Schulich MEDICINE & DENTISTRY

Obstetrics & Gynaecology

21st PAUL HARDING RESEARCH AWARDS DAY 2023

Wednesday, April 12, 2023
Four Points Sheraton London
1150 Wellington Rd, London, ON N6E 1M3
A minimum of 25% of this program is dedicated to participant interaction

Research Day Learning Objectives:

1. Identify transdisciplinary research endeavours within the Department of Obstetrics & Gynaecology

2. Describe the essential nature of research and education in an academic health institution

3. Engage in discussions about relevant research in the field.

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, and approved by Continuing Professional Development, Schulich School of Medicine & Dentistry, Western University. You may claim a maximum of 4.0 hours (credits are automatically calculated).

Each participant should claim only those hours of credit that he/she actually spent participating in the educational program.

Schulich School of Medicine & Dentistry, Western University, Victoria Hospital, Rm. B2-404
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21st ANNUAL PAUL HARDING RESEARCH AWARDS DAY 2023

7:30	Morning Refreshments
8:00 – 8:30	Dr. Tracey Crumley and Dr. Queena Chou - Introduction & Welcome

ORAL SESSION 1 — Chaired by:

Following each presentation there will be a 5-minute question and answer period.

8:30 – 8:45	Maternal Fructose Consumption in Pregnancy and Associations with Maternal and Offspring Hepatic and Whole-Body Adiposity: A Scoping Review **G. Zhao**, S. Chondon, K. Araz, S. Levy, C. Gray, S. Gentili, M. Stanley, T.R.H. Regnault
8:45 – 9:00	Increased Mitochondrial Size is Associated with Mitophagy Suppression in Core Regions of Ovarian Cancer Spheroids **M. Borrelli**, B. Kolendowski, Y. Ramos Valdés, G. DiMattia, T. Shepherd
9:00 – 9:15	In Utero Exposure to Cannabidiol (CBD) in Rats Leads to Impaired Cardiac Function Exclusively in Male Offspring **K. Lee (1,2,5,8),** M. Nashed (3,5,8), S.R. Laviolette (3,5,8), D.R.C. Natale (9) and D.B. Hardy (1,2,5-8)
9:15 – 9:30	ULK1 is Required for Autophagy and Maintaining Cell Viability in Ovarian Cancer Spheroids **J. Webb 1,2,** B. Singha1,2, M. Borrelli1,2, L. Viola1, Y. Ramos Valdés1, and T.G. Shepherd1,2,3,4
9:30 – 9:45	Perinatal Omega-3 Fatty Acid Supplementation Sex-Selectively Prevents the Prenatal Δ9-THC Induced Cognitive, Electrophysiological, And Lipidomic Phenotype **M.H. Sarikahya**; S. Cousineau, M. De Felice, H. Szkudlarek, K.K.-C. Yeung, D.B. Hardy, W. Rushlow, S.R. Laviolette
9:45 – 10:00	Surgical Site Infection Bundle and Pre-Operative Catheter Protocol in Gynaecology: A Quality Improvement Initiative for Combatting Surgical Site and Urinary Tract Infections **S. Moltner**, J. McGee

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10:00 – 11:00 **NUTRITION BREAK & POSTER SESSION**

11:00 – 12:15 **THE EARL R. PLUNKETT LECTURE**

"Adventures with Steroids: Tracking where they need to go."

Dr. Geoffrey Hammond, Ph.D.
Professor Emeritus/a, Department of Cellular and Physiological Sciences,
The University of British Columbia

Objectives:

1. Decribe how hormones access their target cells in different organs and tissues and how this varies in different physiological states.
2. Identify how protein structures provide insight into their function.
3. Realize how genetic abnormalities reveal how proteins act in health and disease.

Following this 60-minute presentation there will be a 15-minute question and answer period.

12:15 – 13:15 **LUNCH**

ORAL SESSION 2 **Chaired by:**

Following each presentation there will be a 5-minute question and answer period.

13:15 – 13:30 To Replace or Not Replace: Intraoperative Catheter Placement at Pelvic Surgery
M. Khojah, M. Tse, Q. Chou

13:30 – 13:45 Gestational Exposure to Cannabidiol Leads to Glucose Intolerance At 3 Months of Age Exclusively in Male Rat Offspring
S. Vanin, K. Lee, B. Tse, S. Brar, M. Nashed, S. Laviolette, E. Arany, D. Hardy

13:45 – 14:00 Safety of Methylene Blue in Pregnancy – Systematic Review
M. Shere, A. Privorozky, F. Garcia-Bournissen, J. Hutson

14:00 – 14:15 The Role of Liver Kinase B1 in Translational Models of Advanced Epithelial Ovarian Carcinoma

C. Trelford, A. Buensuceso, T.G. Shepherd

14:15 – 14:30 "Nothing Comes to Mind…": Challenges with Identifying One's Own Role in Preventable Poor Outcomes and Behaviour, and the Impact on Quality Improvement Initiatives

A. Aqib, L. Columbus, R. Pack, H. Banner, T. Taylor

14:30 – 15:30 **RECEPTION, CLOSING REMARKS & AWARDS**

This program has received an educational grant from:

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RESEARCH DAY ABSTRACTS: ORAL

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Presenters Name: Grace Zhao

Category: Resident

Title: MATERNAL FRUCTOSE CONSUMPTION IN PREGNANCY AND ASSOCIATIONS WITH MATERNAL AND OFFSPRING HEPATIC AND WHOLE-BODY ADIPOSITY: A SCOPING REVIEW

Authors: G Zhao, S Chondon, K Araz, S Levy, C Gray, S Gentili, M Stanley, TRH Regnault

Affiliation: Department of Obstetrics and Gynaecology, Western University, London, ON, Canada

Abstract: Fructose is a major constituent of the Western diet and its increased consumption is associated with negative metabolic outcomes, including alterations in hepatic and whole-body adiposity, in the postnatal environment. However, the effects of excess maternal fructose consumption on the fetus and developing offspring remain poorly understood. Therefore, we aimed to understand the effects of maternal fructose consumption during pregnancy on maternal and offspring hepatic and whole-body adiposity. A systematic search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) was performed, to identify studies that focused on maternal fructose consumption and hepatic and whole-body adiposity in the mother, fetus, and offspring. Two independent reviewers screened citations and abstracted results, with subsequent verification from a third reviewer. After screening 2334 citations, 34 rodent experimental studies were included. Offspring hepatic adiposity was supported in 12 of the 20 articles, with 5 studies demonstrating more severe effects in female offspring. A higher proportion of studies (14 out of 17) supported the association between fructose during pregnancy and maternal hepatic adiposity. Additionally, prenatal fructose exposure was associated with offspring whole-body adiposity and maternal adipocyte hypertrophy. Maternal fructose consumption in pregnancy is associated with changes in maternal and offspring hepatic and whole-body adiposity, with some studies identifying sex-specific effects. As fructose is consumed as part of a diet, and the mechanisms impacting changes in adiposity remain poorly understood, further research is needed to investigate the effects of a Western diet during pregnancy on offspring hepatic and whole-body adiposity.

Funding Sources: None

Presenters Name: Matthew Borrelli

Category: Graduate Student (MSc, PhD)

Title: INCREASED MITOCHONDRIAL SIZE IS ASSOCIATED WITH MITOPHAGY SUPPRESSION IN CORE REGIONS OF OVARIAN CANCER SPHEROIDS

Authors: M Borrelli, B Kolendowski, Y Ramos Valdés, G DiMattia, T Shepherd

Affiliation: The Mary & John Knight Translational Ovarian Cancer Research Unit, London Regional Cancer Program, London, Ontario, Canada

Abstract: Epithelial ovarian cancer (EOC) is infamous for late-stage diagnosis and chemoresistant relapse at metastatic sites, driving its low 5-year survival rate (<30%). Formation of multicellular aggregates (spheroids) provides survival advantages to EOC cells during metastasis; for example, we have identified that spheroids enter a reversible state of dormancy which supports survival during metastasis and chemotherapy exposure. Understanding the mechanisms enabling dormancy and chemotherapy evasion are critical in addressing relapse and chemoresistance. We have identified that autophagy—the "self-eating" stress response comprising degradation and recycling of cellular components—is activated in EOC spheroids, and that mitochondria are among its targets (mitophagy). However, it is unclear if these processes occur uniformly throughout spheroids. In this study, we utilized fluorescent reporter proteins for autophagy (mCherry-EGFP-LC3B) and mitophagy (mCherry-EGFP-FIS1[101-152]), and developed an automated image analysis platform to quantify the localization of each process in spheroids. Analysis revealed that core regions in EOC spheroids suppress mitophagy despite maintaining autophagy activity; previous reports describe mitochondrial fusion as a means of preventing autophagic degradation of mitochondria. Examining mitochondrial morphology in spheroid cryosections via confocal microscopy, we found that large mitochondria comprise a larger proportion of mitochondrial content in core cells than in peripheral cells, aligning with these reports. Furthermore, immunostaining revealed that core regions are largely devoid of the proliferation marker Ki67; thus, mitophagy suppression coincides with cellular dormancy in EOC spheroids. These findings call to question the implications of mitophagy suppression in spheroid core regions, and how it might relate to dormancy and chemotherapy evasion.

Funding Sources: We acknowledge funding support from the CIHR, a Lawson Catalyst Grant from the LHRI, and donations to the Mary & John Knight TOCRU from the LHSF. M Borrelli is currently supported by a PGS-D award from NSERC.

Presenters Name: Kendrick Lee

Category: Graduate Student (MSc, PhD)

Title: IN UTERO EXPOSURE TO CANNABIDIOL (CBD) IN RATS LEADS TO IMPAIRED CARDIAC FUNCTION EXCLUSIVELY IN MALE OFFSPRING

Authors: K Lee (1,2,5,8), M Nashed (3,5,8), SR Laviolette (3,5,8), DRC Natale (9) and DB Hardy (1,2,5-8)

Affiliation: Departments of (1)Physiology and Pharmacology, (2)Obstetrics and Gynaecology, (3)Anatomy and Cell Biology, (4)Biochemistry, (5)Schulich School of Medicine and Dentistry, (6)Children's Health Research Institute, (7)Lawson Health Research Institute, (8)Western University, London, ON, (9)Department of Obstetrics and Gynaecology, Queen's University, Kingston, Canada

Abstract: Studies indicate that 3-22% of pregnant women in North America consume cannabis in pregnancy. We have previously demonstrated that maternal exposure to THC (main psychoactive constituent in cannabis) leads to impaired cardiac function in offspring. However, the effects of maternal CBD (major non-intoxicating constituent in cannabis) exposure remain unknown. Therefore, the objective is to determine if maternal exposure to CBD alone will lead to cardiac dysfunction in offspring. Pregnant Wistar rats were exposed to a clinically relevant dose of 3 or 30 mg/kg CBD or vehicle control i.p. daily throughout gestation (day 6-22). This was followed by echocardiography to assess cardiac function in postnatal day (PD) 21 male and female offspring (n=6-8/group) relative to control. RNA-seq was then performed on PD21 offspring hearts (n=6-7/group). Partek Flow© was used for RNA-seq analysis. RT-qPCR was performed on cardiac targets. CBD exposure did not change birthweight. However, at PD21, echocardiography indicated that both doses of CBD led to impaired cardiac function (significant ($p<0.05$) decrease in cardiac output and ejection fraction), exclusively in male offspring. RNA-seq pathway analysis indicated significantly enriched molecular pathways in hypertrophic and dilated cardiomyopathy. In addition, qPCR data revealed that the endocannabinoid system was significantly altered exclusively in the 30 mg/kg CBD group. Our group has demonstrated for the first time that gestational exposure to CBD, a constituent perceived as safe, leads to postnatal cardiac deficits in the offspring in a sex-specific manner. Associated with these deficits, we revealed mechanistic pathways enriched in cardiac remodeling and a dysregulated endocannabinoid system.

Funding Sources: We acknowledge the funding of the Department of Obstetrics and Gynecology, Women's Development Council (LHSC), the Heart & Stroke Foundation of Canada, Children's Health Research Institute and the Ontario Graduate Scholarship.

Presenters Name: Jack Webb

Category: Graduate Student (MSc, PhD)

Title: ULK1 IS REQUIRED FOR AUTOPHAGY AND MAINTAINING CELL VIABILITY IN OVARIAN CANCER SPHEROIDS

Authors: Jack Webb1,2, Bipradeb Singha1,2, Matthew Borrelli1,2, Lauren Viola1, Yudith Ramos Valdes1, and Trevor G. Shepherd1,2,3,4

Affiliation: 1The Mary & John Knight Translational Ovarian Cancer Research Unit, London Regional Cancer Program, London, Ontario, Canada. Departments of 2Anatomy & Cell Biology, 3Oncology, and 4Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Ontario, Canada

Abstract: Epithelial ovarian cancer (EOC) is the leading cause of death from gynaecologic cancers due to its late-stage diagnosis and no effective strategies for treating chemo-resistant disease. Mechanisms promoting survival of EOC cells during metastasis and following treatment likely support the emergence of resistant disease. EOC spreads by direct dissemination into the peritoneal cavity oftentimes forming multicellular clusters called spheroids. We have demonstrated that autophagy is induced in EOC spheroids as a cell survival mechanism requiring ULK1 (unc-51-like kinase-1) activity. Herein, we have generated new ULK1 knockout EOC cells to further study its requirement during tumour growth and metastasis. CRISPR/Cas9 was used to ablate ULK1 gene expression in OVCAR8, HEYA8 and immortalized fallopian tube secretory epithelial cells (FT190) as a control. ULK1 loss impairs autophagy activation in ULK1KO spheroids as revealed by loss of LC3 processing and p62 accumulation. OVCAR8 and HEYA8-ULK1KO spheroids displayed decreased cell viability and reduced spheroid integrity, which can be attributed to apoptosis induction. Surprisingly, OVCAR8-ULK1KO spheroids are significantly more sensitive to carboplatin treatment, whereas HEYA8-ULK1KO spheroids appear resistant. No differences in EOC spheroid growth were seen due to absence of ULK1. It appears that ULK1 is required for EOC spheroid formation and cell survival while in suspension likely through its regulation of autophagy but may not be as important in precursor fallopian tube secretory epithelial cells. We are currently pursuing an expanded exploration of ULK1 substrates in EOC cells and spheroids, and orthotopic metastasis xenograft studies using ULK1KO cells is on-going.

Funding Sources: We acknowledge funding support from the CRS, and LHSF through donations to the Mary & John Knight TOCRU. J Webb was supported by an OGGS from the Department of Obstetrics & Gynaecology.
Presenters Name: Mohammed Sarikahya

Category: Graduate Student (MSc, PhD)

Title: PERINATAL OMEGA-3 FATTY ACID SUPPLEMENTATION SEX-SELECTIVELY PREVENTS THE PRENATAL Δ9-THC INDUCED COGNITIVE, ELECTROPHYSIOLOGICAL, AND LIPIDOMIC PHENOTYPE.

Authors: M.H. Sarikahya; S. Cousineau; M. De Felice; H. Szkudlarek; K.K.-C. Yeung; D.B. Hardy; W. Rushlow; S.R. Laviolette

Affiliation: Depts of Anatomy and Cell Bio (MHS, SC, MDF, HS, WR, SRL) and Psychiatry (WR, SRL); Depts of Chemistry and Biochemistry (SC, KK-CY); Depts of Obstetrics and Gynaecology, and PhysPharm (DBH)

Abstract: Clinical and preclinical studies indicate prenatal cannabis exposure (PCE) pathologically alters fetal brain development and increases vulnerability to neuropsychiatric disorders. However, underlying mechanisms remain unknown. Research in our lab suggests fetal exposure to Δ9-tetrahydrocannabinol (THC) impairs neurodevelopment, in part, through alteration of the lipidomic structure of cortical synaptic membranes. Considerable evidence demonstrates that abnormal synaptic omega-3 (N3) fatty acid lipidomic structure and function may underlie various neuropsychiatric disorders, with evidence suggesting that dietary N3 interventions may prevent or ameliorate symptom profiles. The present study examined if perinatal maternal N3-fatty acid supplementation may prevent the PCE-induced neuropsychiatric pathophenotypes. Pregnant Wistar rats were assigned to saline (VEH) or 3mg/kg THC (daily, i.p.) from gestational day (GD) 7 to GD22. Dams were given either N3-enriched or standard diets (control: CT) ad libitum from GD5 to postnatal day (PD) 21. Behavioural (e.g., cognitive, and affective capabilities), molecular, in vivo electrophysiological, and cortical lipidomic analyses were conducted to examine the extent of the rescue on PD21, PD35-45, and PD90-120. The behavioural data demonstrates a sex-specific N3-mediated therapeutic effect. PCE N3-treated male and female offspring exhibit significantly improved social, long-term recognition, and spatial working memory. However, only the N3-treated male progeny experience a prevention of the anxiogenic phenotype. The electrophysiological data supports these preventative therapeutic findings, with both male and female progeny exhibiting a mitigation in prefrontal cortical and hippocampal glutamate neuron dysregulation. These findings demonstrate that dietary interventions aimed at N3-fatty acid normalization may be a promising therapeutic option for cannabis-induced neurodevelopmental pathologies.

Funding Sources: NSERC, CIHR

Presenters Name: Stephanie Moltner

Category: Resident

Title: SURGICAL SITE INFECTION BUNDLE AND PRE-OPERATIVE CATHETER PROTOCOL IN GYNAECOLOGY: A QUALITY IMPROVEMENT INITIATIVE FOR COMBATTING SURGICAL SITE AND URINARY TRACT INFECTIONS

Authors: S Moltner, J McGee

Affiliation: Department of Obstetrics and Gynaecology, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada.

Abstract: Surgical site infections (SSI) and urinary tract infections (UTI) are two of the most common healthcare associated infections worldwide, and account for the most common reason for hospital readmission after hysterectomy. Thankfully, modifiable risk factors exist and gynaecology departments, both in Canada and internationally, have created bundles demonstrating significant decline in SSI and UTI. At our institution, a bundle was created and presented through grand rounds and at departmental meetings, in June of 2020. Several steps have been implemented, including standardization of antibiotic prophylaxis, chlorhexidine with and without alcohol surgical site preparation in all operating rooms, closing trays, and Sure-Step Catheter system utilization for indwelling catheters. The National Surgical Quality Improvement Program (NSQIP) data demonstrated 7.2% of gynaecologic procedures at London Health Sciences Centre from January through December 2019 resulted in a UTI, and 9.3% resulted in SSI. NSQIP data for 2021 demonstrates a 3.2% UTI rate, and 7.2% SSI rate. For non-cancer hysterectomy and myomectomy, UTI rate was 6.8% and SSI was 12.8% in 2019, versus a UTI rate of 4.3% and SSI of 8.6% in 2021. Though change is being observed, these rates fall under the category of "needs improvement", making them a high statistical outlier in comparison to other risk adjusted hospitals participating in NSQIP. Limiting factors include resources, protocol formation, and department buy-in. Future changes to improve outcomes could include adherence to the use of sterile closing trays, and tighter glycaemic control. With active buy-in, further decrease can improve financial burden and patient morbidity post operation.

Funding Sources: None

Presenters Name: Mohammad Khojah

Category: Post-Doctoral/Clinical Fellow

Title: TO REPLACE OR NOT REPLACE: INTRAOPERATIVE CATHETER PLACEMENT AT PELVIC SURGERY

Authors: M.Khojah, M. Tse, Q. Chou

Affiliation: Western University

Abstract: Postoperative urinary retention following pelvic reconstructive surgery can result in poor experiences for patients. Complications like urinary tract infections (UTI), vaginitis, ongoing voiding dysfunction and patient discomfort with ongoing reliance on catheterization can lead to an increase in the number of postoperative consultations1,2. Catheterization can be important for draining the bladder to reduce postoperative complications of urinary retention and aid in the return to normal voiding but does contribute to patient distress. In these cases, a catheter is placed at the end of surgery to be left in place postoperatively before discharge. Still, postoperative voiding dysfunction in women undergoing pelvic surgery is estimated to vary between 2.5%-43%3. The current practice in our institution involves the continued use of the same initial catheter placed throughout the entire surgery, even though it may have required removal and reinsertion several times during the procedure, at varying steps, to allow for cystoscopic assessment of bladder wall integrity and ureteral patency. This project aims to compare the rates of postoperative voiding dysfunction and catheter-associated UTI amongst women undergoing pelvic reconstructive surgery for prolapse or incontinence with a the original catheter vs a new, unused catheter. The practice of inserting a new catheter at the conclusion of all pelvic surgery cases in a single urogynecologic surgical practice at Victoria Hospital between October 2022 and February 2023 will be compared with the postoperative outcomes from pelvic surgery cases between May 2022 and September 2022 with the previous protocol of using the same original catheter insertion post-operatively. . The outcomes of voiding dysfunction and catheter-associated UTI rates for each protocol will be compared using the Wilcoxon rank-sum test.

Funding Sources: Patient Data

Presenters Name: Sebastian Vanin

Category: Graduate Student (MSc, PhD)

Title: GESTATIONAL EXPOSURE TO CANNABIDIOL LEADS TO GLUCOSE INTOLERANCE AT 3 MONTHS OF AGE EXCLUSIVELY IN MALE RAT OFFSPRING

Authors: S Vanin, K Lee, B Tse, S Brar, M Nashed, S Laviolette, E Arany, D Hardy

Affiliation: Physiology and Pharmacology, Wester University, London, ON, Canada

Abstract: Up to 20% of young women (18-24 yrs) use cannabis during pregnancy. This is concerning as studies report that maternal cannabis use is associated with metabolic dysregulation in the offspring. Our laboratory published that maternal exposure to Δ9-tetrahydrocannabinol, the main psychoactive component of cannabis, in rat dams led to female-specific deficits in β cell mass and systemic glucose intolerance/insulin resistance. However, the contributions of cannabidiol (CBD) in pregnancy, the primary non-psychoactive compound in cannabis, remain elusive. As such, this study aimed to investigate the effects of gestational exposure to CBD on postnatal dysglycemia. Pregnant Wistar rat dams received a daily intraperitoneal (i.p.) injection of vehicle or CBD (3 mg/kg) from gestational day 6 through parturition. Offspring were followed from postnatal day 21 (PND21) to 3 months (3MO) of age to assess their glucose sensitivity via an i.p. glucose tolerance test (ipGTT), and pancreatic development via immunohistochemical analysis of endocrine pancreas morphometry. Livers were also collected for RNA-sequencing. Gestational exposure to 3 mg/kg CBD led to increased area under the ipGTT curve exclusively in 3MO male offspring, indicating glucose intolerance. These CBD exposed male offspring did not exhibit deficits in pancreatic β or α cell mass. RNA-sequencing analysis is currently ongoing to determine the contribution of the liver to the observed glucose intolerance. Despite its increase popularity, our data suggests that exposure to CBD during pregnancy may not be safe as it leads to glucose intolerance in postnatal life, in part due to dysregulation of hepatic glucose neogenesis.

Funding Sources: Ontario Graduate Scholarship, Obstetrics and Gynecology Graduate Research Scholarship (OGGS), Heart and Stroke Grant

Presenters Name: Mahvash Shere

Category: Resident

Title: SAFETY OF METHYLENE BLUE IN PREGNANCY – SYSTEMATIC REVIEW

Authors: M. Shere, A. Privorozky, F. Garcia-Bournissen, J. Hutson

Affiliation: Department of Obstetrics and Gynecology, Western University, London, ON

Abstract: BACKGROUND: Methylene blue has been used for amniocentesis in twin pregnancies, and for sentinel lymph node biopsies (SLNB) for cancer in pregnancy. Early reports highlighted concerns regarding fetal intestinal atresia and hemolytic anemias, yet a systematic assessment and review of its safety in pregnancy remains lacking. OBJECTIVE: To evaluate the safety of methylene blue during pregnancy. METHODS: We searched MEDLINE, EMBASE, CCRT, CDSR, and CINAHL databases for human studies from inception to August 2021. Case reports, case series, cohort studies and randomized-controlled trials were included. PROSPERO guidelines were followed. Data was extracted by 2 independent reviewers, and the likelihood of adverse reactions establishing causality was classified using the Naranjo algorithm. RESULTS: 445 studies identified initially, 374 studies available after de-duplication. 34 studies available for full-text review, and 14 studies eligible for data extraction. 3 studies described methylene blue use for sentinel lymph node biopsies in pregnancy with no safety concerns. 2 case reports utilized it for identification of PPROM and described neonatal skin discoloration, hemolytic anemia, and respiratory distress. 1 case report highlighted its use in early pregnancy during implantation with no concerns. 5 studies highlighting its use during twin amniocentesis noted increased rates of SGA infants, intestinal atresias, and stillbirth – however, data surrounding this have issues with quality, and clarity of association. CONCLUSIONS: Methylene blue is likely safe for use during SLNB for cancers in pregnancy given the availability of case-series and cohort studies supporting its safety. Intra-amniotic methylene blue injection during twin pregnancies has mixed-quality data.

Funding Sources: Internal Departmental Funding

Presenters Name: Charles Trelford

Category: Post-Doctoral/Clinical Fellow

Title: THE ROLE OF LIVER KINASE B1 IN TRANSLATIONAL MODELS OF ADVANCED EPITHELIAL OVARIAN CARCINOMA

Authors: C Trelford A Buensuceso and T G Shepherd

Affiliation: 2. The Mary & John Knight Translational Ovarian Cancer Research Unit, London Regional Cancer Program, ON

Abstract: Epithelial ovarian cancer (EOC) is usually diagnosed late in tumour development and despite the initial success of surgery and chemotherapy, patients often relapse with chemo-resistance. Late-stage diagnosis compounded with high rates of recurrence after remission make EOCs the most lethal gynecological malignancies in the developed world. Therefore, this project was undertaken to characterize pathways that promote EOC survival and metastasis to efficiently target malignant cells resistant to chemotherapeutics. As revealed by CRISPR/Cas9 genetic knockout of the tumour suppressor, liver kinase B1 (LKB1), EOC cell survival is dependent on intact LKB1 signalling. The loss of LKB1 disrupted cell migration and invasion when assessed under cell adherent conditions. Contrary to these findings, LKB1 was essential to invasion of EOC spheroids imbued in gel-like matrices. Compared to adherent culture, spheroids are three-dimensional models that closely mimic tumour cell-cell contacts and growth kinetics. RNAi-dependent targeting of STE-20-related kinase adaptor protein (STRAD; a pseudokinase that activates LKB1) linked LKB1-STRAD activity to epithelial-mesenchymal transition and extracellular matrix remodelling in both spheroids and adherent culture. Given the need for more precise modeling of LKB1 in EOC pathology, quantitative phosphoproteomics by mass spectrometry was performed using wild-type and LKB1 knockout EOC cell lines. Computational analysis detected numerous alterations to phosphosites and highlighted signalling pathways dependent on intact LKB1 activity. These pathways may regulate EOC chemoresistance which suggests that targeting LKB1 could increase the therapeutic vulnerability of chemotherapy resistant EOC.

Funding Sources: We acknowledge funding support from the CIHR, and LHSF through donations to the Mary & John Knight TOCRU

Presenters Name: Ayma Aqib

Category: Undergrad

Title: "NOTHING COMES TO MIND…": CHALLENGES WITH IDENTIFYING ONE'S OWN ROLE IN PREVENTABLE POOR OUTCOMES AND BEHAVIOUR, AND THE IMPACT ON QUALITY IMPROVEMENT INITIATIVES

Authors: L Columbus, R Pack, A Aqib, H Banner, T Taylor.

Affiliation: Department of Obstetrics and Gynaecology, Schulich School of Medicine and Dentistry, The University of Western Ontario, London, Ontario, Canada.

Abstract: Preventable poor outcomes occur across all healthcare settings and form the basis of many quality improvement (QI) initiatives. While QI initiatives often focus on system issues, health care professionals' attitudes regarding the role of interprofessional communication and team psychological safety within poor outcomes remain largely unexplored. This study investigated the role that sociocultural factors play in preventable poor outcomes within obstetrics. In this intervention-primed, constructivist grounded theory study, members across five professions providing intrapartum care attended an interdisciplinary workshop on improving their fetal health surveillance interpretation, communication, and teamwork skills. Eighteen participants (2-OB, 2-residents, 4-Family Medicine, 4-nurses, 6-midwives) then completed semi-structured interviews which were recorded and transcribed. Participants described errors other team members had made with ease, as well as incidences where they were the recipients of poor treatment but were rarely willing or able to recall their own role in poor outcomes within the team. Poor behaviour and poor outcomes were most often noted in members outside of the participant's own professional group, while strong intraprofessional psychological safety was emphasized by participants. In this obstetrical team setting, individuals struggled to see their role in poor outcomes. QI initiatives aimed at reducing poor perinatal outcomes caused by suboptimal team performance may be of limited efficacy if individual team members struggle to acknowledge their own role in these poor outcomes, as well as the role that their own profession may play. It may be beneficial to develop QI or professional development activities that address this cognitive dissonance.

Funding Sources: We acknowledge the funding of the Department of Obstetrics and Gynaecology, and the Department of Midwifery.

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RESEARCH DAY ABSTRACTS: POSTER

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Presenters Name: Adrian Buensuceso

Category: Post-Doctoral/Clinical Fellow

Title: MYC ONCOGENE DOWNREGULATION IN A SPHEROID CULTURE MODEL OF METASTATIC EPITHELIAL OVARIAN CANCER

Authors: A Buensuceso, M Borrelli, Y Ramos Valdés, B Kolendowski, G DiMattia, T Shepherd

Affiliation: The Mary & John Knight Translational Ovarian Cancer Research Unit, London Regional Cancer Program, London, Ontario, Canada

Abstract: Epithelial ovarian cancer (EOC) is frequently diagnosed at an advanced stage, characterized by metastasis to peritoneal sites beyond the ovaries. Mounting evidence implicates spheroids as important mediators of metastasis in EOC. We have shown that EOC spheroids possess features of a tumour dormancy phenotype that supports cell survival and chemotherapy resistance. As such, greater understanding of spheroid biology may reveal therapeutic vulnerabilities in advanced disease. MYC encodes an oncogenic transcription factor that is frequently amplified or overexpressed in EOC. MYC protein cooperates with dimerization partners to activate or repress specific target genes to elicit pro-tumorigenic functions, yet its regulation and function during metastasis is less clear. We hypothesized that MYC expression and function would be suppressed in EOC spheroids to promote the tumour dormancy phenotype of these structures. Transcriptome analysis revealed a significant decrease in MYC-associated gene expression signatures in EOC spheroids compared with proliferating adherent cells. Immunoblot analysis of 29 cell lines representing high-grade serous and clear cell carcinomas verified a widespread decrease (mean of 54%) in MYC protein in spheroids. Decreased MYC protein is rapid, occurring as soon as 2 h in spheroid culture, and this is mediated by proteasomal degradation. Interestingly, EOC spheroid reattachment quickly restored MYC protein expression and MYC target gene regulation. These results indicate that MYC expression and activity are rapidly but reversibly decreased in EOC spheroids. We postulate that suppression of MYC activity is a key molecular feature of tumour cell dormancy during EOC metastasis.

Funding Sources: Funding support from the CIHR, and LHSF through donations to the Mary & John Knight TOCRU.

Presenters Name: Roisin Dooley

Category: Resident

Title: RESIDENT'S UNDERSTANDING, ATTITUDES, AND BEHAVIOURS TOWARDS NON-INVASIVE PRENATAL TESTING EXPANDED PANEL

Authors: R Dooley, T Burr, R Ho, M Saleh, B de Vrijer

Affiliation: Department of Obstetrics and Gynaecology and Department of Pediatrics, Division of Medical Genetics, Schulich School of Medicine and Dentistry

Abstract: Non-invasive prenatal testing (NIPT) is a screening tool using cell-free DNA (cfDNA) with a high accuracy in detecting trisomy 13, 18 and 21, triploidy and sex chromosomal anomalies. This test, funded by OHIP under certain circumstances, can be ordered with a self-pay 'expanded option', which includes testing for select conditions caused by microdeletions/duplications and imprinting disorders. The clinical utility of this expanded testing option is still uncertain and only NIPT for aneuploidies is supported by the Society of Obstetricians and Gynaecologist of Canada (SOGC) and Canadian College of Medical Genetics (CCMG) at this time. This study aimed to look at the knowledge, attitudes, and behaviours that our residents have towards the expanded NIPT. A questionnaire was developed and distributed electronically to all residents within our department. A total of 25 out of 34 (74%) individuals completed the questionnaire. Only 56% of respondents were aware of the expanded testing option and there was 60% uncertainty regarding the syndromes that it tests for. Furthermore, 76% were uncomfortable explaining the syndromes and their consequences. Only 16% knew that the PPV for the expanded panel is less than the PPV for trisomy 21. Additionally, 100% agreed that practitioners need more information and education around the expanded panel, yet 96% have not been able to find high-quality information on the subject. The results of our study revealed that many residents are lacking knowledge around the expanded NIPT. Proper education on the expanded test will help promote appropriate use and counselling on the screening.

Funding Sources: None

Presenters Name: Jennifer Davis

Category: Undergrad

Title: INVESTIGATING SEQUENTIAL AND COMBINED TREATMENTS OF CARBOPLATIN AND PARP INHIBITORS USING THREE-DIMENSIONAL CULTURE MODELS OF ADVANCED HIGH-GRADE SEROUS OVARIAN CANCER

Authors: J Davis, E Tomas, Y Ramos Valdes, G E DiMattia J McGee and TG Shepherd

Affiliation: Mary & John Knight Translational Ovarian Cancer Research Unit, London Regional Cancer Program, London, ON

Abstract: Epithelial ovarian cancer is a deadly gynecological malignancy with an insidious disease onset and inadequate treatment options. PARP inhibitors (PARPi) are a new class of therapeutics that inhibit single-stranded DNA repair. Using a synthetic lethal strategy, they exploit homologous recombination repair deficiencies like BRCA1/2 mutations which are present in over half of high-grade serous epithelial ovarian cancer (HGSOC) cases. Olaparib and niraparib are currently approved as first-line maintenance therapy in platinum-sensitive ovarian cancer, but clinician decisions regarding their further use is ill-informed by current research. Thus, our objective is to determine the utility of PARPis as sequential or combination therapy with standard-of-care chemotherapy, carboplatin. Ascites-derived malignant cells from eight patients with HGSOC who underwent cytoreductive surgery at London Health Sciences Centre have been established as new cell lines in adherent conditions. The IC50 values for treatment with olaparib and niraparib are heterogeneous across cell lines and variable between the PARPis. A BRCA1 mutant line showed sensitivity to both drugs, while others showed resistance. We then applied our drug treatments by growing cell lines in a matrix-bound 3D organoid culture model. Initial organoid experiments with combination treatment of carboplatin and olaparib have shown increased tumour cell killing. Further studies of varying the sequence and combination are on-going. RNA sequencing data from cell line organoids will be analyzed to identify potential biomarkers for tumour cells resistant or sensitive to PARPis. These results using patient-derived tumour models could inform future clinical trials for using PARPi in sequence or combination in the first-line adjuvant or neoadjuvant setting of women diagnosed with advanced high-grade serous ovarian cancer.

Funding Sources: We acknowledge funding from Ovarian Cancer Canada and Health Canada. J Davis was supported by the Summer Research Training Program from SSMD.

Presenters Name: Jacob Haagsma

Category: Graduate Student (MSc, PhD)

Title: GAIN-OF-FUNCTION P53R175H BLOCKS APOPTOSIS IN A PRECURSOR CELL LINE MODEL OF OVARIAN HIGH-GRADE SEROUS CARCINOMA

Authors: J. Haagsma, M. Pereira, B. Kolendowski, A. Buensuceso, Y. Valdes, G. DiMattia, J. Petrik, T. Shepherd

Affiliation: Department of Anatomy & Cell Biology

Abstract: Ovarian high-grade serous carcinoma (HGSC) is an aggressive malignancy that primarily originates from distal fallopian tube secretory epithelial cells. The earliest genetic event in HGSC is universal TP53 mutation, consisting of missense mutations with gain-of-function properties, and a smaller subset of TP53 deletion. HGSC progression involves the formation of multicellular clusters called spheroids, which shed from their site of origin to seed primary tumours at the ovary and secondary tumours throughout the peritoneal cavity. To assess early mechanisms driving HGSC initiation, we used two mouse oviductal epithelial (OVE) cell lines—OVE4 and OVE16—to delete Trp53 via CRISPR/Cas9-mediated genome editing, or to express mutant p53R175H via lentiviral transduction. Cell transformation was assessed in vitro with soft agar assays. Spheroid formation and survival was assessed by culturing cells in suspension. Pathway analysis was performed by RNA-seq and GSEA, and validated by western blot. Expression of p53R175H produced increased colony growth in soft agar. Either Trp53 deletion or p53R175H expression increased spheroid cell viability compared to cells with wild-type p53. GSEA revealed higher expression signatures related to apoptosis and inflammation pathways in wild-type cells compared to cells expressing p53R175H. Further interrogation of the apoptosis pathway demonstrated decreased apoptosis activation due to p53R175H, and to a lesser degree due to Trp53 deletion. We are currently expanding this work to an in vivo model by injecting OVE cells into syngeneic female FVB/n mice. This work has identified an anti-apoptosis gain-of-function property of p53R175H, and demonstrated this model's utility to investigate early HGSC transformation mechanisms.

Funding Sources: We acknowledge funding support from the CIHR, and LHSF through donations to the Mary & John Knight TOCRU

Presenters Name: Tiffany Johnston

Category: Graduate Student (MSc, PhD)

Title: THERAPEUTIC TARGETING OF ULK1 AND AUTOPHAGY USING MRT-68921 IN EPITHELIAL OVARIAN CANCER

Authors: T Johnston, Y Ramos Valdes, A Buensuceso and T G Shepherd

Affiliation: The Mary & John Knight Translational Ovarain Cancer Research Unit, London Regional Cancer Program, London, Ontario, Canada

Abstract: Epithelial ovarian cancer (EOC) has the fifth-highest death-to-incidence ratio for all cancers in women due to late-stage detection and lack of strategies to treat chemo-resistant disease. EOC metastasizes by cells disseminating into the peritoneal cavity and attaching to distant sites forming secondary lesions. EOC cells within the peritoneal fluid cluster together forming spheroids which potentiate disease as their dormant phenotype promotes chemo-resistance. We identified that autophagy, an evolutionarily-conserved intracellular recycling process, is crucial for spheroid cell viability. Autophagy is initiated by unc51-like kinase 1 (ULK1) and we have identified its activity is important in EOC spheroids. Here, we explore the therapeutic potential of targeting ULK1 and autophagy inhibition using an ULK1 small molecule inhibitor MRT68921 and plan to combine it with chemotherapeutics to test for drug synergy and overcome resistance. We have surveyed six high-grade serous (HGSOC) and four clear cell carcinoma (CCOC) ovarian cancer cell lines in adherent culture and determined the range of IC50 values among cell lines to be between 0.8 and 4 μM. We are currently performing similar MRT68921 treatment of spheroids during and after formation. As spheroids activate autophagy quickly, we expect spheroids to be more sensitive to MRT68921 early during formation as compared with established spheroids. Dose-response and kinetics of MRT68921 inhibitory activity are being performed by evaluating ULK1 phosphorylation target Beclin-1 (S30) and autophagy activation markers LC3B and p62. This MRT68921 characterization will allow for future experiments testing MRT68921 efficacy in combination with chemotherapy as a potential novel strategy to treat chemo-resistant disease.

Funding Sources: We acknowledge funding support from the CRS, and LHSF through donations to the Mary & John Knight TOCRU. T Johnston is supported by an OGGS from the Department of Obstetrics & Gynaecology

Presenters Name: Helen Jiang

Category: Undergrad

Title: INVESTIGATION OF N,N,N-TRIMETHYL-L-ALANYL-L-PROLINE BETAINE (TMAP) AS A POTENTIAL PREECLAMPSIA BIOMARKER

Authors: H Jiang, E Chan, J Hutson

Affiliation: Department of Physiology & Pharmacology, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Abstract: Preeclampsia is a form of new onset hypertension during pregnancy which gives rise to significant complications including acute kidney injury. These complications can only be resolved by delivery of the fetus and placenta. The current lack of tools and biomarkers for the detection of early preeclampsia-induced organ damage presents as a challenge to physicians to time delivery in preeclamptic individuals while balancing fetal risks from premature births and maternal risks from preeclampsia complications. N,N,N-trimethyl-L-alanyl-L-proline betaine (TMAP), a novel molecule with superior sensitivity than creatinine for renal dysfunction, was investigated in this pilot project for its potential as a plasma biomarker of preeclampsia progression. With REB approval, normotensive and preeclamptic participants throughout different trimesters of pregnancy were recruited through obstetrical clinics at London Health Sciences Centre. Plasma TMAP concentrations were determined by collecting and analyzing blood samples via liquid chromatography-mass spectrometry (LC-MS). These TMAP concentrations will be compared between normotensive and preeclamptic participants at corresponding points in gestational age. We anticipate that plasma TMAP concentrations will be increased in preeclamptic participants as compared to normotensive participants due to the renal stress and injury elicited by preeclampsia. This TMAP pilot study will explore plasma TMAP as a potential biomarker for preeclampsia progression, which can help inform the timing of preeclamptic deliveries and reduce preeclampsia-induced maternal and fetal complications in clinical settings.

Funding Sources: Department of Obstetrics and Gynecology, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Presenters Name: Timothy Nunes

Category: Graduate Student (MSc, PhD)

Title: LIFELONG MATERNAL WESTERN DIET IMPAIRS PLACENTAL AND FETAL DEVELOPMENT IN A NON-OBESE GUINEA PIG (CAVIA PORCELLUS) MODEL

Authors: T Nunes(1,2,3), K Nygard(4), M Courchesne(4), B Richardson(2,3), P Kiser(1), T Regnault(2,3)

Affiliation: Departments of (1)Pathology & Laboratory Medicine, (2)Obstetrics & Gynaecology, (3)Physiology & Pharmacology, (4)Biotron Integrated Microscopy Facility; Western University, London, ON, Canada

Abstract: Independent of body mass index (BMI), a "Western Diet" (WD) high in sugars and saturated fats contributes to poor metabolic health. Maternal WD is associated with adverse pregnancy outcomes—including altered placental development. Studies investigating the impact of WD in normal-weight pregnant populations are limited, despite the increasing prevalence of metabolically unhealthy normal-weight persons. To elucidate the BMI-independent effects of WD on fetoplacental development, we utilized a non-obese WD guinea pig model. We hypothesized that lifelong maternal WD would impair placental vascularization and fetal development—independent of maternal BMI. Female Dunkin-Hartley guinea pigs were weaned onto control diet (CD) or WD and mated to CD males at six-months, then necropsied at 36-, 42-, or 63-days gestation (term ~68-days). Placental cross-sections were examined by immunofluorescence microscopy to characterize fetal capillaries and maternal lacunae. Preliminary data are presented for the 63-day cohort (CD n=19 (6 pregnancies), WD n=25 (14 pregnancies), analyzed by linear mixed-model with litter-ID fixed effect. WD pregnancies exhibited significantly decreased fetal-placental weight ratios ($p<0.001$) and 16.8% lower fetal brain-liver weight ratios ($p=0.086$, $g=1.041$). In placental labyrinths, maternal lacunae to fetal capillary area ratios were significantly increased ($p<0.01$) and capillary diameters significantly reduced ($p<0.01$) in WD placentae. Our findings indicate that impaired placental hemodynamics may contribute to adverse gestational outcomes associated with WD pregnancies, and timing of impairments will be further explored. Our work could help to refine pregnancy risk assessments in clinical settings, as we highlight the importance of evaluating maternal lifestyle and metabolic health—rather than BMI alone.

Funding Sources: This research was supported by funds from a National Institutes of Health (NIH) Human Placenta Project Grant (grant No. U01 HD087181-01).

Presenters Name: Akasham Rajagopaul

Category: Graduate Student (MSc, PhD)

Title: DETECTION OF NOVEL DIAGNOSTIC METABOLITES FOR EARLY AND LATE ONSET HYPERTENSIVE DISORDERS OF PREGNANCY

Authors: A Rajagopaul1, S Zhao3, X Wang3, G Eastabrook2, L Li3 T Regnault1, B de Vrijer2

Affiliation: 1 Department of Physiology and Pharmacology, 2 Department of Obstetrics and Gynaecology, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada; 3 The Metabolomics Innovation Centre, University of Alberta, Edmonton, AB, Canada

Abstract: Hypertensive disorders of pregnancy (HDP) are a leading cause of fetal/maternal morbidity and mortality, complicating 7% of Canadian pregnancies. They have a wide range of clinical presentations and severities making diagnosis and management challenging. Current screening and diagnostic tools are less effective at detecting late-onset disease (LO-HDP), which is more prevalent but less severe, compared to early onset disease (EO-HDP). Metabolomic profiling provides insight into the underlying metabolic changes that contribute to the development of HDP and may be a useful tool in HDP diagnostics. Patients with singleton pregnancies admitted to Victoria Hospital were recruited as part of an ongoing cardiometabolic study of HDP. Using this cohort, a metabolomic analyses of plasma samples from non-hypertensive controls (n=36), and women developing EO-HDP (birth <34 weeks; n=12) and LO-HDP (birth ≥34 weeks; n=24) was performed via LC-QTOF-MS. Data were analyzed using Metaboanalyst 5.0 and SPSS 28.0. Distinct metabolomic signatures were observed between all three groups, with one-way ANOVA revealing 73 significant metabolites. PCA and PLS-DA revealed inter-group separation and identified key metabolites associated with EO-HDP and LO-HDP. ROC analysis using a biomarker panel including 2 key metabolites (cystine & 1-methylhistidine), BMI, PWV, and PlGF showed excellent diagnostic performance, producing an AUC of 1.00 for EO-HDP and 0.94 for LO-HDP. Our findings provide new insights into the metabolic changes occurring in EO-HDP and LO-HDP and suggests that metabolomic profiling may be useful for the diagnosis and management of these conditions. Further validation of these biomarkers in an independent cohort will be essential.

Funding Sources: Canadian Institutes of Health Research (CIHR)

Presenters Name: Emily Tomas

Category: Graduate Student (MSc, PhD)

Title: COMPARATIVE EXPLORATION OF CULTURED SPHEROIDS AND ORGANOIDS AS MODELS TO STUDY EPITHELIAL OVARIAN CANCER PATHOBIOLOGY

Authors: E Tomas1,2, Y Ramos Valdes1, J Davis1, G E DiMattia1,4,5 and T G Shepherd1,2,3,4

Affiliation: 1The Mary & John Knight Translational Ovarian Cancer Research Unit, London Regional Cancer Program; Departments of 2Anatomy & Cell Biology, 3Obstetrics & Gynaecology, 4Oncology, and 5Biochemistry, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada.

Abstract: Epithelial ovarian cancer (EOC) is a devastating disease with a unique metastatic progression involving spheroids. Our extensive research into spheroid pathobiology has provided insight into several molecular and cellular changes implicated during EOC metastasis. To further explore the biology of EOC cells between tumour and spheroid states, we have compared several EOC cell lines grown as spheroids on Ultra-Low Attachment plates with organoids using modified patient-derived organoid culture conditions. Among these cell lines, organoids appeared heterogeneous in morphology with dense, cystic, or mixed phenotypes, whereas spheroids often existed as grape-like clusters, with few adopting a compact structure. Next, we performed immunoblotting and immunofluorescence assays to evaluate known altered processes in spheroid biology including bioenergetic stress, cell proliferation and epithelial-to-mesenchymal transition. Interestingly, organoids of established EOC cell lines and patient ascites-derived iOvCa246 have higher AMP-activated protein kinase (AMPK) T172 phosphorylation as compared with spheroids; however, the remaining iOvCa cell lines exhibited increased AMPK activity in spheroids only. As well, transcriptome analysis of seven different iOvCa cell lines showed elevated pathways for G2M checkpoint and E2F target genes in organoids compared to spheroids. Lastly, we treated spheroids and organoids with carboplatin, a common EOC chemotherapeutic, to determine sensitivity within each model. Thus far, spheroids appear to be more carboplatin resistant than organoids, but OVCAR4 cells and iOvCa246 spheroid and organoids are equally sensitive. Given the cellular plasticity of EOC cells during disease progression, parallel assays of spheroid and organoid models will be crucial to discover new therapeutic vulnerabilities in advanced disease.

Funding Sources: We acknowledge the funding from Ovarian Cancer Canada, Health Canada, and Canadian Institutes of Health Research.

Presenters Name: Magdalene Zabek

Category: Graduate Student (MSc, PhD)

Title: THE TRANSFER OF MOLNUPIRAVIR AND NIRMATRELIVIR ACROSS THE HUMAN PLACENTA AND PREDICTION OF SAFETY IN PREGNANCY

Authors: M Zabek, J Hutson, F Garcia-Bournissen, E Chan

Affiliation: Department of Physiology and Pharmacology, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

Abstract: Pregnant individuals are at a higher risk for severe COVID-19, and it is associated with negative birthing outcomes such as low birth weight, pre-term birth and preeclampsia. The antiviral drugs molnupiravir and nirmatrelvir are effective therapeutics for COVID-19, however there is limited data on effects of either drug during pregnancy. This study is undergoing to investigate the maternal-fetal drug transfer of molnupiravir and nirmatrelvir across the human placenta. The ex vivo placental perfusion model and physiological based pharmacokinetic (PBPK) modelling is utilized to accurately predict in vivo placental drug transfer. Written consent from patients was obtained prior delivery. An isolated lobule of a human term placenta from uncomplicated caesarian sections is perfused by introducing the drugs into the maternal circulation. Perfusate samples are taken throughout the experiment, and measurement of each drug in perfusate and placental tissue will be determined by LC-MS. The transport of each drug will be express in two distinct parameters: fetal to maternal concentration ratio at a steady state and drug clearance from maternal circulation. These parameters will be adjusted through PBPK modelling for non-placental physiologic factors that can impact pharmacokinetics which are not able to be included into the perfusion model. The characteristics of molnupiravir and nirmatrelvir during pregnancy will be determined. The adjusted pharmacokinetic parameters from this study can be utilized to estimate fetal drug exposure and be used to create better safety recommendations regarding their use in pregnancy.

Funding Sources: Lawson Research Institute; Department of Physiology and Pharmacology