NIH Symposium on Women's Health Research in Institutional Development Award (IDeA) States
Event Date: June 8, 2024

Welcome
Regine Douthard, M.D., M.P.H., Senior Medical Officer, Office of Research on Women's Health

The NIH Office of Research on Women's Health (ORWH) and National Institute of General Medical Sciences, along with other NIH institutes, centers, and offices, have worked over the past 5 years to expand research capacity in women's health within [Institutional Development Award (IDeA) states](). This inaugural NIH Symposium on Women's Health Research in IDeA States centers on the impact of administrative supplements awarded for women's health research, showcasing presentations from 16 investigators funded in Fiscal Years (FYs) 2020 and 2021.
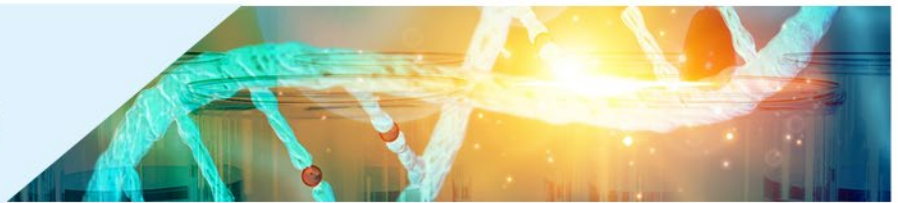
The objectives of the symposium are to facilitate networking and knowledge exchange among IDeA investigators, elevate the visibility of administrative supplement awardees and their research within their institutions and the broader IDeA program, and showcase the program's achievements by highlighting research outcomes. This event aims to underscore the significant progress made in women's health research in IDeA States, promoting further advancements and collaborations in the field.

Introductory Remarks
Janine Clayton, M.D., FARVO, Director, Office of Research on Women's Health; and Michele McGuirl, Ph.D., Acting Director, Division of Research Capacity Building, National Institute of General Medical Sciences

In November 2023, President Joe Biden launched the inaugural [White House Initiative on Women's Health Research](), marking a significant milestone in the focus on women's health in the United States. This initiative was further reinforced by an [Executive Order]() that prioritized investments in women's health research across the federal landscape. At the forefront of this initiative is ORWH, which is collaborating with various NIH institutes and other federal agencies to advance this important cause. Recently, ORWH published the [*NIH-Wide Strategic Plan for Research on the Health of Women 2024–2028*](), a comprehensive 5-year roadmap designed to guide and inform NIH-supported research on diseases and health conditions affecting women. This strategic plan encompasses a wide array of scientific disciplines and research types, ranging from translational to clinical and applied research.

In 2020, ORWH and the National Institute of General Medical Sciences, with support from other NIH institutes and centers (ICs), established the first [Notice of Special Interest (NOSI)]() for Administrative Supplements for Research on Women's Health in the Institutional Development Award (IDeA) States. This initiative aimed to address critical issues such as maternal and infant morbidity and mortality. Building on this success, additional NOSIs were published, offering further funding opportunities for IDeA-funded institutions to research significant women's health issues across the lifespan. From FY20 to FY23, 60 awards totaling $16.5 million were granted to 20 IDeA states and Puerto Rico. In FY24, three new [Centers of Biomedical Research Excellence (COBRE)]() Phase 1 programs received awards to conduct women's health research in IDeA States, specifically at Tulane University of Louisiana, the University of Idaho, and the University of Kansas, Lawrence. These programs exemplify successful collaborations and partnerships,

leveraging resources, research infrastructure, and expertise to improve women's health in IDeA States. The programs also align with the goals of the White House Initiative on Women's Health Research by prioritizing investments and underscoring the importance of women's health research nationwide.

Scientific Session #1
Administrative Supplement Awardee Presenters #1–8

Healthy Moms, Healthy Families
Maribel Campos Rivera, M.D., Professor, Department of Medical Services, University of Puerto Rico

This study investigated the health effects on participants who underwent a lifestyle intervention trial funded by the National Institute on Minority Health and Health Disparities during a period marked by catastrophic events such as Hurricane Maria and the COVID-19 pandemic. Participants in the study had a notably low socioeconomic status, qualifying for federal assistance based on income levels significantly lower than those in other U.S. jurisdictions. The median family income was less than half that of the lowest-income states, with a high percentage living below the poverty line. Unlike the Supplemental Nutrition Assistance Program (SNAP), Puerto Rico's Nutrition Assistance Program (NAP) operates on a block grant basis with stricter eligibility criteria and lower benefits. Nonetheless, NAP continues to provide substantial support, including benefits for many children.

Data collection on food security revealed that 37.7% of participants expressed concerns about running out of food in the previous month, while 31.1% reported experiencing periods without enough food. Social vulnerability was also assessed, with 22.6% indicating high vulnerability due to a lack of support networks. Additionally, measurements of transcutaneous carotenoid levels and body composition highlighted the need for extended postpartum telehealth services and support systems. These services and systems are crucial in addressing potential long-term cardiometabolic effects associated with disproportionate adiposity.

The study recommends transitioning Puerto Rico's food security program from NAP to SNAP, expanding telehealth services, and supporting demonstration projects for broader adoption of Interventions to Minimize Preterm and Low Birthweight Infants through Continuous Improvement Techniques (IMPLICIT). IMPLICIT integrates maternal health screening in pediatric care and promotes shared care models between obstetric and pediatric providers, aligning with the goals of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).

Delivery and Short-Term Maternal and Fetal Safety of Vaginally Administered PEG-PLGA Nanoparticles
Emily Day, Ph.D., Associate Professor, Biomedical Engineering, University of Delaware

This study investigated the use of antibiotic-loaded nanoparticles for treating bacterial vaginosis in both pregnant and non-pregnant women, focusing on the potential of polyethylene-poly (lactic-co-glycolic acid) (PEG-PLGA) nanoparticles in maternal-fetal health. The effectiveness and safety of these

nanoparticles are still under evaluation. Unlike systemic administration, which can result in off-target delivery, vaginal administration was hypothesized to provide targeted delivery to the vagina while minimizing systemic toxicity.

The research involved creating two types of nanoparticles: one loaded with DiD fluorophores as cargo and another where the polymer itself was labeled with fluorophores. This setup facilitated tracking the distribution of the cargo or polymer in the body following vaginal administration in pregnant mice. The study evaluated biodistribution and short-term effects, including maternal weight, fetal weight, placental weight, and indicators of embryo viability such as resorptions per litter. Key findings included the retention of DiD cargo primarily in the vagina post-administration, indicating effective local delivery. In contrast, the polymer component was detected not only in the vagina but also in placental tissues and embryos, suggesting potential systemic trafficking after cargo release. Importantly, within 24 hours of administration, no adverse effects were observed on maternal or fetal parameters compared to control groups receiving saline injections.

The study concluded that vaginally administered PEG-PLGA nanoparticles effectively delivered cargo to the vaginas of pregnant mice without immediate negative impacts on maternal or fetal health. These promising findings advocate for continued research into the potential use of vaginally administered nanomedicines for treating vaginal conditions in both pregnant and nonpregnant women, including bacterial vaginosis. Published in December 2023 in *Drug Delivery and Translational Research*, the study was acknowledged as the journal's top article of the month, highlighting its significance in the field.

Pregnancy Complications in the Strong Heart Study
Emily Harville, Ph.D., Associate Professor, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine

This collaborative project involves Tulane University, the Pennington Biomedical Research Center at Louisiana State University, and researchers from South Dakota, Oklahoma, and Arizona, focusing on pregnancy complications within the Strong Heart Study cohort. The study explores hypertensive disorders, gestational diabetes, and their connections to cardiovascular health. Encompassing 12 American Indian tribes across Arizona, Oklahoma, North Dakota, and South Dakota, the Strong Heart Study provides a comprehensive longitudinal dataset dating back to the late 1980s, offering unique insights over multiple phases of study.

The design of the Strong Heart Study enables the investigation of both post-pregnancy effects on maternal health and preconception factors influencing pregnancy outcomes. Approximately 1,700 pregnancies are included for post-pregnancy effects, while 300 pregnancies are examined for preconception effects. This approach captures pregnancies irrespective of planning, providing a comprehensive view of pregnancy impacts, although it introduces challenges because intervals between study visits and pregnancies vary. Data sources include self-reported reproductive histories, supplemented by medical records, birth certificates, and the National Data Warehouse (Indian Health

Service). This comprehensive approach aims to validate and refine case definitions for conditions such as preeclampsia and gestational diabetes.

Initial findings from the study reveal discrepancies among data sources regarding diagnoses, which affect the reliability of associations with later-life hypertension. Notably, preeclampsia that is self-reported and medically diagnosed shows stronger associations with hypertension compared to symptomatic reports alone. Regarding gestational diabetes, pre-pregnancy factors such as glucose levels were predictive, although associations with later-life cardiovascular disease were less evident despite increased diabetes risks. Key predictors and consequences of gestational diabetes primarily centered around glucose levels and body mass index (BMI) rather than broader cardiovascular risk factors such as blood pressure and lipids. The study highlights the risks of early onset of diabetes in this cohort, suggesting that interventions and further research should focus on early adulthood.

Although the study provides significant insights into pregnancy complications among American Indian populations, ongoing challenges include integrating disparate data sources and refining diagnostic criteria to enhance predictive accuracy for long-term health outcomes. These efforts are crucial for advancing understanding and developing interventions in maternal and cardiovascular health within diverse, underserved populations across IDeA States.

Genetic Variation Modifies Sex Differences in Severity of Viral Infection
Dimitry Krementsov, Ph.D., Associate Professor, Department of Biomedical and Health Sciences, University of Vermont

This study aimed to address the variation in disease severity during infection with influenza A virus, which annually causes significant morbidity and mortality and occasionally leads to pandemics. The study explored why some individuals experience mild symptoms while others require hospitalization or even succumb to the disease. Factors influencing this variation include the genotype of the virus and host intrinsic factors such as biological sex, age, and pregnancy. An underexplored research area is host genetic variation. The study focused on the interaction between host genetic variation and biological sex, noting that females typically exhibit more severe disease because of an overactive inflammatory immune response, a phenomenon observed in both humans and experimental animal models such as mice.

Previous research has largely relied on a single mouse strain, C57BL/6 (B6), which limits the understanding of genetic diversity. To overcome this limitation, the study employed wild-derived strains of mice, such as PWD, and created consomic chromosome substitution strains by crossing B6 and PWD mice. These models enabled the localization of genetic effects to specific genome regions. The study involved infecting 27 consomic strains, covering the entire genome, with a high dose of influenza A virus to examine morbidity and mortality outcomes.

The results demonstrated that disease severity was more pronounced in female mice, mirroring observations in humans. Adjusting the virus dose equalized morbidity and mortality rates between male and female B6 mice, facilitating a more comprehensive analysis. Among the 27 strains tested, significant

genotype-by-sex interactions were observed in two strains, involving portions of the PWD chromosome 5 and a segment of chromosome X on a B6 background. Notably, a male-specific genotype effect was identified in the X chromosome segment ChrX.3 and chromosome 5.

Further investigation into the mechanisms revealed an elevated viral load in males with the ChrX.3 genotype, though this was not significant in females. Whole lung transcriptomics identified differentially expressed genes between genotypes and sexes, notably highlighting *Toll-like receptor 13* (*TLR13*) and *Slc25a53* as potential mediators of these effects. The study concluded that natural genetic variation in the host could modify the impact of biological sex on influenza severity, with variants on the X chromosome playing a pivotal role. These findings hold promise for extending our understanding to humans, potentially leading to more targeted and effective treatments based on genetic profiles.

Maternal Health and Lifestyle During Pregnancy and Offspring Brain Development
Xiawei Ou, Ph.D., Professor of Radiology and Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Research Institute

Over the past decade, significant advancements in neuroimaging have revolutionized our understanding of the developing brain, particularly through the use of advanced magnetic resonance imaging (MRI) techniques. MRI scans can now be conducted on fetuses, neonates, and young infants without sedation, enabling the acquisition of high-quality data for a comprehensive evaluation of both brain structure and function. These advancements provide unprecedented opportunities to study the developing human brain.

Advanced MRI techniques can now detect the effects of various prenatal factors on brain development before any symptoms manifest. This study has shown that maternal mental health during pregnancy significantly impacts offspring brain development. Functional connectivity, which measures synchronization between different brain regions, demonstrates a negative relationship with maternal depression symptoms during pregnancy. Additionally, maternal anxiety and depression are correlated with changes in the offspring's white matter development, which is crucial for neural signaling and overall brain development.

This study also indicates that maternal physical health and lifestyle, such as BMI and physical activity during pregnancy, influence offspring brain development. Babies born to obese women exhibit significantly lower cortical thickness in multiple brain regions, particularly in the frontal lobe, which is important for executive functions. Conversely, higher maternal physical activity during pregnancy is associated with increased cortical thickness in specific brain regions, especially during the first trimester. These findings highlight the significant impact of prenatal factors on early brain development. Future research aims to further characterize how these factors shape brain development, explore the underlying mechanisms, and evaluate interventions to prevent or reverse negative impacts. Additionally, efforts will be made to develop deep neural networks and employ machine learning to predict neurodevelopmental outcomes based on neuroimaging features.

Targeting Fusin Axis in Endometriosis-Associated Ovarian Cancer
Nalini Santanam, Ph.D., M.P.H., FAHA, Professor, Marshall University

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissue outside the uterus, primarily in the peritoneal cavity or ovaries. This disease affects 10% to 15% of women of childbearing age, with more than 200 million women suffering worldwide. Endometriosis increases the risk of several other diseases, including cardiovascular disease and cancer. Although considered benign, the disease exhibits hallmarks of cancer. A 2012 study in the *Lancet Oncology* confirmed an association between endometriosis and increased risk of specific ovarian cancers, but the mechanisms remain unclear.

This study has shown that peritoneal fluid from endometriosis patients can increase the proliferation and migration of human ovarian carcinoma cells. This fluid also increases the expression of *EZH2* and H3K27me3, components of the PRC2 epigenetic complex, and raises levels of inflammatory markers, notably the chemokine receptor CXCR4. The CXCR4/CXCL12 axis (Fusin axis) is involved in tumor growth and migration, and CXCR4 is epigenetically regulated by *EZH2*.

Experiments have demonstrated that blocking the Fusin axis with the CXCR4 antagonist AMD3100 or the selective EZH2 inhibitor EPZ6438 decreases the proliferation and migration of TOV-21G cells. Combining both drugs completely inhibited CXCR4 expression, suggesting that peritoneal fluid increases cell proliferation and migration by modulating the Fusin axis. Blocking this pathway could potentially prevent these effects.

Future research aims to determine whether CXCR4 regulation by *EZH2* is direct or indirect and to validate findings using 3D organoids. Further research is crucial to develop early diagnostic and treatment options for endometriosis and mitigate associated risks of cardiovascular disease and cancer.

A Pilot Study on the Impact of the BumptUP® Mobile App on Physical Activity During and After Pregnancy
Rachel Tinius, Ph.D., ACSM-EP, FACSM, Associate Professor of Exercise Science, Western Kentucky University; CEO, BumptUp® Labs

Maternal morbidity and mortality are significant concerns globally, exacerbated by preexisting conditions such as obesity, which can lead to complications such as hypertension and glucose intolerance during pregnancy. Mental health issues also pose risks during and after pregnancy. Recognizing the potential for lifestyle interventions to mitigate these risks, the BumptUP® mobile app was developed. Designed with input from pregnant women, postpartum women, and obstetric providers, the app aims to promote physical activity in populations in which adherence to exercise guidelines is typically low.

In this pilot study involving 38 women, participants were randomly assigned to either use the BumptUP app or receive alternative education as a control. The study monitored participants from mid-pregnancy through 12 weeks postpartum, assessing outcomes such as objective physical activity levels via

accelerometers, dietary habits, weight management, blood pressure, clinical measures, pregnancy symptoms, self-confidence in exercise, barriers to physical activity, and levels of anxiety and depression. While the pilot study's sample size limited statistical significance, trends indicated that app users were better able to maintain moderate-to-vigorous physical activity levels compared to the control group. Significant improvements were observed in self-efficacy for exercise among app users, who maintained confidence in their ability to exercise throughout late pregnancy and into the postpartum period. These promising findings suggest that the BumptUP app holds potential in promoting physical activity and supporting maternal health. Further validation through a larger clinical trial is currently under way, supported by a Small Business Innovation Research grant aimed at refining and expanding the app's impact.

## A Need for More Than Tele-Text in Postpartum Hypertensive Women
Kedra Wallace, Ph.D., Associate Professor, Department of Obstetrics and Gynecology, University of Mississippi Medical Center

Maternal morbidity and mortality, especially in the postpartum period, are significant concerns in the United States, where approximately 60% of maternal deaths occur during this critical time. Hypertension is a major contributor to these fatalities, complicating pregnancies and underscoring the need for diligent postpartum blood pressure monitoring to prevent emergencies.

In response to these challenges, this study created a program focused on postpartum blood pressure monitoring. This study aimed to enhance patient education and encourage attendance at postpartum visits, essential for monitoring maternal health following childbirth. Because internet access is unreliable in Mississippi, the program opted for text messaging as a communication method instead of mobile apps. Drawing from successful strategies such as those in the Systematic Treatment and Management of Postpartum Hypertension (STAMPP-HTN) trial, the program specifically catered to women who had encountered hypertension during pregnancy.

The study enrolled 250 participants and evaluated their understanding of hypertension management through pre-education assessments and educational materials delivered via video and handouts. Participants were trained to monitor their blood pressure at home and report results via text messages over a 6-week period. Although participants showed some improvement in hypertension knowledge, overall awareness levels remained modest. Of note, although text engagement was robust, many women expressed a desire for more social interaction beyond study-related texts, revealing unmet social needs.

Despite these efforts, the study did not observe a significant increase in postpartum visit attendance, with approximately 77% of women attending scheduled visits, consistent with previous trends. Alarmingly, 17 participants experienced postpartum hypertensive complications necessitating hospital readmission, prompting ongoing retrospective analyses to compare outcomes with previous years lacking such interventions.
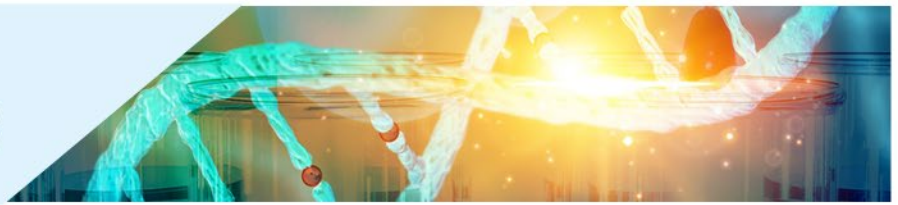
In response to these insights, the program has expanded its scope to include health literacy interventions using randomized trials and artificial intelligence tools such as ChatGPT. These enhancements aim to empower women by improving their understanding of health information and fostering proactive health management beyond pregnancy.

Looking ahead, addressing social needs and enhancing health literacy are pivotal steps toward improving maternal health outcomes, particularly in regions with limited health care access such as Mississippi.

Discussion

What inspired your research focus on women's health within the IDeA States, and what motivated you to pursue administrative supplements for research on women's health in these states?

Dr. Day noted that the decision to apply was largely motivated by a student's interest in bridging nanomedicine research and maternal fetal health. The student's enthusiasm and initiative provided the catalyst for launching the team's project, illustrating the significant impact that student-driven research can have on advancing scientific collaborations and addressing critical health issues.

Dr. Rivera explained that following the completion of the Baby-Act Trial, which centered on lifestyle interventions, researchers became intrigued by the potential impact of the pandemic lockdown on infant growth and maternal health during the postpartum phase. To delve deeper into this area, the team decided to introduce an additional observational arm to assess how managing routine care during pandemic events influences health outcomes.

Could you describe the institutional review board (IRB) process, especially concerning research involving the Indigenous community and the vulnerable population of pregnant women?

Dr. Harville clarified that her team's study primarily involved secondary data and did not require direct interaction with pregnant individuals during the research phase. The study was overseen by IRBs representing the involved Tribes and a joint coordinating center. These IRBs rigorously ensured adherence to ethical guidelines, specifically focusing on safeguarding Indigenous communities and their data.

How do your research findings impact women's health outcome in the IDeA States?

Dr. Krementsov emphasized that influenza virus has consistently been associated with more severe disease in women than in men, prompting an exploration into whether this pattern holds universally or is influenced by human genetic diversity. Emerging evidence indicates that genetic variations among individuals may indeed influence the susceptibility to severe influenza outcomes based on gender. This finding underscores the need for additional experimental research prior to any clinical implications. Understanding these genetic factors could potentially clarify the diverse responses individuals have to influenza infection, thereby enhancing our understanding of disease variability.

Dr. Santanam stated that endometriosis is highly prevalent among women and is characterized by its chronic nature, impacting a woman throughout her life from a young age to menopause. Despite its widespread impact, research funding for endometriosis has historically been limited. However, the disease's broader implications are increasingly acknowledged, given its association with heightened risks of other diseases. Diagnosis of endometriosis is notoriously difficult, and effective treatments are lacking, underscoring the urgent need for advancements in understanding and managing the condition. Addressing these challenges could potentially reduce associated risks such as mental health issues and other chronic diseases, emphasizing the importance of early intervention and research efforts to improve outcomes for affected women.

What strategies are effective for recruiting and retaining minority women in research or health care programs?

Dr. Rivera emphasized that maintaining continuous communication and providing a robust support system for participants were pivotal factors. The strict lockdowns enforced during the COVID-19 pandemic necessitated offering additional tools to help participants manage their transitions in care, particularly with the shift to remote health care services.

Dr. Wallace highlighted that her team benefited greatly from ongoing relationships with repeat patients, particularly among pregnant women in Mississippi. Over the years, researchers have built strong connections with these women, forming a community that is actively engaged and communicative. This long-term approach has fostered a high level of trust and a solid rapport with the population.

Can mobile apps transmit data to a patient portal, enabling providers to read urgent text messages and guide patients on what to do?

Dr. Wallace noted the challenges of using mobile apps, given that many hospitals in Mississippi still rely on paper-based systems instead of electronic medical records. In the original study, maternal-fetal medicine fellows directly contacted individual doctors, with women consenting to this communication with their referring doctors, enabling one-on-one interaction. For future sustainability and to reduce the workload on study participants, integrating this communication system is essential.
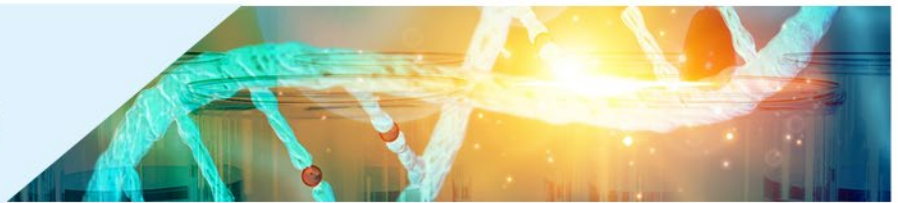
Scientific Session #2
Administrative Supplement Awardee Presenters #9–16

Maternal and Neonatal Outcomes in Women with Metabolic Syndrome and Substance Use Disorder
Usha Murughiyan, M.D., Assistant Dean of Clinical Research, Medical Director Clinical Trials, Marshall University

West Virginia, located entirely within Appalachia, grapples with significant health care disparities, including obesity and substance use disorders, often complicated by metabolic syndrome. Pregnancy exacerbates these risks, increasing the likelihood of conditions such as gestational diabetes and preterm

labor. Despite the prevalence of these issues, little prior research had focused on the outcomes for pregnant women experiencing both metabolic syndrome and substance use disorders.

To address this gap, this retrospective cohort study examined 27,955 pregnant women from January 2010 to November 2021. Participants were categorized into four groups based on their health conditions: metabolic syndrome alone, substance use disorder alone, both conditions concurrently, and a control group without either condition. Variables such as age, BMI, smoking history, alcohol use, and pregnancy complications were analyzed.

The study revealed notable findings, including a high prevalence of obesity (34.5%) and a history of opioid prescriptions (46%) among participants. Pregnant women experiencing both metabolic syndrome and substance use disorder demonstrated significantly elevated odds of complications such as preeclampsia and preterm labor compared to those with either condition alone or the control group. The researchers concluded that while metabolic syndrome on its own posed substantial risks during pregnancy, the combination with substance use disorder magnified these risks even further.

These findings highlight the critical need for comprehensive management strategies targeting both metabolic syndrome and substance use disorder through counseling and clinical interventions during pregnancy in Appalachia. Addressing modifiable factors such as insulin resistance and hypertension promptly could potentially mitigate adverse health outcomes in this vulnerable patient population.

Direct Impact of Mental Stress Triggered by Confinement on the Female Heart and Its Long-Term Cardiac Effects

Diana Cruz-Topete, Ph.D., Associate Professor of Molecular and Cellular Physiology, Louisiana State University Health Sciences Shreveport

Exposure to chronic or acute stress has been strongly linked to adverse cardiovascular outcomes. Following traumatic experiences, individuals may face an increased risk of heart attacks because of heightened psychological stress. Clinical evidence indicates that women are more vulnerable to the negative impacts of stress compared to men. This susceptibility is particularly pronounced in premenopausal women, who typically benefit from the cardioprotective effects of estrogen. Glucocorticoids, primary stress hormones released by the adrenal glands, exert their effects through binding to the glucocorticoid receptor (GR), which is widely expressed in various cell types throughout the body. Normal physiological levels of glucocorticoids are generally higher in women than in men, potentially contributing to women's heightened stress response. Research suggests that elevated glucocorticoid levels diminish estrogen's protective cardiovascular signaling, thereby increasing the risk of cardiovascular disease in stressed premenopausal women.

To explore these mechanisms, this study utilized a rodent model of mental stress involving repeated restraint sessions over a week. Following this stress induction, mice were subjected to ischemia-reperfusion to simulate a heart attack scenario.

Results revealed that female mice exposed to stress prior to ischemia-reperfusion exhibited larger myocardial infarct sizes and more severe morphological changes compared to non-stressed females and stressed males. Stress exposure also altered gene expression related to cell death and increased oxidative stress in female hearts, notably reducing Nrf2 levels, a key regulator of antioxidant responses. Additional investigations demonstrated that female mice lacking GRs in their cardiomyocytes were shielded from stress-induced effects, showing lower levels of superoxide compared to those with intact GR signaling.

These findings underscore the sex-specific impact of stress on cardiac health, highlighting how stress, mediated through the GR in cardiomyocytes, exacerbates myocardial infarction severity in females, particularly among premenopausal women.

Attenuation of Maternal Obesity in BPH/5 Preeclamptic Mice Prevents Cardiometabolic Risk in Female Offspring
Jennifer Sones, Ph.D., Associate Professor of Equine Reproduction, Colorado State University

Preeclampsia is characterized by sudden maternal hypertension and multi-organ dysfunction late in pregnancy. The metabolic mechanisms linking preeclampsia in women with preexisting obesity are not fully understood, yet offspring born to preeclamptic mothers face elevated risks of hypertension and obesity. This study aimed to explore how the maternal obesogenic environment impacts outcomes for both mother and offspring, predisposing them to cardiometabolic diseases. Specifically, the research investigated sex-dependent differences in cardiometabolic health, focusing on the role of the X chromosome and epigenetic modifications.

The study utilized the BPH/5 genetic mouse model, which exhibits superimposed preeclampsia and includes pre-existing hypertension in both sexes, with females additionally exhibiting preexisting obesity. By employing a pair-feeding approach to mitigate excessive caloric intake during pregnancy, researchers prevented gestational weight gain, thereby improving maternal and fetal outcomes associated with preeclampsia. The investigation extended into offspring development through adulthood, employing physiological and molecular analyses.

Key findings highlighted significant disparities in adiposity between male and female BPH/5 offspring. Female BPH/5 mice, under ad libitum feeding conditions, showed notably increased visceral reproductive white adipose tissue compared to males. Whole-genome bisulfite sequencing of adipose tissue identified differentially methylated regions on the X chromosome, with a focus on the androgen receptor. Hypermethylation of this receptor corresponded with reduced gene expression and elevated circulating testosterone levels in female BPH/5 mice across pre-pubertal to post-pubertal stages.

Furthermore, preventing excessive gestational weight gain in BPH/5 mothers led to reduced mass of reproductive white adipose tissue, lower leptin levels, and decreased inflammatory markers. These interventions also significantly lowered blood pressure in BPH/5 offspring. These outcomes suggest that controlling maternal gestational weight gain can mitigate maternal and fetal signs of preeclampsia and

enhance cardiometabolic health in offspring, possibly through epigenetic modifications on the X chromosome in both white and brown adipose tissues.

Explore a Heterologous Prime-Boost Vaccination (HetPBV) Strategy Against Chlamydia
Lin-Xi Li, Ph.D., Associate Professor, Department of Microbiology and Immunology, University of Arkansas for Medical

Chlamydia, the most common bacterial sexually transmitted infection worldwide and in the United States, poses a substantial risk to women's reproductive health, particularly affecting individuals aged 15–24. Despite its prevalence, a vaccine against chlamydia is currently unavailable. This study aimed to investigate how adaptive immune responses, specifically CD4 T cells, can provide protective immunity against this intracellular bacterium. The research focused on a prime/boost vaccination strategy utilizing viral and bacterial vectors—lymphocytic choriomeningitis virus (LCMV) and *Listeria monocytogenes* (Lm), respectively—to augment CD4 T cell responses.

In this study, various prime/boost combinations were evaluated in mouse models to identify the most effective strategy. Results demonstrated that heterologous prime/boost approaches involving the bacterial vector induced superior levels of protective immunity compared to homologous strategies or the viral vector alone. Notably, optimal protection was achieved when mice were primed with a viral vector followed by a boost with a bacterial vector, resembling traditional vaccination methods involving adjuvants and antigens. This heterologous prime/boost method shows promise in eliciting robust CD4 T cell responses crucial for defending against chlamydia infection.

The study leveraged advancements in single-cell RNA sequencing (scRNAseq) to analyze T cell phenotypes and T cell receptor repertoires, linking these characteristics with protective immunity. Insights revealed that the sequence of prime/boost administration profoundly influences the quality and phenotype of CD4 T cells generated. Future research directions include identifying specific gene signatures derived from CD4 T cell scRNAseq datasets that correlate with protective immunity, aiming to facilitate the development of an effective chlamydia vaccine.

Epigenetic Regulation of miRNA Expression and Biogenesis in Lactotrope Cells
Brian Cherrington, Ph.D., Associate Professor, Department of Zoology and Physiology, University of Wyoming

Peptidylarginine deiminases (PADs) are calcium-dependent enzymes known for catalyzing the conversion of positively charged arginine residues into neutrally charged citrulline on proteins. In the context of pituitary lactotrope cells, which produce prolactin crucial for lactation, PAD enzymes play a significant role through post-translational modifications that can alter protein charges, including histone tails, influencing chromatin structure and gene expression.

This study focused on elucidating how PAD-mediated histone citrullination regulates lactotrope cells during pregnancy, a period marked by estrogen-induced hyperplasia and increased prolactin production.

Key findings include the peak expression of PAD2 and PAD4 enzymes in lactotrope cells at pregnancy day 18 (P18), alongside elevated levels of citrullinated histones compared to earlier stages such as pregnancy day 12 (P12). Notably, results also suggest that estrogen stimulation directly regulates PAD2 expression. Further investigation revealed that PAD-catalyzed histone citrullination plays a pivotal role in modulating microRNA (miRNA) expression patterns. Inhibiting PAD activity reduces histone citrullination, thereby relieving repression on specific miRNAs (Let7c2, miR23b, miR29c) involved in regulating growth factors such as IGF-1.

Preliminary data from PAD2 and PAD4 double knockout mice highlight their lower prolactin levels and reduced pup weights compared to wild-type controls, underscoring the essential role of PAD enzymes in maintaining normal prolactin secretion and supporting offspring growth. The study concluded that estrogen-induced PAD expression leads to increased histone citrullination, thereby influencing miRNA expression in the pituitary gland. These findings emphasize the critical role of PAD enzymes in lactotrope function and reproductive health, particularly during pregnancy and lactation.

Mechanism of Tumor Suppressor Function of Progesterone Receptor in Breast Cancer
Motoki Takaku, Ph.D., Assistant Professor, Biomedical Sciences, University of North Dakota

Progesterone and its receptor (PR) are established biomarkers in breast cancer, where PR expression generally indicates a favorable prognosis. Despite its significance, progesterone's role in breast cancer is intricate and less studied compared to the estrogen receptor. Progesterone exhibits dual effects, both inhibiting and stimulating breast cancer cell growth, underscoring the complexity of its mechanisms. Previous studies on the luminal breast cancer cell line T47D have shown sensitivity to progesterone treatment. This study aimed to elucidate how progesterone inhibits cell proliferation in T47D cells. Genomic analysis indicated that progesterone and its receptor modulate miRNAs, which could be pivotal in restraining breast cancer cell proliferation. Examination of miRNA expression unveiled 41 differentially expressed miRNAs upon progesterone treatment, with significant overlap observed with differentially expressed messenger RNAs.

To identify miRNAs involved in cell cycle regulation, this study conducted clustered regularly interspaced short palindromic repeats (CRISPR) screening, highlighting key miRNAs for PR-mediated inhibition of breast cancer cell proliferation. These findings underscore the pivotal role of miRNAs in progesterone's gene regulatory mechanisms in breast cancer.

Targeting these specific miRNAs presents new opportunities for developing therapeutic strategies to augment the efficacy of progesterone-based treatments in breast cancer. Understanding the interplay between progesterone, PR, and miRNAs opens novel avenues for research and potential clinical applications in breast cancer management.

My Best Alaskan Life
Allex Mahanna, University of Alaska Anchorage

[My Best Alaskan Life (MBAL)](#) is a community-based participatory research initiative led by the University of Alaska Anchorage, designed to tailor a reproductive life planning tool specifically for Alaskan youth aged 14–26. This innovative project aims to address the high prevalence of sexually transmitted infections among Alaskan youth, including chlamydia, gonorrhea, syphilis, and HIV.

The centerpiece of MBAL is a self-guided digital health tool featuring an online module system enriched with resources and journaling opportunities. The tool encompasses five key modules: "All About You," "Healthy Relationships," "Your Body and Health," "Substance Use," and "What's Your Next Big Move?" Initiated in response to community concerns and guided by advisory boards composed of youth and community stakeholders, MBAL underwent development from 2019 to 2021. This period included the formation of advisory groups and the creation of a web-based survey platform, ensuring that content was not only relevant but also engaging for its intended audience. In 2022, the project conducted its initial pilot study to assess the feasibility, acceptability, and appropriateness of the MBAL tool among Alaskan youth across rural and urban areas. Valuable feedback from this phase prompted tool refinements.

Building on the insights gained, from 2022 to 2023, MBAL prepared for a statewide launch and initiated a second pilot study focusing on an older age group. This phase involved finalizing analytical tools, conducting recruitment efforts, and commencing data analysis. Results from these efforts indicated that the MBAL tool effectively met the needs of Alaskan youth, bolstering its feasibility, acceptability, and appropriateness across diverse demographics.

Looking ahead, the MBAL project team is enthusiastic about expanding the tool's reach and conducting further randomized studies to validate its effectiveness. The team plans to launch MBAL as a freely accessible statewide resource, empowering Alaskan youth with comprehensive information and support to make informed decisions about their reproductive health and overall well-being.

Microplastic Accumulation in Placentas from Adverse Pregnancy Outcomes
Men-Jean Lee, M.D., Chief of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, John A. Burns School of Medicine, University of Hawaii at Manoa

Plastics play a crucial role in everyday life but are also a significant source of pollution in air, water, and soil. Increasingly, concerns are mounting over the effects of plasticizers and other endocrine disruptors on pregnancy and human development. Recent research has shown a notable increase in microplastic particles found in human placentas from births in Hawaii spanning from 2006 to 2021. Specifically, the presence of plastics in archived placentas was 60% in 2006, rising to 100% in fresh placentas collected during the COVID-19 pandemic in 2021.

This study aimed to investigate whether the content of microplastics varies between complicated and uncomplicated pregnancies, and whether placental calcifications observed via ultrasound correlate with histopathological changes linked to conditions such as preeclampsia and fetal growth restriction. The methodology involved incubating archived placental samples with a pre-filtered 10% potassium hydroxide (KOH) solution for seven days to digest organic material. The digested sample was then filtered through a
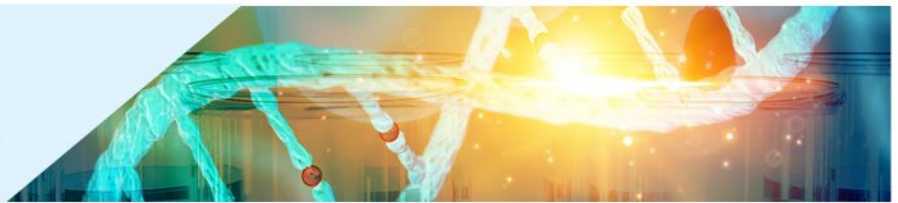
1.6 μm pore glass fiber filter to isolate microplastic particles, which were characterized using Raman spectroscopy and scanning electron microscopy.

Analysis of placental samples included 50 control placentas, 10 from pregnancies with fetal growth restriction, 10 from macrosomic pregnancies, and nine from pregnancies complicated by preeclampsia. Results indicated higher levels of polypropylene and hematite in macrosomic placentas, while pigment Yellow 82 was elevated in samples from fetal growth-restricted pregnancies.

The study suggests widespread contamination of microplastics, and preliminary data suggest that these particles can pass through the placenta from mother to fetus. Future research plans involve prospective placental collections and isolation of trophoblast cells to model and simulate the effects of microplastics on maternal and child health. The aim is to better understand the impact of environmental plastic pollution on women's health outcomes.

Discussion
How does your study integrate statistics on maternal deaths associated with substance use disorder during the postpartum period?

Dr. Murughiyan mentioned her team observed four cases of maternal mortality among pregnant women with both metabolic syndrome and substance use disorder. However, the data were inconclusive regarding the primary cause of death between metabolic syndrome and substance use disorder. Future research will involve collaborating with other institutions to further investigate the correlation between these conditions and maternal mortality in this patient cohort.

What are the feasible components of metabolic syndrome during pregnancy that can be easily modified, given the challenges of addressing BMI in cases of obesity? Do you plan to conduct prospective studies to investigate these modifiable factors?

Dr. Murughiyan highlighted a proposed clinical trial aimed at assessing the effects of managing hypertension, dyslipidemia, and diabetes on enhancing health outcomes for women in the study. Furthermore, the research team plans to offer counseling and regular blood screenings for substance use disorder, with the aim of evaluating the impact of these interventions on the health of pregnant women in future studies

What is your future direction regarding the substance use disorder population in West Virginia, particularly in terms of exploring or intervening in the outcomes of babies born from mothers with substance use disorder, such as neonatal abstinence syndrome?

Dr. Murughiyan noted that in West Virginia, substance use disorder presents a significant challenge, contributing to a substantial population of babies diagnosed with neonatal abstinence syndrome. Future plans include conducting a prospective study to assess not only the health outcomes of mothers affected by substance use disorder but also the health impacts on infants diagnosed with substance use disorder.

Are you interested in studying the outcomes of infants born to mothers exposed to microplastic contamination during pregnancy?

Dr. Lee discussed an ongoing study investigating microplastic presence in the placenta compared to the umbilical cord, exploring potential gradients at the placental interface. The study aims to determine whether the placenta selectively allows smaller particles to pass while retaining larger ones. Future investigations will assess the implications of plastic exposure on infant health. Collaboration with pediatric surgeons is planned to examine appendix specimens for microplastic accumulation, exploring a hypothesized link to appendicitis development from pregnancy through childhood. Moving forward, cell culture models will help clarify whether physical microplastic particles or leached chemicals induce inflammatory changes and impact childhood health outcomes. Despite progress, challenges remain because of Hawaii's isolation and limited recycling infrastructure, posing environmental concerns, particularly for women of Native Hawaiian and other Indigenous backgrounds.

How were the placental samples collected and stored?

Dr. Lee described the study's samples as archive specimens sourced from more than 9,000 placentas and umbilical cords dating back to 2006. These samples were stored in polypropylene tubes for long-term preservation. To mitigate potential contamination from these plastic containers, specimens from scheduled Caesarean sections in 2021 were collected using metal containers and instruments. Despite the use of plastic storage for archive specimens, only half of the archive samples contained microplastics, indicating minimal contamination. In contrast, all 2021 specimens, handled meticulously to avoid plastic contact, showed microplastic presence.

Closing Remarks
Michele McGuirl, Ph.D., Acting Director, Division of Research Capacity Building, National Institute of General Medical Sciences

The symposium featured a diverse range of research topics and methodologies, spanning omics-based studies, investigations using model organisms and human subjects, and collaborative efforts to enhance women's health research. A central focus was maternal health, emphasizing maternal self-care and its broader implications. Presentations underscored the challenge of obesity and the importance of early interventions against environmental toxins affecting maternal and fetal health. Additionally, technological innovations, such as mobile health tools, were highlighted for enhancing rural outreach.

To address challenges with outdated paper-based health records in clinics, ongoing transitions to modern electronic health record systems are supported by initiatives such as the [IDeA Clinical and Translational Research Network (CTR-N) Award program](#). These advancements align with the NIH Director's initiatives to integrate community-based primary care into research, highlighting the critical need for modern electronic health record systems.

The symposium concluded with gratitude to organizers, presenters, and supporters across NIH institutes, centers, and offices for their invaluable contributions to advancing research and health care practices.