a reliable reflection of the medical records. This is of clinical significance because an intervention not recorded could have future implications for these women’s health. Of particular concern was the proportion of major interventions that were not recorded in ObstetriX. The inaccuracy in recording incidence of PPH as well as subsequent interventions also reduces the utility of the ObstetriX database as a source of information about PPH.

5. Implications for practice and recommendation for future research

Our results may not be generalisable to all healthcare settings and electronic databases due to the short study period and small sample size. However, what we found is not an isolated problem. As mentioned earlier, other studies have reported a mismatch between paper-based and electronic records highlighting the likelihood of missing, erroneous and inconsistent electronic data in healthcare systems.

Routine practice data are generally collected for clinical and billing uses, not research, while there is enormous opportunities for using operational electronic records for clinical and translational research. If

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Kappa score</th>
<th>Error rate</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>PPV (%)</th>
<th>NPV (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPH (any location)</td>
<td>0.71</td>
<td>8%</td>
<td>63 (51-74)</td>
<td>100 (99-100)</td>
<td>100</td>
<td>91 (88-93)</td>
</tr>
<tr>
<td>Birth</td>
<td>0.74</td>
<td>8%</td>
<td>62 (50-73)</td>
<td>100 (99-100)</td>
<td>100</td>
<td>91 (89-93)</td>
</tr>
<tr>
<td>Postpartum ward</td>
<td>–</td>
<td>6%</td>
<td>–</td>
<td>94 (92-97)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cumulative total EBL</td>
<td>0.18</td>
<td>18%</td>
<td>13% (6-23)</td>
<td>100 (99-100)</td>
<td>100</td>
<td>81 (80-83)</td>
</tr>
</tbody>
</table>

* PPH was defined as estimated blood loss of ≥ 500 mL. PPV = positive predictive value. NPV = negative predictive value. PPH = postpartum haemorrhage. EBL = estimated blood loss.
Table 4
Error rate in recording of interventions in ObstetriX, compared to medical records, for women who experienced PPH (n = 76).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Error rate$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary catheter</td>
<td>69/71</td>
</tr>
<tr>
<td>IVFT</td>
<td>68/69</td>
</tr>
<tr>
<td>Therapeutic oxytoxics</td>
<td>64/70</td>
</tr>
<tr>
<td>Uterine massage</td>
<td>12/13</td>
</tr>
<tr>
<td>Oral iron supplements</td>
<td>9/11</td>
</tr>
<tr>
<td>Suturing of episiotomy</td>
<td>5/5</td>
</tr>
<tr>
<td>Suturing of lacerations</td>
<td>4/4</td>
</tr>
<tr>
<td>Suturing of second degree tear</td>
<td>2/2</td>
</tr>
<tr>
<td>Blood transfusion$^b$</td>
<td>2/6</td>
</tr>
<tr>
<td>Iron infusion$^b$</td>
<td>2/2</td>
</tr>
<tr>
<td>Bakri balloon$^b$</td>
<td>2/2</td>
</tr>
<tr>
<td>Curettage of uterus$^b$</td>
<td>2/2</td>
</tr>
<tr>
<td>Oral fluids</td>
<td>1/1</td>
</tr>
<tr>
<td>Suturing of first degree tear</td>
<td>1/1</td>
</tr>
<tr>
<td>Suturing of third degree tear$^b$</td>
<td>1/1</td>
</tr>
<tr>
<td>Suturing of vaginal tears (not specified)</td>
<td>1/1</td>
</tr>
<tr>
<td>Cells from cell saver</td>
<td>1/1</td>
</tr>
<tr>
<td>Manual removal of retained products</td>
<td>1/1</td>
</tr>
<tr>
<td>Cryoprecipitate infusion$^b$</td>
<td>1/1</td>
</tr>
<tr>
<td>FFP infusion$^b$</td>
<td>1/1</td>
</tr>
</tbody>
</table>

$^a$ Error rate expressed as a ratio of the number of times each intervention was not recorded in ObstetriX to the number of times that intervention was recorded in medical records.

$^b$ Major medical or surgical interventions performed.

used wisely, with assessment for completeness and appropriate statistical transformation, these data can improve the health of individuals, and promote the function of the larger healthcare system. However, since the timing, quality and comprehensiveness of routinely collected clinical data are often not consistent with research standards, the reuse of these data for clinical research can be challenging.

In this paper, we raised warnings about the accuracy of electronic data and hope that it will lead the healthcare system to endeavour to advance the quality of data, through attention to standards and appropriate health information exchange. We also hope that our report will lead to improved data collection and the more effective use of data for research and further analysis.

The evolve of a national research agenda that aims at the development of guidelines and practices for optimal data entry and structure as well as training of the clinical workforce to understand the importance of clinical data can help identify and implement optimal approaches in the use of electronic health records. Those staff members who enter electronic data at some point during patient care, need to receive appropriate training in medical informatics, and feel competent and confident before using the system.

We suggest further future research to focus on the quality of data from specific electronic health record components and characteristics for quality measurement such as timeliness and comparability. Future research also needs to investigate factors contributing to the poor data quality, in order to identify the causes and develop effective interventions.

6. Conclusion

The ObstetriX database, as used at the Westmead Hospital birth unit, was found not to be a reliable source of data relating to PPH compared to the medical records. Certain areas were found to be less reliable than others, with the EBL at birth being comparable to other NSW databases, while 99% of women with PPH had errors in the recording of interventions for PPH in their ObstetriX records.

Conflict of interest

The authors declare no conflict of interest.

Summary Table

What was already known on the topic:

- Data relating to postpartum haemorrhage are not accurately recorded in hospital databases.
- Coding of hospital discharge data for postpartum haemorrhage has a medium sensitivity.
- Miscoding of postpartum interventions for postpartum haemorrhage has resulted in a high number of false negatives in the coded data.

What this study added to our knowledge:

- The interventions that were recorded in the electronic database were not a reliable reflection of the paper-based medical records. This is of clinical significance because an intervention not electronically recorded could have future implications for these women’s health. The inaccuracy in recording incidence of PPH as well as subsequent interventions also reduces the utility of the electronic database as a source of information about PPH.
- Needing to complete two records creates two potential unreliable sources of information, so it may be better to ask clinicians to complete only one record – either electronic or paper-based. As efforts can be focused on one record, clinicians may be more accurate in their recording and it would also create a more efficient work flow.
- If two parallel methods of recording are used (namely electronic and paper-based), it is important to consider both sources of information when evaluating patient’s history for clinical care or research purposes.

Acknowledgements

We thank the Department of Women’s and Newborn Health at Westmead hospital for their in-kind support.

References

[7] A.A. Chantry, C. Denexh-Tharaux, C. Cans, et al., Hospital discharge data can be used for monitoring procedures and intensive care related to severe maternal
Venous thromboembolism risk and postpartum lying-in: Acculturation of Indian and Chinese women

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ABSTRACT

Objective: many cultures have a set time of traditional rest in the postpartum period. There is limited information on how this activity may potentially increase the risk of venous thromboembolism (VTE). We aimed to investigate VTE risk by determining the prevalence of the cultural practice of postpartum “lying-in”, quantifying activity and determining the factors that influence this tradition in women from China and the Indian subcontinent (India, Bangladesh, Pakistan and Sri Lanka) at an Australian tertiary referral hospital.

Design: we surveyed a prospective cohort of 150 women aged ≥ 18 years who self-identified culturally as from the Indian subcontinent or Chinese, at baseline (≥ 32 weeks gestation) and at follow-up (six to eight weeks postpartum). Demographic details collected included VTE risk factors such as caesarean section, lack of graduated compression stockings (GCS), postpartum haemorrhage greater than 1000 mL, comorbidities and immobility. We quantified postpartum activities and investigated factors that might influence inactivity.

Results: there were 100 women identifying as from the Indian subcontinent and 50 women identifying as Chinese recruited at the baseline of over 32 weeks’ gestation. Most of the study participants (85%) rested in the postpartum period for cultural reasons. Of the women surveyed, 51% rested in bed as much as possible in the postpartum period. We found a significant correlation between increased number of children and decreased overall immobility or rest (P = 0.03). Overall, 91% of participants had relative live-in help, and this significantly increased the risk of immobility by more than six-fold (odds ratio [OR], 6.17; 95% CI, 1.6–23.5; P = 0.008).

Furthermore, a vaginal compared to a caesarean birth increased immobility risk by almost 3.5 times (OR, 3.4; 95% CI, 1.20–9.4; P = 0.021).

Conclusions: acculturation is highly individualised, however postpartum rest remains prevalent in women who identify themselves culturally as from the Indian subcontinent or as Chinese. Inactivity and comorbidities compounded the impact of cultural postpartum rest, and put women at increased risk for VTE. Targeted, culturally appropriate, postnatal education should include VTE-prevention information to women who intend to practise postpartum rest.

Introduction

Venous thromboembolism (VTE) consists of deep vein thrombosis (DVT) and/or the life threatening condition of pulmonary embolism (PE). Inactivity contributes to Virchow triad of risk factors during the puerperium for VTE. This triad includes abnormalities in the vessel wall, abnormalities in the circulating blood and stasis of blood flow (Bagot et al., 2008). These events are well known contributing factors for VTE, increasing the probability of VTE during pregnancy, with the risk greatest during the postpartum period (Heit et al., 2005; Pomp et al., 2008). The reported incidence of VTE in pregnancy and the postpartum period varies between study populations. An Australian study has found the incidence to be 1.14 per 1000 births (Sharma et al., 2008) with estimates in other literature ranging from 0.6 to 1.88 per 1000 births (Chan et al., 2001; Gherman et al., 1999; Jacobsen et al., 2008; James et al., 2006; Meng et al., 2015).

PE continues to be a leading cause of maternal deaths in countries with good maternity resources (Bates et al., 2016; Royal College of Obstetricians and Gynaecologists, 2015; Sultan et al., 2013). Recent targeted strategies have resulted in improved maternal morbidity and mortality and in reductions in preventable deaths (Royal College of Obstetricians and Gynaecologists, 2015). Inactivity (specifically, great-
er time spent sitting or lying down) increases the risk of PE (Kabrhel et al., 2011). Women who are ‘lying-in’ aim to spend as much time as possible sitting and resting. Sultan (2013) found the peak pregnancy VTE risk period was the first three weeks after birth, with a 22-fold increase for a VTE event compared to outside the pregnancy period. A two-fold increase in VTE risk has been reported to continue for up to 175 days compared to similarly aged non-pregnant women (Galambo et al., 2017).

In Australia, the National Health and Medical Research Council (NHMRC) consensus recommendation for prevention of VTE events is to ‘minimise immobilisation of women’ (NHMRC, 2009). To our knowledge there is no published research that quantifies postpartum activity related to cultural constraints, aimed at understanding immobility and VTE risk.

The cultural practice of postpartum resting occurs in the period during which women are most vulnerable to VTE. Traditionally, Indian and Chinese women rest for 30 to 40 days after giving birth. This period is referred to in China as ‘zuoyuezi’ (‘doing the month’) (Chien, 2006; Holroyd et al., 2011; Kathamna 2000). This practice may confer benefits such as improving opportunities for touch, promoting attachment in the mother–infant dyad and promoting breastfeeding. A secluded rest period supports attachment theory, a biological imperative for the mother–infant dyad to be in close contact to promote survival through the secure attachment and close proximity to a primary caregiver (Bowby, 1969). However, the associated immobility of cultural rest may increase the risk of VTE. The prevalence of this embedded practice among migrant women is poorly studied, particularly among women from India.

Acculturation is the process in which members of one cultural group adopt the beliefs and behaviours of another group, often a dominant one (Redfield et al., 1936; Trimble, 2003). The process applies to migrants as a result of exposure to culturally different people and social influences. Some cultural practices are changed by personal desire; others may alter due to more practical reasons as they are no longer feasible to engage in, such as for geographical or financial reasons. Maintaining cultural connection through embedded ritual can add to a women’s sense of identity, reinforce values and provide family connection, support and a sense of belonging (Abraído-Lanza et al., 2006), which can be particularly important during the period of pregnancy and infant care. Mental health is strongly linked to good social support and cohesion (Chen et al., 2013). Even simple traditions can have great meaning, adding strong threads to the sometimes tenuous cultural fabric for migrants. Healthcare providers need to ensure that important support gained from cultural practices are not dismissed or diminished through lack of understanding. To ensure culturally competent best care, accurate information should be provided. The assumptions of healthcare providers relating to cultural practices of migrant groups are best informed by targeted research, which was the basis for our study.

Our primary objective was to investigate the postpartum VTE risk in a group for whom immobilisation is an embedded cultural practice. Our secondary objective was to quantify and assess the factors that influence mobility through understanding ethno-specific postpartum risk factors for VTE during the postpartum time as well as acculturation in respect to immobility practice only.

Methods

Design

We conducted a prospective cohort study at Westmead Hospital, a tertiary referral hospital in the Western Sydney Local Health District, Australia. We administered two surveys that were study-specific: one with baseline information questions and a second postpartum follow-up survey. Survey content was developed in consultation with an expert panel including the hospital midwifery managers for antenatal and postnatal care, a lactation consultant and clinical midwives.

Cultural content was based on literature review and clinical experience of locally observed practices that impacted on movement. Other cultural practices such as dietary restrictions were not included. Questions of support were detailed to more fully understand this practice with survey questions such as ‘Do you plan to have someone other than your husband live with you to help you with the baby?’ including follow-up questions on who they would be, how long they planned to stay, will they come from another country and can they speak English.

Postpartum daily activity questions were separated into sections on any participation in housework, cooking, exercise, food shopping or visiting family/friends and a section on some participation but they were not primarily responsible for activities such as individual questions on ‘Were you the person who: usually bathed your baby, usually was the one who changed your baby’s nappy’ and we also asked if they ‘usually did all the housework’.

Due consideration and care was given to construction of the simple survey to ensure high levels of literacy were not required. The two surveys were pilot-tested and validated with Chinese and Indian women who spoke a language other than English at home. We then modified the surveys to ensure ease of understanding and reduce the complexity of questions, and re-trialed the surveys. Clear questions on postpartum medical history of participants were asked, including diagnosis of VTE, anticoagulant use, graduated compression stockings (GCS) use and reasons for visiting their doctor. Open-ended and free-text response questions were included in the follow-up survey to capture all events, e.g. “What did you spend most of your day doing?” and “Did you feel satisfied with the rest you were able to get?”

Recruitment occurred in the waiting room of the antenatal clinic and on the postnatal ward, and occurred on varying days to capture different groups of high-risk and low-risk women and women from different clinics.

Participants

We recruited women aged 18–45 years who stated that they culturally identified themselves as from the Indian subcontinent (India, Bangladesh, Pakistan and Sri Lanka) or as Chinese, and who were booked to give birth at Westmead Hospital (n = 150). We did not recruit women on the basis of their country of birth. Exclusion criteria included insufficient English literacy or an anticipation that the baby would be admitted to an intensive care unit after birth. To be included in the follow-up survey, women had to be discharged from hospital with their baby. We excluded women whose babies spent time in the intensive care unit because those women tend to have different levels of activity, travelling frequently into hospital to be with their baby. Our sample size was determined by time and funding constraints.

Recruitment and data collection

We collected data from February to September 2013. This process involved the combination of both interview and extraction of routinely collected data from the hospital electronic health records. Information such as smoking status, body mass index (BMI) at first antenatal hospital booking visit, birth details, admission of baby to neonatal intensive care, postpartum haemorrhage and diagnosis on readmission was retrieved.

The first baseline survey was completed at the time when written consent was gained. Women were recruited after 32 weeks’ gestation or in day one or day two of the postpartum period. The follow-up survey took place at six to eight weeks after birth, by phone interview. A single researcher recruited and surveyed 142 women and a further eight were recruited and surveyed by a second researcher. A single researcher conducted all phone interviews for the follow-up survey, ensuring consistency between interviews.

Significant risk factors for VTE were recorded, and included caesarean section (CS) delivery, BMI ≥ 30 at first-visit booking.
postpartum haemorrhage (PPH) ≥ 1000 mL and age greater than 35 years. No participant smoked or had a previous history of VTE.

Data analysis

Descriptive statistics included mean, range and standard deviation (SD). The Student t test was used to compare continuous variables such as age and BMI. The chi-squared and Fisher exact tests were used to compare groups and/or surveys at baseline and at the six-to-eight-week follow up. A multiple regression model with variable selection was used for immobility to identify risk factors. Where required, we included odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All tests were two tailed and a P value of less than 0.05 signified significance. We used SPSS, version 22.0 (SPSS, Inc. Chicago, Illinois) to analyse the data.

Results

Demographics

There were 100 women from the Indian subcontinent recruited who completed the baseline survey, and 50 women who identified themselves as culturally Chinese recruited who completed the baseline survey. Women who were born in India, Sri Lanka, Bangladesh or Pakistan were 95% of the group self-identifying as from the Indian subcontinent, and 96% of the Chinese group were born in China, Taiwan or Hong Kong. Four women were born in an English-speaking country; three of these were from Australia and one from England. The cohort consisted of 59% primiparous women (n = 89) compared to 41% multiparous women (n = 61). Three women (2%) were lost to follow-up and 11 (7.3%) did not meet the criteria for assessment of activity. In total, 91% of women (n = 136) completed the follow-up survey and, of these, 57% were primiparous (n = 77) and 43% were multiparous (n = 59).

In the group identifying as from the Indian subcontinent, 57% (n = 57) had lived in Australia for fewer than five years, which differed from the Chinese group, in which 40% (n = 20) had lived in Australia for fewer than five years (Table 1).

There was no statistical difference in the age of the two groups (P = 0.436). The mean age for Indian subcontinent women was 30.23 years (range, 20–40 years; SD, 4.64 years) and for the Chinese women was 30.78 years (range, 20–42 years; SD, 4.64 years). Women from the Indian subcontinent had a significantly higher BMI than women who identified as Chinese (P = < 0.0001) (Table 2). Although it was not a significant difference, 7% of Indian subcontinent women were obese, as defined by a BMI of ≥ 30, compared to 0% in the Chinese group (P = 0.096).

Postpartum follow up

All pregnant women from both groups planned to breastfeed their infants except one woman who was unsure. At the postnatal follow-up survey, 89% (n = 121) of all women were exclusively or partially breastfeeding (Table 3). There was no overall difference in feeding patterns between the two cultural groups (P = 0.791).

<table>
<thead>
<tr>
<th>Time in Australia (years)</th>
<th>ISC</th>
<th>Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td>1–5</td>
<td>47%</td>
<td>34%</td>
</tr>
<tr>
<td>5–10</td>
<td>35%</td>
<td>24%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>Born in Australia</td>
<td>1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Women in postpartum follow-up n = 136, ISC n = 89, Chinese n = 47

* ISC: Self-Identifies culturally-Pakistan, Sri Lanka, Bangladesh, India

All women, on discharge from hospital, are advised to visit their family doctor for a health check six weeks after giving birth. At the follow-up survey, 82% of the women (n = 112) stated that they attended the six-week check. During the six-to-eight-week postpartum period, 20% of the women (n = 27) stated that they had sought medical care. The main reasons given were painful perineum (33%; 6/27), breast-related problem (22%; 5/27), CS wound infection requiring antibiotics (11%; 3/27), review of essential hypertension (7%; 2/27) and vaginal bleeding (7%; 2/27). We searched the hospital records for the six-month postpartum period for all study participants. There were four women (3%) readmitted after birth; one woman readmitted for antibiotic treatment of mastitis, one woman readmitted to have an ovarian cyst removed and two women were treated for retained pregnancy products. There were no VTE-related readmissions or deaths.

Rest

Most women planned to rest for cultural reasons after their baby was born (84%; n = 126), with 89% of first-time mothers (n = 79) wanting to rest for traditional reasons (Table 4).

Parity influenced intention to rest and actual resting postpartum, with 89% of primiparous women (79/89) versus 77% of multiparous women (47/61) intending to rest for cultural reasons. There was a significant correlation between overall resting rate and the number of children. A greater proportion (91%) of primiparous women (n = 70/ 77) rested, compared to 82% of women with one child (n = 41/50), versus 62.5% of women with two children (n = 5/8) and 0% of women with three or more children (n = 0/1) (P = 0.03). Almost half of all women at follow-up (51%; n = 69) stated that they rested in bed as much as possible (Table 4). Of the four women born in an English-speaking country, three rested for cultural reasons in bed as much as possible and all had live-in mother or mother-in-law help. Most women in the postpartum period (91%; n = 124/136) had live-in relative help with 89% (133/150) antenatally planning live-in support (Table 4).

Of the total cohort, 10% never left home (n = 13) or only left home once (22%; n = 30), during the rest period. Visiting their family doctor was the reason given by most women in this group (93%) who left home once.

Of the women who rested (n = 116) when asked ‘What did you...
**Table 4**

<table>
<thead>
<tr>
<th>Activity and assistance</th>
<th>ISC, n/n (%)</th>
<th>Chinese, n/n (%)</th>
<th>Total, n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan to rest due to cultural beliefs</td>
<td>79/100 (79%)</td>
<td>47/50 (94%)</td>
<td>126/150 (84%)</td>
</tr>
<tr>
<td>Did rest due to cultural beliefs</td>
<td>74/89 (83%)</td>
<td>42/47 (89%)</td>
<td>116/136 (85%)</td>
</tr>
<tr>
<td>Primiparous, planned rest</td>
<td>44/54 (82%)</td>
<td>35/35 (100%)</td>
<td>79/89 (89%)</td>
</tr>
<tr>
<td>Multiparous, planned rest</td>
<td>35/46 (76%)</td>
<td>12/15 (80%)</td>
<td>47/61 (77%)</td>
</tr>
<tr>
<td>Plan to have live-in help</td>
<td>88/100 (88%)</td>
<td>45/50 (90%)</td>
<td>133/150 (89%)</td>
</tr>
<tr>
<td>Paid support person</td>
<td>0</td>
<td>1/45 (2%)</td>
<td>1/133 (0.75%)</td>
</tr>
<tr>
<td>Plan support: other, relative, friend</td>
<td>12/88 (14%)</td>
<td>4/45 (9%)</td>
<td>113/132 (86%)</td>
</tr>
<tr>
<td>Plan to come from another country</td>
<td>77/88 (88%)</td>
<td>37/45 (82%)</td>
<td>114/133 (85%)</td>
</tr>
<tr>
<td>No English spoken by helper</td>
<td>56/88 (64%)</td>
<td>42/25 (93%)</td>
<td>98/133 (73%)</td>
</tr>
<tr>
<td>Support of mother-in-law, mother</td>
<td>76/88 (86%)</td>
<td>40/45 (89%)</td>
<td>116/133 (87%)</td>
</tr>
<tr>
<td>Postpartum rest: in bed as much as possible</td>
<td>43/88 (48%)</td>
<td>26/47 (55%)</td>
<td>69/135 (51%)</td>
</tr>
<tr>
<td>First 30 days never left home</td>
<td>5/89 (6%)</td>
<td>8/47 (17%)</td>
<td>13/136 (10%)</td>
</tr>
<tr>
<td>First 30 days left home ≤ 3</td>
<td>63/89 (71%)</td>
<td>35/47 (74%)</td>
<td>98/136 (72%)</td>
</tr>
<tr>
<td>Usually no nappy changing</td>
<td>4/89 (4%)</td>
<td>8/47 (17%)</td>
<td>12/136 (9%)</td>
</tr>
<tr>
<td>Usually no bathing baby</td>
<td>24/89 (27%)</td>
<td>19/47 (40%)</td>
<td>43/136 (32%)</td>
</tr>
<tr>
<td>No cooking</td>
<td>30/89 (34%)</td>
<td>23/47 (49%)</td>
<td>53/136 (39%)</td>
</tr>
<tr>
<td>No usually no housework</td>
<td>38/89 (43%)</td>
<td>26/47 (55%)</td>
<td>64/136 (47%)</td>
</tr>
<tr>
<td>Feel satisfied with amount of rest</td>
<td>69/89 (78%)</td>
<td>30/47 (64%)</td>
<td>99/136 (73%)</td>
</tr>
</tbody>
</table>

ISC = Indian subcontinent (Pakistan, Sri Lanka, Bangladesh and India).

* Women recruited, n = 150; women in postpartum follow-up, n = 136.

spend most of your day doing? 97% (n = 113) responded with one or two main activities. The four most common activities were looking at the internet (69%; n = 80/116), watching television (36%; n = 42/116), caring for older children (16%; n = 18/116) and reading (9%; n = 10/116).

There was no difference between the women from the Indian subcontinent and the Chinese group in the following characteristics that influenced rest (P = 0.330): type of feeding (P = 0.784), if a relative stayed (P = 0.988) or how many years she had lived in Australia (P = 0.301).

Although it was not significant, the risk of immobility increased by 2.4-fold if women had lived in Australia for one to five years compared to less than one year (OR, 2.4; 95% CI, 0.32–17.35; P = 0.399). This risk decreased to 1.5-fold for women who had lived in Australia for between five and 10 years, compared to less than one year (OR, 1.5; 95% CI, 0.22–9.7; P = 0.688). After controlling for all variables, women who had a relative stay at home significantly increased their risk of immobility by more than six times compared to women who had no relative stay at home (OR, 6.17; 95% CI, 1.6–23.5; P = 0.008). Furthermore, a vaginal birth increased the risk of immobility by almost 3.5 times compared to CS birth (OR, 3.4; 95% CI, 1.20–9.4; P = 0.021).

**Free-text other comments**

**Satisfaction with rest**

Of the 27% (n = 37) of women who stated that they were unsatisfied with the rest period, 54% (n = 20) said when asked to explain further, that it was due to an unsettled baby, with comments such as ‘lack of sleep,’ ‘no sleep at night’ due to ‘baby crying too much’, ‘unsettled baby’ and their support person not assisting at night ‘no help from my mother at night, day good, night time baby unsettled’.

There were 73% of women (n = 99) who were satisfied with the rest they had, 39 offered more comment. Seven stated that they found their husband and relatives very helpful, ‘without my mum at that time, wow I don’t know what I would have done’, ‘had nanny first four weeks, husband changed nappy when daddy not there’, ‘cousin and sister came every day to do housework and look after baby’, ‘quite happy with family support and help, I will miss them when they go’, ‘parents were here, total disaster without them, house maids in India to do the cleaning’, ‘I do nothing at all, mother taking all responsibility of baby I just feed baby’ and ‘my husband doing most things for me’.

**Cultural practice**

There were 38 women (30%) who offered comments on cultural practice such as: ‘they say relaxed, happy, postnatal month, no reading too much or you will have bad eyesight, no crying or [you] will ruin your eyes, no lifting, not to use strength as fragile after birth or in middle age you get body aches. That’s what my mother tells me, I don’t believe, I just did it just in case’, ‘much different in India, more people around you, grandparents look after baby, massage specialists come, can’t do traditional things such as sacrifice lamb, donate food to the poor’, ‘three weeks total bed rest’, ‘traditional practice for baby only’, ‘cultural pressure from everybody to rest inside, in bed as much as possible for 40 days’, ‘very boring, just resting in bed’, ‘first two weeks mother-in-law wouldn’t let me do anything, after 2 weeks I got bored’, ‘mother-in-law didn’t allow use of internet/TV until after 30 days’, ‘resting in bed too boring, can surf the internet only. In our tradition no TV, mother didn’t want any activity no reading or TV, not allowed bathing but I did’, ‘completely different from India, I only left the house for the check-up, parents don’t drive, so here I had to drive them around’, ‘in our village do not touch kitchen first 20 days, want water ask for water, want food ask for food’, ‘my mother is quite modern we don’t do that (traditional rest)’, ‘(I’m) very well and healthy because of resting’ and ‘my mother happy for me not to do traditional rest’.

**Discussion**

During 2013, 5256 women gave birth at Westmead Hospital with 441 babies born to women from China, Taiwan or Hong Kong, and 1205 born to women from countries of the Indian subcontinent (n = 1646). These numbers increased in the following year, 2014, when 5496 women gave birth and 33% of the births were to women from these cultural groups. The Australian Bureau of Statistics states that 28% of the Australian population was born overseas, with India now the biggest source of permanent migrants to Australia (Migration Report 2013–14). The cultural and linguistic diversity within such a population is immense, and specific cultural practices that are maintained within migrant groups are problematic to define. However, we found that there are some common cultural practices that may affect health, particularly those relating to the risk of VTE.

In our prospective study, we were able to recruit women who self-identified their cultural identity rather than limit ourselves to classification by country of birth. It is of interest to note that, although it was
a small group, three of the four women born in an English-speaking country maintained their cultural practice of wanting to rest and have a relative live-in to assist with traditional postpartum care. This small group provides some evidence that acculturation of postpartum practices is a nuanced, complex process, resulting sometimes in bicultural outcomes rather than adhering to the older linear assimilation acculturation theory (Alvaredo-Lanza et al., 2006).

Our data shows that the groups studied highly desire continued support and rest in the first postpartum month. Within these two groups, 84% planned to rest, and 51% stated they rested as much as possible in bed during the first 30 days (Table 4). This is consistent with an Australian study that found that 55% of the migrant Chinese women in their study followed the practice of confinement but did not define what that meant (Matthey et al., 2002).

Some women stated that they would have liked more traditional care but were constrained due to their relatives being unable to come to Australia, or other barriers such as ‘couldn’t find a nanny, if got nanny more happier’, and ‘mother unable to come until next month — looking forward to resting then’. However, there were women who stated that they felt ‘cultural pressure’ to adhere to tradition. One woman said she felt ‘resting in bed too boring, can surf the internet only. In our tradition no TV, mother didn’t want any activity no reading or TV, not allowed bathing but I did.’ The strong influence of family on health practices has been examined in research particularly in China (Raven et al., 2007). Qualitative research in Taiwan (Yeh et al., 2014) supports the results of this study, finding that all participants refrained from household duties and ‘most rested in bed the majority of the time’. In our study, 91% of participants (n = 124) had a relative stay or live-in help to facilitate the mother’s rest. A British study of migrant Gujarati and Bangladeshi women found that relatives expected and influenced adherence to the 40 days’ rest (Kalbannha, 2000). Only three of our study women were born in Australia, and we found that 76% (Table 4) planned to have a support person postpartum from overseas to assist with baby care. This high level of support from country of origin may significantly influence acculturation and may account for the strong adherence to cultural rest in our cohort.

Although most women were satisfied with their rest (73%), women who were not found night time parenting of unsettled infants difficult. This may be due to lack of acquisition of parenting skills during the day such as settling techniques and understanding infant feeding cues, as their support person was primarily responsible for daytime infant care. Further research is required to both understand parenting skill acquisition and the role of the support person at night.

Previous Australian research has shown that migrant Indian-born women have the highest rates of CS among migrant women (Dahlen et al., 2013). We made similar findings; women who culturally identified themselves as from the Indian subcontinent had a CS rate of 47% (Table 2). Although this high rate in our study cohort would be due to a sampling issue, in the same year at Westmead Hospital, when disaggregated for a similar cohort by term gestation (≥ 37 weeks gestation) and country of birth for the Indian subcontinent, the CS rate was 33%, and an overall total population rate for the same year was 28% for term births.

Results from James (James et al., 2006) found a two-fold increased risk of VTE for births by CS compared to vaginal births. Surprisingly, of the 15% of women who did not rest, most had a CS birth. This possibly reflects a higher level of education about VTE for both staff and patients, and about the importance of early mobilisation to decrease DVT risk in the CS group. Despite these findings, our overall results showed that most women in these cultural groups, regardless of birth mode, will rest, thus increasing their VTE risk. Research to understand and reduce the CS rate in women from the Indian subcontinent would ameliorate some of the VTE immobilisation risk.

New British recommendations for more targeted use of low molecular weight heparin (LMWH) and GCS makes this research timely. The green-top guidelines (Royal College of Obstetricians and Gynaecologists, 2015) recommend the use of GCS for all women who have two risk factors in the postnatal period and 10 days or more of LMWH postpartum. No women in our study received LMWH after discharge. Immobilisation has been identified as a risk factor, as has CS. More than half the women (55%) in our study who had a CS were given GCS in hospital but most (65%) did not use them after the first one to two postpartum days. Several women stated that they threw them in the bin, and one woman stated that she was advised by staff to take her GCS off, as her feet were not swollen. However, education about VTE risk and GCS use varied. One Indian woman had the ‘first 20 days total bed rest’ and then ‘20 days of rest’; she had a normal vaginal delivery but a 1.5 L PPH, and she self-initiated GCS use at home for the 40 days of rest. The low rates of GCS use after discharge can be addressed with education together with targeted use of LMWH.

The limitations of our research include its small cohort size; more information could be gained with a larger study that had a comparison cohort who did not practice lying in. Women who did not speak or read English were excluded from the study. This limitation may bias the results, in that cultural practices among non-English speakers are potentially more embedded and therefore our study may have under-reported cultural practices.

The country of birth data were the only data available for comparison. Cultural identification was the defining classification for the study cohort. This enabled a broader range of women to be included and more accurately reflected the population. However, this limits extrapolation to hospital databases. There are potentially more women who identify with the two groups studied than those just born in the defined countries.

Women were interviewed six to eight weeks after giving birth and were asked to identify behaviour and activities during this time. This recollection may be subject to recall bias. The woman’s BMI was recorded at booking and would have changed over the course of the pregnancy and, so discharge BMI would be a more accurate measure of postpartum risk. Research into the introduction of recording maternal weight at postpartum discharge could be investigated as an appropriate measure for VTE risk assessment, and would be a more accurate measure of interpregnancy weight gain for subsequent pregnancy evaluation.

Strengths of our study include the prospective design and the 98% completion rate for the follow-up interviews. Consistency of interviews allowed for more accurate reflection of activity. Questions on activity level were clarified and more information was sought consistently. For example, when one respondent answered that they had exercised daily in the first 30 days, on clarification, the exercise had been pelvic floor exercises.

A very large sample size would be required to study VTE incidence in various cultural groups. We did not evaluate incidence in our research, however a previous study by Heit et al. (2005) suggested that, while the postpartum period remains the period of highest risk for VTE, there has been a reduction in VTE events in the postpartum period over the last 30 years. Short hospital stays and encouragement of early mobilisation may explain this. We have found that early mobilisation does not occur in these cultural groups. There has been no study showing a significantly increased rate of VTE among women who practice lying-in. However, Chan et al. (2001) found, in Hong Kong, a VTE rate in the higher range (1.88 /1000 deliveries) than found in some studies in Caucasian populations. India has one of the highest maternal death rates in the world, and most women in India receive no postnatal care (Iyengar, 2012), so it is impossible to hypothesise about the level of postpartum VTE events in India. One antenatal study in Mumbai (Vora et al., 2007) found a prevalence of DVT of 1 in 1000 births, similar to that found in studies in developed countries. There are no anecdotal reports that VTE is a significant problem in these cultural groups, and some protective mechanisms may be embedded in cultural practices, such as diets including foods that are high in anticoagulant properties, such as garlic and turmeric (Abebe, 2002),
and massage traditions. Another protective factor may include that of not smoking. It is interesting to note that none of our study participants declared that they currently smoked and, in all women who gave birth in 2013 at Westmead Hospital, there were no smokers among the women from the Indian subcontinent or born in China, Taiwan or Hong Kong. Overall, to study the impact of a Western diet and obstetric interventions on this group, together with the varying degrees of adherence to their cultural practices, would require further research on a larger cohort.

Conclusion

Postpartum acculturation is difficult to measure. There are pressures on migrant groups from the dominant cultural practices, and women change them as they adapt to their new environment. However, data from our research show that, for the cohort of women at Westmead Hospital from the Indian subcontinent and of Chinese background, resting is still strongly embedded within the structure of childbirth rituals. The continued perception of the lifelong health benefits of traditional postpartum practices may drive and maintain the easier-to-follow traditions within migrant groups (Heh, 2004). There is a paucity of research in this area, particularly in Indian migrant women (Wells and Dietsch, 2014). Our study provides some understanding of these cultural groups.

The recent introduction of VTE risk-assessment tools within our hospital will improve general awareness among patients and staff of VTE risk factors, but these tools are not culturally targeted. Further development of health promotion inclusive of non-English-speaking influential relatives, sensitive to cultural needs, may improve healthy mobilisation within an appropriate cultural framework. Greater cultural competency will improve health care delivery and outcomes.

Acknowledgment

We thank Monica Hook Maternal Database Custodian for assistance with data retrieval and we are very grateful to Clinical Midwife Consultant Gwen Moody for assistance and support to develop the project and survey tool.

Conflict of Interest

Both authors declare no conflict of interest.

Details of ethics approval and funding

Ethics approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee (HREC2012/9/4.8/3492) AU RED HREC/12WMEAD/104). Signed, approved consent was obtained from every participant in the study. The principal investigator was partly supported by the Covidien (Cardinal Health) VTE Management and Prevention Scholarship. The funders had no role in study design, data collection or analysis, the decision to publish, or in the preparation of the manuscript.

Clinical Trial Registry and Registration number

Not applicable.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.midw.2017.11.006.

References


Westmead research in the media

Why women are spending the first weeks after birth lying flat in bed

A new study suggests many women from China, India, Pakistan, Bangladesh and Sri Lanka are modifying the traditional practices in their west Sydney homes.

The researchers say women should not be discouraged from observing the cultural customs, but they need to be warned that immobility increased the risk of venous thromboembolism (VTE).

VTE is the leading cause of maternal death in countries with good maternity services. Though the condition was rare, with an Australian study finding VTE occurred in 1.14 per 1000 births, women were at greatest risk in the postpartum period.

A series of interviews with 150 new mothers in western Sydney found more than half rested in bed and 85 per cent rested around the home as much as possible in the 30 days after giving birth.

The strict resting practices meant mothers focused on nurturing their babies, and supported breastfeeding, said lead author and Midwife Sarah Melov at the Westmead Institute for Maternal and Fetal Medicine, Westmead Hospital.

“It’s a lovely custom, not having to race around and do everything else,” Ms Melov said.

“Traditionally they would have a whole village looking after them.”

But with its focus on immobility, bed rest could significantly increase the risk of VTE, argued Ms Melov and co-author Associate Professor Kerry Hitos at the Westmead Institute for Maternal and Fetal Medicine.

Women who practised bed rest needed to be warned of the risk of VTE and encouraged to incorporate some activity into their day, similar to advice given on long-haul flights.
Practice gives birth to VTE risk

A new study shows the traditional cultural practice of extended bed rest after giving birth is putting many ethnic women in western Sydney at risk of venous thromboembolism (VTE), a potentially life-threatening condition.

With 63 per cent speaking a language other than English at home, and 25 per cent originating from the Indian subcontinent, educating women about the risks of blood clots developing from lack of movement is critical, says Sarah Melov, a clinical midwife consultant at the Westmead Institute for Maternal and Fetal Medicine.

Ms Melov, and the Department of Surgery’s Associate Professor Kerry Hitos from Westmead Hospital, led the first study of its kind on culturally diverse women who practice traditional bed resting after taking their babies home.

Regardless of how long they had lived in Australia, many mothers still followed this cultural routine, the research found.

“Bed resting after birth is common for African, Indian, Chinese, Korean and Arabic women, who get live-in help, usually from their mother or mother-in-law who may come from overseas,” Ms Melov says.

“However, staying in bed is one of the biggest risk factors for VTE, with a 22-fold increase of risk during the six to eight-week post-partum period.”

VTE is a leading cause of morbidity and mortality in high-income countries and occurs in 1.1 women per 1000 births.

Ms Melov recruited 100 Indian and 50 Chinese women, finding 85 per cent practised traditional rest.

“When I conducted interviews six to eight weeks after they gave birth, I found 51 per cent had rested in bed as much as possible for the first 30 days, putting themselves at increased risk of VTE,” Ms Melov says.

She assessed movement through quantifiable activities such as cooking, cleaning and leaving the house.

Ms Melov found 47 per cent of women did no housework, 39 per cent did no cooking and 89 per cent had live-in help.

One participant stated there was “cultural pressure from everybody to rest in bed . . . not allowed even in the yard” but many found relatives a great support.

“The belief is strongly embedded that if you rest properly, you will benefit all your life with better health,” she says.

“The next step is raising awareness and promoting the message that women can still rest but do it safely by moving more.”
ORIGINAL ARTICLE

Who is and isn’t having babies with Down syndrome in western Sydney: a ten year hospital cohort study

Rebecca M. Moses¹, James H.W. Brown¹, Dale C. Wright², Hayley Diplock¹, Sarah J. Melov³ and Therese Mary McGee¹,⁴

Background: Screening for Down syndrome (DS) is a key component of antenatal care, recommended to be universally offered to women irrespective of age or background. Despite this, the diagnosis of DS is often not made until the neonatal period.

Aims: To retrospectively describe and compare the differences in populations with an antenatal diagnosis (AD) and neonatal diagnosis (ND) of DS and to explore why an antenatal diagnosis was not made.

Materials and methods: The cohorts were women cared for at Westmead Hospital whose pregnancy received a diagnosis of DS between 2006 and 2015. The demographic variables of the AD and ND cohorts were examined and reasons why an antenatal diagnosis was not made in the ND cohort were analysed.

Results: There were 127 diagnoses of DS in the 10-year period, of which 41% were in the ND cohort (n = 52) and 59% in the AD (n = 75). Declaring a religious affiliation rather than Nil Religion was significantly more common in the ND cohort (88.5%) and especially the ND sub-cohort who declined DS screening/testing (95.8%) than the AD cohort (72%, P < 0.05). Women who were not offered screening were significantly younger (P < 0.001) than those who were, with 69% and 20% being ≤30 years, respectively.

Conclusions: The proportion of DS pregnancies diagnosed in the antenatal period in western Sydney could be increased by ensuring younger women are not falsely reassured that DS screening is unnecessary for them. While religious affiliation may be a factor when women decline screening, ensuring appropriate counselling remains important.

KEYWORDS
antenatal screening, Down syndrome, prenatal diagnosis, trisomy 21

INTRODUCTION

Women seek antenatal care for support, advice, and the identification and treatment of pregnancy complications, including fetal aneuploidy. Down syndrome (DS, trisomy 21) is the commonest chromosomal cause of intellectual disability worldwide and is associated with many significant health problems, most notably congenital heart disease in 50% of neonates.¹

Increasing maternal age has long been a recognised risk factor for DS with prevalence at term being 1:1500 in 20-year-old women and 1:100 in 40-year-olds² with this influence largely unaffected by ethnic or temporal factors.³ Prenatal screening has been
widely available around the world since the 1970s, initially with invasive testing being offered based on maternal age ≥ 37 years (or ≥ 35 years). However, because younger women give birth to most babies overall, about 75% of babies with DS are not diagnosed by this testing.4 Since 2001, after the advent of the second trimester serum screen in the mid-1990s and the combined first trimester screen (FTS) around 2000,15,16 obstetric authorities have recommended that all women, irrespective of age, should be offered DS screening.5 The most recent screening option, maternal plasma cell free fetal DNA testing (cfDNA) became commercially available in the USA in late 2011 and in Australia just over one year later.7 Only 2000 women out of 600 000 births in Australia accessed cfDNA in 2013–2014,6 but its utilisation is expected to grow rapidly as its cost falls, owing to its superior detection and low false positive rates, and the attendant reduction in invasive testing.7

At the same time, effective prenatal screening for DS, on both a personal and societal level, requires more than the availability of a highly sensitive, safe, affordable test. It also requires that patients and families from all socio-demographic backgrounds are aware that screening exists, understand its limitations and the implications of a positive screen result, and subsequently have the opportunity to accept or decline it, ideally without consideration of cost.9–14

Even within those affluent countries where both screening programs and pregnancy termination for DS are readily available, DS screening uptake rates vary considerably,15,16 ranging from 90% in Denmark and France,7,18 74% in England,6 to less than 30% in the Netherlands.15 In Australia, screening rates are 60% and 80% in Western Australia and Victoria, respectively.7 In most countries, including Australia, uptake is not equal across the community. Poorer women, rural women, indigenous women and women from non-local ethnic and language groups have lower screening uptake rates than wealthier, urban and locally born women.18,19 In addition, younger women are regularly under-screened.4,20 Failure to provide universal access to DS screening raises both medicolegal and equity issues. While women have the right to decline an offered DS screening test, failure to provide an appropriate screen/test leaves healthcare providers open to litigation.21–23

Westmead Hospital is a large tertiary service in the geographical centre of Sydney undertaking 5500 births a year. It serves a low to middle income area. Approximately two-thirds of pregnant patients are born overseas (over 50 different countries) and 30% speak a language other than English at home. Approximately 90% are public patients. Every year the hospital delivers a number of babies with DS where the diagnosis is not made until after birth; there is concern that some patient cohorts may experience this event more than others.

The aim of this study was to compare pregnancies with a neonatal diagnosis of DS to those with an antenatal diagnosis, to establish the proportion and demographic features of each cohort and to explore possible reasons why the neonatal diagnosis cohort did not receive an antenatal diagnosis. We hypothesised that the cohorts would be demographically different, with overseas-born, religiously affiliated and possibly younger women over-represented in the neonatal cohort.

MATERIALS AND METHODS

Women who gave birth at Westmead Hospital to babies receiving a neonatal diagnosis of DS (ND cohort) over the decade between 1 January 2006 and 31 December 2015 were compared to women over the same time period who received an antenatal diagnosis of DS under our care (AD cohort). Pregnancies where the diagnosis of DS was already known prior to transfer from another hospital (Westmead is the designated state hospital for babies likely to need cardiac surgery soon after birth) were excluded. Additionally, pregnancies where the woman was referred solely for outpatient invasive testing and then returned to the referring service for ongoing care were also excluded.

Both the AD and ND cohorts were identified via laboratory results, maternal and newborn discharge information and the hospital’s Obstetrix database. The medical files of all patients were examined in full.

Demographic variables examined included maternal age and parity, country of birth and language, and religious affiliation. The time period was selected because both FTS and serum screening were well established but cfDNA was not yet making a major impact.

The ND cohort was examined to ascertain why an antenatal diagnosis had not occurred with reasons categorised as: declined screening or testing; not offered screening; low risk FTS result; being overseas in early pregnancy; and patient factors (presented late or failed to attend recommended screen). ‘Not Offered Screening’ was defined as there being no mention of screening anywhere in the referral letter from the general practitioner (GP) or in the hospital record, despite the woman having been seen in time for screening to be offered.

The usual DS screening test offered over this time period was the combined FTS, generally arranged by the woman’s GP and performed at private ultrasound practices, as is common practice in Australia.19 Due to service limitations, only women at increased risk because of age ≥ 35 or past history had their FTS performed by the hospital. A high risk FTS result was taken as greater than one in 300, whereafter the hospital provided counselling and offered invasive testing. Pregnancy termination was available for a confirmed result. Women were offered a serum triple screen by the hospital if they booked in after the FTS window but before 20 weeks without having had prior screening. The triple screen, invasive testing and termination were provided free of charge by the hospital, while a Medicare (government insurance scheme) rebate exists for FTS.

All data were analysed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA) software. Fisher’s exact test or χ² tests were used to analyse the frequencies of patient characteristics in each study group. All P-values were two-sided in tests, and P-values < 0.05 were considered statistically significant.
Approval for the study was granted by the Western Sydney Local Health District Ethics Committee (Human Research Ethics Committee approval number 4681).

RESULTS

Over the 10-year period to 2015, 129 cases of DS were identified in 127 women of which 41% (52 women, 53 babies) were not diagnosed until after birth (ND) and 59% (75 women, 76 fetuses) received an antenatal diagnosis (AD). The proportion of AD was relatively stable over time, being 62% and 57% in the first and second five years, respectively. Over the decade there were 52 846 births after 20 weeks; this gives a DS rate (live births and terminations) of 24 per 10 000 births.

The demographic features of the ND and the AD cohorts are shown in Table 1. The proportion of women who identified with a religion rather than Nil Religion was significantly higher in the ND than the AD cohort (88.5% vs 72%, P < 0.05). However, there was no difference in frequencies of the individual religions between the cohorts.

TABLE 1  Demographic characteristics of the neonatal and antenatal diagnosis cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neonatal diagnosis n = 52 (%)</th>
<th>Antenatal diagnosis n = 75 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>14 (26.9%)</td>
<td>29 (38.7%)</td>
<td>0.719</td>
</tr>
<tr>
<td>MENA†</td>
<td>17 (32.7%)</td>
<td>17 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>South Asia</td>
<td>9 (17.3%)</td>
<td>11 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>Asia (other)</td>
<td>7 (13.5%)</td>
<td>12 (16.0%)</td>
<td></td>
</tr>
<tr>
<td>NZ† or Pacific Islander</td>
<td>3 (5.8%)</td>
<td>3 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>2 (3.8%)</td>
<td>3 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>Language other than English spoken at home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (34.6%)</td>
<td>21 (28.0%)</td>
<td>0.427</td>
</tr>
<tr>
<td>Interpreter used</td>
<td>9 (17.3%)</td>
<td>11 (14.7%)</td>
<td>0.688</td>
</tr>
<tr>
<td>Parity (median)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.256</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>14 (26.9%)</td>
<td>17 (22.7%)</td>
<td>0.583</td>
</tr>
<tr>
<td>Religion declared‡</td>
<td>46 (88.5%)</td>
<td>54 (72.0%)</td>
<td>0.026*</td>
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<tr>
<td>Maternal age (median)</td>
<td>33.5</td>
<td>36</td>
<td>0.134</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td>0.422</td>
</tr>
<tr>
<td>≤30</td>
<td>17 (32.7%)</td>
<td>17 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 to &lt;35</td>
<td>11 (21.2%)</td>
<td>16 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>24 (46.2%)</td>
<td>42 (56.0%)</td>
<td></td>
</tr>
<tr>
<td>Private insurance</td>
<td>5 (9.6%)</td>
<td>8 (10.7%)</td>
<td>0.848</td>
</tr>
</tbody>
</table>

*P < 0.05
†Middle East and North Africa,
‡New Zealand
§Women identified as being Christian (53.8% and 40.0%), Islam (19.2% and 18.7%), Hindu (9.6% and 12.0%), Buddhist (3.3% and 1.3%), Sikh (1.9% and 0.0%), or declared Nil Religion (11.5% and 28%) in the Neonatal and Antenatal diagnosis cohorts respectively. Individual religion subcohorts were too small to demonstrate any significant difference.

Of the 75 AD cohort women, 90.7% (68) were identified via primary screening. This comprised 74.6% (56) via FTS, 2.7% (2) cfDNA, 2.7% (2) triple test and 10.7% (8) via primary invasive testing for maternal age or past history. The other 9.3% (7) were diagnosed after significant ultrasound anomaly before 20 weeks suggested the need for invasive testing. Only 2.7% (2) continued the pregnancy, 96% (72) chose termination while 1.3% (1) demised before amniocentesis.

Of the 52 ND cohort women, the principal reason DS was not diagnosed antenatally was because the woman declined screening/testing (Declined sub-cohort 46.1%, 24 women), comprising declined screening (16) and declined invasive testing (8). The second reason was not having been offered screening (Not Offered Screening sub-cohort 25%, 13 women). Other reasons are demonstrated in Figure 1.

We examined the demographics of the Declined sub-cohort (n = 24) compared to the AD cohort (n = 75) (Table 2). The Declined group were significantly more likely to report having a religious affiliation than the AD cohort (95.8% vs 72%, P < 0.05) but were otherwise no different.

Among the 13 women who gave birth to babies with DS in the Not Offered Screening sub-cohort (seven in first five years, six in second), 92.3% (12) presented to the GP early in the first trimester (10 had first trimester scans) but were not offered FTS, while the other woman presented too late for FTS but attended the hospital in time for triple screen serum testing, which was not offered. Including this woman, a total of 69.2% (9/13) could have been offered triple screen testing by the hospital. Of the Not Offered Screening cohort, all had a normal morphology scan.

FIGURE 1  Reasons antenatal diagnosis not made in the neonatal diagnosis cohort. †Refers to declined screening (16) or declined invasive testing (8), the latter after high-risk combined first trimester screen (FTS) result (3), abnormal 19 week scan (3) or both (2). ‡Refers to no mention of screening in the referral letter or hospital record, despite presentation within adequate time for screening/testing. §Refers to late presentation or failure to attend recommended screening at the right time.
TABLE 2  Comparison of the demographic characteristics of the declined and antenatal diagnosis cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Declined screening and/or invasive testing† n = 24 (%)</th>
<th>Antenatal diagnosis n = 75 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born in Australia</td>
<td>9 (37.5%)</td>
<td>29 (38.7%)</td>
<td>0.919</td>
</tr>
<tr>
<td>Language other than English spoken at home</td>
<td>7 (29.2%)</td>
<td>21 (28.0%)</td>
<td>0.912</td>
</tr>
<tr>
<td>Interpreter used</td>
<td>3 (12.5%)</td>
<td>11 (14.7%)</td>
<td>0.791</td>
</tr>
<tr>
<td>Parity (median)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.658</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>5 (20.8%)</td>
<td>17 (22.7%)</td>
<td>0.851</td>
</tr>
<tr>
<td>Religion declared</td>
<td>23 (95.8%)</td>
<td>54 (72%)</td>
<td>0.015*</td>
</tr>
<tr>
<td>Maternal age (median)</td>
<td>36.0</td>
<td>36.0</td>
<td>0.865</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td>0.556</td>
</tr>
<tr>
<td>≤30</td>
<td>3 (12.5%)</td>
<td>17 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 to &lt;35</td>
<td>6 (25.0%)</td>
<td>16 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>15 (62.5%)</td>
<td>42 (56.0%)</td>
<td></td>
</tr>
<tr>
<td>Private insurance</td>
<td>3 (12.5%)</td>
<td>8 (10.7%)</td>
<td>0.804</td>
</tr>
</tbody>
</table>

*P < 0.05
†Refers to declined screening (16) or declined invasive testing, even after high risk first trimester screen result (3), abnormal 19 week scan (3) or both (2).

TABLE 3  Comparison of the demographic characteristics of the Not Offered Screening and Offered Screening cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Not Offered Screening n = 13 (%)</th>
<th>Offered Screening or Testing† n = 105 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born in Australia</td>
<td>3 (23.1%)</td>
<td>39 (37.1%)</td>
<td>0.318</td>
</tr>
<tr>
<td>Language other than English spoken at home</td>
<td>5 (38.5%)</td>
<td>30 (28.6%)</td>
<td>0.461</td>
</tr>
<tr>
<td>Interpreter used</td>
<td>2 (15.4%)</td>
<td>16 (15.2%)</td>
<td>0.989</td>
</tr>
<tr>
<td>Parity (median)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.336</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>4 (30.8%)</td>
<td>25 (23.8%)</td>
<td>0.582</td>
</tr>
<tr>
<td>Religion declared</td>
<td>10 (76.9%)</td>
<td>83 (79.0%)</td>
<td>0.860</td>
</tr>
<tr>
<td>Maternal age (median)</td>
<td>28.0</td>
<td>36.0</td>
<td>0.006*</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>9 (69.2%)</td>
<td>21 (20.0%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>&gt;30 to &lt;35</td>
<td>1 (7.7%)</td>
<td>24 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>3 (23.1%)</td>
<td>60 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Private insurance</td>
<td>0 (0.0%)</td>
<td>12 (11.4%)</td>
<td>0.198</td>
</tr>
</tbody>
</table>

*P < 0.05
†Refers to antenatal diagnosis (75), declined (24) and low risk first trimester screen result (6) women.

The proportion of neonatally diagnosed DS was 41%, stable over the study period, with 46% of this cohort having declined screening or testing and 25% not having been offered screening. The ND cohort, and particularly the Declined screen/test sub-cohort, were significantly more likely to identify with a religion compared to the AD cohort. In the sub-cohort of women Not Offered Screening, those 30 years or younger were significantly over-represented.

Contrary to our expectation, ethnicity factors were not significantly different between the cohorts. Other studies have found differently, with overseas-born women in European countries less likely to undergo screening – or to accept invasive testing – while in Western Australia, indigenous women are 80% and other non-Caucasian groups 50% less likely to have DS screening than Caucasians. Our inability to show a difference may reflect our relatively small study numbers.

In terms of religious affiliation, the Declined sub-cohort and the overall ND cohort were significantly more likely to report this than the AD cohort (95.8%, 88.5% and 72.0%, respectively, P < 0.05). While intuitive that religious belief influences DS decision-making, there is surprisingly little published data about its impact on screening uptake.

Of the eight women who declined invasive testing, five had undergone FTS and received a high risk result but then declined further investigation. Four of these were approximately 40 years of age. Studies show only 65–85% with a high-risk FTS proceed to invasive testing, with older women more likely to decline. Fear of terminating the pregnancy is clearly a key factor, since, when cfDNA was offered as an alternative to invasive testing after a high-risk FTS result, the number who declined any further testing dropped from 34% to 2.3%.

While acceptance of screening does not always translate to acceptance of invasive testing, acceptance of invasive testing almost always translates to pregnancy termination if DS is diagnosed. The termination rate in the AD cohort was 96% in keeping with 92% in England/Wales and 95% in Victoria, with both rates stable over the past two decades. However, as we move into the cfDNA era and women who would not terminate can receive an almost certain confirmation (or refutation) of the diagnosis without invasive testing, termination as a proportion of antenatally diagnosed DS pregnancies is likely to be considerably lower. Instead, some women will use the information that they are almost certainly carrying a child with DS to prepare for the baby rather than end the pregnancy.
triple screen by the hospital, despite the woman presenting early in pregnancy. The most remarkable feature of this group was its youth, with 69% being 30 years or younger compared to 20% of women offered screening (P < 0.001). While, since 2001, DS screening is supposed to be universal and irrespective of age, failure to diagnose babies with DS in women under 35 years remains common with only 45–60% detected antenatally in both the UK and Australia. Although much higher than the 3% detected in 1980, it is still well below the 70–80% detected in women over 35 years. Failure to offer DS screening to young women is a failure in duty of care. It also renders medical practitioners legally vulnerable.

The main strength of our study is that it provides a real-world, contemporary insight into antenatal versus neonatal DS diagnosis within a large multicultural pregnancy service, and in addition, explores the reasons why antenatal diagnosis may not occur.

Our study has several limitations, in particular being retrospective and relatively small. It provides no information about socioeconomic or educational demographics, nor about why women declined DS screening. Additionally, ‘Not Offered Screening’ was assumed on the basis of screening not being mentioned anywhere in the GP referral or medical record. However, we believe this to be a reliable assumption since clinicians are unlikely to fail to record an offered test being declined. Finally, we do not know the overall DS screen offer and uptake rates within our population which would provide a useful backdrop to the information contained in the study.

Down syndrome screening requires complex counselling by the healthcare provider and complex decision-making by the patient. Ensuring health practitioners have the appropriate knowledge, attitude and time to convey the necessary information can be difficult, especially amid the myriad of competing information-giving tasks of early pregnancy. Our study shows that there is scope to improve antenatal DS detection in the Westmead area by ensuring that young women are not falsely reassured that DS screening is unnecessary for them. At the same time, it is also important to ensure that women who decline screening have received appropriate counselling. While cfDNA will change the nature of DS screening over the next decade, as it becomes an affordable and possibly routine test, it may also bring its own issues. In the meantime, ensuring access to currently available screening options remains a priority.

ACKNOWLEDGEMENTS

We acknowledge the significant contributions from Monica Hook, ObstetriX Database Midwife, Westmead Hospital and Emma Gibbs, Statistician, Westmead Hospital, for their work towards data obtainment, collection and statistical advice for this study.

REFERENCES


Women’s experience of their sexual function during pregnancy and after childbirth: a qualitative survey

Abstract

Background Women’s sexual function can be dramatically affected during and after pregnancy.

Aims To explore Australian women’s personal experience of changes in their sexual function during pregnancy and childbirth.

Methods This was an online qualitative survey in which women across Australia who had given birth in the previous 12 months were invited to take part. A total of 273 responses were included.

Findings The five main themes that emerged were: mental health changes; obstetric violence (including lack of support from caregivers, violation of privacy, instrumental delivery and episiotomy); relationship issues (including lack of support from partner, lack of intimacy and domestic violence); physical changes (including birth trauma and negative body image); and role conflict (including role incompatibility, breastfeeding and lack of sleep). Mental health changes were reported to have both positive and negative impacts on women’s sexual function.

Conclusions Women experience many changes in their sexual function during and after pregnancy. Health professionals should take an integrated approach to improve women’s sexual function and overall wellness.

Keywords Australia | Childbirth | Pregnancy | Postpartum | Qualitative | Sexual function
There has been increasing interest in conducting research on the sexual function of women during and after pregnancy. While international studies report a high prevalence of perinatal sexual dysfunction (Echeverry et al, 2010; Ishak et al, 2010; Asselmann et al, 2016), the majority of these studies have adopted a quantitative approach. Quantitative studies emphasise objective measurements and statistical analysis of collected data, but they fail to collect data based on the participants’ own words and experiences and fail to reveal underlying ideas through analysing words and phrases (Neuman, 2011). This type of research methodology is possibly premature in an area where authenticated theoretical frameworks are not yet entirely developed (Morof et al, 2003; Barrett et al, 2000; Klein et al, 2009). Unlike quantitative methodology, qualitative research does not deal with numbers. It involves collecting, analysing and interpreting data related to the concepts, experiences and behaviours of individuals (Anderson, 2010). During recent years, there has been a worldwide tendency towards collecting qualitative data on women’s sexual function in order to learn from their experiences (Woolhouse et al, 2014; Liu et al, 2013; Martínez-Martínez et al, 2017). Since there are a small number of qualitative studies with up-to-date data from Australia among the literature (Woolhouse et al, 2014), this qualitative study was conducted to obtain women’s personal experience of changes in their sexual function during pregnancy and childbirth. It is hoped that these findings will provide a more in-depth understanding and better description of women’s personal experiences of pregnancy and childbirth.

Methods

Design
This was a population-based qualitative survey of postpartum women in Australia.

Ethics
This research involved human participants and we received ethical approval from the Human Research Ethics Committee at Curtin University before its commencement. Informed consent was obtained from all individual participants included in the study.

Participants
Postpartum women were invited to participate in this study. Inclusion criteria were that the woman must be between 18 and 40 years old; have given birth to a live baby at 37 weeks or later of pregnancy; have given birth during the past 12 months; be in a relationship with a partner (either heterosexual or homosexual relationship); not be using any antipsychotic medicines; not be pregnant at the time of the study; and must live in Australia.

The National Health and Medical Research Council (NHMRC) guidelines (2007: 19) state that ‘consent should be a voluntary choice’, and because the legal age of consent in Australia is 16 years, women who were 16 years of age or older were invited to voluntarily participate in this study. Women who were older than 40 years were excluded from the study since they were more likely to experience pre- and peri-menopausal changes that have been shown to affect sexual life and mental health (Avis et al, 2009; Hess et al, 2012).

Responses from women were excluded from the study if they met the exclusion criteria of being clinically diagnosed with any psychiatric illness, such as obsessive compulsive disorders (OCD) and anorexia nervosa; or if they were Aboriginal or Torres Strait Islander. This exclusion was based on the National Statement on Ethical Conduct in Human Research (National Health and Medical Research Council, 2007: 69) indicating that ‘researchers should address relevant issues of research design, ethics, culture and language’ if they aim to study Aboriginal and Torres Strait Islander individuals.

Main outcome measures
After a comprehensive literature review, questions were designed to capture data on the topic of pregnancy, childbirth and sexual function (Table 1). A panel of experts, including three sexologists, two midwives and three psychologists, reviewed all aspects of the study and investigated the content validity of the questions. The questionnaire was then reviewed for face and content validity by another 15 researchers who had previously used online questionnaires.

Procedure
After the study received ethics approval, women from across Australia who had given birth in the previous 12 months were invited to take part. An invitation letter containing information about the study and the link to the online questionnaire was posted and distributed on Facebook pages, various search engines, public places and community papers. Snowball sampling also occurred, as participants were asked to pass the website’s link onto their friends, family members and relatives who might be interested in participating.

The first two pages of the study website contained information on the research project, including its general purpose, methods and demands, conditions of entry, risks, possible harms and benefits, confidentiality and anonymity, ethics approval, dissemination of the results and consent to participate. Participants were asked to read the information about the study and then provide consent by ticking the ‘consent to participate’ box if they
agreed to participate. Since this was an anonymous study, the participants were asked not to provide their names or contact details. Participants were then directed to the next pages to answer the questions.

Data considered for inclusion and exclusion were derived from responses to the questions seeking information on the woman's age, country of residence, ethnicity, relationship status, pregnancy, the gestational age at birth of their last child, age of the child and presence of a mental health condition. These criteria were clearly listed on the study website before the participants answered any questions. Women who were not eligible were requested not to participate by an instant screen message. Despite this, some women chose to answer the study questions. Therefore, at the time of data analysis a total of 128 women were excluded: 67 of whom lived in other countries; 12 of whom were of Aboriginal or Torres Strait Islander background; 8 who were not in a relationship; 5 who were pregnant; 8 who had given birth before the 37th week of pregnancy and 28 who reported mental health problems such as OCD, anxiety, phobia and post-traumatic stress disorder (PTSD). The online questionnaire was available for four months from May–August 2012.

Data analysis
Providing responses to the questions was not mandatory because the researchers assumed that creating and inputting responses might have added a burden for some women, especially those who experienced undiagnosed or undeclared mental health issues or postpartum depression. As a result, a different number of participants responded to each question. Table 2 shows a summary of the responses given to each question. More than one-third of the women (35%) reported that their last pregnancy affected their sexual function, 33% experienced changes in their sexual function after childbirth, 24% reported changes in their mental health during pregnancy and 26% had their mental health affected by childbirth. Women who reported not being affected by pregnancy and childbirth (answered 'No' to questions 3, 5, 7 and 9), either did not provide additional information, or mentioned that they had not resumed sexual activity after childbirth. The themes were then explored among the responses from women who answered 'Yes' to those questions and provided further details. Some women typed a few sentences and a few women wrote up to two pages. The average response length was one paragraph.

Data were analysed using Colaizzi’s (1978a; 1978b) process for thematic analysis. All participants’ descriptions of the changes in their sexual function during pregnancy and after birth were read, reviewed, coded and assigned to major, broad categories, which were identified by different colours. Next, important statements that related directly to the changes in sexual function were extracted, to help formulate definitions for these important statements, which were then categorised into clusters of themes. During this process, each reviewer conducted an inductive analysis that resulted in emergence of the descriptive themes to answer the research questions. Each reviewer first did this independently and then as a group. Through group discussions, more analytical themes emerged. This cyclical process was repeated.

Table 1. Online survey questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What makes you most happy (satisfied) in your sexual relationship with your partner?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. What makes you most unhappy (unsatisfied) in your sexual relationship with your partner?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you think your last pregnancy affected your sexual function?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4. If your answer to the previous question is ‘yes’, in what way it affected your sexual function?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you think your last childbirth or delivery affected your sexual function?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6. If your answered ‘yes’ to the previous question, in what way it affected your sexual function?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you think that your last pregnancy affected your mental health?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8. If your answered ‘yes’ to the previous question, in what way it affected your mental health?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you think that your last childbirth or delivery affected your mental health?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. If your answered ‘yes’ to the previous question, in what way it affected your mental health?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Do you have any other comments?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
until the new themes were sufficiently described and all initial descriptive themes were explained. Integrating the findings into a comprehensive description of the changes in women’s sexual function during pregnancy and after birth was the next step. Finally, modifications were incorporated into the final description of the changes in women’s sexual function. The emergence of patterns resulted in a more sophisticated level of coding, which assisted the development of sub-themes and conclusions.

Results
Of the participants, 52% were aged 21-30 years old, 67% had a university degree, 51% had no formal occupation, 69% had annual income of ≥50,000 AUD and 73% were multiparous (Table 3).

The data generated five main themes and several sub-themes (Figure 1). The themes were: mental health changes, obstetric violence, relationship issues, physical changes and role conflict. The contents of each theme and its sub-themes are described below and explained using quotes from the participants.

Mental health changes
Mental health changes had two main sub-themes: positive changes and negative changes. The positive changes in mental health and sexual function during pregnancy and after childbirth were reported to be due to role transition, new responsibilities and feeling empowered, confident, happier, a better person, more relaxed and centred, clearer in mind and more mature after going through the process of labour and birth. For example, one woman said:

‘It [childbirth] made me happier. I felt more loved and in love with my husband. This caused my mind to be at ease and for me to relax.’

Another woman commented:

‘I feel more confident in myself and my sexuality. I felt very empowered in my childbirth. And when I go through tough times in motherhood I look at the situation and say if I overcame and conquered in birth then I can overcome and conquer in anything that comes my way.’

On the other hand, the mental health of some women (n=37) was negatively affected by factors such as the experience of birth, hormonal fluctuation, brain–body disconnection, difficult emotions, depression, fears and stress, violation of privacy during labour and lack of confidence. These negative changes had a negative impact on the women’s sexual function, which made the women concerned for when their sexual function would return to normal. For example, one woman commented:

‘Childbirth seems to have completely removed my libido! It’s like the hormones are not there! I want to have sex, but not because I feel like having sex. I just want to be close to my husband and be with him in that way, I just wish my body was into it. I don’t get turned on at all … I’m not used to having no libido and I’m scared it will never come back.’

Another woman said:

‘To me it feels like there is a broken connection between my brain and my vagina! … I find it hard to get aroused and in the mood for sex … I also find it very hard to orgasm now.’

Obstetric violence
Obstetric violence was described by respondents as neglected needs and wishes, verbal humiliation, invasive practices and forced medical intervention. These, in turn, resulted in the violation of women’s right to make voluntary choice and have reproductive autonomy during pregnancy, childbirth and the postpartum period. Subthemes of obstetric violence were shown to be: lack of support and understanding from caregivers, violation of privacy during labour, instrumental delivery and episiotomy that evoked an image of rape. One woman mentioned that:

‘It left me feeling like a failure, a sexless eunuch, not a true woman … The birth rape, the lack of support from hospital staff and family.’

Another woman said:

‘I was pretty traumatised by the actions of my caregivers in the last hour of my birth. I was forced to push on my back, I was forced to ‘purple push’, I was cut without being asked for consent. My daughter

| Table 2. Participants’ responses to quantitative questions |
|---------------------------------|------------------|------------------|
| Questions                        | Yes n (%)        | No n (%)         |
| Do you think your last pregnancy affected your sexual function? (n=273) | 114 (35%)        | 159 (49%)        |
| Do you think that your last pregnancy affected your mental health? (n=267) | 79 (24%)         | 188 (58%)        |
| Do you think your last childbirth or delivery affected your sexual function? (n=265) | 106 (33%)        | 159 (49%)        |
| Do you think that your last childbirth or delivery affected your mental health? (n=266) | 84 (26%)         | 182 (56%)        |
was born via vacuum, the feeling of her literally being dragged out of me while a team of people held me down was horrific. The episiotomy took months to come together, I had swelling for almost a year. I had pelvic pain for months after giving birth. Whenever I tried to talk about these things I was chastised and told that I should be thankful for a healthy baby. I don’t see how the two are related … I am traumatised by the actions of my caregivers. There is a total lack of support when it comes to helping women process their birth experiences.’

Another woman complained that the issue was taken for granted and not talked about by clinicians:

‘I think everyone seriously underestimates the changes that will happen to your mind and body after being pregnant. Everyone talks about during the pregnancy and straight after but nothing about months and years down the track how it can really change your body so much.’

Relationship issues

The theme of ‘relationship issues’ contained other subthemes, including lack of support from partners, lack of intimacy and communication, and domestic violence.

Lack of support from their partner after birth was reported to cause sexual problems. One woman mentioned that:

‘My husband works away so he is only home once a month or so and wants to get his ‘quota’ in before he leaves again.’

Some women (n=24) reported that their sexual problems were due to the lack of emotion in their relationships during pregnancy and after childbirth. They were dissatisfied that their partners considered only the physical aspect of sex and ignored their needs for intimacy and closeness. They reported that they felt pressured into being a receptacle for their partners’ needs. For example, one woman said that she was affected by:

‘The lack of remembering by my partner that a woman is all about the entire body, not just the vagina.’

Other women commented that:

‘He counts quantity over quality … I do wish he would want to spend time not just having sex but intimacy, romance, cuddling as well.’

Lack of communication with the partner accompanied by mismatched libido caused sexual problems. Some women (n=8) reported they wanted their partners to initiate sex more often, while others (n=23) reported sexual dissatisfaction due to their partners being absent from home, having long working hours, nagging, expressing a lack of interest, or having an affair. For example, one woman mentioned:

‘Pain during and after intercourse due to anxiety around my partner looking elsewhere for sexual intimacy … he turned to pornography, and because he wasn’t working it was more often than I would [have] liked, so that was degrading.’

Violence and abuse within the relationship, and not receiving enough support from the community were noted as other factors that caused sexual problems among the participants. For example, one woman stated:

Table 3. Demographic characteristics of participants (n=273)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>18–20</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>21–30</td>
<td>143 (52%)</td>
</tr>
<tr>
<td>31–40</td>
<td>117 (43%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Diploma or lower</td>
<td>90 (33%)</td>
</tr>
<tr>
<td>University degree</td>
<td>184 (67%)</td>
</tr>
<tr>
<td><strong>Career</strong></td>
<td></td>
</tr>
<tr>
<td>No formal occupation</td>
<td>138 (51%)</td>
</tr>
<tr>
<td>Formal occupation</td>
<td>135 (49%)</td>
</tr>
<tr>
<td><strong>Annual income of family (AUD)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ $50 000</td>
<td>84 (31%)</td>
</tr>
<tr>
<td>≥ $50 000</td>
<td>189 (69%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Oceanian (Australia and New Zealand)</td>
<td>128 (47%)</td>
</tr>
<tr>
<td>American</td>
<td>63 (23%)</td>
</tr>
<tr>
<td>European</td>
<td>52 (19%)</td>
</tr>
<tr>
<td>African and Middle Eastern</td>
<td>16 (6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>16 (6%)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>74 (27%)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>199 (73%)</td>
</tr>
</tbody>
</table>
‘Domestic abuse [is a] big factor for many women and sex is affected. My partner became borderline abusive, verbally and [was] throwing things with terrible scary threats … left me with no desire for sex … very little help given, [clinicians’] response is only to study us more and make us fearful of them.’

Physical changes
Physical changes was another major theme, which could be divided into sub-themes including birth traumas and negative body image. Birth trauma caused by different modes of birth was reported to cause physical changes and affect women’s sexual function. For some women (n=18), caesarean section was a negative event that affected their sexual function. One woman, who had given birth by caesarean, said that:

‘Following my caesarean delivery, my lower abdomen between my pubic bone and navel were completely numb and flaccid for 8 months … I feel that the numbness in my lower abdomen extends somewhat below the pubic bone, deadening my clitoral sensation which makes it difficult to orgasm.’

Others (n=22), however, reported that their sexual problems, lack of desire, painful intercourse and lack of orgasm were due to a traumatic vaginal birth, particularly if their baby was reported to be large. A few women (n=7) reported that birth trauma resulted in urinary incontinence and this has made them self-conscious during sex, saying, that giving birth to a larger baby was:

‘A very traumatic birth … do not feel the same. It is very tight inside and penetration feels like the skin is stretching … I think I may have urinated once during orgasm because my muscles aren’t as strong.’

Negative body image was reported by the women as another factor that they felt contributed to their sexual dissatisfaction. Some women (n=13) did not feel comfortable with the physical changes that had taken place and reported a lack of confidence in their body due to weight gain and changes during pregnancy and after...
Research

birth. As one woman commented:

‘I don’t feel sexy anymore; I feel fat and I am not satisfied with my physical appearance at all.’

Another woman stated:

‘Confidence! That I would still be enough for my husband and not stretched beyond all recognition! … Less confidence around the rest of my body.’

Role conflict
Adapting to the new motherhood role was a further major theme identified in this study, and could be divided into subthemes that included the incompatibility of multiple roles, the challenges of breastfeeding, and a lack of sleep. As reported by the women, childbirth meant less sleep, less free time and more fatigue. Consequently, instead of having sex, women wanted to sleep or have time for themselves, and that led to a changed sex pattern. For example, one woman mentioned that it was:

‘Hard to separate being a mum, being a wife and still being me … I also just don’t feel like myself anymore.’

Another woman said that she felt:

‘Like everyone wants a part of you. No time on your own. Go to bed you rest from kids but feel like you need to be there for hubby then … I feel depleted and tired yet I can’t sleep … no energy for sex.’

Some women who breastfed (n=19), reported that sharing a bed with the baby resulted in an unsatisfactory sex life, as they were concerned about accidentally waking or harming the baby. Other breastfeeding women reported that their sexual activity was negatively affected by both breastfeeding and having a toddler at home. For example, one woman said:

‘We bed-share with our son. Plus, he’s a poor sleeper and that the baby and toddler seem to always wake up when we try to have sex! It definitely has a negative impact on our sex-life.’

Discussion
In this study, 273 women were recruited through an online survey to investigate the changes in their sexual function during pregnancy and the first year after childbirth. Five main themes were identified: mental health changes, obstetric violence, relationship issues, physical changes and role conflict.

Some women found that pregnancy and giving birth helped them to gain a new perspective and improved their sexual function by making them feel empowered and relaxed. These findings support previous research (Ngai et al, 2011) indicating that childbirth-induced changes were considered to be empowering and could contribute to improved sexual function.

Other women reported that pregnancy and childbirth had negative effects on their sexual function. Adapting to their new roles as parents, taking care of the newborn, tiredness, lack of sleep and less free time were mentioned, which meant that mothers preferred to sleep or look after themselves in their limited free time. This reportedly conflicted at times with the partner’s sexual desire, with negative consequences on their sexual life, a finding that corroborated previous research (Olsson et al, 2005). Indeed, becoming a mother, a mismatch between expectations and realities of motherhood, women’s attitudes to pregnancy, birth-related changes and the ability to adapt to new responsibilities may play a significant role in negative experiences of pregnancy and childbirth (Amankwaa, 2003; Luyben et al, 2011; Ngai et al, 2011). It has been reported that being a mother makes many women ‘feel isolated, alone and depleted rather than nurtured and supported’ (Barclay et al, 1997: 727; Olsson et al, 2005; Williamson et al, 2008; Zuriati, 2017).

An Australian study by Williamson et al (2008) reported that pregnancy and childbirth affected the sexual function of the many couples who participated in the study and negatively influenced their relationships. Feeding the baby at night, perineal tears, tiredness, dedicating more time to the baby and less time to the partner, and loss of sexual desire were mentioned as factors that interfered with couples’ sexual lives and relationships. In that study, only one couple declared that their sexual desire and activity increased after childbirth and their relationship became stronger, as they had abstained from sex during pregnancy due to the fear of hurting the baby and they looked forward to resuming sex after birth. Similar results were also shown in a study by Muise et al (2017). These reports agree with the findings of our study, indicating that interpersonal issues, birth-related trauma and the need to care for the baby affect the sexual function of women after birth.

The women in this study stated that they needed to be assured of being loved and appreciated outside the bedroom. The women reported wanting their life with their partner to be their focus, not just their sex life, especially as women need to connect emotionally, mentally and intellectually before they can connect sexually (Ramsey and Hoyt, 2015). Earlier literature has shown that women have an inclination towards keeping sex and love separate and that emotional connection and being loved are the determinants of a satisfactory
intimate relationship for many women (Basson, 2000; Brotto et al, 2008; Schoenfeld et al, 2017).

Obstetric violence, another theme that was discovered in this study, is a frequently disregarded type of violence against women in maternity care. Performing an episiotomy without woman’s consent, being held down during birth, extracting the baby from the mother’s body, and having a caesarean section while the threat of vaginal birth (if any) to the baby or mother was not communicated or made obvious (or when a caesarean contradicted their birth plans) were examples of obstetric violence reported by participants. These discriminations and violation of women’s rights and privacy are not limited to these cases and can happen anytime during pregnancy, childbirth and postpartum period (Pérez D’Gregorio, 2010). Research has shown that mistreatments such as verbal humiliations, physical violence and forced medical interventions can result in degrading childbirth, postpartum health complications and severe psychological trauma. According to the World Health Organisation (WHO) (2017), violence and discrimination that occurs during birth may not be documented in medical notes or may not be reported by the women due to fear and shame. WHO recommends providing support for further research on defining and measuring obstetric violence worldwide in order to better recognise its effects on women’s health experiences and choices (WHO, 2017).

Despite the significance of the issue, most women choose not to discuss obstetric violence during routine antenatal and postpartum visits because of factors such as embarrassment, lack of trust, or fear of a lack of empathy from clinicians (Khajehei et al, 2015). Health professionals have also been shown to be reluctant to talk about these issues due to potential barriers such as cultural factors, embarrassment, lack of knowledge and time limitations (Pauleta et al, 2010). The information obtained from this study can help shape future interventions and enhance knowledge and awareness of the problems among nurses, midwives and other health professionals.

Sexual health education has been shown to promote women’s sexual and marital satisfaction and improve their quality of life (Mahmodi and Valiee, 2016). Educational sessions can be held to inform pregnant or postpartum women and their partners about changes in sexual function, mental health and the quality of relationships, while providing information on adapting to their new roles and responsibilities during and after pregnancy. Training should include strategies for providing active, woman-centred counselling with an open atmosphere to enable postnatal women to freely discuss their issues, needs and expectations (Edvardsson et al, 2011), to help women pursue more effective coping strategies. Peer support groups can also provide postnatal women with support and guidance to help them find answers to their questions, resolve their problems and increase involvement in community activities (Doornbos et al, 2013). Providing timely and appropriate professional counselling and support can help women maintain a good quality of life.

**Implications for practice**

Primary care services and health professionals should consider how the sexual function of women may change during and after pregnancy, with an integrated approach to improve their overall wellness (Wincze and Weisberg, 2015). Assessment of sexual function needs to be included in perinatal visits, where appropriate and timely education, counselling and support should be provided. Health professionals should initiate conversations in a confidential and friendly environment, asking open questions and shaping the dialogue so that the women feel comfortable to express their concerns and seek support (Bahadoran et al, 2015; Rivas et al, 2016). To address obstetric violence, appropriate education and training are required to enhance awareness, improve interactions, promote respectful practice and enhance the quality of services provided (Sadler et al, 2016).

**Limitations and strengths**

Similar to other studies, the present study has some limitations. First, the online nature of the questionnaire excluded women who were not computer literate or had no access to a computer. The study also relied on self-reported data, which has inherent limitations. However, as the study was anonymous, with no face-to-face contact, it is reasonable to conclude that the participants provided honest, trustworthy responses. Furthermore, because participants were not selected randomly across Australia, women with negative experiences might have been over-represented and women who reported symptoms of depression might have been under-represented due to a selection bias. Thus, the results obtained from this study cannot be generalised to the entire population of postpartum women in Australia, but can operate as an informative aspect within the greater body of knowledge.

Despite these shortcomings, it is fair to conclude that the present study offers important contributions to the literature and supports the case for future studies in this
Key points

- Positive effects such as feeling empowered, confident, more relaxed and centred made some women clearer in mind and more mature after going through the process of labour and birth.
- Some other women were negatively affected by the birth experience, hormonal fluctuation, difficult emotions, depression, fears and violation of privacy during labour.
- Obstetric violence, such as neglected needs and wishes, verbal humiliation, invasive practices and forced medical intervention, negatively affected women’s mind and body.
- Some women reported that their sexual problems were due to lack of support from partners, lack of intimacy and communication, and domestic violence.
- Physical changes, incompatibility of multiple roles, the challenges of breastfeeding, and a lack of sleep were other factors affecting women’s sexual function.

This indicates that pregnancy and childbirth cannot necessarily be negative experiences. Pregnancy and giving birth can help women feel empowered and relaxed and have better sexual function. To achieve this, women need to be assured of being loved and appreciated outside the bedroom and need to connect emotionally, mentally and intellectually before they can connect sexually.

Declaration of interests: The authors have no conflicts of interest to declare.

Ethical approval: This research involved human participants and received ethical approval from the Human Research Ethics Committee at Curtin University.

Funding: This research was done whilst Manjan Khajehei was a Curtin International Research Scholar.

Review: This article was subject to double-blind peer review and accepted for publication on 20 March 2018.

CPD reflective questions

- How do pregnancy and childbirth affect the sexual function of perinatal women?
- How do pregnancy and childbirth affect the mental health of perinatal women?
- What approaches can be taken into consideration to improve the pregnancy and birth experiences and promote sexual function and mental health of perinatal women?


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At Westmead Hospital, the majority of our patients were born overseas and this proportion is steadily increasing. Migrant population can be remarkably different from general population in terms of prevalence of some health conditions and healthcare outcomes, such as gestational diabetes (GDM) (1, 2, 3). In the present research, we used routinely collected data of 51,577 women who birthed at Westmead hospital between July 2006 and June 2016. Data were coded and analysed using SPSS software. We used descriptive statistics to show prevalence of gestational diabetes amongst our population. Our study showed that out of 4,978 women who were diagnosed with GDM, the majority of them were born in countries on Indian subcontinent (34%, n = 1,665) or Asia (24%, n = 1,187). Australia-born women accounted for 37% of general population of our patients, however they represented less than 20% of women with GDM. We applied a multinomial logistic regression analysis to evaluate the effect of mother's country of birth on mode of birth amongst women diagnosed with GDM. In our analysis, we adjusted for maternal age, parity, gestational age, birth weight and use of epidural analgesia. Our results showed statistically significant differences.