FETAL AND NEONATAL WORKSHOP
OF AUSTRALIA AND NEW ZEALAND

33RD ANNUAL MEETING

PERINATAL SOCIETY of Australia & New Zealand PSANZ

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

LIONS MEDICAL RESEARCH FOUNDATION

The FNWANZ is proudly affiliated with the Perinatal Society of Australia and New Zealand

The 23rd Annual PSANZ Congress | 17-20 March 2019 | Gold Coast Convention Centre Broadbeach | Australia

Terms of reference

Fetal and Neonatal Workshop of Australia and New Zealand (FNWANZ)

- The FNWANZ provides a forum for discussion of new ideas and presentation of experimental and clinical data in fetal and neonatal biology
- The FNWANZ aims to encourage discussion and establish collaborations between basic scientists and researchers from all disciplines of perinatal medicine
- The FNWANZ is an informal, multidisciplinary meeting with workshop-style presentations and discussion sessions from scientists and researchers from all disciplines of perinatal medicine
- The FNWANZ meetings consist of oral communications on completed studies, works in progress or planned studies

The Fetal and Neonatal Workshop gratefully acknowledge financial support from:

FNWANZ 2019 Program Outline

Mantra Legends, Surfers Paradise, Queensland, Australia

Friday March 15th		
8.00 – 8.50am	Registration	Pre-function area
8.50 – 9.00am	Welcome & Official Opening	Apollo Ballroom
9.00 – 10.30am	Session 1	Apollo Ballroom
10.30 – 11.00am	Morning Tea	Pre-function area
11.00 – 12.15pm	Session 2	Apollo Ballroom
12.15 – 1.15pm	Lunch	Pre-function area/Terrace
1.15 – 3.00pm	Session 3	Apollo Ballroom
3.00 – 3.30pm	Afternoon Tea	Pre-function area
3.30 – 4.45pm	Session 4	Apollo Ballroom
6.00 – 10.00pm	Workshop Dinner	Seascape

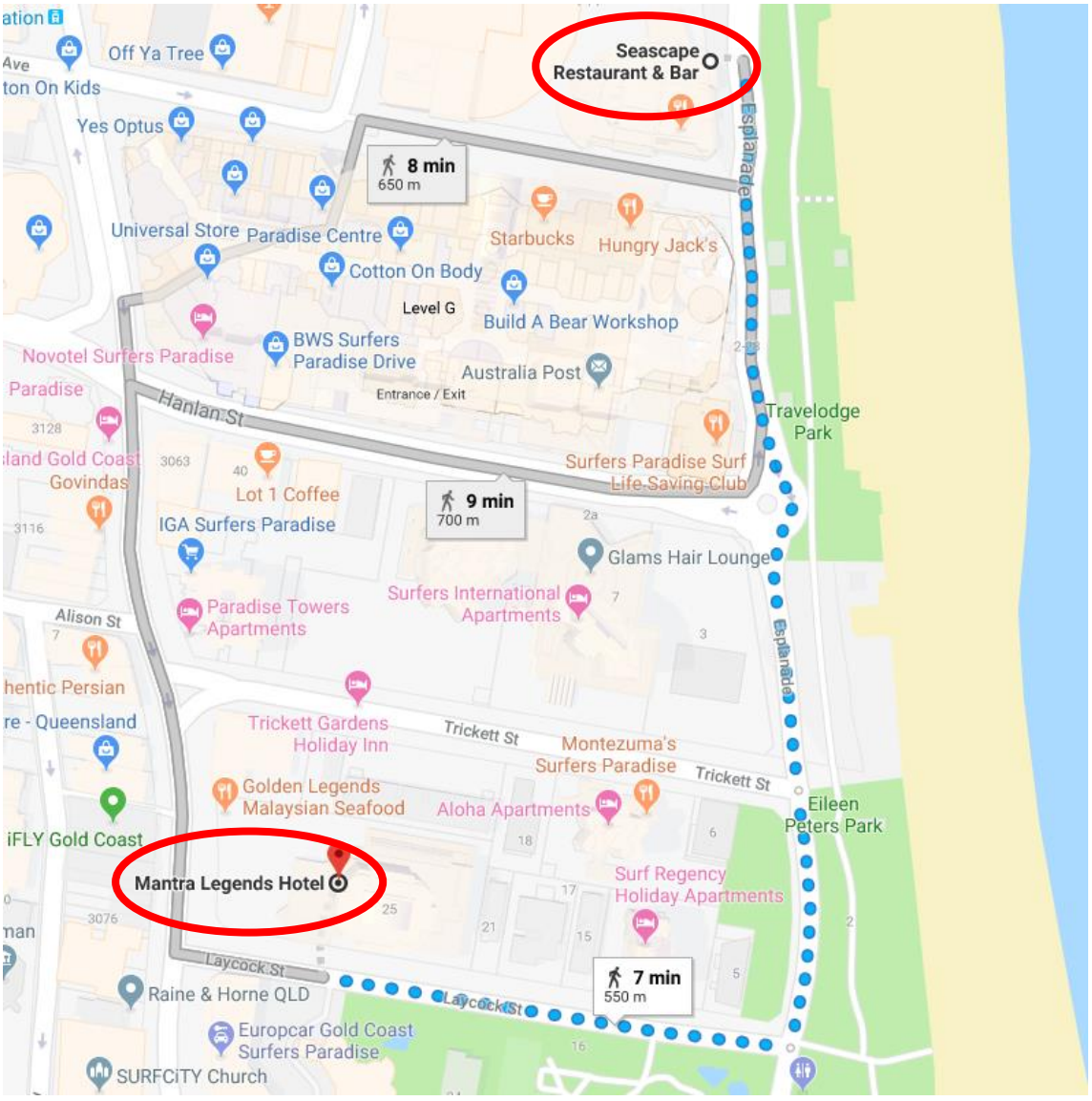
Saturday March 16th		
9.30 – 10.00am	Registration	Pre-function area
10.00 – 10.45am	Session 5	Apollo Ballroom
10.45 – 11.15am	Morning Tea	Pre-function area
11.15 – 1.15pm	Session 6	Apollo Ballroom
1.15 – 2.15pm	Lunch	Pre-function area/Terrace
2.15 – 4.00pm	Session 7	Apollo Ballroom
4.00 – 4.30pm	Afternoon Tea	Pre-function area
4.30 – 5.00pm	Awards & Official Close	Apollo Ballroom

Information for Delegates

Conference Location:

Mantra Legends Hotel
Cnr Surfers Paradise Blvd & Laycock Street
Surfers Paradise, QLD 4217, Australia

Wifi Details: FNWANZ



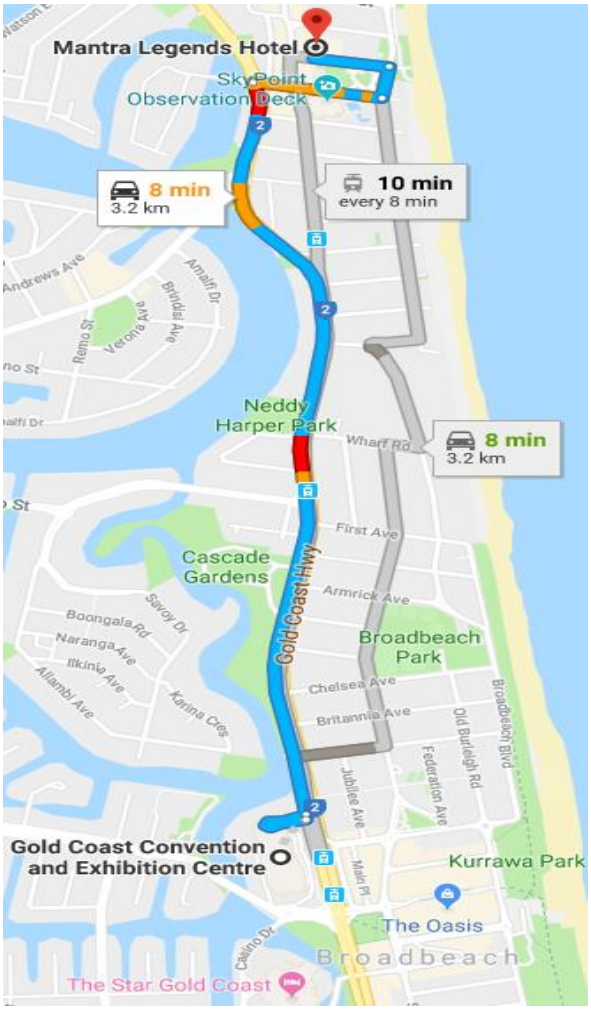
Conference Dinner:

Seascape Restaurant + Bar
4 The Esplanade, Surfers Paradise, QLD 4217
Lvl 1 – Bistro Bar, Lvl 2 – Restaurant; Lvl 3 – Rooftop

*** 6.00 pre-dinner drinks on the rooftop for 6.45pm dinner**

PSANZ 2019 Conference:

Gold Coast Convention & Exhibition Centre



Transport:

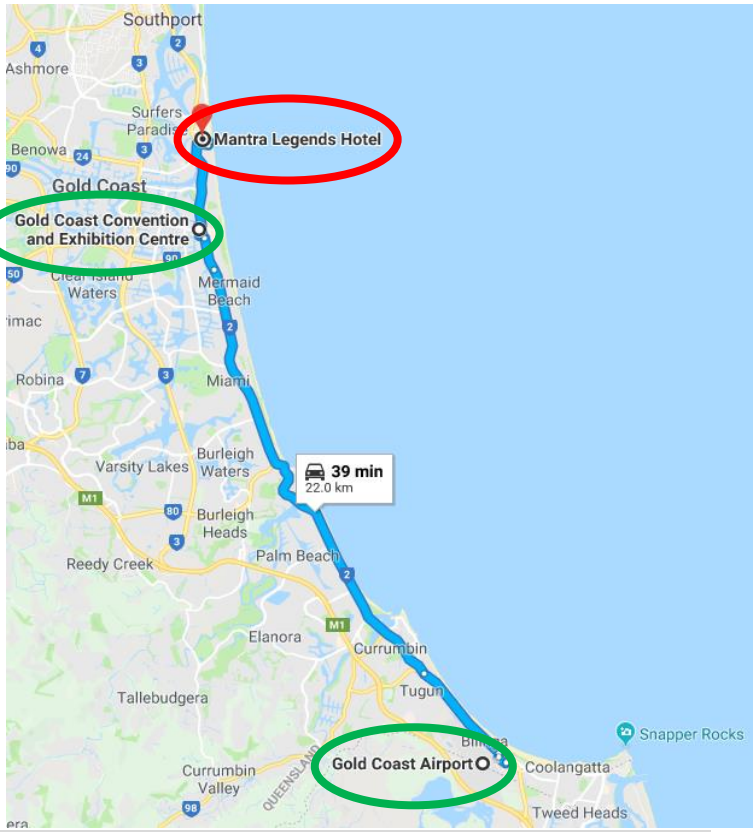
Bus

Route 705 Broadbeach to Sea World/Main Beach
Runs every 30 mins from 4.07am – 11.07pm

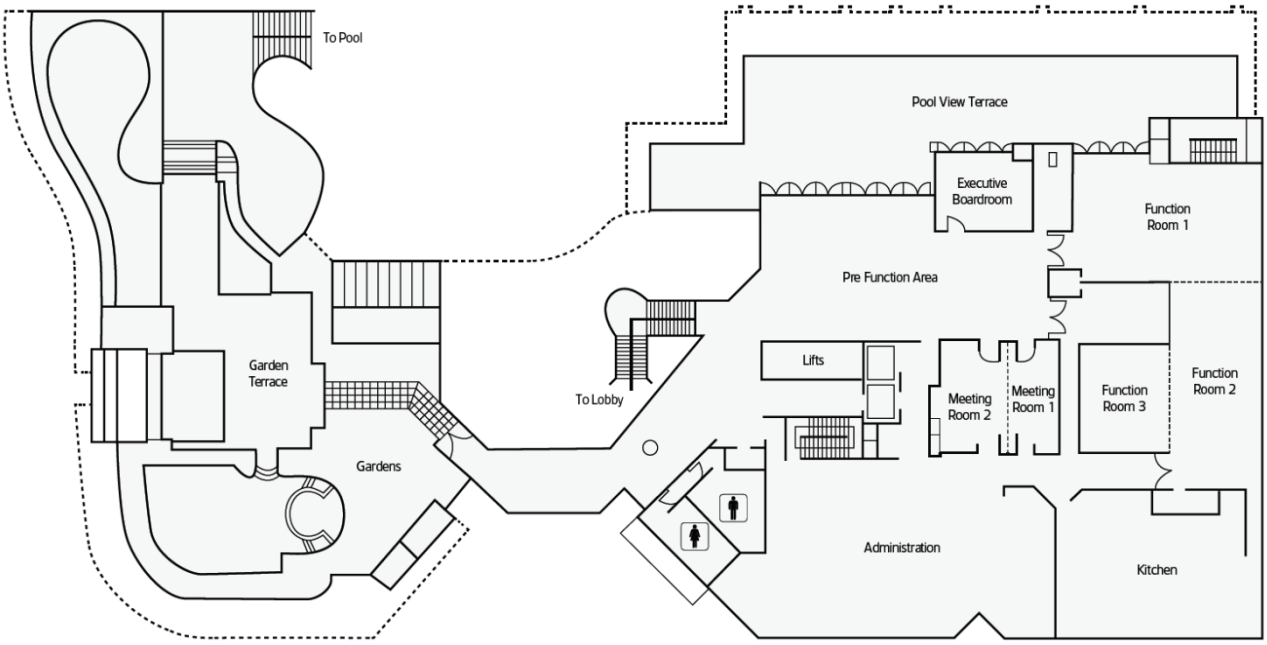
Gold Coast Light Rail

Weekdays: Every 7.5 mins from 7am – 7pm
Every 15 mins from 5am – 7am & 7pm – midnight

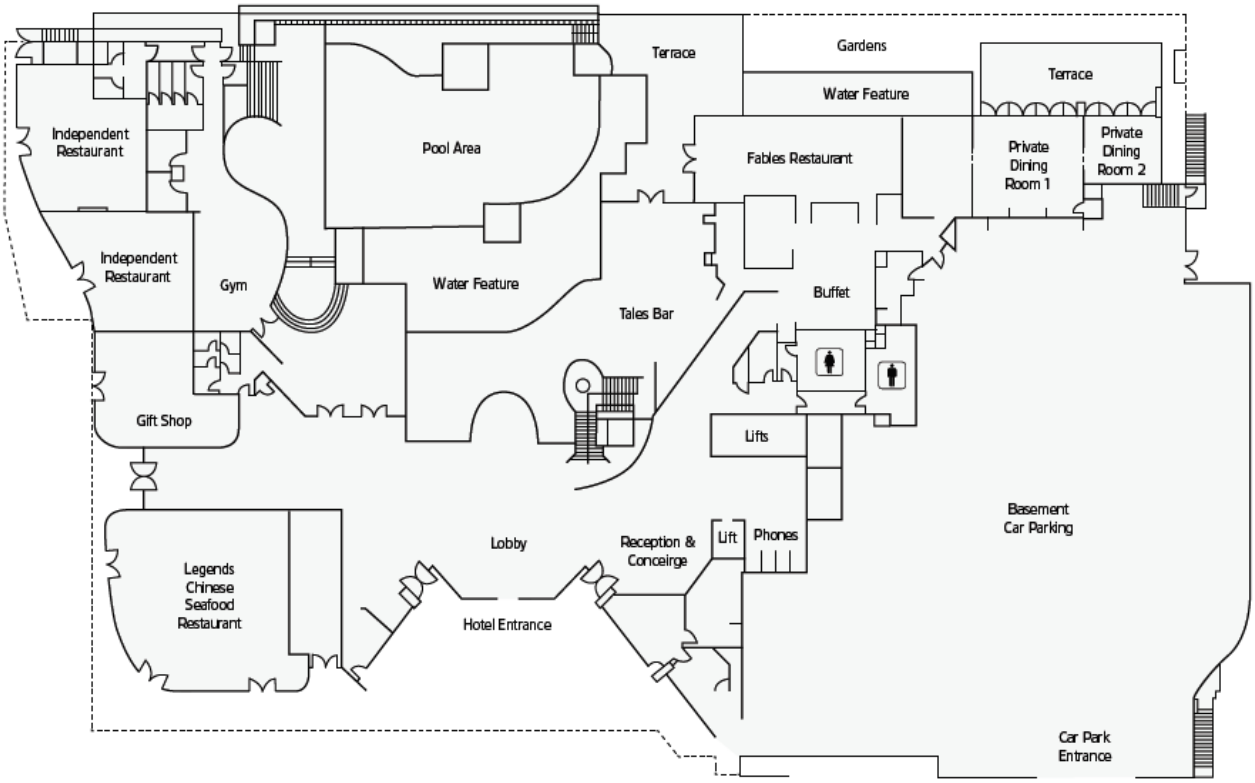
Weekends: Every 10 mins from 7am – 7pm
Every 15 mins from 5am – 7am & 7pm – midnight



Venue Floorplans:



Level 1



Ground Floor

FNWANZ 2019 Program

Day 1 – Friday 15th March

8.00 – 8.50am Registration (Pre-function area)
8.50 – 9.00am Welcome & Official Opening (Apollo Ballroom)

Session 1 (Apollo Ballroom)			
Chairs – Dr Bobbi Fleiss & Dr Kirat Chand			
Time	**Abstr #**	**Speaker**	**Title**
9.00 am	A1	Tayla Penny (L)	Is multiple doses of UCB needed; Designing effective UCB clinical trials using preclinical data
9.15am	A2	Steph Miller (ECR)	Preterm Hypoxia- how detrimental is it?
9.30am	A3	Madeline Smith (E)	Neural and mesenchymal stem cell therapy in a rodent model of HI brain injury
9.45am	A4	Lara Jones (E)	Investigating the effect of placental stem cells on the blood brain barrier in a model of HIE
9.52am	A5	Leo Cooper (H)	Neuropathology and behaviour associated with fetal growth restriction
10.00am	A6	Julie Wixey (ECR)	Placental stem cells to protect the newborn IUGR brain
10.15am	General Discussion		
10.30am	*Morning Tea (Pre-function area)*		

Session 2 (Apollo Ballroom)			
Chairs – A/P Michael Stark & Dr Stacey Ellery			
Time	**Abstr #**	**Speaker**	**Title**
11.00am	A7	Mariana Muelbert (L)	NIRS for detection of olfactory activation in moderate to late preterm infants: A pilot study
11.15am	A8	Nykola Kent (E)	Does mid-gestational selenium supplementation improve adverse maternal and fetal outcomes following gestational hypothyroidism?
11.22am	A9	Shreya Rana (L)	The development of cortical folds: a cross-species comparison
11.37am	A10	Shamina Albeloushi (E)	Effect of branched chain amino acid (BCAA) supplements on growth and development of preterm lambs
11.44am	A11	Kathryn Gatford	Relationship between size at birth and postnatal allergy – an update
11.51am	A12	Tamara Varcoe (ECR)	Meloxicam provides superior analgesic effects for sheep recovering from indwelling catheter surgery
11.58am	General Discussion		
12.15pm	*Lunch (Pre-function area & Terrace)*		

FNWANZ 2019 Program

Day 1 – Friday 15th March

Session 3 (Apollo Ballroom)			
Chairs – Prof Kathy Gatford & Dr Julie Wixey			
Time	**Abstr #**	**Speaker**	**Title**
1.15pm	Guest Speaker	Prof Rebecca Simmons	Fetal Programming: We Can Work It Out
1.45pm	A13	Harleen Kaur (L)	Sexual dimorphism in fetal growth responses in a mouse model of IUGR
2.00pm	A14	Delphi Kondos-Devcic (L)	Assessment of neonatal growth and wellbeing following thyroid hormone-based therapy in a rodent model of IUGR
2.15pm	A15	Abi Ratnasingham (L)	Infant body composition predicts childhood obesity
2.30pm	A16	Kate Highfield (H)	Simulated shift work during pregnancy does not alter circadian rhythms in young adult sheep progeny
2.45pm	General Discussion		
3.00pm	***Lunch (Pre-function area & Terrace)***		

Session 4 (Apollo Ballroom)			
Chairs – A/P Leo Leader & Dr James Cuffe			
Time	**Abstr #**	**Speaker**	**Title**
3.30pm	A17	Nirajan Shresta (L)	High maternal linoleic acid alters maternal lipid profile and hepatic cytokines in rat model
3.45pm	A18	Nadia Bellofiore (ECR)	Pseudopregnancy and reproductive cycle synchronisation cannot be induced using conventional methods in the spiny mouse
4.00pm	A19	Ashley Meakin (E)	Human placental androgen receptor variants: potential regulators of male fetal growth
4.15pm	A20	Lisa Akison (ECR)	Prenatal alcohol exposure and female reproductive potential: Are there impacts on ovarian reserve or fertility?
4.30pm	General Discussion		
6.00pm for 6.45pm	***Conference Dinner – Seascape*** 4 The Esplanade, Surfers Paradise **6.00pm – pre-dinner drinks*		

FNWANZ 2019 Program

Day 2 – Saturday 16th March

Session 5 (Apollo Ballroom)			
Chairs – Prof Janna Morrison & Dr Yvonne Eiby			
Time	**Abstr #**	**Speaker**	**Title**
10.00am	A21	Simone Sleep (M)	The effect of high maternal concentrations of linoleic acid on endocannabinoid signalling in heart tissue of offspring rats
10.07am	A22	Kelsee Shepherd (L)	Does prone sleeping affect baroreflex sensitivity in preterm infants in NICU?
10.15am	A23	Jack Darby (L)	Selection of an appropriate anaesthetic agent for cardiac magnetic resonance imaging in the fetal sheep
10.30am	A24	Aidan Kashyap (L)	The effect of antenatal sildenafil on neonatal pulmonary haemodynamics in an ovine model of diaphragmatic hernia
10.37am	A25	Aidan Kashyap (L)	Physiologically based cord clamping improves pulmonary haemodynamics during the neonatal transition in lambs with diaphragmatic hernia
10.30am	General Discussion		
10.45am	*Morning Tea (Pre-function area)*		

Session 6 (Apollo Ballroom)			
Chairs – Prof Alistair Gunn & Dr Nathan Stevenson			
Time	**Abstr #**	**Speaker**	**Title**
11.15am	A26	Nathanael Yates (ECR)	White matter neuropathology following chorioamnionitis and postnatal dexamethasone in preterm lambs
11.30am	A27	Simerdeep Dhillon (L)	Neural effects of delayed recombinant human erythropoietin treatment after asphyxia in preterm fetal sheep
11.45am	A28	Maria Petraki (H)	Inhibiting the inflammasome as a novel treatment for neonatal hypoxic-ischemic brain injury
12.00pm	A29	Benjamin Lear (M)	The evolution of neuroinflammation and myelination after hypoxia-ischaemia in preterm fetal sheep
12.15pm	A30	Victoria King (E)	Investigating ultradian periodicity in the preterm fetal sheep EEG
12.30pm	A31	Anna Muccini (L)	Using creatine to preserve mitochondrial function in the fetal brain following acute in utero hypoxia
12.45pm	A32	Nhi Tran (E)	Neuroprotective capacity of creatine to reduce perinatal hypoxia-related encephalopathy: a microdialysis study
1.00pm	General Discussion		
1.15pm	*Lunch (Pre-function area & Terrace)*		

FNWANZ 2019 Program

Day 2 – Saturday 16th March

Session 7 (Apollo Ballroom)			
Chairs – Prof Dawn Elder & Dr Stephanie Miller			
Time	Abstr #	Speaker	Title
2.15pm	A33	Nathan Stevenson	Predicting post-menstrual age in preterm infants using EEG analysis
2.25pm	A34	Joe Smolich	Asphyxial state after immediate cord clamping accelerates onset of ductus arteriosus left-to-right shunting after birth in preterm lambs
2.40pm	A35	Yvonne Eiby	Does the vascular response to adrenergic agents explain their ineffectiveness in preterm piglets?
2.55pm	A36	Shaun Sandow	Endothelial vasodilator mechanisms as targets to control uterine blood flow in preeclampsia
3.10pm	A37	Karen Moritz	Prenatal alcohol exposure and child health outcomes: results of a national survey
3.25pm	A38	Janna Morrison	Fetal hepatic flow in sheep assessed using 4D flow MRI
3.40pm	General Discussion		
4.00pm	*Afternoon Tea (Pre-function area)*		
4.30pm	*Awards & Official Close*		

Guest Speaker FNWANZ 2019

Professor Rebecca Simmons, MD

Dr. Simmons completed her M.D. at the University of Arizona in Tucson and then went on to a Residency in Pediatrics at the University of Arizona Health Sciences Center followed by a Neonatal-Perinatal Medicine Fellowship at the Cardiovascular Research Institute in San Francisco, California.

Dr. Rebecca Simmons is now the Hallam Hurt Endowed Chair and Professor of Pediatrics at the Perelman School of Medicine and an Attending Physician at the Children's Hospital of Philadelphia. Her research focuses on the causal mechanistic links between the intrauterine milieu and type II diabetes and obesity in the adult with a focus on epigenetics and mitochondria function. She has received many awards for her research and is a member of several academic honorary societies including the Perinatal Research Society and the Academic Physician Society. She has also been a member of the Endocrine Society and the American Diabetes Association for over 25 years.

The Simmons' laboratory has been continuously funded for the past 25 years by the NIH and has also received funding from the American Diabetes Association and the March of Dimes. In addition, Dr. Simmons is a PI of the March of Dimes Preterm Birth Research Center at the University of Pennsylvania. She is also the Co-Director of the Center for Excellence in Environment and Toxicology Research at the University of Pennsylvania. Over the course of her research career Dr. Simmons has mentored over 50 postdoctoral fellows, graduate students, medical students, and undergraduate students.

A1

IS MULTIPLE DOSES OF UCB NEEDED; DESIGNING EFFECTIVE UCB CLINICAL TRIALS USING PRECLINICAL DATA

Tayla Penny[1,2], Amy Sutherland[1], Jamie Mihelakis[1], Yen Pham[1], Graham Jenkin[1,2], Suzanne Miller[1,2] and Courtney McDonald[1].

[1] *The Ritchie Centre, Hudson Institute of Medical Research, Clayton, Australia*
[2] *Department of Obstetrics and Gynaecology, Monash University, Clayton, Australia*
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Background: Cerebral palsy (CP) is the most common childhood motor disability, resulting from injury to the brain during the perinatal period. Currently there are clinical trials underway that are investigating umbilical cord blood (UCB) as a treatment for established cases of CP. A few of these trials in subsequent analysis, have suggested that multiple doses of UCB is more effective at improving motor outcomes than a single dose. Pre-clinical studies investigating UCB for neonatal brain injury most commonly administer a single dose of UCB cells. For this study, we administered multiple doses of UCB in order to more closely match current clinical trial data.

Aims/Hypothesis: This study aimed to determine whether a single dose or multiple doses of UCB would be more efficacious for improving neuropathology and behavioural outcomes in the setting of neonatal brain injury. By doing this, we will provide robust pre-clinical evidence that can help guide future clinical trials.

Methods: Neonatal brain injury was induced in postnatal day (PND) 10 rats by left carotid artery ligation, followed by 90 min of hypoxia (8% O_2). 24h later, pups were administered 1 million hUCB cells intranasally and received 1 dose (PND11), or 3 doses (PND11, 13, 20). Rats were monitored until PND50; throughout this period, they underwent behavioural testing. On PND50, brains were collected for immunohistological analysis.

Results: HI injured pups showed a significant decrease in brain weight (P=0.004) and increase in tissue loss (P=0.001) compared to sham animals. This was modulated my multiple doses of UCB (P=0.006, P=0.02) but not by a single dose. In the somatosensory cortex of the brain, there was a reduction in neuron numbers (P=0.008) and an increase in activated microglia (P=0.0007) and apoptosis (P<0.0001) in the HI injured animals compared to sham. Multiple doses of UCB were able to significantly modulate these neuropathologies (P=0.007, P=0.002, P=0.01, respectively), whereas a single dose was not. In addition, HI injured animals also showed significant behavioural deficits compared to sham (P=0.0008), which were modulated by multiple doses of UCB (P=0.02) but not by a single dose.

Conclusions: Multiple doses of UCB cells is more beneficial than a single dose for improving neuropathology and behavioural outcomes in the setting of neonatal brain injury.

A2

EFFECT OF STEM CELLS ON VASCULAR STABILITY IN THE PRETERM

Stephanie Miller[1], Yvonne Eiby[1], Julie Wixey[1], Kirat Chand[1], Seen-Ling Sim[2], Jatin Patel[2], Kiarash Khosrotehrani[2], Paul Colditz[1], Barbara Lingwood[1], Tracey Björkman[1]

[1] *Perinatal Research Centre, UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Herston, QLD Australia.*
[2] *The University of Queensland Diamantina Institute, Faculty of Medicine, The University of Queensland, Herston, QLD Australia*
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Background: Preterm birth is associated with numerous complications and poor long term outcomes. Providing adequate care of the preterm involves ensuring sufficient blood flow and oxygenation to vital organs – hypotension and hypoxaemia are common clinical problems in the first days of life. Our previous research has identified that vascular integrity is compromised in preterm neonates. Placentally derived stem cells display distinct properties, and are a source rich in mesenchymal stem cells (MSCs) and endothelial colony forming cells (ECFCs). ECFCs possess vascular network forming potential, significant engraftment properties and have superior proliferative capacity, making them an ideal candidate for supporting the integrity of the preterm vasculature.

Hypothesis: Systemic placental stem cell treatment in the preterm piglet within the first hours of life improves vascular integrity and supports cardiovascular function leading to better brain outcomes.

Methods: Preterm piglets delivered by caesarean section (99d gestation, term 115d) will be ventilated, catheterised and maintained in standard NICU conditions in our neonatal PigICU. Stem cells (placental ECFCs and MSC; 2.5 million) will be administered intravenously 2-3h after delivery. Animals will be recovered for 14 days (term equivalent)- magnetic resonance imaging, EEG and behavioural analysis will be undertaken before euthanasia. Cardiovascular function will be evaluated by measuring blood pressure, heart rate, and cerebral oxygenation with near-infrared spectroscopy (NIRS). Vascular integrity will be examined using fluorescent-labelled dextrans, and immunohistochemistry and qPCR in brain, skin, muscles, kidneys and lung.

Results: Preliminary studies in our lab have demonstrated the feasibility of recovering preterm piglets to term equivalent age. IgG extravasation has been observed in the preterm piglet in both brain and skin.

A3

NEURAL AND MESENCHYMAL STEM CELL THERAPY IN A RODENT MODEL OF HI BRAIN INJURY

Madeleine Smith, Amy Sutherland, Graham Jenkin, Michael Fahey, Suzie Miller, Courtney McDonald

The Ritchie Centre, Hudson Institute of Medical Research, Monash University, Clayton, Australia.
madeleine.smith@hudson.org.au

Background: In Australia this year, approximately 60 babies will be affected by perinatal stroke, leading to significant neurological and cognitive deficits. Mesenchymal stem cells (MSCs) and neural stem cells (NSCs) have anti-inflammatory and neuroregenerative properties and are therefore promising therapeutic treatments for perinatal stroke. We aimed to determine whether NSCs and MSCs could reduce hypoxic ischaemic (HI) injury in a rodent model of perinatal stroke.

Aims/Hypothesis: To determine whether NSC or MSC treatment is more effective in reducing HI brain injury in a perinatal rat model.

Methods: HI surgery was performed on PND10 rats to permanently ligate the left carotid artery, followed by exposure to 8% oxygen for 90 minutes. Human fetal derived NSCs or MSCs (2 x 10^5 cells) were delivered intranasally 24 hours after HI injury. To assess behavioural deficits, negative geotaxis was performed at PND17, followed by a post-mortem where the brain was collected for immunohistochemistry.

Results: HI injury led to increased behavioural deficits compared to sham ($p<0.05$), which was improved by NSCs ($p=0.06$), but not MSC treatment. HI led to significantly increased microglial activation in the motor cortex ($p<0.05$) and significant neuronal cell loss in the somatosensory cortex and hippocampus ($p<0.05$) compared to sham. We observed a trend that NSC therapy reduced microglial activation and increased neuronal cell numbers following HI injury. However, MSC treatment did not modulate any histological indices of inflammation and injury.

Conclusions: NSC treatment 24 hours after HI injury improved behavioural deficits and indices of inflammation and injury. MSCs showed no significant benefit. This study highlights that not all stem cells are equal and certain stem cells may be more effective for treating perinatal stroke.

A4

INVESTIGATING THE EFFECT OF PLACENTAL STEM CELLS ON THE BLOOD BRAIN BARRIER IN A MODEL OF HIE

Lara Jones[1], Stephanie Miller[1], John Luff[1], Kirat Chand[1], Elliot Teo[1], Seen-Ling Sim[2], Jatin Patel[2], Kiarash Khosrotehrani[2], Paul Colditz[1], Julie Wixey[1], Tracey Bjorkman[1]

[1] Perinatal Research Centre, University of Queensland Centre for Clinical Research, The University of Queensland, St. Lucia, 4067, Australia.
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Background: Hypoxic-ischemic encephalopathy (HIE) is a devastating neurological injury, the result of oxygen deprivation and diminished blood supply to the neonate around time of birth. The blood brain barrier (BBB) is a highly regulated defence pivotal for brain homeostasis, a disruption in this barrier reduces its protective function and can contribute to neurological damage in newborns. Stem cells have been trialled in various models as a potential treatment for newborn HIE injury however results are conflicting. Placental stem cells are a unique stem cell source rich in mesenchymal stem cells (MSCs) and endothelial colony forming cells (ECFCs) which have properties distinct from other stem cell populations. Given that these cells possess vascular network forming potential and superior proliferative capacity, this makes them a prime candidate for neuroprotective effects at the BBB in the HIE neonate.

Hypothesis: Administration of stem cells isolated from human placenta following neonatal HIE will provide neuroprotection and improved outcomes through attenuation of BBB disruption. Stem cells will provide both reparative actions and contribute to the formation of new blood vessels.

Methods: Newborn piglets (<24h old) will undergo a 30 minute hypoxic insult (HI) before receiving treatment. At 2 hours post HI insult, animals will receive either a single dose of stem cells (MSCs & ECFCs) or vehicle (saline) intravenously. All pigs will undergo 24 hour therapeutic hypothermia (33.5°c). MRI, EEG and behavioural analysis will be undertaken before euthanasia on day 8 post HI insult before collection of brain for laboratory analysis. Alterations to BBB permeability post HI will be assessed using immunohistochemistry, western blotting and qPCR, focussing on cells of the NVU and targeting markers of BBB integrity and permeability.

Results: We have established an 8 day survival model of neonatal HI and animal experiments are ongoing. IHC techniques are currently being worked up with several antibodies already optimised including Chanel 5, CD31, CD34, IgG, Iba1, Ki67, NeuN and Caspase 3.

A5

NEUROPATHOLOGY AND BEHAVIOUR ASSOCIATED WITH FETAL GROWTH RESTRICTION

Leo Cooper, Amy Sutherland, Beth Allison, Yen Pham, Atul Malhotra, Graeme Polglase, Graham Jenkin, Margie Castillo-Melendez, Suzie Miller

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Background: Fetal growth restriction (FGR) is a significant risk factor for physical disability, such as cerebral palsy, and also for cognitive and behavioural deficits. Knowledge of the consequences of FGR on the structure of the developing brain is accumulating from experimental animal studies and human imaging studies, however, the link between structural and functional deficits associated with FGR remains poorly described.

Aims/Hypothesis: The aim of the current study is to examine and characterise the neuropathology underlying functional deficits in FGR.

Methods: We induce FGR in fetal sheep at 88d gestation (term = 150d) via the surgical procedure termed single umbilical artery ligation. This causes placental insufficiency, chronic fetal hypoxia and hypoglycaemia analogous to that in human FGR. Moderate- to late- preterm birth at 133d is induced using betamethasone and mifepristone. FGR and control lambs remain with their mum for 4 weeks, during which time they undergo behavioural assessment tasks at 2, 3 and 4 weeks after birth, including simple maze and T-maze tasks described in *Camm et al, Reprod Fert Dev 2000, 12:165*. At 4 weeks, the brain is collected for MRI and histological analysis.

Results: This study is ongoing. Numbers to date include n=4 control lambs (3M, 1F) and n=4 FGR lambs (2M, 2F). Birth weight is reduced with FGR (4.4±0.2kg vs 3.3±0.2kg), and FGR lambs do not achieve catch-up growth by 4 weeks of age. To date, behavioural results indicate FGR lambs show a deficit in learning and memory ability characterized by an increase in maze errors and greater time to complete the tasks. FGR lambs are observed to be less careful and risk-adverse compared with control lambs who are more considered in their decision making. We are currently assessing neuronal morphology within the hippocampus of the brains from these animals, and early analysis suggests altered neuronal morphology and fewer synapses in FGR brains compared with control.

Conclusions: This study provides us with the basis for correlating brain structure with functional outcomes in offspring affected by FGR. The results will allow potential neuroprotective therapies to be tested.

A6

PLACENTAL STEM CELLS TO PROTECT THE NEWBORN IUGR BRAIN

Julie Wixey[1], Kirat Chand[1], Elliot Teo[1], Lara Jones[1], Rinaldi Pretorius[1], Stephanie Miller[1], John Luff[1], Seen L. Sim[2], Jatin Patel[2], Kiarash Khosrotehrani[2], Paul Colditz[1], S. Tracey Bjorkman[1]

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Background: Intrauterine growth restriction (IUGR) is commonly caused by placental insufficiency, resulting in an inadequate supply of oxygen and nutrients to the fetus. The fetal brain is particularly vulnerable to IUGR conditions and abnormal neurodevelopment is common in the IUGR infant. Recent evidence suggests inflammation may be a key mechanism responsible for the progression of brain impairment in the IUGR newborn. We hypothesised placental stem cell treatment will reduce inflammation and neuronal and white matter impairment in the IUGR newborn piglet brain.

Aims/Hypothesis: Placental stem cell therapy reduces inflammation and improves neuropathology in the IUGR brain.

Methods: We used the preclinical piglet model of growth restriction where IUGR occurs spontaneously. Newborn IUGR (<5th centile) and normally grown control piglets were collected on day of birth (P1) and received either i.v. vehicle (saline) or stem cells (1 million mesenchymal stem cells and 1 million endothelial colony forming cells). Animals were monitored and cared for until euthanasia on postnatal day 4 (P4). Neuronal and white matter impairment and markers of inflammation were investigated using IHC and qPCR.

Results: IUGR brains demonstrated increased microglial activation and astrocyte reactivity, suggestive of a pro-inflammatory status. Treatment with stem cells resulted in a dampening of these pro-inflammatory markers toward levels observed in controls.

Conclusions: Preliminary findings suggest administration of placental stem cells reduces neuroinflammation and attenuates poor neuropathological outcomes we have previously reported in IUGR piglet brains.

A7

NEAR INFRARED SPECTROSCOPY FOR DETECTION OF OLFACTORY ACTIVATION IN MODERATE TO LATE PRETERM INFANTS: A PILOT STUDY

Mariana Muelbert[1], Jane E Harding[1], Frank H Bloomfield[1]

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Background: In response to sensory stimulation such as smell and taste of food, a cascade of preabsorptive physiological responses are activated by the brain, referred to as cephalic phase responses (CPR). Preterm infants often require nutrition through feeding tubes until coordination of oral skills, and thus may miss activation of CPR. Previous studies have demonstrated that activation of the olfactory cortex can be detected using Near Infrared Spectroscopy (NIRS). Yet it is not known if activation of the olfactory cortex can be detected in moderate to late preterm (MLP) infants exposed to smell and taste of milk prior to tube feeding.

Aims/Hypothesis: To describe changes in cerebral oxygenation in the olfactory cortex measured by NIRS in MLP infants exposed to smell and taste of milk prior to tube feeds, compared to infants not exposed.

Methods: Pilot observational study in a sub-cohort of MLP infants enrolled in the DIAMOND trial and randomly assigned to be exposed or not exposed to smell and taste of milk prior to tube feeds. Smell of milk was provided with a gauze soaked with milk placed close to infant's nose; taste of milk was provided by placing a few drops of milk on the infant's lips with a syringe. Cerebral oxygenation levels were monitored at the bedside using a NIRS device (NIRO-200, Hamamatsu, Japan) before and during sensory stimulation and during tube feeding. Light optodes were placed over the right and left orbito-frontal cortical regions of the brain. Concentrations of oxygenated haemoglobin (O_2Hb) were recorded every second and described as average changes from baseline.

Results: 13 moderate to late preterm infants (32-35 weeks' gestation) were assessed on day 5 after birth. In the intervention group (n=4), asymmetry was observed between left and right sides with increases in average concentrations of O_2Hb for the left side when exposed to sensory stimulation. No consistent pattern was observed in the control group (n=9).

Conclusions: Preliminary data suggest that there might be activation of the olfactory cortex when MLP babies are presented with smell and taste of milk prior to tube feeds. Analysis of the larger cohort is required to support or refute these preliminary observations.

A8

DOES MID-GESTATIONAL SELENIUM SUPPLEMENTATION IMPROVE ADVERSE MATERNAL AND FETAL OUTCOMES FOLLOWING GESTATIONAL HYPOTHYROIDISM?

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Background: Maternal hypothyroidism is linked to a number of adverse fetal outcomes including fetal growth restriction and impaired neural function. Hypothyroidism affects approximately 3% of pregnant women and is currently treated by restoring thyroid hormone concentrations using thyroxine. Approximately 8% of pregnant women are thyroid antibody (TPOAb) positive in pregnancy with adverse fetal and maternal outcomes more likely in TPOAb positive women. Current treatments do not reduce TPOAb levels suggesting additional treatments are required. Selenium supplementation has been shown to diminish TPOAb concentrations in non-pregnant women but how it affects outcomes in pregnant women is poorly understood.

The purpose of this investigation is to use an animal model to determine the effect of maternal hypothyroidism during pregnancy on maternal and fetal outcomes. Using this animal model, this project will then determine whether mid-gestational selenium supplementation can reduce adverse outcomes.

Methods: Hypothyroidism will be induced in nulliparous female Sprague-Dawley rats by exposure to 0.02% methimazole in their drinking water for seven days prior to mating and throughout pregnancy. A subset of animals will receive selenium supplementation in their chow from E10 up until E20 when fetal weight will be assessed, and tissues collected for assessment of organ impairment. Maternal blood will be collected throughout pregnancy for analysis of thyroid hormone and TPOAb concentrations. Dams will be subjected to metabolic cage testing and oral glucose tolerance testing to evaluate maternal metabolic outcomes.

Expected Outcomes: It is anticipated that selenium supplementation from mid-gestation will reduce TPOAb and prevent adverse fetal and maternal outcomes.

A9

THE DEVELOPMENT OF CORTICAL FOLDS: A CROSS-SPECIES COMPARISON

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Background: Cortical folding, or gyrification, allows for an increase in cortical surface area-to-volume ratio, and the locations of specific folds allow for delineation of different functional regions of the brain. Gyrification is not unique to the human brain, with folding complexity varying between species. Little is known about the underlying mechanisms of cortical folding. Previous studies suggest that MRI-derived fractional anisotropy (FA, a measure of the direction of water diffusion) in the developmentally transient subplate layer in the brain can predict where folds will form.

Aims/Hypothesis: We compared FA in three species with different folding complexities and to identify the specific microstructure(s) identified by FA. We hypothesised that: (1) FA would vary more in the cortices of species with complex folding than in a species without folding, and; (2) that FA would reflect axonal density and directionality through the subplate.

Methods: FA was measured in sheep and ferrets (both have gyrencephalic brains), and compared with FA measurements from spiny mice (which have smooth, lissencephalic cortical hemispheres) using diffusion tensor imaging (DTI). In the fetal sheep, axonal density and directionality, and subplate cell densities were then histologically characterised below sulci and gyri to complement imaging findings.

Results: FA variability between adjacent cortical regions was higher in cortices of sheep and ferrets than in spiny mice, and in sheep and ferrets focal FA maxima corresponded with the locations of incipient development of gyri. Microstructurally, axonal density was greater below gyri than sulci through the subplate, but only after folds had begun to develop; uniformity of axonal directionality did not differ. Subplate cell density was consistently higher below gyri than sulci from the onset of cortical folding.

Conclusions: Structures influencing water diffusion are not uniformly arranged in gyrencephalic brains, but the cause of FA variation is unlikely to be axons. The subplate may be involved in cortical folding through a mechanism other than axonal guidance.

A10

EFFECT OF BRANCHED CHAIN AMINO ACID (BCAA) SUPPLEMENTS ON GROWTH AND DEVELOPMENT OF PRETERM LAMBS

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Background: Preterm birth occurs during a critical period for the development of metabolic systems and organ maturation, in which nutrition plays a key role. Preterm birth predisposes to impaired pancreatic function and diabetes. BCAA are important nutrients for neonatal growth and development of the endocrine pancreas, especially β-cells.

Aims: To determine, in male and female preterm lambs, the effect of postnatal BCAA supplementation on:

1. Development and function of the endocrine pancreas (primary outcome).
2. Early postnatal growth (secondary outcome and the focus of this abstract).

Methods: Preterm born lambs were randomized to receive daily oral supplements containing BCAAs (leucine, isoleucine and valine in a ratio of 1: 1.1: 1.9), maltodextran (M), or an equivalent volume of water (Preterm Control (W)) for the first 2 weeks after birth. Term Control lambs (T) received an equivalent volume of water. During the intervention period, weight, crown rump length (CRL), chest girth, abdominal girth, hock-to-toe length (HT), hind limb length (HL), and biparietal diameter (BPD) were measured. Milk intake was assessed using deuterium oxide dilution. At post mortem, pancreatic tissues were collected for immunohistochemistry (IHC) to measure islet number and composition, β-cell proliferation and apoptosis.

Results: At birth and at 15 days, T had the highest weight (T vs Preterm $P < 0.001$) but there was no difference in weight among preterm groups (table). Growth velocity (GV) for weight and CRL was less in T than in preterm (all groups combined $P < 0.05$). Milk intake and IHC data are pending.

	Term-water		Preterm-water		Preterm-BCAA		Preterm-Malto	
	(n=7) ♀	(n=6) ♂	(n=7) ♀	(n=9) ♂	(n=7) ♀	(n=7) ♂	(n=8) ♀	(n=7) ♂
Weight At Birth (kg)	6.11 ± 0.2	6.45 ± 0.3	4.4 ± 0.2	4.84 ± 0.2	4.34 ± 0.2	4.71 ± 0.2	4.76 ± 0.2	5.25 ± 0.2
Weight At Day 15 (kg)	10.89 ± 0.23	11.65 ± 0.63	8.7 ± 0.6	9.54 ± 0.37	8.59 ± 0.56	9.34 ± 0.2	9.36 ± 0.31	9.54 ± 0.26
GV (g*Kg-1*day-1)	17.96 ± 0.98	18.3 ± 1.62	21.1 ± 1.14	21.3 ± 1.5	20.99 ± 1.41	21.31 ± 1.01	21.03 ± 0.7	18.53 ± 1.03

Conclusions: Neither BCAA nor maltodextran supplements accelerated early postnatal growth in preterm lambs. Milk intake data will be helpful to interpret these results. BCAA supplements may affect pancreatic endocrine function and development independently of lamb growth.

A11

RELATIONSHIP BETWEEN SIZE AT BIRTH AND POSTNATAL ALLERGY – AN UPDATE

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Background: Data from animal models and some human literature suggests that *in utero* growth restriction is protective against allergy. Human literature is variable and has not been systematically reviewed to assess effects of birth weight on allergy, with correction for gestational age a particular issue in separating relationships reflecting *in utero* growth restriction from those due to prematurity.

Aims/Hypothesis: We therefore designed and registered (1) a systematic review to assess existing studies and provide clarity on the relationship between size at birth or fetal growth rate, relative to gestational age, and postnatal allergic disease (eczema/atopic dermatitis [AD], hay fever/atopic rhinitis [AR], allergic asthma [AA] and food allergy [FA]). We used the generalized least-squares method (2) to estimate the linear association of birth weight [BW] with each outcome.

Methods: We searched 11 databases for literature describing our exposures (size at birth or fetal growth), and outcomes of interest (physician diagnosis/clinical symptoms allowing specific diagnosis of AD, AR, AA or FA).

Results: Of the 15093 studies identified from our search, 42 were eligible for inclusion in the narrative review. Only two studies reported AA. In meta-analysis of data from four studies, an increase of 1 kg in birth weight was associated with a 1.44-fold increase in the risk of FA in children (OR 1.44; 95% CI 1.04-1.99, P=0.001). Sixteen studies investigated AR outcomes, with 14 able to be included in meta-analyses. There was no evidence that risks of AR ever in childhood, current AR in childhood, or AR ever in adulthood, were altered by BW ($P > 0.5$ for each). Meta-analysis of relationships between BW and AD is ongoing.

Conclusions: The protective effect of low BW relative to gestational age at birth on food allergy is consistent with reduced susceptibility to allergy in animal models of IUGR. Data to date suggests effects of fetal growth vary between allergic diseases that differ in age of onset.

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2. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. *Am J Epidemiol* 2012; 175:66-73.

A12

MELOXICAM PROVIDES SUPERIOR ANALGESIC EFFECTS FOR SHEEP RECOVERING FROM INDWELLING CATHETER SURGERY

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Background: Sheep are routinely used as an animal model in pregnancy and fetal development studies. Catheterisation of both the maternal and fetal vasculature allows repetitive sampling from non-anaesthetised ewes. However, due to the invasive nature of this procedure, an effective analgesic is required post-operatively. The α2 adrenergic receptor agonist Xylazine, and the non-steroidal anti-inflammatory drug Meloxicam both have demonstrated efficacy in reducing pain in sheep.

Aims/Hypothesis: The aim of this study was to compare the analgesic actions of Xylazine and Meloxicam in sheep following maternal and fetal indwelling catheter surgery.

Methods: In this retrospective study, ewes were administered Xylazine (20 µg/kg, intramuscular, n=50) upon recovery from anaesthesia, or Meloxicam (0.5 mg/kg, subcutaneous, n=55) at 1600 h on the day prior and of surgery. Routine clinical records were collected for 3 days prior and up to 10 days following surgery. Ewes were assessed each morning by a trained animal technician and scored on a scale of 0 to 3 for Appetite, Drinking, Defecation, Urination and Alertness, where 0 is normal and 3 is severely affected. Total clinical scores were calculated for each animal and food consumption was determined by weighing daily residual feed.

Results: Surgery significantly increased total clinical score and reduced food consumption for up to 4 days (P<0.05). Compared to Xylazine, Meloxicam administration reduced total clinical score at day 1 (-1.4 AU, P<0.001), day 2 (-1.2 AU, P<0.001) and day 3 (-0.6 AU, P=0.008), and increased food consumption at day 1 (+166 g, P=0.035) and day 2 (+262 g, P=0.01) post-surgery.

Conclusions: These results demonstrate that Meloxicam is superior to Xylazine in reducing the impact of fetal surgery on routinely collected clinical measures and food consumption in the ewe, particularly within the first 3 days following surgery.

A13

SEXUAL DIMORPHISM IN FETAL GROWTH RESPONSES IN A MOUSE MODEL OF IUGR

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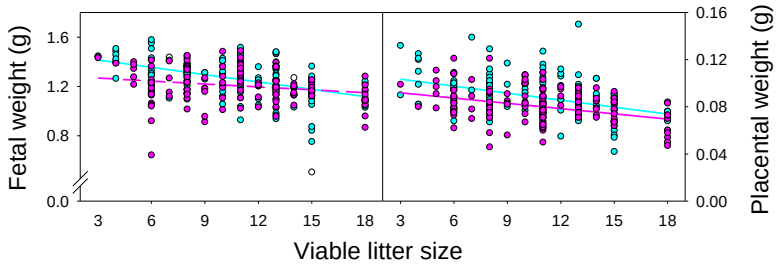
Background: Intrauterine growth restriction (IUGR) affects 5-15% of babies, and increases their risk of perinatal death and poor health in later life. In order to test potential interventions, we have established a murine model using embryo transfer-generated pregnancies where increased litter size induces an IUGR phenotype. In humans, birth weights are higher in male than female babies at every gestation [1], and adverse exposures such as maternal asthma have sex-dependent effects [2].

Aims/Hypothesis: To investigate whether increasing litter size constrains fetal growth in a sex-specific manner.

Methods: CBAF1 embryos were collected at gestation day 0.5 (GD0.5) and 6, 8, 10 or 12 embryos transferred into each uterine horn of pseudopregnant CD1 mice (n=32). Fetuses and placentas were collected and weighed at GD18.5. Fetuses were genotyped for sex by PCR for *Sry*.

Results: Effects of viable litter size on fetal weight differed between sexes (interaction *P*=0.002). Weights of males (P=0.002), but not females (P=0.233), correlated negatively with litter size (Figure). Placental weight decreased with increasing litter size (P<0.001) and was lower in females (P=0.020), but effects of litter size did not differ between sexes (Figure).



Conclusions: In this model, the pattern of female growth is not affected by maternal constraint. In contrast, males are heavier when unconstrained, and their placentas are always heavier than those of females, suggesting the male fetus extracts maximal available nutrients, whereas the female maintains placental reserve capacity. This strategy is likely to place the male fetus at risk in the event of a "second hit".

[1] Verburg et al., PLoS One 11(7) (2016) e0158807-e0158807.

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A14

ASSESSMENT OF NEONATAL GROWTH AND WELLBEING FOLLOWING THYROID HORMONE-BASED THERAPY IN A RODENT MODEL OF INTRAUTERINE GROWTH RESTRICTION (IUGR)

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Background: We have shown that the thyroid hormone (TH) transporter - monocarboxylate transporter-8 (MCT8) is decreased in the neonatal IUGR rat brain, perhaps contributing to impaired brain development in IUGR. We also found that the TH analogue, diiodothyropropionic acid (DITPA), which does not require MCT8 to enter cells promotes myelin recovery by P7. However the preclinical safety profile of DITPA is unknown.

Aims/Hypothesis: To determine if DITPA treatment in IUGR rats affects neonatal growth and wellbeing.

Methods: At day 18 of pregnancy (term=22 days), rats underwent bilateral uterine vessel ligation (n=29 litters) or sham surgery (n=15 litters) to generate IUGR or control pups. DITPA (0.5mg/100g; i.p.) or saline was administered daily from P1-P13 to IUGR (DITPA, n=60; Saline, n=57) and control (DITPA, n=42; Saline, n=46) pups. Body weight, brain weight, body composition, thyroid function (serum free T_3 and T_4), and serum liver enzymes (alanine transaminase, ALT; alkaline phosphatase, ALP) were assessed at P14.

Results: In IUGR vs control pups, there was a significant reduction in body weight, brain weight, bone mineral content, bone mass, lean tissue mass and fat mass; DITPA did not improve or worsen these effects. In IUGR vs control pups, free T_4 and ALT were significantly decreased, and ALP was significantly increased; DITPA treatment significantly increased free T_3, ALP, and ALT (IUGR only), but reduced free T_4.

Conclusions: DITPA does not adversely impact neonatal growth or wellbeing following IUGR, despite altering free thyroxine levels and showing hepatic thyromimetic activity.

A15

INFANT BODY COMPOSITION PREDICTS CHILDHOOD OBESITY

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Background: Obesity is a growing epidemic associated with several cardiovascular and metabolic diseases. Early detection and intervention may help reduce later cardiometabolic risk. While low birth weight is associated with poor health in later life, early body composition (fat mass [FM] and fat-free mass [FFM]) may be a better predictor.

Aims/Hypothesis: This study aimed to: (1) determine whether infant body composition is a better predictor of childhood obesity than birth weight, (2) determine which infant body composition factors predict childhood obesity and (3) determine what other early life factors predict childhood obesity.

Methods: This was an observational follow-up study of 130 children recruited as newborns at the Royal Brisbane and Women's Hospital in 2007-2010. Body composition was measured by air displacement plethysmography using the PEA POD® during infancy (at birth, 6 weeks, 3 months and 4.5 months old) and the BOD POD® at 8-11 years old. Maternal risk factors (e.g. maternal body mass index [BMI]) and infant feeding information were also recorded. Backward stepwise multiple regression analysis was used to identify significant predictors of childhood obesity.

Results: There was no association between childhood percentage fat (FM/body weight) and either birth weight or birth weight z-score. Increased percentage fat at 6 weeks old was a significant predictor of increased childhood percentage fat as were higher maternal BMI and earlier exposure to formula feeding.

Conclusions: Adiposity at 6 weeks old may identify infants at risk of developing childhood obesity. This may enable timely intervention to prevent obesity before it develops. Interventions aimed at reducing maternal BMI prior to pregnancy and facilitating continued breastfeeding may also help reduce the risk of later obesity in children.

A16

SIMULATED SHIFT WORK DURING PREGNANCY DOES NOT ALTER CIRCADIAN RHYTHMS IN YOUNG ADULT SHEEP PROGENY

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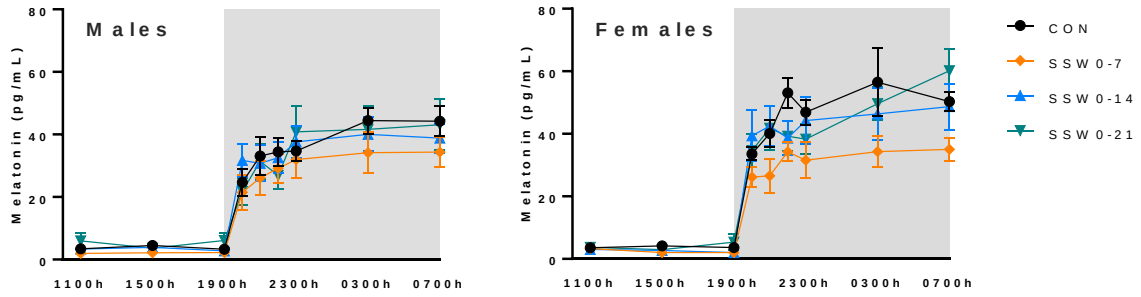
Background: Exposure to shift work perturbs central and peripheral circadian rhythms, including during pregnancy. Circadian disruption in rodent pregnancy impairs progeny metabolic and neurodevelopmental outcomes and alters circadian rhythms in progeny (1).

Aims/Hypothesis: We investigated whether progeny circadian rhythms are altered following maternal shift work in species that are more mature at birth, and the critical periods for programming of circadian rhythms.

Methods: Pregnant ewes were randomised to either control (CON, 12h light:12h dark) or simulated shift work (SSW) conditions for 1/3 (SSW 0-7 weeks), 2/3 (SSW 0-14 weeks) or throughout pregnancy (SSW 0-21 weeks) (2). Melatonin was measured by radioimmunoassay over a 20 h period in 12 month-old young adult progeny.

Results: Plasma melatonin (Figure below) rose at the onset of the dark period (grey area; time $P < 0.001$), but did not differ between treatment groups, sexes or litter sizes, or change differently over time in any group ($P > 0.05$ for each). Similarly, the area under the melatonin profile was similar between groups ($P > 0.05$ for each).



Conclusions: Although simulated shift work disrupted maternal circadian rhythms (2), we saw no effects on melatonin levels or rhythms in young adult progeny. This is profoundly different from effects of similar exposures in rats, where the normal rise in dark-phase melatonin is lost in progeny of SSW dams (3).

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A17

HIGH MATERNAL LINOLEIC ACID ALTERS MATERNAL LIPID PROFILE AND HEPATIC CYTOKINES IN RAT MODEL

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BACKGROUND: Linoleic acid (LA) is an essential polyunsaturated fatty acid that has vital roles during pregnancy for fetal development. The major sources of LA are vegetables oils, nuts and seeds. The consumption of LA has been increasing gradually worldwide due to its increased bioavailability. Previous studies have shown that elevated intake of LA may be detrimental for human health, however its effect on pregnant women and the developing fetus have not been fully determined yet.

AIM/ HYPOTHESIS: The main objective of this study was to explore whether high maternal LA affects maternal metabolic health, inflammation and fetal development.

METHODS: Female Wistar Kyoto rats were fed with high LA diet (HLA-6.21%) or control LA diet (LLA-1.44%) with matched omega 3 (0.3%), for 10 weeks prior to mating and during pregnancy. Animals were sacrificed at E20, and maternal body and organ weights, fetal body and organ weights, placental weight, maternal blood and fetal sex-ratio determined.

RESULTS: There were no significant differences in maternal, foetal and placental weight. There were no changes in maternal circulating cytokines, however, TNF-α and IL-7 levels were increased in the maternal liver from HLA rats. Total cholesterol, LDL – cholesterol, HDL- cholesterol and urea were decreased in the maternal plasma from rats fed with HLA. The relative mRNA expression of sterol regulatory element binding transcription factor 1 (SREBF-1) was significantly decreased in the maternal adipose tissue from the rats fed with HLA. The proportion of male fetuses was significantly decreased in HLA treated group.

CONCLUSION: HLA diet before and during pregnancy alters maternal lipid profile, liver cytokines and fetal sex ratio suggesting that the amount of LA intake should be considered during pregnancy.

A18

PSEUDOPREGNANCY AND REPRODUCTIVE CYCLE SYNCHRONISATION CANNOT BE INDUCED USING CONVENTIONAL METHODS IN THE SPINY MOUSE

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Background: Pseudopregnancy is a pro-gestational state in which the female mimics endometrial and endocrinological changes of early pregnancy in the absence of a fertilised embryo, and is particularly useful in research, allowing for the transfer and implantation of embryos into surrogates. We have recently identified the menstruating spiny mice is the first rodent identified to exhibit natural spontaneous decidualisation, cyclical endometrial shedding and regeneration. These characteristics make the spiny mouse a particularly relevant laboratory rodent for studies of reproductive biology. However, it has not been established whether pseudopregnancy can be induced in this species, or if their cycles can be synchronised as in other small laboratory rodents.

Aims/Hypothesis: To induce pseudopregnancy and cycle synchronisation (i.e. Whitten effect) in spiny mice.

Methods: Virgin females (n = 3-8 per group) underwent one of: daily vaginal lavage only (control); progesterone injection; mechanical stimulation of the cervix, or; sterile mating to induce pseudopregnancy. A separate cohort were also exposed to male-soiled bedding to assess the Whitten effect. Pseudopregnancy was deemed successful if females presented with extended (>12 consecutive days) leukocytic vaginal cytology.

Results: No female from any method of induction met this criterion. In addition, females' menstrual cycles could not be synchronized, nor immediate ovulation induced via exposure to male-soiled bedding.

Conclusions: Our study highlights the importance of animal model selection when applying broadly used laboratory techniques. The spiny mouse does not behave as a typical rodent. These responses emphasize their comparability to higher order primates including humans, who do not experience pseudopregnancy or cyclical synchronization, and further advocates for their versatility in translational studies of menstruation and fertility. The development of a similar *in vitro* fertilisation protocol in this human-like rodent would be required for embryo transfer studies in this species and remains an exciting prospect.

A19

HUMAN PLACENTAL ANDROGEN RECEPTOR VARIANTS: POTENTIAL REGULATORS OF MALE FETAL GROWTH

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Introduction: Numerous studies show that males have increased intrauterine growth compared to females, and that pregnancy complications may further these growth differences, but the regulatory mechanisms underlying these differences remain unknown. We propose that these growth outcomes may be due to sex-specific differences in androgen sensitivity – giving rise to altered growth signalling pathways – mediated by the differential expression of placental androgen receptor (AR) variants.

Methods: Placental protein and mRNA were used to identify AR protein variant levels and AR-downstream target gene expression, and were then analysed against neonatal measurements. Dihydrotestosterone (DHT)-induced AR protein variant expression and downstream growth factors were examined *in vitro*.

Results: Four known AR variants (AR-FL, AR-V1, AR-V7, and AR-45), and three unknown proteins (120, 90 and 55kDa) immunoreactive to the anti-AR antibody were identified in human placentae. Male placentae from controlled asthmatic pregnancies had increased AR-45 and decreased AR-V1 and AR-V7 nuclear expression. Increased nuclear AR-45 expression was associated with increased *IGF-1*, *IGF-1R*, and *IGFBP-5* mRNA expression and normal male growth. AR-45 mRNA and protein did not change in the presence of uncontrolled maternal asthma and associated with an increase in SGA male fetuses. *In vitro* DHT stimulation increased AR-45 protein and *IGF-1R* and *IGFBP-5* mRNA expression.

Conclusions: Collectively, our data shows altered AR protein expression and downstream signalling targets may contribute to sex-specific fetal growth outcomes in response to an adverse environment, and that AR-45 appears central in mediating these changes.

A20

PRENATAL ALCOHOL EXPOSURE AND FEMALE REPRODUCTIVE POTENTIAL: ARE THERE IMPACTS ON OVARIAN RESERVE OR FERTILITY?

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Background: Alcohol consumption is endemic in Australia, including 80% of reproductive age women. Our recent systematic review has identified a paucity of studies examining the impact of prenatal alcohol exposure (PAE) on reproductive outcomes in female offspring (1). To-date, there are no studies examining impacts on ovarian reserve, the finite pool of oocytes in primordial follicles that a woman is born with and can influence her reproductive lifespan. With women increasingly delaying child-bearing, it is important to understand if alcohol consumption impacts the establishment of ovarian reserve and subsequent fertility of offspring.

Aims/Hypothesis: We utilised 2 clinically relevant rat models of PAE to examine female offspring fertility. We hypothesised that PAE would reduce ovarian reserve in neonates & impact on puberty onset and/or adult fertility.

Methods: Sprague-Dawley dams were either treated with a 1g/kg BW EtOH gavage (peak BAC ~0.06%) at days 13.5 and 14.5 of pregnancy (binge); or 12.5% v/v EtOH in a liquid diet (peak BAC of ~0.2%) for 4 days prior to mating until 4 days after (periconceptional – PC). Unbiased stereology was used to quantify primordial and early growing follicles in postnatal day 3-10 ovaries; expression of factors regulating ovarian reserve was measured by RT-PCR; puberty onset was determined by age at vaginal opening; estrous cycles were monitored in adults via vaginal electrical impedance; and mating success and number of implantations or litter size were used as measures of fertility.

Results: The binge exposure did not impact on ovarian reserve, puberty onset or reproductive function in adulthood. However, the PC exposure resulted in aberrant ovarian expression of factors involved in follicle apoptosis (*Bax*, *Bcl2*) and growth (*Amh*, *Inha*). There was also a moderate increase in estrous cycle length in PC offspring, although overall fertility was not affected.

Conclusions: This study highlights that dose and timing of exposure may be critical to potential programming of female reproductive dysfunction in offspring. Given that ~50% of pregnancies are unplanned, alcohol is likely to be a common exposure in the 1st trimester and may contribute to a reduction in ovarian reserve.

(1) Akison LK, Moritz KM and Reid N (2019) Adverse reproductive outcomes associated with fetal alcohol exposure: a systematic review. *Reproduction,* Online Jan 2019.

A21

THE EFFECT OF HIGH MATERNAL CONCENTRATIONS OF LINOEIC ACID ON ENDOCANNABINOID SIGNALLING IN HEART TISSUE OF OFFSPRING RATS

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BACKGROUND: During pregnancy, linoleic acid (LA) is vital for fetal and postnatal development. Overconsumption of LA has increased worldwide due to the availability of LA in food products. LA can be pro-inflammatory, and therefore pregnant mothers consuming diets high in LA may alter the development of their fetuses. Metabolites of LA modulate the endocannabinoid system. This study investigated the role of high maternal LA consumption and its effects on endocannabinoid signalling in heart tissue of offspring rats.

METHODS: Female Wistar Kyoto rats fed a diet high in LA (HLA-6.21%) or control LA diet (LLA-1.44%) with matched omega 3 (0.3%), for 10 weeks prior to mating and during pregnancy. At E20, maternal rats were sacrificed, and body and organ weights determined. mRNA was extracted from offspring heart tissue, which was reverse transcribed and analysis of endocannabinoid signalling targets was undertaken using real time PCR.

RESULTS: There was no change in body weight or heart weight in offspring from mothers consuming a high LA diet. There was no change in mRNA expression of GPR18 in heart tissue in the offspring. The mRNA expression of FAAH is significantly decreased in heart tissue of male offspring rats compared with females. NAPE-PLD mRNA is significantly decreased in female offspring hearts from mothers consuming a high LA diet. NAPE-PLD mRNA is significantly increased in male offspring hearts from mothers consuming a high LA diet. There was no significant changes in diacylglycerol-lipase alpha and beta mRNA expression in offspring hearts. mRNA expression of CB2 was significantly decreased in both sexes from mothers consuming a high LA diet.

CONCLUSION: This study advances our understanding of the effect of LA on endocannabinoid signalling in heart tissue and allows new perspectives regarding the effects of HLA diet on offspring.

A22

DOES PRONE SLEEPING AFFECT BAROREFLEX SENSITIVITY IN PRETERM INFANTS IN NICU?

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Background: Preterm infants are frequently placed prone in the neonatal intensive care unit (NICU) to improve respiratory function. However, prone sleeping is associated with impaired blood pressure (BP) control in both term infants and preterm infants after term-corrected age. The baroreflex is the primary mechanism for the autonomic control of BP and is immature in preterm infants after term-equivalent age. Currently, there is a paucity of data on the effect of prone sleeping on baroreflex sensitivity (BRS) in preterm infants during their early postnatal weeks in NICU when they are most vulnerable to cardiovascular instability.

Aims/Hypothesis: To determine the effect of prone sleeping on BRS in preterm infants in NICU.

Methods: Fifty five preterm infants (born at 25-33 weeks of gestation) were studied weekly for 3 weeks after birth with cardiorespiratory monitoring and non-invasive BP measurement. Infants slept for 1 hr in both the prone and supine positions and data were analysed for both active sleep and quiet sleep. Cross-spectral power analysis between systolic BP (SBP) and R-R intervals were used to estimate of BRS. Effects of sleeping position, sleep state and postnatal age were compared using linear mixed model analysis.

Results: Overall, BRS was lower when prone compared to supine (4.2 ±0.3 vs 5.1±0.3 ms/mmHg, $p<0.05$), with no interaction between position and postnatal week. BRS decreased with increasing postnatal age, being higher at week 1 compared to week 3 (5.2±0.3 vs 3.9±0.3 ms/mmHg, $p<0.01$). R-R interval was shorter in the prone compared to supine position (380.1±1.5 vs 387.1±1.5 ms, $p<0.01$). There was no effect of position on SBP or sleep state on R-R, SBP or BRS.

Conclusions: Compared to supine, the prone position was associated with lower BRS and higher heart rate, though the differences were small. Reduced BRS, in the prone position may potentially increase vulnerability to cardiovascular instability within the first 3 postnatal weeks. However, further studies are required to determine the clinical significance of reduced BRS in the prone position in clinically unstable preterm infants.

A23

SELECTION OF AN APPROPRIATE ANAESTHETIC AGENT FOR CARDIAC MAGNETIC RESONANCE IMAGING IN THE FETAL SHEEP

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Background: Acquisition of high-resolution fetal magnetic resonance (MR) images relies on the subject remaining still throughout the scan sequence. In the clinical setting, the patient can be asked to remain still. However, when performing fetal MRI on animals, anaesthesia is required but these agents cause cardiac suppression and hemodynamic instability. As such, fetal cardiovascular measures obtained by MRI may be confounded by maternal anaesthesia.

Aim: We aimed to compare the fetal cardiovascular response to 4 commonly used anaesthetic regimes.

Methods: Pregnant ewes underwent surgery to implant vascular catheters in the maternal carotid artery, jugular vein and trachea, fetal femoral artery and vein as well as the amniotic cavity. Flow probes were implanted around the uncatheterised fetal femoral artery. Each ewe underwent cardiovascular monitoring during three of four different anaesthetic regimes (Isoflurane (n=7), Isoflurane + Ketamine (n=7), Ketamine+ Midazolam (n=6), & Propofol (n=8)) as well whilst conscious (n=15) on separate days, in random order, separated by at least 2 days from 110 to 120 days gestation (term, 150d).After a one hour baseline period of anaesthesia, maternal hypoxia was induced by infusing nitrogen gas (N_2) into the maternal trachea. The fetal cardiovascular response to one hour of maternal hypoxia was recorded under each anaesthetic regime.

Results: Fetal blood gases were not different between anaesthesia groups during baseline. Administration of N_2 gas to the maternal trachea decreased both maternal and fetal oxygen saturation. In response to maternal hypoxia, mean fetal femoral arterial pressure increased in all anaesthesia groups except for Propofol.

Conclusions: These data indicate that the normal fetal response to acute hypoxaemia is blunted by maternal Propofol administration. Further investigation is required to determine how fetal cardiac function and blood flow measures may be affected by each anaesthetic agent.

A24

THE EFFECT OF ANTENATAL SILDENAFIL ON NEONATAL PULMONARY HAEMODYNAMICS IN AN OVINE MODEL OF DIAPHRAGMATIC HERNIA

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Background: Congenital diaphragmatic hernia (CDH) is associated with lung hypoplasia that impairs pulmonary vascular development, which predisposes these infants to pulmonary hypertension after birth. Antenatal sildenafil treatment attenuates abnormal pulmonary vascular development in rabbit and rodent CDH models.

Aims/Hypothesis: We aimed to evaluate the effect of antenatal sildenafil on pulmonary haemodynamics during the fetal to neonatal transition in lambs with a diaphragmatic hernia (DH).

Methods: DH was surgically created at ≈80 days gestational age (GA; term≈147d) in 13 ovine fetuses. From 105d GA, ewes received either sildenafil (5 mg/kg/day intravenously; n=6) or saline infusion (n=6). At ≈138d GA, all lambs were instrumented and then delivered via caesarean section, with physiological and ventilatory parameters recorded for 120 min during the neonatal transition.

Results: Lung-to-body-weight ratio was not significantly greater in DH-sildenafil lambs compared to DH-saline controls (0.016±0.001 vs. 0.013±0.001; p=0.06). Pulmonary vascular resistance (PVR) decreased in both groups following lung aeration, however subsequently increased in DH-saline lambs after 60 min of ventilation. By the end of the 120 min ventilation period, PVR was 4-fold lower (0.5±0.1 vs. 2.2±0.6 mmHg/(L/min); p<0.001), pulmonary arterial pressure ~10 mmHg lower (47.3±2.3 vs. 59.7±2.8 mmHg; p=0.04) and pulmonary blood flow (PBF) 3-fold greater (26.4±2.7 vs. 7.5±2.0 mL/min/kg; p=0.004) in DH-sildenafil compared to DH-saline lambs. End-diastolic PBF, which correlates with low PVR and reflects left-to-right shunting across the ductus arteriosus, was greater in DH-sildenafil lambs from 20 min into the ventilation period.

Conclusions: In these DH lambs with lung hypoplasia, antenatal sildenafil treatment reduced PVR and increased PBF during the fetal to neonatal transition. These findings suggest that antenatal sildenafil treatment may reduce the likelihood of neonatal pulmonary hypertension in infants with CDH.

A25

PHYSIOLOGICALLY BASED CORD CLAMPING IMPROVES PULMONARY HAEMODYNAMICS DURING THE NEONATAL TRANSITION IN LAMBS WITH DIAPHRAGMATIC HERNIA

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Background: Lung hypoplasia associated with congenital diaphragmatic hernia (CDH) results in respiratory insufficiency and pulmonary hypertension after birth. Aerating the lung before removing placental support (physiologically based cord clamping; PBCC) may improve the cardiopulmonary transition and protect the underdeveloped pulmonary vasculature in CDH infants.

Aims/Hypothesis: We aimed to investigate the impact of PBCC on cardiopulmonary physiology in a lamb model of CDH. We hypothesised that PBCC would protect the pulmonary vascular bed from high pressures during the fetal to neonatal transition and avoid severe hypoxia at birth.

Methods: At ≈138 days of gestational age, 17 lambs with surgically induced left-sided diaphragmatic hernia (≈d80) were delivered via caesarean section. The umbilical cord was clamped either immediately prior to ventilation onset (ICC; n=6) or after achieving a target tidal volume of 4 mL/kg, with a maximum delay of 10 min (PBCC; n=11). Lambs were ventilated for 120 min with real-time physiological monitoring.

Results: At 5 min after cord clamping, PBCC lambs had higher cerebral tissue oxygen saturation (60 ± 6 vs. 24 ± 4 %, p<0.001) and lower systemic arterial blood pressure (60 ± 4 vs. 76 ± 5 mmHg, p=0.02) compared to ICC lambs. After 120 min of neonatal ventilation, pulmonary blood flow (PBF) was 3-fold greater (23 ± 4 vs. 8 ± 2 mL/min/kg, p=0.01) and pulmonary vascular resistance (PVR) was 3-fold lower (0.6 ± 0.1 vs. 2.2 ± 0.6 mm Hg/(mL/min), p<0.001) in PBCC lambs compared to ICC lambs.

Conclusions: PBCC prevented the severe hypoxia at birth associated with cord clamping and increased PBF by reducing PVR, and this difference persisted for at least 120 min after birth in lambs with diaphragmatic hernia.

A26

WHITE MATTER NEUROPATHOLOGY FOLLOWING CHORIOAMNIONITIS AND POSTNATAL DEXAMETHASONE IN PRETERM LAMBS

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Background: Chorioamnionitis is a common antecedent of preterm birth, and impairs brain development. The effect of postnatal glucocorticoids on brain growth and injury after chorioamnionitis is unknown.

Aims/Hypothesis: To determine if postnatal glucocorticoids improve or exacerbate preterm brain development and injury after chorioamnionitis.

Methods: Pregnant ewes received an intra-amniotic injection of LPS (4 mg: 2 mg/mL) or saline (SAL) at 126 d gestation at least 6 hours prior to intramuscular betamethasone (5.7mg x 2, q24h). Preterm lambs delivered operatively at 128 d gestation received 7 days of tapered postnatal dexamethasone (DEX) (0.15 mg/kg/d x 3 d; 0.10 mg/kg/d x 2 d; and 0.05 mg/kg/d x 2 d) or equivalent volume of saline (SAL), resulting in 4 groups: SAL/SAL, SAL/DEX, LPS/SAL, and LPS/DEX (N = 7-8 /group). Brains were collected and fixed on day 135. White matter injury throughout the brain was quantified with MRI and also with histology in the prefrontal cortex (PFC).

Results: T1-weighted MRI showed that LPS reduced total brain width and cortical thickness (all $p < 0.05$), whilst DEX increased the anterior-posterior length of the brain ($p < 0.05$). White matter lesions were more common in LPS exposed animals (SAL/SAL = 14 %, SAL/DEX = 22%, LPS/SAL = 60 %, LPS/DEX = 44 %). LPS reduced white matter and grey matter volume in the PFC ($p < 0.01$). Myelin basic protein (MBP) in the PFC white matter was unchanged, but LPS reduced MBP in the grey matter ($p < 0.05$). There was an interaction between LPS and DEX in the PFC white matter oligodendrocyte density ($p< 0.05$), but no significant post-hoc effects.

Conclusions: LPS increased prevalence and severity of injury in the preterm brain. Postnatal dexamethasone did not have neuroprotective effect against LPS exposure in the PFC. However, ongoing work indicates that LPS and DEX have regional-specific outcomes. Funding: NHMRC 1057759, 1057514, 1077691, TPCHRF

A27

NEURAL EFFECTS OF DELAYED RECOMBINANT HUMAN ERYTHROPOIETIN TREATMENT AFTER ASPHYXIA IN PRETERM FETAL SHEEP

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Background: Recombinant human erythropoietin (rEpo) has been shown to be neuroprotective in preclinical studies. Two large ongoing trials in preterm infants are now testing whether 1000 IU/Kg rEpo given every 48 hours is neuroprotective. However, rEpo concentration drops below the therapeutic range for prolonged periods between intermittent injections. A continuous infusion maintaining rEpo concentration within the therapeutic range for the duration of treatment may have better neuroprotective efficacy.

Aims: To compare the neural effects of delayed rEpo treatment when given as continuous infusion versus intermittent bolus injections after HI brain injury in preterm fetal sheep.

Methods: Chronically instrumented preterm (0.7 gestation) fetal sheep received sham asphyxia (n = 8) or asphyxia induced by complete umbilical cord occlusion for 25 minutes. Six hours after asphyxia, fetuses received intravenous bolus injection of saline (n = 8) or 5000 IU rEpo (n = 8) with repeated doses given every 48 hours for 5 days, or a continuous infusion of rEpo (loading dose 2000IU, infusion at 520U/h) (n=8) from 6 to 72 hours after asphyxia. Post-mortems were performed for tissue collection at seven days after asphyxia.

Results: Compared with diffuse white matter injury in the asphyxia-rEpo infusion group, rEpo bolus treatment was associated with severe bilateral cystic injury in the lateral white matter in 4/8 fetuses. The asphyxia-rEpo bolus group had greater neuronal loss in dentate gyrus of the hippocampus than the asphyxia-rEpo infusion group ($P < 0.05$). EEG power in asphyxia-rEpo bolus group was lower than both the asphyxia-rEpo infusion and asphyxia-saline groups from 72-168 hours after asphyxia ($P < 0.05$). Delayed treatment with rEpo infusion did not improve the histological outcome compared with the asphyxia-saline group.

Conclusions: Delayed treatment with rEpo after asphyxia was not neuroprotective, furthermore, high dose rEpo boluses were associated with a prolonged reduction in cerebral perfusion, impaired recovery of EEG power and increased neural damage. These data support the need for further preclinical examination of different doses and treatment regimens of rEpo for the treatment of hypoxic-ischaemic encephalopathy.

A28

INHIBITING THE INFLAMMASOME AS A NOVEL TREATMENT FOR NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

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Background: Neuroinflammation plays a key role in the development of injury in the neonatal brain and can lead to cerebral palsy. The inflammasome, a novel pathway in the inflammatory process, is a key signalling platform which matures pro-inflammatory cytokines into their bioactive forms.

Aims/Hypothesis: Our current project aims to explore the therapeutic efficacy of a specific inflammasome inhibitor, MCC950. We hypothesise that inhibition of the inflammasome pathway following neonatal hypoxic-ischemic (HI) brain injury will reduce neuroinflammation, neuropathology and improve behavioural outcomes.

Methods: To induce brain injury, postnatal day 10 Sprague-Dawley rats (n=42) underwent single carotid artery ligation surgery, followed by exposure to hypoxia (8% oxygen, 90 mins). At 6 and 24 hours post HI, pups received MCC950 (20mg/kg) or saline. Behavioural testing was performed 72 hours later to examine motor control. Following this, rats were humanely killed and brains and serum collected. Immunohistochemistry was performed on brain tissue and serum will be used for cytokine analysis. qRT-PCR will be performed for gene analysis.

Results: HI injury significantly impaired motor control compared to sham ($p=0.0198$) and MCC950 treatment did not improve this deficit. HI injury also reduced brain weight ($p=0.0072$) and increased left hemisphere tissue loss ($p=0.0025$) compared to sham, MCC950 treatment did not improve this. Immunohistological analysis revealed that HI injury significantly decreased neuron cell counts ($p=0.0005$) and increased microglial activation ($p<0.0001$) in the somatosensory cortex and treatment with MCC950 had no effect on these outcomes.

Conclusions: We have shown that the inflammasome pathway is active following neonatal brain injury and the inhibition of this pathway using MCC950 given 6 and 24 hours post HI injury does not appear to be effective. Further research into different timing and dosing of MCC950 as a therapy for neonatal brain injury is warranted.

A29

THE EVOLUTION OF NEUROINFLAMMATION AND MYELINATION AFTER HYPOXIA-ISCHAEMIA IN PRETERM FETAL SHEEP

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Background: Many cases of cerebral palsy and impaired neurodevelopment are associated with hypoxia-ischemia (HI) well before birth, during preterm development. HI leads to long-term impairment of myelination and neuroinflammation, both of which likely contribute to poor connectivity.

Aims/Hypothesis: To determine the evolution of neuroinflammation and myelination after an acute HI insult in preterm fetal sheep.

Methods: Chronically instrumented fetal sheep (0.7 gestation) underwent sham HI or HI induced by 25 min of umbilical cord occlusion. Fetal brains were processed for histology post-HI at 3 days (n=9, sham n=12), 7 days (n=8, sham n=8) and 21 days (n=9, sham n=10).

Results: Large cystic lesions were observed in 3/9 fetuses within the temporal lobe at 21 days post-HI. Marked white matter atrophy were also observed in 4/9 fetuses by 21 days post-HI. No lesions were observed at earlier time points. Caspase-3 apoptosis was significantly increased at day 3 post-HI ($p<0.05$), but returned to sham levels by 7 days. HI was associated with a significant increase in Iba-1 positive microglia at 3, 7, and 21 days post-HI ($P<0.05$). A reduction in brain weight (39.5 ±0.89 vs. 32.5 ±1.7 g, day 21), CNPase area fraction ($p<0.05$), MBP area fraction ($p<0.05$), and SMI312 area fraction ($p<0.05$) was observed post-HI vs. shams at all post-HI time points.

Conclusions: Bulk neural cell death is thought to largely occur during the first 3 days after an HI insult. However, our study has demonstrated that significant evolving injury is observed weeks after an HI insult with diffuse white matter injury at three and seven days, evolving into a spectrum of severe white matter degeneration including cystic white matter lesions, white matter atrophy, and ventriculomegaly by 21 days post-HI. This study, therefore, highlights a potential window of opportunity for treatment in the tertiary phase.

A30

INVESTIGATING ULTRADIAN PERIODICITY IN THE PRETERM FETAL SHEEP EEG

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Background: Our 24-hour circadian rhythms are important for our physiological health, but less is known about shorter cycles (milliseconds to hours) throughout a 24-hour day, known as ultradian rhythms. They are postulated to be endogenously generated, self-sustained oscillatory processes, allowing more labile partitioning of metabolism within the circadian cycle, and may support brain maturation and development. Impaired ultradian rhythmicity is associated with adverse behavioural outcomes. Little is known about fetal ultradian rhythms.

Aim: To evaluate the occurrence and maturation of ultradian periodicity in the fetal electroencephalogram (EEG).

Methods: Ewes carrying singleton fetuses were acclimatised to the laboratory for a week before surgery. They were housed in individual metabolic crates with companion animals, fed *ad libitum* and entrained to a 12h:12h light:dark cycle (lights off 18.00h). Fetuses were then surgically instrumented to allow continuous post-surgical recording of the EEG. Recordings started 5-d post-surgery at 104d gestation and continued for 21d. Wavelet transformation, using the analytical Morlet wavelet, was carried out on the EEG on 24h windows at 3 gestational periods (104-110d, 111-120d, and 121-125d) to examine the presence of ultradian periodicity.

Results: At 104-110d the EEG is discontinuous, and we observed ultradian rhythms of ~0.5 to ~1.5h periodicity, the power of which was greater at night between 00.00h to 06.00h. Between 111-120d we observed shorter (~8min) rhythms that had no circadian timing. In the 121-125d group there was development of the ultradian rhythm related to sleep state cycling (rapid-eye movement (REM: ~20-30min cycles) and non-REM cycling (~10-15min cycling), with superimposed shorter ultradian rhythms mostly seen in REM.

Conclusions: Our preliminary data show the existence of ultradian rhythms in fetal EEG which change with age. The changes in their morphological appearance reflect the different phases of neural network development, such as the transition from discontinuous to continuous sleep-state activity. Further studies are required to characterise these rhythms, and to examine how adverse events such as hypoxia and inflammation, and neuroprotection treatments, may modify them.

A31

USING CREATINE TO PRESERVE MITOCHONDRIAL FUNCTION IN THE FETAL BRAIN FOLLOWING ACUTE *IN UTERO* HYPOXIA

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Background: Acute *in utero* fetal hypoxia can adversely impact on the integrity of the fetal brain. A primary manifestation of hypoxic injury is cellular energy failure mediated by mitochondrial dysfunction. Creatine is a naturally occurring dietary metabolite that acts as a spatial and temporal energy buffer by generating ATP anaerobically. It has been shown to be neuroprotective against neonatal and adult brain trauma by maintaining mitochondrial integrity but is yet to be investigated as a treatment to prevent hypoxic-induced injury in the fetus.

Aims/Hypothesis: It is hypothesized that creatine supplementation protects the fetal brain against mitochondrial dysfunction caused by acute *in utero* hypoxia in late gestation, by improving mitochondrial respiration.

Methods: At 118 days of gestation (term = 147), surgically prepared singleton fetuses of 22 pregnant ewes were randomly allocated to receive an intravenous infusion of either creatine (6mg/kg/h) or saline. After 13 days of infusion, fetuses were subjected to 10 minutes of severe fetal hypoxia by complete occlusion of the umbilical cord (n=6 of creatine and n=7 saline infused). Control fetuses did not receive a hypoxic insult (n=6 of creatine and n=3 of saline infused). 72-hour post-injury, fetal brains were collected, and mitochondria freshly isolated from grey matter, white matter and the hippocampus for assessment of basal, complex-II mediated, ADP-linked and uncoupled respiration. Data were analysed by Two-Way ANOVA with Turkey's multiple comparisons.

Results: In the white matter, basal ($P<0.05$), complex-II mediated ($P<0.05$), ADP-linked ($P<0.01$) and uncoupled respiration ($P<0.05$) were all significantly reduced following UCO. Basal respiration in the grey matter is also reduced following UCO ($P<0.01$). No differences have been observed in the hippocampus at this stage of the project, nor does creatine treatment impact on these outcomes.

Conclusions: Preliminary results suggest that white matter mitochondrial respiration is adversely impacted by acute hypoxia *in utero*. Further characterisation of mitochondrial injury through gene expression and immunohistochemical analysis is now underway.

A32

NEUROPROTECTIVE CAPACITY OF CREATINE TO REDUCE PERINATAL HYPOXIA-RELATED ENCEPHALOPATHY: A MICRODIALYSIS STUDY

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Background: Acute perinatal asphyxia can cause significant encephalopathy, leading to life-long morbidity or even death. The hypoxia-ischemia associated with asphyxia can result in oxidative and metabolic stress, mitochondrial dysfunction and cell death. Creatine is a dietary metabolite that is able to sustain intracellular ATP to meet metabolic demand during oxygen deprivation and has been proposed as a prophylactic treatment during pregnancy to prevent or ameliorate the effects of hypoxia-ischemia on the fetus and newborn.

Hypothesis: We hypothesise that creatine can prevent hypoxia-related neuropathology by buffering cellular ATP levels, thereby reducing reactive oxygen species (ROS) production and associated neuropathology.

Methods: Fetal sheep (118 days gestation) were implanted with brain microdialysis probes, brachial arterial and vein catheters and a silastic umbilical cord cuff using sterile surgical procedures. Creatine (6mg/kg/h; n=5) or saline (9mg/kg/h; n=6) was infused IV to the fetus from 122 to 134 days gestation. Cerebral microdialysis fluid was collected at 1 h intervals from 130 to 134 days gestation, and a 10 minute umbilical cord occlusion (UCO) was performed on day 131. Microdialysis fluid was analysed for hydroxyl radical (OH•) production by fluorescent HPLC using the terepthalic acid trapping method. Data were analysed using area under the curve (AUC) as a combined measurement of duration and magnitude.

Results: UCO caused immediate respiratory acidosis, hypotension and bradycardia. Between 0 and 72hr post-UCO, creatine infusion demonstrated significantly lower OH• production levels compared to saline-infused fetuses (24.56 ± 1.23 [SEM] vs 40.41 ± 2.84 uM.h, $p<0.0001$).

Conclusions: Systemic creatine pretreatment reduced the overall cerebral production of cytotoxic OH• resulting from global fetal hypoxia. More research is needed to establish creatine supplementation during human pregnancy as a clinically realistic approach to reducing the neuropathology arising from intrapartum hypoxia/asphyxia and for improving the health outcomes of newborns.

A33

PREDICTING POST-MENSTRUAL AGE IN PRETERM INFANTS USING EEG ANALYSIS

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Background: In Australia, 8.5% of births are preterm. Infants with gestational age (GA) less than 32 weeks are at a high risk of long term neurological delays and, therefore, will be closely monitored until they are more mature. Methods of tracking the developing neurological function in these at-risk infants provide a potentially, important tool for clinicians.

Aims/Hypothesis: To develop a multi-variate model of post-menstrual age (PMA) from computer analysis of EEG recordings.

Methods: The electroencephalogram (EEG) was recorded at weekly intervals (where possible) from 65 preterm infants at the Medical University of Vienna, Austria between 2011 and 2015 (gestational age, 23-28 weeks). Neurodevelopmental outcome was assessed at 1y of age (Bayley Scales of Neurodevelopment III). Several variables were calculated from 1h epochs of EEG. Variables were derived from burst shapes and the distribution of burst area. A multi-variate model was constructed (Gaussian process regression) to combine EEG variables into a prediction of PMA. Model accuracy was assessed using correlation.

Results: A total of 1140, 1h EEG epochs from 177 EEG recordings were used in the cross-validation. Individual EEG features were highly correlation with PMA (skewness of burst shape, Pearson's r = 0.872, 95%CI: 0.832-0.903). The correlation between the multi-variate EEG model output and PMA was 0.905 (Pearson's r; 95%CI: 0.874-0.928) and was significantly higher than a uni-variate model based on only the skewness of burst shape (Δr = 0.031, 95%CI: 0.009 to 0.059; n=177). Models based on EEG from only infants with normal outcome did not result in higher prediction accuracy (p = 0.208 and p = 0.393; n=78).

Conclusions: Automated methods of EEG analysis provide an accurate, real-time assessment of maturity based on cortical activity. Analysis of maturation has potential for diagnosis and prognosis.

A34

ASPHYXIAL STATE AFTER IMMEDIATE CORD CLAMPING ACCELERATES ONSET OF DUCTUS ARTERIOSUS LEFT-TO-RIGHT SHUNTING AFTER BIRTH IN PRETERM LAMBS

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Background: Recent findings in preterm lambs have suggested that, after immediate cord clamping (ICC) followed by a brief, non-asphyxial cord clamp-to-ventilation (CC-V) interval, left-to-right (L➞R) ductal shunting after birth arises from: 1) direct systolic LV inflow, 2) retrograde diastolic discharge from a lower body arterial reservoir/windkessel (LBres), and 3) diastolic discharge from an upper body arterial reservoir (UBres). However, it is unknown if a longer and asphyxial CC-V interval affects L➞R ductal shunting, or its sources, after birth.

Aim: To determine if an asphyxial CC-V interval after ICC alters the pattern of L➞R ductal shunting after birth.

Methods: Ductal and aortic isthmus flows were measured with transit-time probes in 18 anaesthetized preterm lambs after ICC with a non-asphyxial (~40 sec) or asphyxial (~90 sec) CC-V interval prior to mechanical ventilation for 30 min after birth. Flow in the descending thoracic aorta (DTA) was obtained as the sum of isthmus and ductal flows. L➞R (i.e. negative) segments in the ductal flow profile were related to the timing of isthmus and DTA profiles, with a direct LV contribution indicated by positive isthmus flow in systole, retrograde LBres discharge by negative DTA flow in diastole, and UBres discharge by forward (positive) isthmus flow in diastole,.

Results: In the non-asphyxial CC-V group, L➞R ductal flow was initially unchanged after birth but then rose steadily to peak at 437±164 ml/min by 15 min ($P < 0.001$). However, in the asphyxial CC-V group, L➞R ductal shunting increased from 24±21 to 199±93 ml/min with onset of ventilation ($P < 0.001$) and rose further to 471±190 ml/min by 2 min after birth ($P < 0.001$). This accelerated onset of L➞R ductal shunting occurred in conjunction with an earlier appearance and greater magnitude of an LV systolic flow contribution ($P < 0.001$) and retrograde LBres discharge ($P < 0.001$), but no change in the UBres discharge component ($P > 0.5$).

Conclusions: An asphyxial CC-V interval after immediate cord clamping in the preterm birth transition was accompanied by an earlier emergence and greater magnitude of post-birth L➞R ductal shunting that was supported by 1) a greater systolic LV flow component, and 2) enhanced diastolic retrograde LBres discharge.

A35

DOES THE VASCULAR RESPONSE TO ADRENERGIC AGENTS EXPLAIN THEIR INEFFECTIVENESS IN PRETERM PIGLETS?

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Background: Adrenergic inotropes are administered to preterm infants to support cardiovascular function despite being ineffective at improving blood pressure or neurodevelopmental outcomes. The capacity of the preterm vasculature to respond to adrenergic agonists is unknown.

Aims/Hypothesis: The aim of this study was to determine the capacity of the vasculature to respond to α- and β-adrenergic agents in preterm and term piglets and to determine if the preterm vascular response to adrenergic agents explains the poor response to treatment with dopamine or dobutamine.

Methods: Preterm (97/115 d gestation) and term piglets were ventilated and maintained in intensive care. Approximately 3h after birth, changes in skin blood flow were measured during local administration of isoprenaline (β-adrenergic agonists) and then phenylephrine (α-adrenergic agonist) by iontophoresis. Piglets subsequently received infusions of either dopamine or dobutamine during which cardiovascular function was measured, including contractility and arterial blood pressure.

Results: Female preterm piglets had a decreased vasodilator response to the β-adrenergic agonist compared to female term piglets. The vasoconstrictor capacity of preterm piglets was similar to term piglets. Blood pressure during dopamine treatment was positively correlated with the α-adrenergic agonist response in term piglets only, and negatively correlated with the β-adrenergic agonist response only during dobutamine infusion in preterm piglets.

Conclusions: In preterm piglets, the vascular response to adrenergic agents does not explain their response to dopamine but may influence the response to dobutamine.

A36

ENDOTHELIAL VASODILATOR MECHANISMS AS TARGETS TO CONTROL UTERINE BLOOD FLOW IN PREECLAMPSIA

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Background: Preeclampsia (PE) can cause significant maternal and fetal morbidity and mortality. Diffuse maternal endothelial-dysfunction is the hallmark of PE, including in the uterine myometrial vasculature, resulting in systemic organ dysfunction. No direct therapies have been identified and treatment remains supportive. Early data support beneficial effects of the cholesterol-lowering drug pravastatin in reducing blood pressure and moderating PE by altering vascular endothelial (dys)function, although the mechanism is unknown.

Aims/Hypothesis: This work identifies key endothelial signalling pathways in human myometrial radial arterioles and how they are altered by pravastatin in PE, to reflect potential mechanisms for improving uterine vascular endothelial function.

Methods: Myometrial radial arterioles from caesarean-section normotensive (NT), gestational (GH) and PE hypertensive patients were examined as control and *in vitro* pravastatin (2mM/6h)-incubated segments. Electron microscopy, immunohistochemistry and pressure myography with pharmacological intervention characterized vessel structure and function. Protocols were approved by UNSW and Health District Human Ethics Committees.

Results: Caveolae density and caveolin-1 expression is reduced in PE and GH, and further reduced by pravastatin incubation. PE is accompanied by decreased vasodilator NO and endothelium-derived hyperpolarization (EDH) activity; and altered expression of NO and EDH signalling components, including myoendothelial gap junctions, eNOS, IK_{Ca}, SK_{Ca}, TRPC3 and V4 channels. Endothelium-independent-smooth muscle relaxation is unchanged in radial arterioles from GH/PE compared with NT pregnancies. Pravastatin incubation restored endothelium-dependent relaxation by ~50% in PE samples.

Conclusions: These data suggest that pravastatin acts at caveolae and non-caveolae sites to change their form and microdomain- and endothelium-dependent signalling functions as a key contributor to myometrial radial artery activity in PE.

A37

PROGRAMMING OF HEALTH OUTCOMES IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER (FASD): PRELIMINARY RESULTS

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Background: Prenatal alcohol exposure is known to affect neurocognition and behavioural outcomes in children. Less is known about effects of prenatal alcohol on chronic health outcomes. Recent data from preclinical models of alcohol exposure suggest alcohol may affect develop of other organs including the heart and kidney and result in long term outcomes such as high blood pressure, diabetes and obesity. At a recent conference in Canada, a group of young adults with fetal alcohol spectrum disorder (FASD) highlighted they suffered from a range of health issues leading to the suggestion FASD should be considered a whole body disorder rather than just a brain disorder.

Aim: To investigate chronic health outcomes in children with diagnosed FASD

Methods: We have taken two approaches; firstly, we have conducted an on-line survey which has been completed by caregivers or adults with FASD. This asked questions around a range of health outcomes across the lifespan. Second, we have commenced a study investigating aspects of health (blood pressure, body composition, renal function) in children with FASD in Brisbane.

Results: In the first 6 months, we have 64 respondents to the survey with a range of 5-21 years of age. Approximately 60% of respondents were male. Caregivers reported a wide range of issues in children with FASD. Most common were sleep issues (66%), allergies/asthma (32%), joint pain (32%) and recurrent infection (32%). In addition, parents reported high levels of stress in their lives due to caring for a child with FASD. For our second study, we have conducted consumer engagement (with parent supporter groups), obtained ethics and recruited out first 5 patients.

Conclusion: These preliminary results suggest that young people with FASD may be at increased risk of a range of health disorders in childhood. Further research examining specific health outcomes will give further insights into the risk of children with FASD for chronic diseases.

A38

FETAL HEPATIC FLOW IN SHEEP ASSESSED USING 4D FLOW MRI

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Background: Assessment of fetal hepatic flow poses difficult technical problems due to the small nature of vessels, slow blood flow within the liver, and sources of motion present *in utero*.

Aims/Hypothesis: 4D flow MRI **[1]** is coupled with specialized animal preparation to capture 3D fetal hepatic haemodynamics in a late gestation sheep model of human pregnancy.

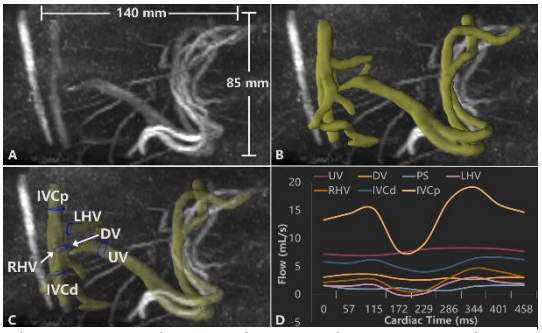

Fig. 1. a: Angiogram, b: Vascular segmentation, c: Vessels labelled, d: Measured blood flow.

Methods: Pregnant Merino ewes (singleton pregnancies, n=11; 137-139 days gestation; term=150 days) underwent surgery to implant catheters into the fetal femoral artery to trigger the MRI as previously described **[2, 3]**. Data was collected using a 3T MR scanner (Skyra, Siemens) at high resolution. Whole-heart assessment followed recently published work **[4]** and included segmentation, blood flow measurements, and visualisation of fetal shunts with particle traces. Measured flows were indexed to fetal weight and internally validated using conservation of mass at the DV-IVC junction.

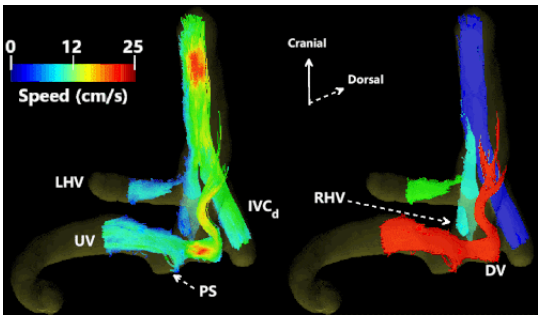

Fig. 2. Fetal ventral-oblique blood flow particle trace visualisation in hepatic vessels, coloured based on blood speed (left) or origin of blood (right).

Results: Example image quality and 4D flow MRI processing is shown in Fig. 1, with flow evaluation over the cardiac cycle at multiple vessel locations. Exemplary flow visualisations using particle traces (Fig. 2) display the fine detail of helical DV flow and swirling flow in the portal sinus. Across 10 measurements of internal consistency at the DV-IVC junction, the average (± standard error of the mean) difference was 17.3 ± 2.4%.

Conclusions: Here we present the first use of 4D flow MRI for comprehensive evaluation of fetal hepatic haemodynamics in a large animal model, and present visualisation of umbilical shunting through the DV.

References: [1] Markl, JMRI 2012. [2] Duan, *AJP* 2017 [3] Duan, *JCMR* 2017. [4] Schrauben, *JCMR* 2019.

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