Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) National Institutes of Health (NIH)

Inaugural Stakeholder Meeting for the Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating (PPL) Persons

Meeting Summary

July 9-10, 2024

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Meeting Summary

Purpose: This meeting, organized with NICHD's Office of the Director, Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), and Pregnancy and Perinatology Branch (PPB), will begin discussions on prioritization of drugs, vaccines, and dietary supplement research needs for use in pregnant, postpartum, and lactating (PPL) people. The effort directly addresses recommendations from the NICHD-led Task Force on Research Specific to Pregnant Women and Lactating Women to identify gaps in knowledge and needs and prioritize research on therapeutics for PPL persons.

Day 1: Tuesday, July 9, 2024

Welcome, Introductions, and Goals for Meeting

Camille Fabiyi, Ph.D., M.P.H. - Program Officer, OPPTB, NICHD
Diane Gumina, Ph.D. - Program Officer, PPB, NICHD
Alison Cernich, Ph.D. - Deputy Director, NICHD
Aaron Pawlyk, Ph.D. - Branch Chief, OPPTB, NICHD

Dr. Fabiyi welcomed participants to the Inaugural Stakeholder Meeting for the Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating Persons. She noted that the topics for this meeting directly address recommendations from the NICHD-led Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). She introduced Dr. Gumina, PPB Program Officer, and thanked her for her help in preparing for the meeting.

Dr. Cernich thanked the staff at OPPTB and PPB and the PRGLAC members who have been engaged in this work for several years. NICHD's mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all. This is reflected in its 2020 Strategic Plan's five research themes, three of which have particular relevance to this meeting: promoting gynecologic, andrologic, and reproductive health; setting the foundation for healthy pregnancies and lifelong wellness; and advancing safe and effective therapeutics and devices for pregnant and lactating women, children, and people with disabilities. NICHD is heavily invested in research to address the maternal morbidity and mortality (MMM) crisis in the United States. In addition to its broad and robust maternal health research portfolio and its data and network infrastructure, NICHD engages in partnerships both across NIH to advance

development and implementation of effective therapeutics and with external groups to help guide clinical recommendations that providers need to deliver care.

In coordination with the National Institute of Nursing Research (NINR) and the Office of Research on Women's Health (ORWH), NICHD co-leads the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative. The core principles of the initiative are reducing preventable causes of MMM, ensuring community involvement, focusing on implementation research, and addressing disparities. IMPROVE has funded 12 Maternal Health Research Centers of Excellence, issued a technology challenge for postpartum diagnostics and monitoring, built research infrastructure in communities, increased intervention uptake in community settings, and developed electronic health record (EHR) standards for pregnancy to enable real-world research. NICHD is also developing Common Data Elements (CDEs) for use in pregnancy studies in the Maternal Health Research Centers of Excellence. The CDEs are standardized, precisely defined questions, paired with a set of allowed responses to ensure consistency. They are currently in the first round of Delphi voting to prioritize constructs, and plan to share final recommendations by September 2024.

Dr. Cernich shared several NICHD maternal health research initiatives that are advancing the goals of PRGLAC, including the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub and the Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE) study. NICHD also leverages the following networks for MMM research: the Maternal-Fetal Medicine Units (MFMU) Network; the Neonatal Research Network (NRN); and the Global Network for Women's and Children's Health Research. The Institute is also advancing research through the NICHD Data and Specimen Hub (DASH), a centralized resource for researchers to share de-identified data from NICHD-funded studies.

NICHD has also used public-private partnerships to accelerate and sustain maternal health research efforts. One example is the Azithromycin-Prevention in Labor Use Study (A-PLUS), which partnered NICHD's Global Network for Women's and Children's Health Research with the Bill & Melinda Gates Foundation and the Foundation for the National Institutes of Health (FNIH). The A-PLUS Study was stopped early due to clear maternal benefit when it found that a single dose of azithromycin can reduce the risk of postpartum sepsis and death by one-third. NICHD is also working with FNIH to look at biomarkers for risk stratification and detection of early-onset preeclampsia.

Due to historical exclusion from clinical trials, researchers and clinicians do not have a good understanding of how disease pathophysiology may differ in pregnant and lactating people, and evidence for safety, efficacy, and dosing of medicinal therapies for these individuals is severely lacking, which complicates their medical decision-making. The PRGLAC Task Force addressed these issues in its 2018 Report to Congress by recommending the inclusion of pregnant and lactating people in clinical research, as well as the expansion of the workforce of clinicians and researchers with expertise in obstetric and lactation pharmacology and therapeutics. Dr. Cernich noted that public-private partnerships and international collaborations will be necessary to advance the 15 recommendations included in the 2018 report. Partnership is also

critical in changing the existing culture to protect pregnant and lactating people and their fetuses through research, rather than from research.

Dr. Pawlyk highlighted this meeting's central issue, which is that physicians and patients must often make decisions on drug, dietary supplement, and vaccine use without rigorously conducted regulatory studies and approval. Although approximately 60% of pregnant and lactating people take one or more prescription medications for pre-existing or pregnancy-induced conditions, approximately 90% of clinically approved medications do not have appropriate drug labeling information for this population. Dr. Pawlyk noted that two of PRGLAC's recommendations focused on the need for a prioritization process. NICHD has charged OPPTB and PPB with developing this process, expanding on OPPTB's work with prioritization under the Best Pharmaceuticals for Children Act (BPCA). The MPRINT Hub also addresses several of PRGLAC's recommendations, as well as aspects of the BPCA mandates, and has the potential to play a pivotal role in the next round of prioritization for pregnancy and lactation.

NICHD and ORWH published a Request for Information (RFI) on prioritization to address the changes that have occurred since the inception of the BPCA prioritization process in 2004. The information collected through this RFI helped assess the landscape of needs, engage key stakeholders, incorporate new data sources and analytical approaches, consider integrating new processes, and discuss who would use a list of therapeutics priorities. Congress has not authorized any new programs specifically focused on therapeutics in response to the PRGLAC recommendations, and NICHD is focusing on leveraging existing programs for the study of existing medications using existing approaches to prioritizing research. Dr. Pawlyk gave specific examples of prioritizing research needs for existing medications: if there is not sufficient pharmacokinetic (PK) data about Drug X during pregnancy to design a large, controlled trial, then obtaining PK data is a priority research need for Drug X and could be achieved via opportunistic studies. If there is a significant amount of PK data on Drug Y during pregnancy and real-world evidence suggests positive outcomes for mothers and newborns at higher doses with no safety signal, a pivotal randomized controlled trial (RCT) is a priority research need to assess the efficacy of Drug Y. He also gave examples of discussions that NICHD did not want to engage in during this meeting, such as designating Drug Y as a higher priority to study than Drug X, or prioritizing the development of a new drug for a condition that does not currently have any drugs. Following this meeting, NICHD anticipates soliciting suggestions for revision of the prioritization framework, establishing working groups to discuss all therapeutic areas, and expanding available curated knowledge on the MPRINT Hub. Ultimately, these efforts will result in the release of an initial list of priority research gaps for drugs, vaccines, and dietary supplements for PPL persons.

PRGLAC Overview: History and Current Status

Emma Carpenter, Ph.D. - Health Science Policy Analyst, Office of Legislation, Public Policy, and Ethics, NICHD
Leyla Sahin, M.D. - Deputy Director for Safety, Division of Pediatrics and Maternal Health, U.S. Food and Drug Administration (FDA)

Dr. Carpenter provided an overview of PRGLAC's history, the PRGLAC Implementation Working Group of the National Advisory Child Health and Human Development (NACHHD) Council, and the status of several PRGLAC recommendations. PRGLAC was formed in 2016 via the 21st Century Cares Act and was led by NICHD, with representation from multiple sectors. The committee developed a Report to Congress in 2018 and an Implementation Plan in 2020 before its charter expired in 2021. The PRGLAC Implementation Working Group was established under the 2023 Consolidated Appropriations Act and reports to the NACHHD Council. The working group's objectives are to review publicly available materials pertaining to implementation progress, invite speakers from relevant federal agencies or non-federal entities to discuss progress on the implementation plan, report their findings to the NACHHD Council, and ultimately submit a report to Congress.

The working group used a cluster format to group their recommendations around common themes; these were discussed at three stakeholder meetings held between November 2023 and March 2024. Five overarching themes emerged: 1) distinguishing between pregnancy and lactation; 2) assigning clear ownership over recommendations; 3) engaging multiple, diverse stakeholders; 4) requiring additional resources and congressional action; and 5) continuing assessment of implementation progress. Dr. Carpenter shared several examples of recommendation subparts that had been implemented, some that were in progress, and others that have not yet been implemented. She noted that the two subparts that formed the basis of this meeting have been implemented: 8B, Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women; and 9A, Create separate prioritization processes for pregnant women and lactating women. The working group is currently working to finalize their progress report, which the Council voted to accept at its June meeting, and it will be published and disseminated in late July.

Dr. Sahin spoke about the FDA's regulatory framework regarding pregnancy and lactation studies and FDA's efforts to address the PRGLAC recommendations. A recent FDA review of pregnancy safety postmarketing requirements showed that it took 11 years after approval of a new drug to update the labeling with human pregnancy safety data. Most of the FDA's pregnancy and lactation data collection activities occur in the postmarketing phase of the drug life cycle. This includes case reports and series published by healthcare providers, clinical trials of approved drugs that may be repurposed, opportunistic lactation studies, pregnancy PK studies, and observational studies. FDA can require pregnancy safety studies under the Federal Food, Drug, and Cosmetic (FD&C) Act and, historically, pregnancy registries have been issued as postmarketing requirements/commitments (PMRs/PMCs). Recently, two types of pregnancy PMRs have been issued in FDA's Center for Drug Evaluation and Research (CDER).

The FDA is involved in several efforts to advance the conduct of studies. These include publishing guidance for industry, conducting workshops and webinars, conducting outreach at scientific meetings, and collaborating with entities such as NICHD. Dr. Sahin provided several examples where FDA is addressing specific PRGLAC recommendations, including their collaboration with NICHD on BPCA lactation studies of off-patent drugs, an FDA Pregnancy Registry Public Workshop planned for March 2025, and several ongoing Pregnancy Safety Demonstration Projects. FDA will also hold a public workshop on Evaluating Immunosuppressive Effects of In Utero Exposure to Drug and Biologic Products on July 11 and 12, 2024. On the global scale, FDA is participating in the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E21 guideline working group. This working group includes global regulatory agencies and industry, and the purpose is to provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials.

Dr. Meg Grabb (National Institute of Mental Health (NIMH)) asked whether the FDA encourages companies to establish registries. Dr. Sahin said that FDA makes recommendations related to issuance of PMRs and pregnancy and lactation during the New Drug Application (NDA) review process, as part of discussions with applicants about what data are missing. Their recent policy is to issue a PMR for a database study as well as a pregnancy registry, as both study designs have their own strengths and limitations.

Overview of Nominations from the RFI and Prioritization Process

Camille Fabiyi, Ph.D., M.P.H

Under the recent RFI, NIH invited nominations of drug, vaccine, and dietary supplement research needs to be considered in the development of a priority list to advance PRGLAC recommendations 8B and 9A. A total of 136 nominations were received during the public comment period, which ran from May 8, 2023, through September 29, 2023. Dr. Fabiyi noted that many of the nominations had incomplete or unclear information and some nominators may have misclassified information in the nomination, highlighting the importance of the discussion and input received during this meeting to shape the prioritization framework. She presented a breakdown of the nominations by type (drug, vaccine, or dietary supplement) and condition category (general medical condition, pregnancy/postpartum-specific, or lactation-specific).

PRGLAC Recommendation 8B specifically recommended considering NIH's BPCA program as a model for developing a prioritization process for testing therapeutics in pregnant and lactating people. The BPCA legislation requires NIH, in consultation with FDA and experts in pediatric research, to develop a priority list of needs in pediatric therapeutics, establish a program for pediatric drug development studies (primarily of off-patent medications) and submit clinical trial findings to the FDA for drug label change consideration. The legislation also mandates the training of experts in pediatric pharmacology research. BPCA's prioritization process emphasizes three guiding principles: 1) a well-defined process that includes a systematic approach and clear objectives and outcomes; 2) well-defined objective criteria for measuring

priorities; and 3) a dynamic but legitimate and fair process that incorporates expert stakeholder input, transparency, and strong leadership. Unlike the BPCA program, the current efforts around prioritization of research needs for PPL people do not have legislative authority or associated funding. The BPCA has an established process for expert involvement and a dedicated research network (the Pediatric Trials Network or PTN). This process is still evolving within the PPL program, and it does not yet have a research network dedicated to the study of therapeutics in PPL persons.

Dr. Fabiyi summarized the objectives of this meeting. NIH is seeking input to identify pharmacological gaps and make prioritization decisions so that they are prepared to facilitate research i, as well as to address pharmacological gaps around existing medications and inform existing NIH research prioritization processes. This meeting will begin discussion with select drug nominations submitted as lactation and pregnancy-specific conditions due to their alignment with the NICHD mission, with plans to discuss the remaining drug nominations across all condition categories at future meetings.

Study Design for Research on Therapeutics in Pregnant and Lactating People, Part 1

CUDDLE Study

Kevin Watt, M.D., Ph.D. - Chief, Professor, Division of Clinical Pharmacology, University of Utah

Dr. Watt presented an overview of opportunistic studies in lactation, including the CUDDLE study. CUDDLE, which is sponsored by NICHD through the PTN, is an opportunistic study that enrolls lactating people who are already on one of several drugs of interest, with samples collected at the time of standard care visits. Participants can provide maternal breastmilk, maternal plasma, and/or infant plasma, and the study also leverages standard of care procedures like laboratory tests. The study began with 10 initial drugs of interest and an additional 12 medications are now open for enrollment. Drug selection criteria included knowledge gaps in the FDA label, frequency of use in the breastfeeding population, potential to cause harm to the infant, and other scientific priorities such as those aligned with BPCA. The primary outcome of the study looks at infant exposure using metrics such as milk to plasma ratio, total infant dose, and relative infant dose.

Dr. Watt shared study results for oxycodone, where researchers found that, even though oxycodone concentrates in milk at a 3:1 ratio, the daily infant dose was orders of magnitude lower than the dose that would be prescribed to an infant to treat pain. They were also able to simulate oxycodone exposure for various doses at the individual as well as the population level using a physiologically-based PK model, which confirmed their observed findings in the CUDDLE study. They submitted these data to the FDA, which resulted in a label change for oxycodone. Dr. Watt and Dr. Tina Chambers (University of California, San Diego) have also been working on an R21 opportunistic study that looks at collecting breastmilk samples in participants' homes, which could greatly increase the number of lactating people who can participate in these studies. The NIH R21 is an exploratory/developmental grant that supports exploratory and

developmental research projects by providing support for the early and conceptual stages of these projects.

Glyburide and Metformin Studies

Mary Hebert, Pharm.D., FCCP - Professor of Pharmacy, Adjunct Professor of Obstetrics and Gynecology; Director, University of Washington Obstetric-fetal Pharmacology Research Unit, Department of Pharmacy, University of Washington

Dr. Hebert spoke about study design in the context of her group's work with glyburide and metformin. In order to have the appropriate data to evaluate changes in PK and pharmacodynamics (PD), the group first had to conduct studies to evaluate glyburide enzymatic pathways and transport and metformin transport. After having done this, they expected both drugs to be altered by pregnancy. Their ideal comparator group was the non-pregnant population for which the drug is approved. They conducted extensive sampling for glyburide both in pregnant people with gestational diabetes mellitus (GDM) and non-pregnant people with Type 2 diabetes mellitus (T2DM), and found significant changes in the PK of the drug. In order to determine the impact on dosing, they used modeling followed by Monte Carlo simulations that found more than double the approved dosage would be needed for pregnant populations and non-pregnant concentrations to match. They also looked at potential gestational age-dependent changes with drugs that are used chronically, such as metformin. They performed intensive PK sampling in individuals who were taking 500 mg of metformin twice daily during early pregnancy, mid-pregnancy, and late pregnancy. In all three phases, the concentration time profiles were significantly lower than the control group of individuals who were three or more months postpartum.

Dr. Hebert noted that metformin has non-linear PK, and while they found that the peak for 1,000 mg of metformin twice daily in the pregnant population was comparable to 500 mg twice daily in the non-pregnant population, it did not mean that the starting dose should be doubled for pregnant individuals. She emphasized the importance of interpreting the data correctly, noting that recommendations have come out of this data that do not align with the results' actual indications. It can be helpful for clinicians to have a correlate with a clinical marker. In addition to PK, PD are important; when looking at drugs for treatment of diabetes Dr. Hebert's group examined the effects of pregnancy on insulin and glucose concentrations. Although GDM is similar to T2DM, they found significant differences in the ability of the pancreas to produce insulin in the setting of high sugars, indicating that the underlying condition is not the same. They included a healthy pregnant arm in their study to account for gestational age-dependent changes and saw a significant change in the overall disposition index between 30 weeks gestation and 36 weeks gestation. They looked at relative oral treatments being used at the time and found that metformin monotherapy brought patients closer to what's considered normal insulin sensitivity in pregnancy, while glyburide did not. They also looked at equal effects on clinical biomarkers, including glucose concentration. Following a mixed-meal tolerance test, patients receiving metformin monotherapy had significantly lower glucose Area Under the Curve (AUC) compared to pre-treatment, as did the combination therapy group.

Looking at fetal exposure, they found that the average umbilical cord to maternal concentration ratio was 0.7 and suggested that neonatal risks should be considered for dosage changes.

Tranexamic Acid (TXA) and Pravastatin Studies
George Saade, M.D. - Professor and Chair, Associate Dean for Women's Health, Obstetrics and Gynecology, Eastern Virginia Medical School

Rates of postpartum hemorrhage (PPH), a major cause of MMM, are increasing while therapies and preventative strategies are decades old. Trials have looked at TXA to treat PPH, which decreases bleeding and saves lives in the case of traumatic injury. Dr. Saade within the MFMU Network published a study in the *New England Journal of Medicine* in 2023 looking at TXA to prevent obstetrical hemorrhage after cesarean delivery. While they could not confirm the benefit of TXA in preventing maternal death or blood transfusion, they did see improvements in interventions in response to bleeding and in the change in pre- and post-operative hemoglobin levels. Incorporating pregnancy into their study design introduced several challenges. They wanted an outcome of clinical relevance, but this is rare in obstetrics, and longer-term follow-up for risk of thromboembolism added to the cost and study size. They also had to delay administration of TXA until cord clamping to avoid exposure to the neonate.

Similar to PPH, rates of hypertensive disorders of pregnancy (HDP) are also rising and a major cause of both maternal and perinatal mortality and morbidity, with a lack of innovative therapies. There is also a pronounced racial disparity in HDP. Dr. Saade's team at the University of Galveston in Texas studied the use of statins to prevent preeclampsia and found that pravastatin improved endothelial function and uteroplacental function in mice. They proposed a PKPD study to the Obstetric-Fetal Pharmacology Research Unit (OPRU) and obtained an Investigational New Drug Application (IND) from the FDA for a Phase I randomized trial. They found an 80% reduction in incidence of preeclampsia in the individuals who took pravastatin, a decrease in preeclampsia with severe features, and a decrease in indicated preterm delivery. Following this study they proposed a Phase III trial with the MFMU Network using pravastatin 20 mg and a composite primary outcome of preeclampsia, maternal death, or fetal loss. This study is currently on a partial clinical hold from the FDA until they can conduct further animal studies and analyze long-term outcomes in the offspring; however, a long-term neurodevelopmental follow-up study of children exposed to pravastatin in utero was conducted and significant negative effects were not observed.

Dr. Saade summarized several of the challenges in obstetrical trials: eligible patients are uncommon, screening and enrollment are expensive, a need for balance between efficacy and safety, clinically relevant outcomes are rare, and long-term follow-up is needed. All of these factors drive up cost and uncertainty, and the return on investment is small for drug companies due to the short duration of treatment and limited number of patients who will use the medication making large scale funding uncommon. Dr. Saade emphasized the need for solutions, similar to the Cancer Moonshot initiative, to overcome these challenges.

Real-World Evidence

Shaun Grannis, M.D., M.S., FAAFP, FACMI, FAMIA - Vice President, Data and Analytics; Regenstrief Professor of Medical Informatics and Professor, Family Medicine, IU School of Medicine
Chris Bartlett, Ph.D., MHA - Associate Chief Data Sciences Officer, Abigail Wexner Research Institute at Nationwide Children's Hospital; Professor of Pediatrics and Biomedical Informatics, The Ohio State University (OSU) College of Medicine

As defined by the FDA, real-world data (RWD) refers to data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, while real-world evidence (RWE) is clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD. Since 2005 there has been an increase in reliance on RWD/RWE in RCTs as well as externally controlled trials and observational studies. In the MPRINT Real-world Evidence Core, Drs. Grannis and Bartlett are using RWD to develop a hybrid deterministic and algorithmic method of identifying mother-child linkages. This method uses commonly available public health natality data, information from EHRs, and a machine learning method that utilizes demographic data.

While RWE is not the gold standard, it is timely and cost effective; it can be used to identify discrepancies in care, and to work with special populations. It also includes data on patients with multiple comorbidities and drug interactions, which are often excluded from RCTs, and RWE allows for the analysis of different dosing regimens as practiced in real-world studies, helping to optimize dosage recommendations. Dr. Bartlett presented an example of RWD where information on drugs prescribed during pregnancy, pulled from the OSU EHR, could be compared to the MPRINT Knowledgebase data to see what drugs are most often prescribed in the pregnancy interval and how often those drugs are studied during pregnancy and lactation intervals. This can allow researchers to identify real-world patterns, discuss possible new priorities, and find over-studied outliers.

Discussion

Ms. Julie Grimes (Lactation Education Resources) asked Dr. Watt if his team documents the stage of lactation for the milk collected during CUDDLE, and if they use any time intervals shorter than 24 hours in their at-home milk collection study. Dr. Watt said they do collect information about the lactation stage in CUDDLE, primarily as age of the infant or days postpartum. They were not able to get to a more granular level than 24 hours in the at-home condition study, but that would be fairly easy to do in a more in vitro way. Dr. Kaytlin Krutsch (Texas Tech University Health Sciences Center) asked if they looked at any lab work for mammary epithelial permeability in the course of their studies, and Dr. Watt explained they had not done this but acknowledged that it would be important.

Dr. Hebert asked if the FDA was requiring Dr. Saade's team to do further pravastatin studies before a Phase III trial because the drug company was not asked to do those studies before, or because they could not get the data from the drug company. Dr. Saade said that FDA would not share the data from the drug company, and his group did not have access to the past

developmental and reproductive toxicity (DART) studies. He argued that, regardless of those DART studies' results, they should be able to rely on the data that his group has collected through their own studies. They need to accept the fact that medications will be used in pregnancy before there is 100% certainty of safety, because 100% certainty is impossible to achieve.

Dr. Grannis asked if NICHD had a specific strategic plan related to RWD and RWE. Dr. Pawlyk said that one use the NIH is interested in is using RWD/RWE as a regulatory tool to address issues like the one that Dr. Saade brought up with pravastatin. NIH is developing a network to validate and qualify tools for regulatory use, and while NICHD is still exploring its place in those efforts, it will likely be involved in generating linkages and building partnerships. The NIH Common Fund is also starting the Complement Animal Research in Experimentation (Complement-ARIE) Program, which will include an in silico component with RWD.

Introduction to the Review of Drug Nominations within Therapeutic Areas

Overview of Review of Drug Nominations within Therapeutic Areas

Camille Fabiyi, Ph.D., M.P.H.

Dr. Fabiyi gave an overview of the review sessions which are intended to generate input on research needs for drug nominations within the therapeutic areas, with the aim of defining therapeutics and therapeutic needs and gathering data to identify knowledge gaps. Moderators and discussants will cover the background, research landscape or key literature, and proposed recommendations for each area. Following each presentation participants will engage in open discussion, guided by the following questions:

- What information is needed to make prioritization decisions for this area? (i.e., new report on the knowledge gaps, epidemiology, and current treatment option landscape; updates to a existing reports, workshops, or other modes of reaching consensus)
- What considerations are most important for determining topic and therapeutic prioritization? (i.e. severity of condition, population(s) impacted, time to impact, ethical considerations, etc.)
- What types of research infrastructure are needed to address the primary questions? (i.e. utilizing existing clinical trial networks, formation of new networks, retrospective reviews to guides on prospective study design, etc.)
- What types of studies are needed for this topic area (i.e., PK, efficacy, safety)?
- Are the drugs represented in the RFI nominations representative of the topic area and align with standards of care? If not, what is needed to assess missing therapeutics?

The Role of MPRINT Hub's Knowledgebase Portal and Pharmacoepidemiologic Analytic Capabilities in the Review of Drug Nominations

Lang Li, Ph.D. - Professor and Chair, Department of Biomedical Informatics, College of Medicine, The Ohio State University

Dr. Li presented an overview of the silver and gold versions of MPRINT Hub's Knowledgebase-Portal (KBP) and its pharmacoepidemiologic analytic capabilities. The silver version was generated by artificial intelligence (AI). An initial PubMed query using a series of key terms generated nearly 3 million maternal publications and 2.2 million pediatric publications. Dr. Li summarized the large language models (LLMs) and active learning methods that his group used to scan the PubMed abstracts and identify a total of 758,560 publications and 5,062 drugs. Users can conduct queries of the database by drug or more sophisticated queries by both drug and disease. The gold version of the KBP was manually curated and contains 252 drugs and a total of 2,573 publications screened from a pool of 7,966 abstracts.

Dr. Li's group has used the KBP to help identify knowledge gaps in a number of areas. They looked at the frequency of drugs studied from the BPCA priority list in the pediatric population since 2019 and found that out of a total of 157 drugs, only 31 had greater than 20 publications. They also sorted opioid PK studies, pharmacoepidemiology (PE) studies, and clinical trial (CT) publications by subpopulations and maternal pregnancy stages, and divided opioid PE/CT publications into different categories by outcomes and data sources to see how information on various topics was collected.

Dr. Li's institute also has access to the MarketScan Database, which draws from private insurance claims with over 58 million enrollees, including insured employees and their dependents. The database contains person-specific clinical utilization, expenditures, and enrollment information across inpatient, outpatient, and prescription drug services. Paid claims and encounter data can be linked over time across sites and types of providers, and there are 576,869 mom-baby pairs linked through family ID. Dr. Li acknowledged that family ID was a crude mechanism for linkage, but the data are still valuable for longitudinal studies. His group analyzed medication usage data in MarketScan to include in the silver version of KBP and calculated frequencies for five populations: 1) pregnancy, 2) postpartum, 3) infants younger than one year, 4) children 1-12 years, and 5) adolescents 12-17 years. They are also participating in a multi-institutional PE drug safety study. Using electronic medical record (EMR) data from these institutions, the study will investigate medication safety in maternal and pediatric patient populations, including approximately 800,000 linked mom-baby pairs.

Review Selected Nominations by Therapeutic Area

Low Milk Supply, Nutritional, Hyperemesis/Vomiting
Moderator: Andrew Bremer, M.D., Ph.D., M.A.S. - Director, Office of Nutrition Research, NIH
Discussant: Sara Quinney, Pharm.D., Ph.D. - Professor and Director, Disease and Therapeutic Response Modeling Program, Indiana University School of Medicine

Low Milk Supply

Background
Many lactating people perceive that their breastmilk supply is too low; a commonly cited reason for early cessation or decreased exclusivity in breastfeeding. Establishing, monitoring, validating, and quantifying milk production is very difficult, and it is often unclear whether milk production is insufficient, or if the problem with the breastfeeding process is insufficient stimulation. As of 2023, there are no FDA-approved medications to treat low milk supply. Eight nominations were received: any supplements directed to pregnant or lactating people to increase milk production; herbal supplements such as galactagogues for insufficient breastmilk; Mother's Milk Tea; shatavari; domperidone (nominated twice); galactagogues, herbs, and drugs (such as Fenugreek); and galactagogues (synthetic and natural).

Key questions still exist around the safety and efficacy parameters of herbal, pharmaceutical, and dietary supplements used as galactagogues, their benefits, and their effectiveness. There are knowledge gaps around studies on effectiveness and safety, predictors of insufficient milk supply such as biomarkers and polymorphisms, and underlying mechanisms of insufficient milk supply.

Research landscape/key literature
An MPRINT analysis of clinical trials, PE studies, and PK studies on milk supply showed that there is a lack of information on most galactagogues, many of the clinical studies that have been conducted lack stringency, and it is difficult to define clinical outcomes.

Discussion
Ms. Grimes noted the importance of asking which supplements mothers are actually using and which ones other countries have shown to be effective. The answers to these questions should help to inform priorities, dispel myths, and prop up research that has already been done. While Fenugreek has more studies than other supplements, it is controversial in the lactation space because of its side effects. Domperidone is studied more frequently outside of the United States and there is good evidence behind it, but it is not approved for use in the United States. Dr. Quinney agreed that turning to resources like the MotherToBaby helpline would be useful to ascertain which products are actually in use.

Dr. Hebert said that even if they are studied in the proper way, herbal supplements present challenges because often the information on the label does not match what is in the product. Dr. Pawlyk asked whether enough was known about milk composition to objectively address

outcome measures like biomarkers. Dr. Bremer said that in this era of omics, the medical and scientific community is better poised than ever before to answer important questions about the contents of human milk, the variability of milk composition among individuals, and the biological function of individual milk components. It is still difficult to quantify the amount of milk a baby is receiving, but if this could be done then milk volume could start being linked to composition and function. Dr. Quinney added that part of the issue with quantifying milk intake is the variability in how and when a baby is being fed, and this has implications when looking at the PK of various drugs.

Dr. Jennita Reefhuis (Centers for Disease Control and Prevention (CDC)) asked if it would be possible to identify the components of herbal supplements that are effective for lactation, making them more measurable and therefore easier for the FDA to regulate. Dr. Quinney said that for some herbal supplements there is synergism between multiple active constituents, and it may be difficult to tease out those dynamics. Dr. Krutsch said that her group heard a large number of requests for information from mothers and providers about herbal supplements. They also know that lactating people in the United States are using domperidone, and there is currently a Phase II trial for a deuterated version of the drug. Dr. Bremer noted that it is challenging but also very necessary to address the psychosocial elements and other maternal factors that influence human milk composition and production.

Dr. Saade said that regulatory agencies had an accelerated approval process that could incentivize more innovation, but this depends on the scientific community coming together to define clinical outcomes. Dr. Bremer said that from a milk composition standpoint, there is now an economy of scale of researchers who are asking those questions, and talking to regulators and investing in long-term studies is extremely important. Dr. Sahin said that it would be difficult to proceed with further study of domperidone, as the FDA has a strong stance that it should not be used due to its pro-arrhythmic properties. Dr. Krutsch said that what she found most concerning with domperidone use was the lack of consultation with providers, which makes it difficult to stratify risk.

Nutrition

Background

Iodine deficiency can lead to hypothyroidism and iron deficiency can result in anemia, both having negative health effects for mothers and babies. Vitamin supplementation is currently a commonly used therapeutic agent for nutritional support. The nominated agents are prenatal multivitamins/minerals with iodine (over-the-counter and prescribed) and prenatal vitamins.

Key questions concern evaluating iodine status in pregnant individuals and infants and assessment of nutritional status. Knowledge gaps exist around which nutrients should be considered for optimal health outcomes in pregnancy and infancy and the potential effects of contamination in dietary supplements.

Research landscape/key literature

The research landscape includes clinical trials and PE and PK studies, though these often focus on individual elements instead of taking a more holistic approach to nutrition. Dr. Quinney stated that it was important to understand how a person's diet informs which micronutrients they need and how much they should consume.

Discussion

Ms. Grimes suggested looking at iodine in lactation as well as in the prenatal context, as iodine levels in breastmilk are affected by the mother's diet. Dr. Jaime Gahche (NIH) said that the Office of Dietary Supplements (ODS) was interested in looking at prenatal vitamins holistically to study the best forms, absorption rates, and what is actually needed. ODS is hosting a prenatal workshop in 2025 to understand the nutrient requirements for a healthy pregnancy and which nutrients are helpful for certain health conditions. Dr. Daniel Robinson (Northwestern University) suggested that the nutrition model that has been developed for precision health could be appropriately applied in this area. Dr. Bremer said that precision medicine elevates the importance of nutritional assessments. The Nutrition for Precision Health study, powered by the *All of Us* Research Program, is currently still enrolling and is a model to capture deep phenotyping of the pregnant person, the lactating person, and the infant.

Dr. David Weinberg (NIH) emphasized the importance of clear messaging to the public, who are bombarded with disinformation about this topic, particularly from the internet. Dr. Quinney added that non-scientific clinicians are an important audience that does not currently receive this information. Dr. Hebert said that her group at the University of Washington has a paper under review that found that prenatal vitamins often do not match well with nutritional intake during pregnancy and lactation.

<u>Hyperemesis/Vomiting</u>

Background

The 2018 PRGLAC Report discusses nausea and vomiting in pregnancy, including in its most severe form, hyperemesis gravidarum, which has the potential to impact a pregnancy in harmful ways for mothers and babies. In addition to the nominated agents, doxylamine and pyridoxine (vitamin B6) are currently used for hyperemesis/vomiting. Dopamine antagonists, antihistamines, serotonin 5-hydroxytryptamine type 3 receptor antagonists, and steroids are also in the clinical guidelines. The nominations are growth differentiation factor 15 (GDF15)/glial cell line-derived neurotrophic factor (GDNF)family receptor alpha-like (GFRAL) inhibitors; and metformin. Dr. Bremer noted that GDF15 and GFRAL are used as antiemetics in oncology but have not been looked at in pregnancy and lactation.

Limited research is available on medicinal therapies for nausea and vomiting in pregnancy. Although supplement products may be widely used for these purposes, few studies have been reported on their composition, safety, or efficacy.

Discussion

Dr. Quinney noted that metformin can increase nausea as a side effect and the group who submitted the nomination hypothesize that giving metformin before pregnancy prevents nausea and vomiting during pregnancy, as those receptors have already been stimulated. The inhibitors are currently in Phase I clinical studies for cancer cachexia and nausea, but little is known about them at this point, and using them in pregnancy may be premature.

Mental Health
Moderator: Meg Grabb, Ph.D. - Program Officer, NIMH, NIH
Discussant: Matthew Rudorfer, M.D. - Chief, Psychopharmacology, Somatic, and Integrated Treatment Research Program, NIMH

Background
Although there is little data to establish whether medications for mental health disorders are safe during pregnancy, untreated mental illness may pose risks for both the pregnant person and the fetus. The decision of whether a pregnant person should take mental health medication during pregnancy is made on a case-by-case basis, taking into account the severity of the symptoms, their ability to take care of themselves, and whether or not they are able to go to OBGYN appointments. Overall, the data on psychotropics has not been conclusive as to potential harm to the infant, except with specific agents. The nominations for mental health are selective serotonin reuptake inhibitors (SSRIs); serotonin and norepinephrine reuptake inhibitors (SNRIs); bupropion; amphetamines; atomoxetine; guanfacine; benzodiazepines; hydroxyzine; buspirone; and gabapentin. The nominated agents include both specific drugs and large drug classes and fall into three therapeutic areas: 1) treatment of mood disorders, 2) treatment of anxiety disorders, 3) and treatment of attention-deficit/hyperactivity disorder (ADHD). Within each area, the amount and quality of data available for use in pregnancy and lactation are highly variable.

Research landscape/key literature
SSRIs and SNRIs (SRIs) are commonly used antidepressants, and the frequency of SRI use during pregnancy in the United States has increased by a third in the last decade. This has been extensively studied, but sample sizes have been small. A 2024 paper on SRI use in late pregnancy found an increased risk of delayed neonatal adaptation and a dose dependent relationship. Another study found evidence that tapering SRI dose to lower fetal exposure reduced NICU admissions, though the impact on maternal postnatal depression was unclear. The SSRI paroxetine has been associated with congenital malformations when used in the first trimester in two studies, while bupropion received reports of cardiac birth defects when used in the first trimester in a small sample.

In the category of mood stabilizers, lithium, which was formerly used to treat bipolar disorder, is widely regarded as safe in pregnancy, though it is contraindicated in nursing mothers due to risk of toxicity to the newborn. Carbamazepine, valproate, and lamotrigine were originally approved as anti-seizure medications and then for treating bipolar disorder. Carbamazepine and valproate are lithium alternatives and should be avoided in pregnancy due to risk of birth defects. Lamotrigine has not been associated with birth defects or pregnancy complications,

and typically requires dose increases during pregnancy, which are lowered after delivery. While it does enter breastmilk, no adverse effects have been seen in nursing newborns.

Brexanolone and zuranolone, both $GABA_A$ receptor positive modulators, have recently been approved for use in treating postpartum depression. While the FDA has endorsed the safety and efficacy of these approaches, their place in treatment protocol remains to be established.

Benzodiazepines can be used intermittently for episodes of anxiety, and they rapidly cross the placenta. Multiple studies have shown lower gestational age at delivery, lower birth weight, and slight to moderately higher risk of preterm delivery associated with use during pregnancy, primarily driven by exposure in the second and third trimester. There is no systematic data available for buspirone, hydroxyzine, or gabapentin, which are all non first-line anxiolytic agents.

Stimulants, the most commonly used drugs to treat ADHD, are of particular concern to infant health as they may impact neurodevelopmental outcomes and growth. A cohort study of Medicaid-insured individuals in the United States observed a small increase in the risk of cardiac malformations during exposure to methylphenidate in the first trimester. The same effect was not observed for amphetamines. Small studies have observed reduced serum prolactin in postpartum women treated with amphetamines.

Nominated agents guanfacine and atomoxetine are both non-stimulants, which are not first in line treatments, and there is currently no systematic data available on their reproductive safety.

Proposed recommendations

- In a clinical context, understanding patients and their mental health challenges during the perinatal period is important for developing optimal safe and effective use of pharmacotherapy options.
- Align with the standard of care.
- More medication registries; the lamotrigine registry in particular helped to establish the drug's safety for use in pregnancy.
- Case-control series, tracking the course of patients on medication throughout pregnancy (or portions of pregnancy) compared with patients who declined medication.
- More PK studies, tracking changes in medication concentrations across pregnancy. There is a particular research gap with regard to mood stabilizers.
- Benefits and risks of combination treatments (e.g., medication and psychotherapy).
- Consider diversity.
- Clinical research should not increase risk to participants; this should be taken into consideration in the timing of medications, timing of nursing, and tapering of medications.
- Follow neonatal health over time.
- Always consider benefit-to-risk ratio, including the risk of untreated mental illness for mothers and their babies.

- Mood stabilizers and atypical antipsychotics should be considered. Many of the latter now have FDA indications for use as adjuncts in depression and bipolar disorder, and were not included in the nomination list.

Additional discussion questions

- Are the examples in the RFI nominations representative of standard of care in psychiatry?
    - Should off label, occasionally used (not regarded as mainstream) drugs be considered? (e.g., intravenous ketamine?)
    - What disorders, drug classes, and drugs are missing?
- Given ethical considerations, what study designs should be prioritized? (e.g., tapering?)
- Would an intensified diagnostic process in patients with perinatal depression identify more cases of bipolar disorder, with implications for treatment?
- What is the role of device-based neuromodulation interventions during pregnancy, including transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and bright light therapy?

Discussion

Dr. Saade advised caution when looking at data that associates drug exposure to outcomes in children; most of this data comes from administrative data sets where it is difficult to know if the mother actually took the medication, for how long, and the outcomes in children are not rigorously assessed. It is difficult to account for all confounders, and researchers often do not adjust for multiple comparisons. Dr. Grabb agreed, stating that the intent of their presentation was to highlight the multiple gaps existing in this area.

Dr. Reefhuis said that there are case control studies that look at antidepressants and birth defects, and there are methodologies to analyze published studies, though they are not perfect. Studies looking at multiple designs, data sets, and countries are needed before making clinical decisions, but all epidemiological studies should not be discounted. She suggested venlafaxine as an additional medication for consideration; though the case control studies are small and have limitations, they have shown some association with birth defects. Dr. Rudorfer agreed and noted that, while non-pregnancy clinical studies are able to design efficacy trials to control for as many variables as possible, they do not have that luxury in studying people during pregnancy and postpartum.

Hypertensive Disorders
Moderator: Jasmina Varagic, M.D., Ph.D., FAHA - Program Director, National Heart, Lung, and Blood Institute (NHLBI)
Discussant: George Saade, M.D.

Background
Hypertensive disorders of pregnancy (HDP) include gestational hypertension, preeclampsia-eclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia. Preeclampsia is a new onset of high blood pressure (>140/90 mmHg) after 20 weeks of gestation with signs of damage to another organ system, typically kidney or liver. Delivery is the only cure for preeclampsia and may lead to neonatal morbidity and mortality. HDPs are very common in pregnancy in the United States, and all pose health risks for pregnant people and fetuses. In addition to immediate adverse effects, people with HDP are at risk of developing cardiovascular risk factors very soon after delivery, as well as full-blown cardiovascular disease in subsequent years. Current commonly used therapeutic agents for treatment of hypertension in pregnancy include methyldopa, labetalol, nifedipine, verapamil, clonidine, hydrochlorothiazide, and hydralazine. The nominated therapeutic agents for treatment of HDPs are labetalol, nifedipine, and Procardia XL (the extended release version of nifedipine). The nominations for prevention of preeclampsia are acetylsalicylic acid (aspirin) and statins.

Labetalol and nifedipine, first-line therapies for hypertension in pregnancy and postpartum, cross the placental barrier in humans, and are transferred through breastmilk. No evidence of fetal malformations were observed in animals that received several times the maximum human recommended dose of labetalol, though there are no adequate and well-controlled studies in pregnant people. Some non-teratogenic effects have been observed in infants of mothers who were treated with labetalol during pregnancy. For nifedipine, embryotoxic, placentotoxic, and fetotoxic effects were found in animal models when they received several times the recommended human dose, but there are no adequate and well-controlled studies in humans.

Aspirin is a nonsteroidal anti-inflammatory drug, and at low dose (81 mg/day), initiated after 12 weeks of gestation, is recommended by both the United States Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) for use in persons who are at high risk for preeclampsia. Aspirin does not significantly increase serious bleeding complications, and at a low dose is not excreted in breastmilk. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and some studies suggest they could be used in prevention of preeclampsia. They are found to cross the placenta in animal studies and may cause fetal harm when administered to pregnant patients. Pravastatin has a favorable safety profile, good PK properties, and was found to be present in human milk in one study. A series of case reports and observational cohort studies on the use of statins in pregnant people found no major congenital malformations. There is no information on the effects of statins on breastfed infants or milk production.

Research landscape/key literature

A 2018 Cochrane systematic review of 58 trials concluded that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension. The Chronic Hypertension and Pregnancy (CHAP) trial examined the safety and effectiveness of antihypertensive medication compared to no medication in pregnant women with chronic mild hypertension. Before this trial, chronic hypertension in pregnant people was only treated if the blood pressure exceeded 160/110 mmHg (severe hypertension), but the results from the CHAP trial showed that antihypertensive treatment with a blood pressure target below 140/90 mmHg leads to better pregnancy outcomes and has no negative effect on fetal growth. This led to immediate changes in ACOG's clinical practice guidelines. A recent small RCT compared labetalol to extended-release nifedipine in patients with persistent postpartum hypertension and found that both agents were effective, though labetalol had fewer adverse effects and achieved control more often with the starting dose. The Giant Pregnancy ANtihypertensive Drugs: which Agent is best? (PANDA) trial is currently ongoing in the United Kingdom; this is a pragmatic, open-label, multicenter, RCT in women with pregnancy hypertension which evaluates the effects of labetalol and nifedipine on maternal and fetal/neonatal outcomes.

There are still knowledge gaps about whether labetalol or nifedipine is safer and more effective, and the long-term effects of both in children. While most people are now using the extended release form of nifedipine, it has not been adequately studied in pregnant people. There is a need for research in the United States comparing labetalol and nifedipine, but an individualized approach may be more useful than a direct comparison. In addition to prevention of preeclampsia, interventions are needed to improve outcomes once preeclampsia has already developed.

A meta-analysis of the effectiveness of antiplatelet agents (mostly aspirin) performed by the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration found that antiplatelet agents produce moderate reductions in preeclampsia. The recent Aspirin Supplementation for Pregnancy Indicated risk Reduction In Nulliparas (ASPIRIN) trial in low- and middle-income countries found that low dose aspirin similarly reduced the risk of preterm birth, HDP, and perinatal mortality in women with and without additional risk factors. For statins, animal studies and human pregnancy exposure cohorts do not support previous teratogenicity claims. NICHD's Obstetric-Fetal Pharmacology Research Centers Network performed a series of pilot double-blind randomized trials using pravastatin as a prophylactic treatment in pregnant women at high risk for preeclampsia and found that the treated group had lower rates of preeclampsia and indicated preterm delivery and no identifiable safety risks.

With regard to aspirin's effectiveness in preventing preeclampsia, questions remain about whether aspirin should be given to all pregnant people versus only those at risk, and which dose is more effective, 81 mg versus 162 mg. For statins, there are questions around the efficacy in preventing preeclampsia, long-term effects on children exposed during pregnancy, and effects on breastfed infants.

Considerations for prioritization of research needs:

- HDP are carrying high risk for moms and babies.
- MMM in the United States is high.
- HDP is a significant contributor to MMM.
- HDP is associated with future cardiovascular disease (CVD).
- CVD is the number one cause of death for women in the United States.
- Lack of high-quality, large, RCTs focused on: 1) head-to-head assessment of antihypertensive drugs in pregnancy and 2) efficacy of statins to prevent preeclampsia in high-risk women and improve maternal and neonatal outcomes.
- Need for additional studies on the effect of hypertension medications on lactation and breastmilk
- Need to study statins viamaternal-fetal transfer, safety, and PK/PD studies.
- Potential of leveraging MFMU Network infrastructure.
- 2018 PRGLAC Report:
    - Need to establish more effective treatment/prevention strategies.
    - Substantial gap in the effect of hypertension medications on lactation and breast milk.

Discussion

Ms. Grimes said that she was surprised to hear a caution attached to using nifedipine during lactation, as it is used routinely and the amount present in breastmilk is only 2% of the pediatric dose. She expressed similar thoughts about the prohibition with statins and breastfeeding, as the relative infant dose of statins in breastmilk is 0.2%, which is much lower than the normal cutoff of 10%. She also noted that her organization advises against taking aspirin while breastfeeding due to the possibility of Reye's syndrome.

Dr. Quinney said that one thing missing from studies on labetalol and nifedipine is the effect of precision therapy and personalized therapy; some patients will most likely respond better to one medication than the other because of their different mechanisms of action, metabolic pathways, et cetera. Dr. Saade agreed that different patient populations would benefit from one versus the other. Dr. Quinney added that immediate release nifedipine is not used in any other population other than tocolysis of pregnancy, it has a short half-life, and it has a variable absorption pattern. She suggested looking at the nifedipine extended-release (XL) with more frequent dosing. Dr. Megan Clowse (Duke University School of Medicine) commented that many processes can lead to preeclampsia, including rheumatological conditions such as lupus. She encouraged the group to keep these other pathways in mind and think about different agents that might be able to interfere with them to prevent preeclampsia, such as immunosuppressant medications.

Cardiovascular

Moderator: Jasmina Varagic, M.D., Ph.D., FAHA

Discussant: Courtney Thornburg, M.D., M.S., Chief Medical Research Officer, Division of Blood Diseases and Resources, NHLBI

Background

Increasing incidents of arrhythmia in pregnancy have been noted in the United States over the past two decades. Maternal arrhythmias include supraventricular tachycardia (SVT), which is the most common arrhythmia during pregnancy; atrial fibrillation; and ventricular arrhythmias (VAs). Fetal tachyarrhythmia occurs in less than 0.1% of pregnancies; the majority of these are benign, but some can lead to adverse fetal outcomes. Beta-blockers are commonly used to treat SVT and VAs, with flecainide as a non first-line therapeutic. For fetal tachyarrhythmia, digoxin and flecainide are recommended. Flecainide is the nominated therapeutic agent for treatment of arrhythmia in pregnancy.

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism. The risk of VTE increases with pregnancy, and VTE is a leading etiology of preventable MMM. Anticoagulation is used to treat or prevent VTE before, during and after pregnancy, and commonly used anticoagulants include the low molecular weight heparin enoxaparin (given subcutaneously) and unfractionated heparin (given subcutaneously or intravenously). Rivaroxaban is the nominated therapeutic agent for treatment of VTE.

Flecainide is an antiarrhythmic medication that is safely used to treat maternal and fetal arrhythmias, with rare reports of neonatal cardiotoxicity, though there are no adequate and well-controlled studies in pregnancy. It is not known whether the use of flecainide acetate during labor and delivery has immediate or delayed adverse effects on the mother or fetus. Flecainide is excreted in human breastmilk in concentrations as high as four times the corresponding maternal plasma levels, and absorption into neonatal plasma is very low. Milk may inhibit absorption of flecainide in infants, so a reduction in dose should be considered when milk is removed from an infant's diet if it is used to treat arrhythmias in infants.

Rivaroxaban is a direct oral anticoagulant (DOAC) that decreases thrombin generation to prevent thrombus formation.

Key questions:

- Are more PK data needed to optimize treatment of fetal tachyarrhythmia with flecainide?
    - Considerations for placental transfer and accumulation in the amniotic fluid.
    - Optimal methods for measurement of fetal drug exposure.
- Are more data needed to define the fetal, maternal, and neonatal safety profiles?
    - Fetal echocardiography (ECHO) or fetal magnetocardiography (fMCG) could be optimal methods for measurement of flecainide efficacy and toxicity.

- Does flecainide have immediate or delayed adverse effects on the mother or fetus, affect the duration of labor or delivery, or increase the possibility of forceps delivery or other obstetrical intervention?
- Is rivaroxaban safe and effective in treating and/or preventing VTE in pregnancy? Is the PK/PD the same in pregnancy? Could anticoagulation lead to subclinical placental bleeding and associated complications?
- Is rivaroxaban safe and effective in treatment and/or preventing VTE in postpartum period? Is the PK/PD the same in postpartum period?
- Does rivaroxaban cross the placenta? If so, does it cause harm in the fetus such as teratogenic effects or bleeding, including intracranial hemorrhage?
- If a pregnant person is exposed to rivaroxaban, what should be the monitoring?
- If a pregnant person is on rivaroxaban at the time of delivery, what precautions should be taken? Considerations include risk of bleeding with epidural placement or Cesarean section and risk of post-partum hemorrhage.
- Does rivaroxaban cross into breast milk? If so, does it increase harm in the newborn/infant, particularly related to bleeding?

Knowledge gaps:

- Flecainide:
    - Lack of studies:
        - Limited PK studies.
        - No general guidelines on optimal dosing of flecainide and timing of discontinuation prior to delivery.
        - RCTs evaluating and comparing efficacy and safety of antiarrhythmic drugs for pregnant and lactating persons are needed.
            - Awaiting results of Fetal Atrial Flutter & Supraventricular Tachycardia (FAST) Therapy Trial for fetal arrhythmia.
    - When evaluating the risks and benefits of flecainide, how to account for effects of the underlying arrhythmia on fetal and neonatal outcomes.
        - It is often difficult to tease out outcomes related to the condition versus side effects of medication.
- Rivaroxaban:
    - VTE represents a wide range of conditions that can present as a pre-existing condition at the time of pregnancy or develop during pregnancy or in the postpartum period. Each condition and associated timing of presentation will have specific knowledge gaps.
    - It is known that rivaroxaban passes into breastmilk; currently available preclinical and incidental exposure data in pregnancy are very limited and insufficient to conclude safety of rivaroxaban in this population.
    - The limited available data on rivaroxaban in pregnancy are insufficient to inform a drug-associated risk of adverse developmental outcomes. Adverse effects have been seen in animal studies and reported in a few human case reports.

- There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production.

Research landscape/key literature

Much of the research landscape data for flecainide focuses on fetuses and infants. Case reports indicate flecainide is safe to use to treat fetal tachyarrhythmia, and that it penetrates the placental membrane easily without accumulation in fetal blood. Small observational studies of 14 women who were given flecainide for fetal SVT concluded that it should not be the first drug of choice for atrial flutter. A systematic review and meta-analysis comparing the efficacy, safety, and fetal-maternal tolerance of first-line therapies for fetal SVT and atrial flutter found that flecainide may be more effective than digoxin as a first-line treatment for fetal SVT. The prospective RCT of FAST RCT recently completed enrollment, though no results have been published yet. The study included 600 fetuses with SVT or atrial flutter from at least 70 centers. Flecainide concentration in human milk averages 2.5 times that found in maternal plasma, with a calculated infant plasma level that is negligible for a nursing infant.

The research landscape for rivaroxaban consists of animal studies, database reviews, pharmacovigilance reports, and case reports, with some case reports including drug concentration in breastmilk. As a DOAC, rivaroxaban is not considered safe for pregnant or lactating people, and multiple medical societies recommend against its use in these populations.

Considerations for prioritization of research needs:

- Flecainide:
  - Maternal and fetal arrhythmias are rare but could lead to significant maternal, fetal, and neonatal adverse events.
  - Flecainide is deemed relatively safe during pregnancy and lactation and used in clinical practice. Additional preclinical and clinical data could be used to optimize administration and clinical outcomes.
  - Future studies should consider routes of maternal fetal transfer to inform additional PK studies.
  - Better pharmacological and electrophysiological models could be developed and used to predict effects.
  - To garner more RWE, expand drug usage registries to accurately assess the clinical effects of antiarrhythmic drug treatment on both mother and fetus, including data during the breastfeeding period.
  - Conduct randomized trials evaluating the superiority in efficacy and safety of antiarrhythmic in pregnancy.
  - Leverage MFMU Network infrastructure.
- Rivaroxaban:
  - Consulting with experts in hematology, obstetrics, and perinatology to gather more information, specifically asking if there is additional rationale to study rivaroxaban further, given that is considered unsafe based on limited data.

- Consider multiple levels of efficacy and safety risks to the pregnant person, fetus, and neonate.
    - There are rare contraindications to heparin, as well as special populations with very high risk of thrombosis.
- Research infrastructure is needed.
    - Additional safety and efficacy data may come from RWE, including claims data, pharmacovigilance, and registries/cohort studies and PK studies to inform whether interventional studies may be safely pursued.
    - Investigators should consider available networks and FDA guidance.

Discussion

Dr. Saade noted that antiarrhythmic medications are supposed to treat the fetus without harming the mother, while anticoagulants are supposed to treat the mother without harming the baby. There is an opportunity to develop methods and formulations of these medications to either limit or facilitate their transplacental passage. Dr. Hebert asked if the DOACs should be studied further. Dr. Thornburg said that it was important to get more preclinical data in animal models to look at safety, both in terms of teratogenicity and bleeding risk, before embarking on any clinical trials. Dr. Reefhuis said that they need to prioritize finding a way to capture data on women who are on a drug and happen to get pregnant.

Day 1 Summary and Instructions for Day 2

Diane Gumina, Ph.D.
Camille Fabiyi, Ph.D., M.P.H.

Dr. Gumina summarized key points from the day's discussion. Dr. Fabiyi thanked the presenters and attendees for their time and adjourned the meeting at 4:33 p.m.

Day 2: Wednesday, July 10, 2024

Summarize Day 1 and Discussion

Camille Fabiyi, Ph.D., M.P.H
Diane Gumina, Ph.D.

Dr. Fabiyi welcomed participants to the second day of the meeting. Dr. Gumina summarized the presentations and discussions from Day 1. She noted that, while there were subject-specific discussions around the RFI-nominated therapeutics, some common themes emerged, including: the rigor of prior studies and how that informs the future of research; the possibility of a role for precision medicine; considering preconception health in studies; accounting for and including multiple comparisons; and rooting prioritizations in the standard of care.

Overview and Instructions for Remaining Nomination Review

Camille Fabiyi, Ph.D., M.P.H.

Dr. Fabiyi summarized the format for the nomination presentations and discussions. She thanked the moderators and discussants for their insight and expertise in organizing this meeting.

Review Selected Nominations by Therapeutic Area - Continued

Preterm Birth

Moderator: Monica Longo, M.D., Ph.D. - Medical Officer, Project Scientist, Maternal-Fetal Medicine Units Network; PPB, NICHD
Discussant: Maisa Feghali, M.D. – Assistant Professor, University of Pittsburgh

Background

A preterm delivery, also known as a premature birth, occurs when a baby is born before 37 weeks of pregnancy have been completed. Preterm deliveries can be categorized into different subcategories based on gestational age, including:

- Extremely preterm: Less than 28 weeks
- Very preterm: 28 to less than 32 weeks
- Moderate to late preterm: 32 to 37 weeks

Preterm delivery is the leading cause of neonatal morbidity and mortality and the most common reason for antenatal hospitalization. It accounts for 25-50% of cases of long-term neurologic impairment, cerebral palsy, breathing problems, feeding difficulties, and/or impaired vision or hearing. Current practice for preterm labor involves the use of tocolytic drugs to delay labor and allow for the administration of corticosteroids and magnesium sulfate and transport to a tertiary facility. Common medications to treat preterm birth include nifedipine and indomethacin; terbutaline can be used in acute settings, and magnesium is now used only for neuroprotection for 12 hours. These medications have limited effectiveness in preventing preterm birth and there is a lack of consensus on the optimal tocolytic drug to use, leading to variability in practice. There is a need for more research and evidence-based

guidelines to guide the use of these drugs effectively and safely. The nominated therapeutic agents for this category are hydroxyzine; aspirin; statins; azithromycin; novel synthetic progestin; progesterone; choline/phosphatidylcholine; and prenatal multivitamin/mineral (over-the-counter and prescribed).

Hydroxyzine use during pregnancy has been associated with an increased risk of preterm delivery, but some studies have found different results. One study found that hydroxyzine use during pregnancy was associated with an increased risk of preterm delivery. However, another study found no significant difference in pregnancy outcomes between women who were exposed to hydroxyzine and those who were not. Although the mechanism of action for aspirin is not fully understood, the ASPIRIN trial found that it reduced the incidence of preterm birth and perinatal mortality. Statins are used to treat high cholesterol and prevent heart disease, and in pregnancy they may increase risk of preterm labor. However, some studies suggest that they may help delay premature birth by reducing inflammation and uterine muscle contractions. Azithromycin is an antibiotic used to treat perinatal infection in preterm premature rupture of membrane (PPROM) or advanced cervical dilation. Novel synthetic progestin is another agent to be explored, especially given the FDA final decision ordering the withdrawal of approval for Makena (hydroxyprogesterone caproate). Vaginal progesterone can still be used, but it has not been well-studied for use to prevent preterm labor in women with prior preterm delivery. A series of dietary supplements were also nominated: choline/phosphatidylcholine, which have been studied for prevention of birth defects and preterm birth, have been shown to improve postnatal growth and neuro-cognitive development of infants; and prenatal vitamins/minerals, including vitamin D, vitamin C, iodine, calcium, iron, and folate.

Key questions:

- What are the best therapeutic options for efficacy and safety?
- What are the PK/PD and safety considerations?
    - Transfer of medication across the placenta
    - Transfer of medication across breast milk
    - Long-term neonatal/children follow-up
- Dosage and timing guidelines for administration.
- Route of administration leading to change in PK.

Research landscape/key literature

The research landscape includes several PK and epidemiology studies on progesterone, aspirin, folate, iron, and calcium. Progesterone has been the subject of the most clinical trials in this area, but there is still a significant limitation in understanding what other medications, vitamins, and supplements can be used to prevent preterm birth. Although the research literature on preterm birth is relatively large compared to other conditions covered in the 2018 PRGLAC Report, there is still limited scientific understanding of the underlying mechanisms. There is also a knowledge gap around PK, PD, and pharmacogenetic (PG) considerations specific to pregnant and lactating physiology.

Discussion

Dr. Feghali noted that in the clinical setting there is a distinction between spontaneous preterm delivery related to preterm labor or placental conditions and iatrogenic situations where preterm delivery is indicated, such as preeclampsia. The same medications and interventions would not necessarily apply to both of these scenarios. Dr. Saade emphasized the need to determine what outcome would be adequate to allow regulatory agencies to approve any medication preventing preterm delivery. Dr. Feghali agreed that clinical outcomes related to the success of preterm delivery prevention have varied significantly, and it has become harder to find effective therapies as the goals are moved with higher expectations. The population that is studied can affect these outcomes, as there are baseline differences in preterm delivery risk and recurrence.

Dr. Weinberg said that he did not hear enough compelling evidence to test any of the nominated agents, and the field needs to support more research on the mechanisms of action. He added that he would encourage the group not to treat preterm delivery as a single category, echoing Dr. Feghali's comments about clinical distinctions. Dr. Krutsch encouraged the group to reconsider the justification for excluding parents with preterm delivery from clinical lactation trials, because that population needs better information. Dr. Robinson said that he had expected to see the N-3 fatty acid DHA (docosahexaenoic acid) in the nomination list, as it has a strong foundation of literature for prevention of preterm delivery. Dr. Saade said that there were many other therapeutic agents for preterm delivery that were not on the nomination list. He added that better methods are needed to study pregnancy in utero prospectively, similar to the Human Placenta Project.

Ms. Becky Abbott (Society for Maternal-Fetal Medicine) said they needed to think about whether they are prioritizing obstetric research generally or helping to guide the decision-making process between clinicians and patients. Dr. Feghali said that part of the challenge with preterm delivery is that, because it is a pregnancy-specific condition, it is difficult to use interventions from other areas. In addition, the overall regulatory environment and the concern about research and pregnancy have negatively impacted the ability to evaluate interventions for its treatment and prevention. Dr. Reefhuis said that recurrence is a good starting point because they already know there is increased risk and inequity. Dr. Feghali said that the avoidance of intervention because of theoretical risk comes at the cost of exposure to active conditions with known risks. Studies that are well-organized and well-regulated can still allow for the protection of research participants while advancing knowledge of how to care for these patients. Dr. Krutsch commented that there is a push for more patient-centered research, and they need to make sure they are answering the questions that patients and lactation consultants are actually asking.

Dr. Quinney echoed earlier comments that the nominated agents are not the right drugs to study; instead they should be looking at medications that they already know have the potential to be effective. Dr. Longo asked how they could best reach out to get input about the right drugs to study. Dr. Quinney said that her group was using MPRINT to look at RWE on use of medications and trying to match that up with what is presented in the research. She also

suggested surveying clinicians directly. Dr. Krutsch said that organizations like InfantRisk and MotherToBaby are collecting data on what questions are asked, and this can complement the MPRINT data. Dr. Weinberg suggested that a study could look at why some people have severe adverse side effects to nifedipine while others do not, as this could be valuable from a precision medicine standpoint. Dr. Saade recommended continued focus on treatment or management to improve the outcomes for preterm neonates, as this is where they have been the most successful in the area of preterm delivery.

Infectious Disease

Moderator: Tara DeYampert, M.D. - Program Officer, Division of Extramural Research, NICHD
Discussant: Jeanna Piper, M.D. – Senior Medical Officer, Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID)

Background

Infections during pregnancy and lactation are common, and infectious diseases in pregnant women can cause substantial maternal and fetal morbidity and mortality. There is limited scientific information for pregnant women and their providers on how and whether to treat infectious diseases during pregnancy and lactation. Other than the well-documented risk of HIV transmission via breastmilk, there are few data available on the effects of infections and their treatment on breastmilk and lactation, as mentioned in the 2018 PRGLAC Report. The nominated therapeutic agents fall into three categories: HIV prevention and treatment (cabotegravir and lenacapavir); hepatitis C treatment (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir); and syphilis treatment (cefixime).

Multiple antiretroviral drugs are currently approved for treatment of HIV, and a few drugs approved for prevention. Cabotegravir has been approved by the FDA for treatment and prevention of HIV, with testing prior to starting its use. Lenacapavir has also been approved for treatment by the FDA and is under investigation for prevention. In June 2024, data from the PURPOSE 1 (https://www.purposestudies.com/purpose1/) study showed a significant reduction in HIV acquisition in cisgender women compared to oral pre-exposure prophylaxis (PrEP). Of the 133,000 estimated perinatal infections worldwide in 2022, 20% were due to acute infection during pregnancy or lactation. Perinatal transmission of HIV has decreased dramatically in the United States since 1995. HIV acquisition during pregnancy and lactation has a higher risk of perinatal transmission due to high viral loads from acute infection and late timing of diagnosis and treatment. Pregnancy and lactation also include physiologic changes that increase the risk of HIV infection if exposed.

In 2022, the CDC reported 67,400 estimated acute hepatitis C infections in the United States. Direct acting antiviral agents have cure rates greater than 95%, but access to diagnosis and treatment is low. Sofosbuvir/velpatasvir was approved by the FDA for treatment of hepatitis C, with ribavirine added for people with decompensated cirrhosis. A sustained virologic response was found in more than 90% of people across multiple clinical studies. Glecaprevir/pibrentasvir is also approved by the FDA and also has a sustained virologic response rate of greater than 90%. 15 million people of child-bearing potential have chronic hepatitis C, and perinatal

transmission occurs in 5-7% of pregnancies with active hepatitis C. There is limited data on the impact of hepatitis C on pregnancy, as well as the impact of pregnancy on hepatitis C, though there is evidence of increased risk of intrahepatic cholestasis of pregnancy associated with hepatitis C infection.

The CDC reported 203,500 new syphilis cases in the United States in 2022, which is a 79% increase from 2018. Maternal syphilis rates in the United States increased by 222% from 2016 to 2022. According to CDC guidelines, benzathine penicillin G is the preferred treatment for all stages of syphilis and the only treatment for syphilis in pregnancy. Outside of pregnancy doxycycline, tetracycline, and ceftriaxone may be used. Syphilis is associated with adverse birth outcomes, including stillbirths, neonatal deaths, low birth weight, and congenital syphilis. The majority of congenital syphilis cases are related to lack of adequate diagnosis and treatment during pregnancy. Cefixime was approved by the FDA in 1986 for bacterial infections and is currently being studied as an alternative treatment for syphilis in non-pregnant people.

Research landscape/key literature
Animal studies done on cabotegravir in pregnancy and lactation have shown generally reassuring results. Data is currently being collected in the Antiretroviral Pregnancy Registry and through International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) studies. The HIV Prevention Trials Network (HPTN) 084 pregnancy substudy is currently collecting safety and PK data from the original Phase III trial and the open-label extension study. Animal studies have shown negative results for reproductive toxicity of lenacapavir, but there is inadequate human data for safety evaluation. The excretion in human breastmilk is unknown, as is the impact of pregnancy and lactation on PK or efficacy in humans. Data is being collected in the Antiretroviral Pregnancy Registry and the PURPOSE 1 and 3 studies. There are gaps in knowledge for both cabotegravir and lenacapavir around the safety for fetuses and infants exposed via pregnancy and lactation, though data is currently being collected for both via registry and from ongoing clinical trials. Data is currently being collected on the impacts of pregnancy on PK and effectiveness for cabotegravir through clinical trials, but the same has not yet been done for lenacapavir.

Animal studies have shown negative results for reproductive toxicity of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, but there is inadequate human data for safety evaluation. Components of both drugs were detected in animal breastmilk, with unknown excretion in human breastmilk. Data is being collected for both agents in the Treatment in Pregnancy for Hepatitis C (TiP-HepC) Registry. The Hepatitis C in Pregnancy (HIP)-2 PK study of sofosbuvir/velpatasvir (SOF/VEL) in pregnancy has been completed and found that the PK was not clinically significantly different from non-pregnant individuals and there were no concerning adverse events in mothers or fetuses/infants. The SOF/VEL Treatment of Chronic Hepatitis C During Pregnancy (STORC) study of safety of sofosbuvir/velpatasvir in pregnancy is ongoing. There are only case reports of glecaprevir/pibrentasvir use in pregnancy thus far, but an IMPAACT 2014 study to assess PK and safety in pregnancy and lactation is in development. Data is being collected from ongoing clinical trials to assess safety for fetuses/infants exposed during pregnancy/lactation, and the impact of pregnancy on PK and effectiveness for

sofosbuvir/velpatasvir. More trials are needed to collect data on these same areas for glecaprevir/pibrentasvir.

Due to drug shortages of benzathine penicillin G, alternative therapies with adequate placental transfer are needed for treatment of syphilis in pregnant women. Animal studies have found negative results for reproductive toxicity of cefixime, but there is inadequate human data for safety evaluation. There are no controlled studies for treatment of syphilis in pregnancy, but a trial is currently underway to look at cefixime use in non-pregnant women, with a plan to study pregnant women subsequently if successful.

Recommendations

- Prioritization in the infectious disease category should be guided by population frequency, impact on pregnancy/lactation, impact on the fetus/infant, and feasibility.
- The three conditions discussed today were all high priority examples with drugs at different stages in their pregnancy/lactation pathway.
- Other drugs submitted are also high priority, particularly the multiple tuberculosis (TB) drugs submitted, which will need quite a bit of time to fully consider.

Discussion

Dr. Pat Flynn (St. Jude Children's Research Hospital) noted that Gilead, the sponsor of the PURPOSE studies, has significant data on lenacapavir in pregnancy. IMPAACT has some studies on first- and second-line TB drugs, but, given some of the very complex drug regimens TB patients are on, there is an opportunity for more research on drug-drug interactions. She added that she was surprised by the lack of vaccine nominations, particularly flu and COVID vaccines. Dr. DeYampert said that they did receive a nomination for the mRNA vaccine for RSV and one for the COVID vaccine. Dr. Piper mentioned NIAID's Multisite Observational Maternal and Infant Study for COVID-19 (MOMI-VAX study), which is currently analyzing breastmilk data and will be published later this year.

Dr. Saade asked if there were any nominations for the treatment of cytomegalovirus (CMV), which is just as much a problem as syphilis. He added Group B strep to the list of vaccines that should be considered. He said that it was important to determine which was better, giving an RSV vaccine to the mother or treating the baby prophylactically after delivery. Dr. Piper said that CMV did not have any nominations, nor did they see nominations for infectious disease conditions that are specific to pregnancy and lactation, such as mastitis, endometritis, and chorioamnionitis.

Dr. Michael McVoy (Virginia Commonwealth University) suggested prioritizing ways of finding money to support not just the studies but the cost of some of the drugs needed to conduct the studies. Dr. Piper said that PRGLAC often discussed the topic of pharmaceutical companies' attitudes towards testing their products in pregnancy and lactation. They talked about trying to de-risk the process and making it more feasible for companies to put their products into studies. Dr. Hebert commented that companies are responsible for ensuring the safe and effective use of their products. When a drug is approved in the adult population, it is approved

for pregnant and lactating people, and the liability data shows that it is riskier not to study these individuals than to study them. Dr. Sahin added that a recently published report by the National Academies of Sciences, Engineering, and Medicine found no evidence to support an increased risk of liability for including pregnant and lactating people in clinical studies. The real liability occurs once the product is out on the market without data on how it affects this population.

Dr. Saade said that it was not actually an issue of liability, since liability is inherent for drug companies, but there is no financial return on investment in pregnancy. They need to find a way of incentivizing companies to get a return on investment through programs like BPCA or by making trials less costly, which depends on regulation. Dr. Pawlyk said that developing better nonclinical models will also help, and there is potential to improve DART assays, which are currently very expensive. He commented that pregnancy and lactation research could be viewed as being at the point where pediatrics was 30 years ago, and it took congressional action to create incentives and requirements for industry doing clinical trials. One large incentive for the pharmaceutical industry is the extension of exclusivity, which has a high market value for companies.

Dr. Krutsch said that she was surprised not to see treatment for mastitis on the nomination list, as it is currently at the center of a controversy in the lactation world and more information is needed about its physiology. She also talked about the ways that risks and benefits are communicated from studies on the effects of antibiotics in breastmilk, noting that InfantRisk hears from many lactating people who choose to suffer without their antibiotics rather than risk harming their baby.

Dr. Saade noted that many medications used in non-pregnant people were able to progress because they were used first in healthy volunteers, and he wondered if something similar could be done for pregnancy. Dr. Sahin noted that in pediatrics there is a provision of a minor increase over minimal risk where there is potential generalizable knowledge. This topic was raised in PRGLAC but the discussions have not moved forward.

Dr. Krutsch said that she has asked the BPCA program whether lactation trials could qualify for pediatric exclusivity, but she has not received any solid answer. Dr. Feghali said that these discussions highlight just how isolated the pregnancy and lactation world is when it comes to regulatory language. It would be helpful to remedy this to allow more flexibility, given the lack of availability of regulatory space to try to investigate treatments in the setting of pregnancy-specific conditions.

Dr. Fabiyi shared comments from the online chat. One commenter noted that the World Health Organization has a working group focused on drugs for treating and preventing HIV, hepatitis, and STIs in pregnancy and lactation. Another shared that one of the key antibiotics used in multidrug-resistant TB is a later generation fluoroquinolone, which is also relevant to other infections in pregnancy. The commenter asked if any of the nominated drugs cut across several different infectious diseases, as that would seem to give them higher priority. Dr. Piper said

that she did not recall any drugs being submitted for multiple conditions. Another online commenter pointed to a consensus statement on the inclusion of pregnant people in TB research, available on the Treatment Action Group (https://www.treatmentactiongroup.org/) website.

Substance Abuse/Exposure & General Areas
Moderator: Sunila Nair, Ph.D. - Program Officer, Integrative Neuroscience Branch, National Institute on Drug Abuse (NIDA)
Discussant: Carmela Reichel, Ph.D. – Program Officer, Division of Therapeutics and Medical Consequences, NIDA

Substance Abuse/Exposure

Background
The use of alcohol, tobacco, and illicit drugs during pregnancy and lactation is a significant public health concern in the United States, as mentioned in the 2018 PRGLAC Report. In the 2013 National Survey on Drug Use and Health, 5.4% of women reported using illicit drugs (including cocaine, methamphetamine, and marijuana) during pregnancy, 9.4% reported using alcohol, and more than 15% reported using tobacco. The opioid epidemic has also spread among pregnant women, and the incidence of neonatal opioid withdrawal syndrome (NOWS) has increased nationally. Therapeutic agents currently used to treat substance use disorders (SUDs) are nicotine replacement therapies and medication-based treatments for opioid dependence, including methadone and buprenorphine. The nominated therapeutic agents in the abuse category are vape pens (mods, pods, e-cigarettes), medications foropioid use disorder (MOUD), and naltrexone. For the exposure category, the nominations are cannabidiol (CBD), cannabis, marijuana (all components - delta-9 tetrahydrocannabinol (THC), delta-8 THC, et cetera.), and over the counter cannabidiol and/or medical cannabis.

Key questions:
- What is the impact of vaping on the fetus?
- What are the consequences of regular maternal use of CBD on the pregnancy?
- What are the long-term effects of marijuana and its components? Does marijuana have long-term adverse effects on the fetus?
- Do the benefits of cannabis use for hyperemesis gravidarum outweigh the risks to the pregnancy and the fetus?

There are few studies that address how SUDs and their medicinal therapies affect lactation and breastmilk. Basic mechanistic studies of substance use in pregnancy are limited, and relatively few studies of any type exist to inform understanding of possible therapeutic approaches in pregnant people who used several commonly abused illicit drugs.

Research landscape/key literature
This category did not have an associated MPRINT analysis. An electronic search of research articles for studies of naltrexone compounds compared with methadone and buprenorphine in pregnant individuals with opioid use disorder (OUD) yielded a total of five studies that met eligibility criteria. No significant differences in gestational age at delivery were detected, and all

studies with data on neonatal abstinence syndrome (NAS) detected a lower risk of NAS in the naltrexone group compared to methadone and buprenorphine. The data available are limited, and further comparative studies of pregnant people with OUD taking MOUDs and large RCT trials are necessary. In non-pregnant people, methadone and buprenorphine are associated with lower overdose rates and decreased opioid health problems than naltrexone, but all forms of MOUD are superior to no treatment for overdose prevention.

Prenatal cannabis exposure after the middle of the first trimester is associated with attentional, social, and behavioral problems in affected children, which persist as they progress into early adolescence. Analysis using baseline data from the Adolescent Brain Cognitive Development (ABCD) study found an association between prenatal cannabis exposure and behavioral problems in children 9-10 years of age. Other preclinical studies have reported that Delta-9 THC can cross the placenta and potentially affect brain development. The incidence of opioid use at labor and delivery has steadily increased since 1999, with stimulant use in pregnancy characterized as an under-recognized epidemic. Two separate studies found that drug overdose mortality increased in pregnant and postpartum people during the COVID pandemic, with the highest rates during the late postpartum period.

Recommendations

- Additional studies are required prior to forming a consensus on prioritization
    - Studies targeted at delineating changes in the PK of SUD therapeutics during pregnancy and in the postpartum period
    - Studies targeted at the transfer of addictive substances as well as therapeutic agents through the placenta and into breast milk
    - Influence of polysubstance use on maternal and fetal outcomes
    - Identification of brain changes during pregnancy and postpartum
    - Identification of specific windows of vulnerability and biological factors that increase vulnerability during pregnancy and in the postpartum period
    - Mechanisms underlying individual differences in vulnerability
    - Influence of comorbidities such as postpartum depression, sleep disturbances, etc.
- Consideration of non-pharmaceutical interventions:
    - Circumvent polydrug use and exposure as well as drug-drug interactions
    - Cognitive behavioral and digital behavioral therapies
    - Neuromodulation (e.g., TMS, focused ultrasound and low intensity focused ultrasound, phrenic nerve stimulation, etc.)

<u>General</u>

Background

This category is not included in the PRGLAC Report. The nominated agents are drugs frequently taken by pregnant people and drugs used for general anesthesia. Key questions arose from the nomination about studying the mechanism and extent of changes in the PK of drugs in the maternal-fetal unit, including fetal exposure through phenotyping studies and in vitro studies, rather than studying each drug separately. For general anesthetics, there was a question of

whether the advice to pump and dump breastmilk is backed up by actual evidence of transfer or harm to the baby.

Research landscape/key literature
Data from MPRINT studies on general anesthetics showed more studies conducted during pregnancy than in the postpartum period, with almost none during lactation.

Discussion
Ms. Grimes said that lactation circles were moving away from the idea of pumping and dumping breastmilk for surgeries, with the exception of certain procedures and drugs. Dr. Krutsch added that the American Society of Anesthesiologists (ASA) has a new slogan, "sleep and keep," and their guidelines no longer recommend pumping and discarding milk. Dr. Hebert said that they do not want to push pregnant and lactating people into less than optimal treatment strategies. She added that, under the current state of the art strategy for OUD, taking away buprenorphine increases recidivism. Dr. Grabb asked if the ABCD study collects data on the amount of cannabis use in a certain time period. Dr. Nair said that she was not sure about the granularity, but they do collect that information. Dr. Reichel said that they ask participants to self-report cannabis use and then attempt to quantify this with hair samples.

Ms. Grimes asked if anyone was looking at whether the benefits of treatments for withdrawal also pass into breastmilk for babies with NOWS. Dr. Nair said that they needed more small- and large-scale studies to answer that question with respect to individual drugs and polysubstance combinations. Dr. Reichel added that lofexidine is one of the only FDA-approved treatments for opioid withdrawal. While she did not know if it passed into breastmilk, it is under consideration for treatment in younger populations.

Study Design for Research on Therapeutics in Pregnant and Lactating People, Part 2

Mary Hebert, Pharm.D., FCCP

Dr. Hebert summarized the study designs that were discussed on Day 1 and noted that clinicians often face challenges when preclinical work has not been done or is not accessible. Most of the preclinical and clinical work with the pregnant and lactating population is done during the postmarketing period, after the drugs have been approved. DART studies are done during drug development, but the information is often considered proprietary. Phase I studies of safety and dosage have been done for very few medications during pregnancy. Most of the medications used in pregnancy are FDA-approved for the adult population, but their place in therapy, what dose to use, and the safety for pregnant, postpartum, and lactating persons, as well as the embryo, fetus, and neonate, have not been established. Evaluating each individual medication to collect the missing data will be costly and require careful consideration of prioritization. The following elements should be taken into account:

- Pharmacological gaps in knowledge for PK, PD, dosing, efficacy, and safety of each drug in pregnancy and lactation.
- Timing of studies (PK, PD, efficacy, safety) during pregnancy and lactation.

    - Do studies need to be done in all three trimesters? What is the time course of changes postpartum?
- What factors are important to consider in the selection of study design?
    - Dedicate versus nested PK/PD studies? Single dose versus steady state? Population versus intensive sampling?
    - RWD versus prospective, randomized studies for efficacy and safety information?
- Selection of the appropriate control or comparator group depends on the question you are trying to answer.
    - Is the PK/PD changed during pregnancy?
    - Is the PK, PD, dosage, efficacy and safety the same as the population for which the drug has received FDA approval?
    - Is the efficacy/safety better with new treatment versus the standard of care?
- Dosage selection strategies: extensive sampling PK/PD, population PK, non-linear PK, modeling and simulation, cross-sectional dosage studies.
- Consideration of PD changes:
    - Is there a good surrogate marker? Is the underlying condition the same as the improved condition? Is the response to therapy the same as the approved population?
- Efficacy study considerations: Have PK/PD studies been completed? Have dosage and safety been determined during pregnancy/lactation? Is the drug being used for an approved indication?
- Safety study considerations: What are the effects of the drug (maternal, embryo, fetal, neonate)? Is this a first-in-pregnancy study?

Dr. Hebert opened the floor for a discussion on strategies NIH can use for prioritization. Dr. Pawlyk asked how to assess whether sufficient nonclinical studies have been done to initiate additional research studies in pregnant and lactating people. Dr. Sahin said that FDA's M3(R2) guidance discusses the nonclinical studies that need to be done before pregnant individuals can be included in clinical trials. There is a question around when the available RWD from a drug on the market becomes sufficient to obviate the need for those nonclinical studies. Dr. Li said that his group used machine learning to curate six or seven categories of maternal/pediatric information from drug labels, and this is included in the silver version of the KBP. The KBP also contains many well-defined phenotypes curated from published epidemiology studies, and these can serve as a preliminary starting point for future epidemiology studies. Dr. Pawlyk asked if MPRINT could extract a summary of the nonclinical data from the labels, and Dr. Li said that they were already doing that automatically. All of this information can be accessed by querying the silver version of the KBP.

Dr. Reefhuis noted that a case control study is almost always needed to study a specific birth defect because they are such rare outcomes. It is important to keep talking to PPL people to find out whether they are taking their medication, as this can ebb and flow over time and it can be different for different medications. She reiterated the importance of starting a registry for

people who get pregnant during trials and would otherwise be removed from the trial. Dr. Hebert noted that currently that data is owned by the drug companies and cannot be released because it is proprietary. Dr. Reefhuis added that the link to stillbirths is missing from pregnancy outcomes, and they are difficult to find in maternal medical records.

Dr. Saade commented that one of their problems is the lack of standards and guidance to assess how much nonclinical research or RWD is sufficient to proceed with human studies. Dr. Krutsch noted that the public comment period is currently open for the USCDI+ core data elements for the maternal health domain, and they would appreciate feedback on Dr. Reefhuis' point about stillbirths in medical records. She also suggested applying natural language processing to the lactation information from the National Library of Medicine's LactMed database. In response to Dr. Saade's comments, Dr. Pawlyk noted that several NIH Institutes and Centers do have contract services that conduct trials with regulatory consultants, although NICHD does not. There is a knowledge gap when it comes to investigators accessing that regulatory expertise to design studies.

Ms. Grimes echoed Dr. Li's comments about looking at RWD first to see which of the most commonly used drugs have not been studied and then prioritizing those medications for further research. She suggested looking at medications that have already been shown to be efficacious, such as heparin for the treatment of VTE. Dr. Hebert added that conditions that are less common but life-threatening should also be prioritized. Dr. Krutsch suggested looking at drugs for which there are no alternatives, where clinicians currently advise people to stop breastfeeding so that they can continue to use the medication. Dr. Reefhuis commented that, as a pregnancy-only issue, preterm birth should be prioritized. Dr. Hebert agreed and added that the same was true for preeclampsia and hyperemesis gravidarum. Dr. Fabiyi shared a comment from the online chat that they can build in PK early safety assessment among consenting people who become pregnant in registrational trials, especially Phase III. Once dosing is established in non-pregnant adults, and if no concerns are raised by nonclinical fertility and early embryonic development (FEED)/embryo-fetal development (EFD) studies, they could stay on the study drug with consent.

Open Discussion and Plans for the Future

Dr. Fabiyi invited participants to raise questions or comments about topics discussed during the meeting. Dr. Saade said that many studies in this area are negative because the availability of funds determines study design factors such as eligibility, outcome, and sample size. Trials are often stopped early because of poor recruitment, or they are underpowered because investigators picked an outcome and overestimated its rate to keep the budget below the funding requirement. Dr. Krutsch suggested that more lactation physiology expertise should be included in ongoing discussions.

Meeting Adjourned

Dr. Fabiyi thanked the participants for their attendance and noted that they will continue to have future discussions about the remaining nominations, most likely via virtual working groups. There being no further business, she adjourned the meeting at 11:51 a.m.