Obstetrics, Gynaecology and Maternal Health Services

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OGM02	Natasha de Alwis, Yeukai TM Mangwiro, Natalie K Binder, Sally Beard, Sarah A Marshall, Natalie J Hannan	Assessing long-term cardiovascular effects of hypertension in an L-NAME mouse model of preeclampsia	Preeclampsia, L-NAME, Pregnancy, Animal models
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OGM04	Fato BR, De Alwis N, Binder NK, Beard S, Tong S, Kaitu'u-Lino TJ, and Hannan NJ.	New human models of preeclampsia; offering physiologically relevant assays for the development of therapeutics to ameliorate vascular dysfunction that occurs in preeclampsia.	Preeclampsia
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OGM10	Associate Professor Lisa Hui, Mr Melvin Barrientos Marzan, Dr Daniel L. Rolnik, Dr Stephanie Potenza, Dr Natasha Pritchard, Associate Professor Joanne M. Said, Dr Kirsten R Palmer, Dr Clare L. Whitehead, Dr Penelope M. Sheehan, Dr Jolyon Ford, Professor Ben W. Mol, Professor Susan P. Walker	This abstract is not included at the request of the author	COVID-19, lockdown, stillbirths, preterm birth, pregnancy, obstetrics, fetal growth restriction, newborn

Lik-Hui (William) Lau [1], Suet-Wan Choy [1]

Renal cell carcinoma in pregnancy: A case report and summary of cases

[1] Mercy Hospital for Women, Melbourne, VIC, Australia

Introduction:
Renal cell carcinoma (RCC) is a rare diagnosis in pregnancy. We report a case of a pregnant woman with RCC and summarised characteristics of 40 other published case reports over the last 20 years

Our case:
A 34 year old primigravid woman presented with a left solid renal mass (56x71x55mm) discovered incidentally on a dating scan at 9weeks gestation. Fine needle aspirate was suggestive of clear cell RCC. An abdominal MRI at 13weeks gestation demonstrated growth of the solid heterogeneous renal mass (80x52x47mm). Chest x-ray was normal. After discussion in a multi-disciplinary team, the patient underwent a successful laparoscopic partial nephrectomy at 23weeks gestation with post-operative ileus and chyle leak but without obstetric complication. Histopathology confirmed type 1 papillary RCC, grade 2, stage pT2aNx. She delivered a 3kg baby girl at 395 weeks gestation via caesarean section due to obstructed labour. She remained in remission 12 months post-operatively.

Summary of cases:
Women had a median age of 32 years with median gravidity of 2 and were diagnosed at a median gestation of 17weeks. Seventy-three percent were operated on antenatally at a median gestational age of 20 weeks while 27% were post-natally. Most tumours were detected incidentally on ultrasonography(39%), followed by flank, groin or abdominal pain(27%), haematuria(29%), hypertension(13%), palpable flank mass(8%) and urinary symptoms. Right sided tumours occurred more frequently(54%). Most RCCs were clear cell type(59%), followed by chromophobe(27%), papillary(7%) and cystic(2%).

Sixty-three percent had open, while 37% had laparoscopic nephrectomies and 78% were radical while 22% were partial nephrectomies. Pregnancies reached a median gestational age of 39weeks with half delivering vaginally and one third via caesarean. There were 3 terminations, 2 spontaneous abortions and one neonatal death. Two women died from metastatic disease.

Conclusion:
RCC in pregnancy remains rare and a database to collate additional RCC data may help inform future practice.

Natasha de Alwis[1,2], Yeukai TM Mangwiro[1,2], Natalie K Binder[1,2], Sally Beard[1,2], Sarah A Marshall[3] and Natalie J Hannan[1,2]

Assessing long-term cardiovascular effects of hypertension in an L-NAME mouse model of preeclampsia

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Aim
Preeclampsia is associated with increased long-term risk of maternal cardiovascular disease. This study investigates the use of N(ω)-nitro-L-arginine methyl ester (L-NAME), a nitric oxide scavenger associated with vasoconstriction, in modelling preeclampsia and its effects on long-term maternal cardiovascular health.

Methods
Pregnant CBA/C57BL6 (F1) mice were injected subcutaneously with L-NAME (50mg/kg/day; n=41) or phosphate buffered saline (vehicle control; n=46) from E7.5-E17.5 gestation. Mice were culled at E17.5, or 1-, 2-, 4- or 10-weeks post-delivery. Fetal and placenta size was measured. Blood pressure was recorded during pregnancy and post-delivery. Urine, blood and organs were collected for assessment of cardiovascular markers and organ morphology. Mesenteric arcade was collected to test vascular reactivity via wire myography.

Results
L-NAME administration significantly increased blood pressure, and circulating endothelin-1 (vasoconstrictor), C-Reactive Protein (inflammatory marker) and sFLT-1 (anti-angiogenic factor) levels in pregnancy, but did not induce proteinuria. L-NAME reduced fetal/pup weight and length. L-NAME reduced placental weight and increased placental *Flt1* and *Hmox-1* (anti-oxidant) expression. Post-delivery, blood pressure and levels of circulating ET-1 and CRP returned to control levels. We detected no changes in cardiovascular disease risk indices until 10 weeks post-delivery, where L-NAME mice had increased cardiac and renal expression of inflammatory markers, and increased mesenteric artery vasoconstriction to phenylephrine.

Conclusion
Blocking nitric oxide simulates gestational hypertension and fetal growth restriction, hence can be used to assess efficacy of therapeutics to mitigate preeclampsia-induced hypertension. However, this model does not accurately recreate the breadth of adverse long-term cardiovascular effects we expect after a pregnancy complicated by preeclampsia, thus further study is required to develop models of long-term effects.

Bridget Arman[1,2], Natalie Binder[1,2], Natasha de Alwis[1,2], Sally Beard[1,2], Stephen Tong[2], Tu'uhevaha Kaitu'u-Lino[2], and Natalie Hannan[1,2]

Developing a pipeline to examine the therapeutic potential of repurposing drugs to prevent preterm birth.

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2. Mercy Perinatal, Mercy Hospital for Women, Heidelberg 3084, Australia

Aim

Spontaneous preterm birth (delivery before 37 weeks gestation) is the leading cause of perinatal morbidity and mortality. Current treatments to prevent preterm birth are limited, with significant side effects. This work aims to explore repurposing drugs to attenuate preterm uterine contractions through the development of a robust pipeline of *in vitro*, *in vivo* and *ex vivo* human and mouse models of preterm birth. These models will assess the anti-inflammatory and anti-contractile abilities of current therapies to validate the model that will test novel candidate therapeutics.

Methods

Nifedipine, currently used clinically, was tested to determine if it can reduce the inflammation central to the pathophysiology. Nifedipine's effects on inflammatory cytokine gene expression were evaluated in a myometrial cell line using qPCR. Contraction assays utilising collagen gel embedded with myometrial cells assessed nifedipine's ability to relax contractions induced by pro-inflammatory mediators tumour necrosis factor-alpha (TNFα) and lipopolysaccharide (LPS). We developed a mouse model of preterm birth to determine the effect of nifedipine on the timing of delivery and the expression of contraction-associated genes in uteri collected from the dams after littering.

Results

Treatment of myometrial cells with TNFα (0.1ng/ml) and LPS (100ng/ml) induced a significant increase in gene expression of pro-inflammatory cytokines (interleukin (IL)-1B, IL6 and CXCL8) compared to vehicle control treatment. Nifedipine treatment (10μM) did not reduce expression of these pro-inflammatory cytokines. In myometrial contraction assays, TNFα (1ng/ml) and LPS (100ng/ml) triggered contractions in the myometrial cells. Nifedipine treatment reduced these contractions back to baseline levels. Our preliminary findings indicate nifedipine delays inflammatory-induced preterm birth in ~25% of mice (similar to its clinical efficacy).

Conclusion

Inflammation-induced contractions can be elicited in various myometrial cellular and tissue models, providing an innovative pipeline of drug evaluation to assess the actions of current drugs and the potential of novel repurposed therapies. Nifedipine reduces myometrial contractions, but does not show evidence this is done by diminishing inflammatory pathways.

Fato BR[1,2,3], De Alwis N[1,2,3], Binder NK[1,2,3], Beard S[1,2,3], Tong S[2,3], Kaitu'u-Lino TJ[2,3], and Hannan NJ[1,2,3].

New human models of preeclampsia; offering physiologically relevant assays for the development of therapeutics to ameliorate vascular dysfunction that occurs in preeclampsia.

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AIM:

The onset of maternal hypertension is a hallmark of preeclampsia, as a result of widespread endothelial dysfunction and systemic vasoconstriction. Central to this study, we set out to create a new model depicting the vascular dysfunction in preeclampsia to test new therapies for preeclampsia.

METHODS:

Human omental arteries were collected from normotensive pregnant women at term (n=9). Blood serum was collected from women complicated by preterm preeclampsia (delivery gestation <34 weeks, n=8), term preeclampsia (delivery gestation >37 weeks, n=5) and healthy gestation matched controls (n=15). We performed *ex vivo* whole vessel wire myography (DMT 620M) to investigate the vascular effects of treatment with serum from pregnancy. Omental vessels were treated with increasing doses of serum (2-20%) to assess vasoconstriction. Vessels preconstricted with serum were then treated with candidate preeclampsia therapeutic, esomeprazole (0.1-100uM).

RESULTS:

All vessels constricted in response to serum. There was no significant difference in constriction of human omental blood vessels in response to preterm or term preeclamptic serum, compared to their gestation matched controls. Esomeprazole enhanced relaxation of vessels pre-constricted with preterm preeclamptic serum compared to vehicle. However, when control serum from normotensive pregnancies was used, esomeprazole did not alter vasodilation.

CONCLUSION:

Pregnant serum induced vasoconstriction of omental vessels, demonstrating vascular treatment with pregnant serum provides a useful model to assess pregnant vasoactivity. However, the use of preeclamptic serum demonstrated a superior response to therapeutic assessment and thus provides a more relevant model for the complex pathophysiology underpinning preeclampsia.

Sally Beard [1,2,3], **Matthew J Wakefield** [4,5], **Natalie J Hannan** [1,2,3]

The antiplatelet medication prasugrel induces an antioxidant response in placental cells: a candidate preeclampsia therapy?

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Aim
Preeclampsia is a serious complication of pregnancy and a leading cause of disease and death in mothers and babies. Oxidative stress has been implicated in the disease.(1) There is no known effective cure. Prasugrel, a new-generation antiplatelet agent used to treat heart attack has shown promising results in *in vitro* and *in vivo* models of preeclampsia, although the mechanisms of action are not yet known. The aim of this study was to investigate changes in the transcriptome of primary human placental cells cultured *in vitro* in response to prasugrel using RNA-Seq.

Methods
We isolated cytotrophoblast cells from placentas of seven uncomplicated term pregnancies and cultured *in vitro* with and without prasugrel for 24 hours. RNA was sequenced and mapped to the genome using *HISAT2* and *HTSeq-count*. Differential expression analysis using *limma-voom* with a paired sample design and *camera* gene set testing identified genes and pathways altered with prasugrel treatment.

Results
2592 genes were upregulated and 2808 downregulated by prasugrel with a false discovery rate < 0.05. Of these, 11 were upregulated and 5 downregulated with a fold change > 2. Among the upregulated genes: *NQO1*, *TXNRD1*, *GCLM, OSGIN1*, *SLC6A6, PIR*, *TRIM16L*, *KIAA0319, AKR1C2* are all known to be regulated by the transcription factor NFE2L2 via antioxidant response elements located in their promoter regions. Additionally, a gene set comprising 266 genes activated by NFE2L2 was enriched with upregulated genes (FDR = 0.013) in this study.

Conclusion
We identified a large change in expression of NFE2L2-regulated genes in response to prasugrel in primary placental cells, which has not previously been reported outside our group. These findings support the continued investigation of prasugrel as a treatment for preeclampsia. Further work will be required to clarify whether the pathway identified is relevant beyond cytotrophoblast cells in the whole placenta to combat preeclampsia.

References
1. Guerby P, Tasta O, Swiader A, Pont F, Bujold E, Parant O, et al. Role of oxidative stress in the dysfunction of the placental endothelial nitric oxide synthase in preeclampsia. Redox Biology. 2021 Apr;40:101861.

Natasha Pritchard, [1,2], **Susan Walker,**[1,2,] **Stephen Tong,** [1,2,] **Anthea Lindquist**[1,2,]

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Growth Charts Based on Individual Gestational Day Improve Correlation with Adverse Perinatal Morbidity and Mortality: A Statewide Population Study.

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Aim
Growth charts either provide a single centile for each completed week of gestation or a centile for each day of gestation. A fetus gains weight throughout each week; use of week charts may overestimate the proportion of SGA infants at the beginning of the week, and underestimate at the end. We aimed to quantify the differences, and to see if day charts improved the prediction of perinatal mortality.

Methods
Retrospective cohort study of all infants born in Victoria, Australia, from 2005-2015 (529,261 cases). We applied growth charts, either using an average for each completed week of gestation ("week" charts), or an individual centile for each gestational day ("day" charts). We compared all infants born on the first day of a completed week of gestation (+0 ie. 24+0, 25+0...42+0), with those born at the end of a completed week of gestation (+6 ie. 24+6, 25+6...42+6).

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Results
Using week charts, of all newborns born on the first day of a gestational week, 12.1% were considered <10th centile (SGA), compared to 7.8% of all infants born on the final day of a gestational week. In relative terms, an infant born at the end of the week compared to the beginning is 44% less likely to be considered SGA ($p<0.001$). If day charts were used, a similar proportion was considered SGA regardless of when the infant was born (9.5% SGA at +0, 9.9% SGA at +6). Out of those classified as <10th centile by week charts, the RR of stillbirth was higher at the end of the week than the beginning (1.47, 95%CI 1.09–2.00, $p=0.01$), suggesting a distortion of risk if week charts were used. Day charts corrected this; no difference in stillbirth risk was seen based on when in the week an infant was born.

Conclusion
Using week charts creates an unequal distribution in the proportion of SGA infants throughout the gestational week; this is corrected if day charts are used. Week charts also lead to an unequal relative risk of adverse outcomes, including stillbirth, for infants born at the beginning or end of the week. Day charts should be used.

Natasha Pritchard, [1,2], Susan Walker,[1,2,] Stephen Tong, [1,2,] Anthea Lindquist[1,2,]

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Adjusting Growth Standards for Fetal Sex Better Correlates with Perinatal Morbidity and Mortality: An Australian State-Wide Population Study.

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Aim
Sex plays a role in determining birthweight, with male babies heavier on average than females. However, not all growth standards are sex-specific; some use mean birthweight for both male and females. We aimed to identify the proportion of infants would be re-classified if sex-specific charts were used, and if this had a measurable impact on perinatal outcomes.

Methods
Retrospective cohort study on all infants born in Victoria, Australia, from 2005-2015 (529,261 cases). We applied GROW centiles, either adjusted or not adjusted for fetal sex. We compared overall small for gestational age (SGA) populations, and then the populations of males considered small only by sex-specific charts, and females considered small only by sex-neutral charts.

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Results
Of those <10th centile by unadjusted charts, 39.6% of the population were male, and 60.5% female. Using sex-specific charts, 50.3% of those <10th centile were male and 49.7% female. 19.2% of females that were SGA according to sex-neutral charts were reclassified as average for gestational age (AGA) using sex-specific charts. These female newborns were not at increased risk of stillbirth or other adverse outcomes compared with an infant AGA by both charts (AGA_{all}), but were at greater risk of being iatrogenically delivered on suspicion of growth restriction (RR 4.90, 95%CI 4.39 – 5.48). 8,048 male infants were reclassified as SGA by sex-specific charts, which increased the male SGA population by 25%. Compared to the AGA_{all} infants, these male newborns were at greater risk of stillbirth (RR 1.94, 95%CI 1.30-2.90), combined perinatal mortality (RR 1.80, 95%CI 1.26–2.57), NICU admissions (RR 1.38, 95%CI 1.12-1.71), Apgars<7 at 5 minutes (RR 1.40, 95%CI 1.25-1.56) and emergency Caesarean (RR 1.12, 95%CI 1.06-1.18).

Conclusion
Sex-specific growth standards improve correlation with perinatal outcomes, over growth standards unadjusted for fetal sex. They newly classify a high risk cohort of male infants as SGA, and exclude a cohort of female infants, whose risk is no greater than an appropriately grown infant.