

TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING
WOMEN

MEETING

August 21-22, 2017

The Task Force on Research Specific to Pregnant Women and Lactating Women (Task Force) convened its first two-day meeting on August 21 and August 22, 2017 at the National Institutes of Health (NIH) 31 Center Drive, Building 31, Room 6C6, Bethesda, Maryland 20892. In accordance with the provisions of Public Law 92-463, the meeting was open to the public. The public could attend in person by registering in advance or by viewing online by NIH videocast. A video archive is available online for Day 1

(<https://videocast.nih.gov/summary.asp?live=24815&bhcp=1>) and for Day 2

(<https://videocast.nih.gov/summary.asp?live=24820&bhcp=1>).

Task Force Members Present:

- Terry Adirim, MD, MPH, Department of Defense (DOD)
- Shelli Avenevoli, Ph.D., National Institute of Mental Health (NIMH)
- Diana Bianchi, MD, NICHD
- Karin Bok, Ph.D., M.S., HHS
- Andrew Bremer, MD, PhD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Camille Fabiyi, PhD, MPH, Agency for Healthcare Research and Quality (AHRQ)
- Elena Gorodetsky, MD, PhD, Office of Research on Women's Health (ORWH), NIH
- Marjorie Jenkins, MD, MEHP, Food and Drug Administration (FDA)
- Athena Kourtis, MD, PhD, Centers for Disease Control and Prevention (CDC)
- Linda Lipson, MA, Department of Veterans Affairs (VA)
- Joan Nagel, MD, MPH, National Center for Advancing Translational Sciences (NCATS), NIH
- Victoria Pemberton, MS, RNC, CCRC, National Heart, Lung, and Blood Institute (NHLBI), NIH
- Jeanna Piper, MD, National Institute of Allergy and Infectious Diseases (NIAID), NIH
- Catherine Y. Spong, MD, NICHD
- Sayeeda Uddin, MD, MPH, HHS

Task Force Members Absent:

- Lee Andrew Wilson, MS, Health Resources and Services Administration

Other Members of the Public Present:

See attachment A.

Welcome and Opening Remarks

Lawrence Tabak, D.D.S., Ph.D.

NIH Principal Deputy Director

Dr. Tabak welcomed the Task Force meeting participants. He noted that although pregnant women take between three and five medications, very little research has been conducted on the appropriate dosing, safety, and efficacy in pregnant or nursing women. Dr. Tabak explained that the Task Force had been created by the 21st Century Cures Act to address these gaps in knowledge and reviewed the mandates of the new law. He said that the Secretary of Health and Human Services (HHS) had delegated authority for the Task Force to the NIH, and that Dr. Francis Collins, Director of the NIH, had asked the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to lead the effort.

Introductions

Dr. Catherine Spong, NICHD, stated that the federal members of the Task Force have been named, and that the slate for the non-federal members is pending approval.

Dr. Spong noted that NICHD is hosting a website for Task Force activities:

<https://www.nichd.nih.gov/about/advisory/PRGLAC>.

The Task Force will hold four meetings, including this one. Future dates are:

- November 6-7, 2017
- February 26-27, 2018
- May 14-15, 2018

Background, Timeline, Goals, and Report

Dr. Spong provided further details on the legislative mandate for the Task Force in the 21st Century Cures Act, which was signed into law in December 2016. The Act spelled out categories of Task Force membership, including specific Federal agencies, professional societies, nonprofit organizations, and industry. The NIH was delegated the authority to lead the Task Force in January 2017, the Task Force Charter was filed in March 2017, and Federal members were designated in May 2017.

The Task Force's report is due to the Secretary of HHS and Congress by September 2018, and the Secretary must act on the Task Force recommendations by December 2018. The Task Force will sunset by March 2019 unless the Secretary chooses to extend it. All Task Force meetings will be open to the public, videocast, and archived. Each meeting will include time for public comments. NIH may also issue a Request for Information to get further input.

Each of the four Task Force meetings will focus on one of the topics identified in the legislation:

- Identification of Federal activities
- Discussion of ethical issues
- A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant and lactating women
- Recommendations to improve the development of these therapies

Scope of the Task Force – Legislative History

Kathryn Schubert, MPP

Society for Maternal Fetal Medicine

Ms. Schubert provided background on how the 21st Century Cures Act mandate was developed. Several nonprofit advocacy organizations and professional societies identified the gap in knowledge regarding prescription drug use by pregnant and lactating women. Ms. Schubert noted that without this information, women may stop taking the medications they need, may not initiate breastfeeding, or wean early. The Coalition to Advance Maternal Therapeutics was formed to address this issue, and immediately began to gather information from federal health agencies about current activities. The Coalition developed its guiding principles, educated members of Congress, identifying champions on Capitol Hill, and organized grassroots advocacy to get the Task Force provision into the Cures Act.

Dr. Spong led a discussion about the potential scope of the Task Force, stating that it is important to define a scope of work that is feasible within the time allowed.

Task Force members engaged in an active discussion, although all agreed that there are few data about medications used by pregnant or lactating women, including pharmacokinetic and pharmacodynamic studies. Although the majority of pharmaceutical research is done by industry, there are few studies that include these populations. One participant stated that the Task Force should promote the notion of protecting women through research, rather than from research.

Participants stated that in addition to prescription medications, other substances used by pregnant and lactating women should be considered for inclusion in the scope of the Task Force's work, such as herbal preparations, alternative and complementary therapies, dietary supplements, over the counter medications, immunizations/vaccines, prenatal vitamins. An active discussion followed about how to prioritize the range of possible issues to be considered, e.g. to focus on medications that women must take during pregnancy, medications used to treat the most prevalent conditions, medications to treat the most serious conditions, therapies on which high-quality research has been done, or conditions for which animal models are available. Other considerations include the impact on the fetus, drug-drug interactions, and the long-term impact on the woman of not taking a medication. A risk-benefit approach also was suggested, where the burden posed by a particular health condition on a pregnant or lactating woman would be balanced against the treatments (and their safety) that women may use for that condition, including non-prescription therapies. This would present a model that could be used for other conditions later.

Among the possible approaches that could be taken to obtain this needed information were a clearinghouse of evidence-based treatments, or comparative effectiveness research, especially for those medications where there are already a lot of data. Identifying the best research that has been done with pregnant women would be an excellent place to begin. All agreed that individuals who are pregnant or breastfeeding need a place to obtain accurate information.

State of Research on Pregnancy and Lactation
Anne Zajicek, MD, PharmD, NIH

Dr. Zajicek's talk focused on the state of knowledge about prescription medications used in pregnancy and breastfeeding, their impact, determining effective and safe dosing, maternal-fetal and maternal-infant drug transfer, and new drug development for medications to be used during pregnancy. She confirmed that many medications are used off-label during pregnancy, and that there is sparse basic science on pregnancy-related conditions. Among the most commonly taken prescriptions medications were anti-infectives, anti-nausea, and those taken for asthma and pain. For many women, it is not feasible to stop taking their medications.

A major area needing further exploration is whether physiological changes during pregnancy affect the effectiveness of drugs. Basic science is lagging in this area, such as pharmacokinetic and pharmacodynamics studies. There is still a fear that inclusion of pregnant women in research studies will lead to a higher incidence of birth defects in their offspring. This must be balanced against the concern about short- and long-term consequences for the woman if she decides to stop taking medications during pregnancy or while breastfeeding. Having preclinical data to show there might be some teratogenic effect of a drug would be helpful.

Dr. Zajicek also presented data on lactation, stating that the prevalence of breastfeeding drops from 79% after a baby is born, to 27% when the infant is 12 months old. Very few studies specifically include lactating women, making it virtually impossible to advise women about drugs used postpartum. One issue is how to determine drug exposure levels to the baby received through breast milk; assays are difficult to develop. The research needs in this area include novel drug targets, including placental drug transport inhibitors, validated short- and long-term clinical trial outcome measures, improved and more feasible clinical trial designs, and improved tracking of research conducted in pregnancy and during lactation.

During the discussion that followed, one participant noted that the "holy grail" of drug development is a drug that does not pass the placenta to the fetus. There is evidence that higher doses of medications are needed for pregnant women, but that a bottleneck is occurring for clinical trials. Further, women may be receiving incomplete information about breastfeeding and their medications. Among the suggested approaches for addressing these issues were to encourage more collaboration across NIH Institutes, conducting translational research from preclinical findings to humans, and increasing post-market surveillance of drugs that may be used by pregnant or lactating women. The NICHD's Human Placenta Project, which is supporting "placenta on a chip" studies, might be an avenue to studying drugs and their ability to cross the placental barrier.

Identification of Federal Activities

Overview

Catherine Y. Spong, MD

Dr. Spong provided an overview of current federal activities related to safe and effective therapies for pregnant and lactating women. Federal agencies are engaging in activities in these topics relevant to PRGLAC:

- Birth defects and adverse effects of prenatal exposures
- Substance abuse: effects and treatment

- Postpartum depression
- Preterm birth
- Mechanisms of action for preeclampsia and other pregnancy-related conditions
- Responses to infection and inflammation in pregnancy
- Sleep disorders and pregnancy
- Global health – malaria and HIV in pregnant and lactating women
- Access to prenatal care

NIH

Dr. Bianchi described ongoing NIH activities, providing examples of clinical networks and other research aimed at informing clinical practice. The NIH also engages in collaborations across agencies and with professional societies, and has created communications campaigns related to pregnancy and lactation.

CDC

Dr. Kourtis described CDC's research activities, which include assessing risks to pregnant women and their offspring, treatments for specific conditions, and surveillance and data collection. CDC also conducts epidemiological studies of medication use during pregnancy and lactation, and studies the safety and effectiveness of vaccines. The agency has issued clinical guidance in many formats, and other communication materials and collaborative efforts.

FDA

Dr. Jenkins stated that pregnancy and lactation research at the FDA includes studies on the mechanisms of therapies, pharmacokinetic, pharmacodynamic, exposure risk, and impact of tobacco use. The agency creates policies and guidance for its stakeholders, communicated through a wide variety of media, and maintains a Pregnancy Registry List. It should be noted that FDA does not conduct any pregnancy registries. The registries posted are based on a sponsor or investigator's request to list their registry. FDA does not endorse any registry and is not responsible for the content of registries listed on this webpage. Since January 2014, CDER's Drug Trial Snapshots webpage provide demographic information (e.g., race, ethnicity, age, and gender) about who participated in clinical trials that supported the new molecular entities. The information provided in these Snapshots also highlights whether there were any differences in the benefits and side effects among sex, race and age groups. The Pregnancy And Lactation Labeling Rule (PLLR) requires changes to the content and format for information presented in prescription drug labeling to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication. The changes required by the PLLR include:

- removes pregnancy letter categories – A, B, C, D and X.
- a new section is being added to the prescription drug labeling (Females and Males of Reproductive Potential) to include information, when necessary, about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug.

HHS Office of the Assistant Secretary for Health (OASH)

Dr. Uddin said that the National Vaccine Program Office has conducted multiple studies of vaccine use during pregnancy, and the Office for Human Research Protections oversees

protection of human subjects in research. OASH also engages in pregnancy provider training and breastfeeding outreach efforts.

Agency for Healthcare Research and Quality (AHRQ)

Dr. Fabiyi stated that AHRQ invests in research, including studies on the use of medications and vaccines by pregnant women, creates training materials for health care professionals, and generates measures and data to evaluate and improve the health system. It also supports the work of the USPSTF, which has issued recommendations on therapies for pregnant and lactating women.

HRSA

Dr. Lopata pointed out that although HRSA is not a research agency, it supports health care to people who are economically or medically vulnerable through grants and cooperative agreements. It also supports the Maternal and Child Health Research Network on Pregnancy-Related Care and, through several programs, clinical care specifically for pregnant and lactating women. HRSA is a partner in the text messaging application, Text4baby.

DOD

Dr. Adirim described DOD's active research program that includes studies on pregnant and lactating women, part of its integrated health care system that provides clinical care and other supports.

National Vaccine Program Office

Dr. Bok said that the balancing act with vaccines is to protect the pregnant woman from disease while also protecting the fetus. The office is collaborating with CDC on studies, and exploring how to better survey vaccinations during pregnancy.

Department of Veterans Affairs

Dr. Zephyrin stated that although the VA does not provide obstetrical care, studies are being done on pregnancy and PTSD (which increases risk of preterm birth) and the use of opioids among pregnant veterans. She suggested that the Task Force include military status as one variable when looking at groups of pregnant women.

Discussion

One attendee raised concerns about whether a pregnant woman's medical records, showing the medications she is taking, would follow her if she left a health system. Dr. Zephyrin stated that the VA has policies in place about tracking medications. Regarding long-term health outcomes of medications taken during pregnancy, baseline data are needed and the health of children must be followed for years.

Other Federal Efforts

Dr. Sarah Glavin, NICHD, provided an overview of other Federal agencies' activities affecting pregnant and lactating women.

The Substance Abuse and Mental Health Services Administration published an evidence review on interventions for pregnant women who use opioid drugs, and has a large clinical care portfolio.

The Indian Health Service has a substantial clinical portfolio.

The Centers for Medicaid and Medicare collects data, and the Office of the National Coordinator for Health Information Technology coordinates national health records information; these activities are helpful for large database studies.

The U.S. Department of Agriculture collaborates with NIH on research on the effects of antibiotics and other medications (including drug treatment of parasites) on placental and fetal growth in farm animals and humans. Its work also includes food safety and healthy diets for pregnant and lactating women.

The Environmental Protection Agency (EPA) supports basic physiological research on pregnancy, including the effects of anticonvulsants on pregnancy in animal models. In collaboration with NIEHS, the EPA is conducting the Healthy Baby, Healthy Pregnancy Study.

The U.S. Consumer Product Safety Commission has information on breast pumps.

The U.S. Agency for International Development supports global health research on preventing transmission of infection (e.g. HIV) from mother to child.

Meeting participants suggested other federal agencies that may have some work in this area.

Recap

Dr. Spong summarized the discussions, pointing out that basic science is limited on medications used during pregnancy and lactation, including the physiologic changes of pregnancy and how it affects metabolism of medications used during this period. There are even more limited data on breastfeeding and breastmilk. She suggested that the Task Force report should define the scope of its efforts, while acknowledging that information is needed on a wide variety of therapies used during pregnancy and lactation. The Task Force is charged with recommending ways to improve the development of safe and effective therapies for pregnant women and lactating women.

Coordination and Collaboration

The second day began with a panel discussion on recommendations for coordination of and collaboration on research.

NIH Perspective

Dr. Bianchi pointed out that NIH staff participate in thousands of interagency and other collaborations, which are reported to Congress annually. She provided several examples, including the 2016 scientific workshop on opioid use in pregnancy, research infrastructure, public education campaigns, and research registries (PregSource™).

FDA Perspective

Dr. Jenkins stated that the FDA collaborates internally and externally to develop a variety of programs to benefit pregnant and lactating women. Research priorities include advancing the safety and efficacy of products, emerging technologies, biomarkers, and health communications. The FDA maintains a list of pregnancy registries which are owned and managed by the drug sponsor or other organizations and Pregnancy Registries include observational data on women and infants who have been exposed to medications, and that the agency utilizes several sources of science across the research spectrum, such as that which is developed by NIH and industry, in its work.

Industry Perspective

Dr. Christina Bucci-Rechtweg, Novartis, reviewed *industry*-sponsored clinical trials, finding little research on lactation. She suggested that public-private collaborations might be organized using trade associations, and provided several examples of successful partnerships.

Panel discussion on opportunities for and challenges to coordination and collaboration.

Participants agreed that there is a paucity of data about pregnancy and lactation, and that the federal government could be instrumental in fostering collaborations in this area, including condition-related registries and multi-site clinical trials to test therapeutics in pregnant and lactating women. NIH's current research network infrastructure could be encouraged to partner with industry to achieve mutual goals. Several participants encouraged the group to think about the needs of pregnant and lactating women from bench to bedside when developing new drugs, not just post-market. There are many data sources available that are drawn from diverse populations.

Summarizing the discussion, Dr. Spong reiterated the suggestion to take advantage of ongoing collaborations, and to look for opportunities to share data across federal agencies. Much more research needs to be done specific to pregnant and lactating women, but legal and ethical challenges need to be resolved, and expertise expanded to design and conduct trials in these populations.

Public Comments

Several individuals offered public comments about the need for research that includes pregnant and lactating women who need to use medications for a range of health conditions:

- Dr. Amita Gupta - Johns Hopkins Center for Clinical Global Health Education
- Dr. Graeme Moffat – Health and Environment Science Institute
- Ms. Lindsay McKenna – Treatment Action Group
- Mr. Nathan Nelson and Dr. Jonathan Bortz – Balchem Corporation/Women's Choice Pharmaceuticals
- Dr. Jennifer Radin – Scripps Translational Science Institute
- Dr. Sharon Nachman – Family Health International
- Ms. Kate O'Brien – We Are TB
- Ms. Sheila Heitzig – American Academy of Allergy, Asthma, and Immunology

The written comments are posted on the PRGLAC website.

Dissemination of Research and Information

Professional Society Perspective

Dr. Michael Greene provided a perspective as a health care professional, referring to a 2015 American College of Obstetricians and Gynecologists Committee Opinion that states that pregnant women should be included as “scientifically complex” participants in research. Professional guidelines recommend that health care providers discuss their patients’ prescription and non-prescription medications.

Patient Perspective

Ms. Jamie Zahlaway Belsito offered a patient perspective, stating that 20 percent of women have a mental health issue during pregnancy and postpartum. The Task Force should recommend health care provider training and support so that they can provide evidence-based care.

CDC Perspective

Dr. Kourtis described CDC’s approach to disseminating science, studying communication strategies to inform and influence decisions that enhance health. CDC uses partnerships and collaborations to accomplish this goal.

During the panel discussion, Dr. Siobhan Dolan, March of Dimes, emphasized that often, use of a medication entails a risk-benefit analysis. Tekoa King, American College of Nurse-Midwives, pointed out that health literacy and health numeracy must be considered when developing health education materials. Audiences do not like to see separate materials for consumers and health care providers. Many people access health information through their cell phones, and the new PregSource™ registry has an extensive resource library of materials from trusted national organizations. However, work also needs to be done to determine how women use health information once they receive it.

Overarching Recommendations from Meeting 1

- Case studies may be used to show how little data exists on therapies used by pregnant and lactating women. Begin with common conditions experienced by pregnant women and delve into all of the medications/therapies/supplements they take.
- Explore why many studies are not completed.
- Consider alternative study designs (opportunistic sampling, simulation studies).
- Infrastructure to share standardized information and techniques across government should be developed, as well as a shared data warehouse. Existing clinical trial networks and data resources should be utilized.
- Focus on disseminating information through the Internet.
- A comprehensive communications strategy should be developed.
- Harmonize the use of definitions.
- The Task Force should define success, provide specific action items, focus on unmet medical needs, and identify gaps in therapies.

Adjournment

The meeting adjourned on August 22, 2017 at 3:00 p.m.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.ⁱ

Lisa Kaeser, JD
Executive Secretary, Task Force on Research Specific to Pregnant Women
and Lactating Women
Director, Office of Legislation and Public Policy, *Eunice Kennedy Shriver*
National Institute of Child Health and Human Development

Attachment: Participant List

ⁱ These minutes will be considered formally by the Task Force at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.