

## **Task Force on Research Specific to Pregnant Women and Lactating Women**

### **Meeting**

**November 6-7, 2017**

The Task Force on Research Specific to Pregnant Women and Lactating Women (Task Force or PRGLAC) convened the second of four two-day meetings on November 6 and 7, 2017, at the National Institutes of Health (NIH), 6001 Executive Boulevard, Rooms C-D, Rockville, Maryland. In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Interested individuals could attend in person by registering in advance or by viewing the meeting online by NIH videocast. A video archive is available for Day 1 at: <https://videocast.nih.gov/summary.asp?Live=26437&bhcp=1>, or for Day 2 at: <https://videocast.nih.gov/summary.asp?Live=26441&bhcp=1>.

Task Force members present:

- Catherine Spong, M.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Chair
- Diana Bianchi, M.D., NICHD
- Marjorie Jenkins, M.D., MEHP, Food and Drug Administration (FDA)
- Sayeeda Uddin, M.D., MPH, Department of Health and Human Services (HHS)
- Joan Nagel, M.D., MPH, National Center for Advancing Translational Sciences (NCATS)
- Andrew Bremer, M.D., Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Karin Bok, Ph.D., M.S., HHS
- Jeanna Piper, National Institute of Allergy and Infectious Diseases (NIAID)
- Athena Kourtis, M.D., Ph.D., Centers for Disease Control and Prevention (CDC)
- Victoria Pemberton, M.S., RNC, CCRC, National Heart, Lung, and Blood Institute (NHLBI)
- Linda Lipson, M.A., Department of Veterans Affairs (VA)
- Lee Andrew Wilson, M.S., Health Resources and Services Administration (HRSA)
- Elena Gorodetsky, M.D., Ph.D., Office of Research on Women's Health
- Lisa Kaeser, J.D., NICHD

Task Force members absent:

- Terry Adirim, M.D., M.P.H., Department of Defense
- Camille Fabiyi, PhD, MPH, Agency for Healthcare Research and Quality

Ad Hoc members present:

- Bridgette Jones, M.D., University of Missouri- Kansas City
- Melissa Gorman, M.S.N., RN-BC, CCRN, Shriners Hospitals for Children
- Susan Givens, RN, Mount Carmel St. Ann's
- Steven Foley, M.D., FACOG, Prowers Medical Center
- Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation
- Diane Spatz, Ph.D., University of Pennsylvania

- Robert Ternik, Ph.D., Eli Lilly and Company
- Lois Tschetter, Ed.D., RN, IBCLC, South Dakota University
- Jeanne Sheffield, M.D., Johns Hopkins University

Other members of the public present:

See attachment A.

*Welcome and Opening Remarks*

Dr. Catherine Spong welcomed the Task Force to its second meeting, noting that the public members are serving as ad hoc members pending approval.

*Review and Approval of Minutes*

The Task Force unanimously approved the minutes from the August 2017 meeting with the incorporation of edits from the FDA.

*Work Products from the August 2017 Meeting*

Dr. Spong reminded the Task Force that its report to the HHS Secretary and Congress must be submitted by September 2018. She also noted that at the August meeting, the Task Force had recommended exploring federal activities related to the use of vitamins, herbal medicines, and dietary supplements by pregnant and lactating women. This information was gathered in the interim, sent out to the members prior to the meeting and Dr. Sarah Glavin presented the findings at this meeting.

*Scientific Research and Federal Activities on Drugs, Vaccines, Vitamins, and Other Supplements for Pregnant and Lactating Women*

Sarah L. Glavin, Ph.D., NICHD

Dr. Glavin led the literature search and analysis by medication-treated conditions common to pregnant and lactating women. The review evaluated the quantity of existing literature, identifying 13,628 therapy-related studies over the past 10 years. Research gaps were identified by condition, type of research, and subtopic, concluding that the prevalence of a condition among pregnant or lactating women does not correlate with the number of published studies. Gaps exist in research on vitamins, herbals, and dietary supplements, and less than four percent of original research involving pregnancy and medications addressed lactation. There are few pharmacokinetic or pharmacodynamic studies, and no studies of new drugs for pregnancy-related conditions.

*Overview of Draft Section of Federal Activities for Secretary's Report*

Dr. Spong reviewed the provisions of the 21<sup>st</sup> Century Cures Act that mandated formation of the Task Force, which will sunset in March 2019 unless the Secretary chooses to extend it.

The report will be divided into five sections, each reflecting a subsection of the legislation:

- Current federal activities, including the state of the research;
- Ethical issues surrounding the inclusion of pregnant and lactating women in research;
- Communications strategies for health care providers and the public of information relevant to pregnant and lactating women;

- Recommendations to improve the development of safe and effective therapies for pregnant and lactating women; and
- A plan to address gaps in knowledge and research regarding safe and effective therapies for pregnant and lactating women.

Dr. Spong presented a draft of the section of the report regarding federal activities, which provides a summary of current research through the literature review, and identification of research gaps and funding sources. It also summarizes communications and trans-federal collaborative efforts. Three appendices will list research therapies in pregnant and lactating women, federal activities by agency, and pregnancy registries in the United States and elsewhere.

Among the suggestions made by Task Force members were to provide statistics on conditions affecting pregnant women for context, noting a lack of research on low milk supply, and inclusion of a recommendation in the Task Force report on pregnancy registries, such as a centralized site listing all known registries. Meeting participants were encouraged to send in reports of additional studies and registries to the Task Force, and Dr. Jenkins agreed to distribute a recent review on registries conducted by the FDA Office of Women's Health. A suggestion was made to recommend disease-focused registries, not drug-centered registries. Half of the registries on the FDA website are the result of post-marketing study requirements, and half are voluntary.

Dr. Spong reviewed Task Force recommendations made at the August meeting, including establishment of clinical trial networks, implementing incentives to engage in this research for industry and agencies, and facilitating collaboration. The Task Force also identified a need for new product development, post-market evaluation, a federal database on medication safety, and tapping the potential of social media for sharing information, taking health literacy into account.

During the discussion, Task Force members were encouraged to look at models for research in under-developed areas that are encapsulated in current legislation, such as the Best Pharmaceuticals for Children Act, and the Orphan Drug Act. Concerns around ethics and liability remain two obstacles to more research on therapies for pregnant and lactating women.

#### *Public Comment Period*

Two individuals offered comments about the need for research that includes pregnant and lactating women:

- Kathryn Schubert, M.P.P., Society for Maternal-Fetal Medicine
- Sarah Mancoll, M.Sc.

These comments are posted on the PRGLAC website.

#### *The Inclusion of Pregnant Women and Lactating Women in Clinical Research: Ethical Issues*

Amina White, M.D., M.A., University of North Carolina at Chapel Hill

Dr. White pointed out that few drugs are approved by the FDA for use by pregnant women, and most of them are for obstetrical indications. In addition, there are very limited data on dosing and safety of medications while breastfeeding, yet the majority of drugs are not contraindicated for breastfeeding women.

Dr. White reviewed some of the history of ethical issues involving research in the United States, including the so-called “Common Rule” provisions of the Code of Federal Regulations for the Protection of Human Subjects. These provisions were updated in 2001 to allow pregnant women to be involved in research if 10 conditions were met. There is currently no presumption that pregnant women should be included in research. Dr. White stated that there has been a paradigm shift in pediatric research, from it being unethical to include children in drug research to it being unethical not to. She pointed to several statements from professional societies, scientists, and bioethicists that advocate for the responsible inclusion of pregnant women in research, and said that the proposed revision of the Common Rule, which is scheduled to go into effect in January 2018, will remove pregnant women from the list of vulnerable populations (although the conditions in Subpart B still apply).

Dr. White discussed inclusion and exclusion of pregnant and lactating women in clinical trials. Of over 4,000 studies recruiting women and girls that were conducted in 2017, six specifically excluded pregnant women, and three excluded lactating women. However, these populations are not clearly included, either.

Dr. White stated her concerns about the research gaps that exist for pregnant and lactating women, including their need for safe and effective therapies, that untested therapies jeopardize fetal safety, and that research equity is a matter of justice. While risk assessment is challenging in pregnancy, bioethicists often apply the informed clinician test, which involves trade-offs on the risk and benefit to both the pregnant woman and fetus. Reluctance to include pregnant women in research due to concerns for the fetus paradoxically may increase adverse outcomes for both.

During the discussion, Task Force members suggested relying on comparative effectiveness research rather than a risk-benefit calculation, and to be sure to include long-term benefits in any calculation of risk.

*Panel: Federal and Local Requirements Related to Pregnant and Lactating Women Participating in Clinical Research*

Lisa Buchanan, M.A.O.M., CIP, HHS

Ms. Buchanan stated that the proposed revisions to the Common Rule and Subpart B were meant to promote individual autonomy, reduce administrative burden, and streamline the IRB process. The revision no longer includes pregnant women as a population that is potentially vulnerable to coercion or undue influence; however, the Subpart B protections still apply. She then reviewed what IRBs must consider when reviewing research, such as consent from both the pregnant woman and father.

*Consent Requirements for Both Pregnant Woman and Father*

Anne Drapkin Lyerly, M.D., M.A., University of North Carolina at Chapel Hill

Dr. Lyerly explained the paternal consent requirement, which is meant to recognize that parents share an interest in the fetus’ health. There have been objections raised, including that this requirement is inconsistent with standards of clinical care; one parent may give consent for their child to participate in research. One model for paternal involvement could be that the pregnant woman could consult with the father if she wishes.

*IRB Interpretation of 45 CFR 46 Subpart B*

Karim Calis, Pharm.D., MPH, FDA

Dr. Calis noted that IRBs must be independent and knowledgeable about the ethical principles and expertise in relevant areas of science and medicine, including consideration of risks and benefits to the pregnant woman and fetus of proposed research. An IRB can approve research under Subpart B if: preclinical studies that include pregnant animals and clinical studies that include non-pregnant women have been conducted first, and that any risk to the fetus is caused only by interventions or procedures that hold the prospect of direct benefit to the woman or fetus. These protections are in place because of the complex nature of research with this population.

*IRB Interpretation of Minimal Risk to the Fetus*

Maggie Little, Ph.D., Georgetown University

A critical issue is determining how much research-related risk to the fetus is ethically acceptable, since the fetus cannot consent. The minimal risk standard serves to cap the risk for an individual or fetus with no prospect of direct benefit. The “minor increase over minimal risk” category does not apply to Subpart B, which potentially could allow research in pregnant or breastfeeding women to go forward.

*Regulatory Perspective*

Tamara Johnson, M.D., M.S., FDA

Dr. Johnson provided background on the FDA’s role in studies involving pregnant and lactating women. It requires that Subpart B be satisfied in studies supported by HHS. She outlined the conditions under which a PK trial in a clinical setting can involve pregnant women, but that these studies should not enroll healthy pregnant women. Clinical trials in lactating women must not involve greater than minimal risk to the breastfeeding infant.

*Lactating Women and Research*

Victoria Pemberton, M.S., RNC, CCRC, NHLBI

One study found that women take an average of four medications during lactation, yet half of the drugs have no data on breastfeeding on their labels. Ms. Pemberton noted that research in lactating women is important to determine the degree of drug transfer into breast milk, how a drug affects the composition or volume of milk, the amount of drug that infants are exposed to in breast milk, and how changes in breast milk composition over time can affect drug transfer. She described steps for establishing research priorities in this area.

*Discussion*

Ruth Faden, Ph.D., MPH, Johns Hopkins University, led the discussion, asking first whether removing pregnant women as a “vulnerable population” from the Common Rule regulations would change research. Most Task Force members felt that it would be a signal to IRBs and others to do more research with pregnant and lactating women. One suggestion was to reframe IRBs’ charge to make them responsible for inclusion of these populations in research studies. The panel also discussed issues around consent, noting that timing of obtaining consent is important. Women in labor may not have the opportunity to understand what she is being asked to consent to. Lactating women may not face the same hurdles as pregnant women in joining a research study, since it may be easier to predict risk in this population. Task Force members were also encouraged to remember that an investigational new drug may pose very different risks than a drug that is already on the market.

Dr. Faden suggested that the Task Force define what type of preliminary evidence would be needed to conduct first-in-pregnant women, or first-in-lactating women studies, and that scientists need to make use of other available data, such as data from inadvertent exposure, opportunistic prospective studies, incident pregnancies, or physiological modeling. PK studies may be especially difficult given the length of time required for blood draws. Animal data are helpful to inform trial designs, but animals may not transfer the drug across the placenta the same way that humans do. However, most research with pregnant and lactating women could meet the minimal risk standard. Studies should include a research question specific to pregnant or lactating women before including them; pregnant and lactating women must be built into the research study during the design.

Currently, the disincentives for inclusion outweigh the incentives. Participants identified the need for a new ethical framework to emphasize the importance of including pregnant and lactating women in research.

In summing up the day's discussion, Dr. Spong noted that the Task Force can learn from what has been done in other fields (e.g. pediatrics), and public health crises.

## *DAY 2*

### *Recap and Discussion*

Dr. Spong summarized the key points from the first day's discussions. Dr. Bianchi began the discussion by suggesting that changing the consent requirement to maternal consent alone would align with current practice in pediatric research, and that investigators should determine the lactation status of women who participate in their studies. Another suggestion was made to adopt the "minor increase over minimal risk" category from pediatric research.

### *Panel: Inclusion of Pregnant and Lactating Women in Research*

#### *Reluctance to Include Pregnant Women in Clinical Research: Physiological Changes and Complexity*

David M. Haas, M.D., M.S., Indiana University School of Medicine

Dr. Haas provided an overview of the physiologic changes experienced by a woman during pregnancy, such as increase in blood volume, cardiac output, and stroke volume. Pregnancy can change drug transit time, and drug metabolism changes, making study design difficult. He urged researchers to design more consumer-friendly studies to encourage more pregnant and lactating women to participate.

#### *Research Science, Ethics, and Litigation*

Michael F. Greene, M.D., Massachusetts General Hospital

Dr. Greene stated that biomedical research, no matter how well designed and ethically conducted, carries uncertainty and exposes participants to risk of injury. He noted that the National Vaccine Injury Compensation Program might be one model to compensate research participants who are injured during trials; other universities self-insure. There has been a rise in human subjects research litigation.

#### *Vaccines, Pregnancy, and the Research and Development Agenda*

Carleigh Krubiner, Ph.D., Johns Hopkins University

Dr. Krubiner said that although vaccines can offer significant benefits to both pregnant woman and fetus, not a single vaccine is licensed for use in pregnancy, making women reluctant to get vaccinated. There are not enough data on background rates of adverse maternal, fetal, and infant outcomes, so harm that occurs may be misattributed to vaccines. Innovations in vaccine development also present a challenge. Dr. Krubiner suggested development of vaccines specifically for pregnant women, injury compensation programs, including pregnant women in efficacy trials, and collecting data from inadvertent exposures.

*Why is There No Research on Lactating Women?*

Diane Spatz, Ph.D., University of Pennsylvania

Dr. Spatz stated that over three million women in the United States each year initiate breastfeeding and could face decisions about medication use. About half of mothers who stop breastfeeding during the first year do so because of low milk supply, yet research on this issue is limited. Due to little information, many women take herbal supplements to increase milk supply, which have not been tested.

*Discussion*

The question of how to lower the risk of liability and compensate those injured in research are important considerations for the Task Force. In addition, panelists agreed that scientists need incentives and disincentives to make the research more attractive and protect both scientists and participants. Women are interested in studies that could benefit their health and their children's health. The science of lactation can inform the design of good studies. The dogma that pregnant women should not receive live vaccines is now being challenged because evidence from incidental pregnancies does not indicate higher risks. Transfer of antibodies from pregnant woman to fetus is across the placenta, not through breastmilk or the gut. One participant suggested that milk banks could form a network to do opportunistic studies on the transfer of drugs through breastmilk.

Participants noted caution among researchers due to thalidomide and other negative research history. A universal consent for pregnancy and lactation studies might be preferable given state law differences (including those affecting minors). Because research related to pregnancy can be more expensive for individual researchers, networks might be the most cost-effective way of conducting these studies.

*Panel: Ethical Issues of Specific Clinical Research Designs*

Jeanne Sheffield, M.D., Johns Hopkins University

Dr. Sheffield reviewed different study designs. A cohort study is one in which investigators enroll a group of subjects and follow them over time. Observational studies can be cross-sectional or case-control studies in which the investigators compare those who have the outcome in question and those who do not. Clinical trials apply an intervention and prospectively observe the outcome. Each design has benefits (time required) and drawbacks (expense). Observational studies do not carry the same level of risk because no intervention is applied. Risks to participants (including risk of not including in the study), and consent issues must be considered.

*Ethical Issues Related to PK and PD Studies in Pregnant and Postpartum Women*

Steve Caritas, M.D., University of Pittsburgh Medical Center

Dr. Caritas explained that PK measures what the body does to the drug, including how it is absorbed and distributed through the body, and how it is metabolized and eliminated. PD studies measure what the drug does to the body, requiring a measurement of a target organ or tissue response and its relationship to drug concentration in blood or tissue. Most PK studies pose little risk, except those measuring fetal blood or amniotic fluid. Ethical issues include fasting, and changing the timing or dose of the medication. Without good PD studies in pregnant women, drugs could be ineffective or unsafe. Postpartum breastmilk studies may present some of the same issues.

#### *Convenience Studies: Ethical Considerations*

Amina White, M.D., M.A., University of North Carolina at Chapel Hill

Dr. White explained that convenience sampling involves collecting data from individuals who are easily accessible to the investigator, and can be helpful to generate data to develop hypotheses. However, convenience sampling can be more prone to selection bias. It might be used to begin filling research gaps.

#### *Issues of Inclusion in Clinical Research*

James Griffin, Ph.D., NICHD

Dr. Griffin provided a timeline of NIH inclusion policies and participant data collection. The 21<sup>st</sup> Century Cures Act required NIH to convene a workshop on age groupings/exclusions in clinical research, and revise its policies by the end of 2017. The culture may be shifting from “protection from research” to “protection through research.” Problems recruiting sufficient numbers of sub-populations may be addressed by doing meta-analyses in combination with other studies. Workshop participants noted the need to include pregnant and lactating women in research, as well as challenges associated with their enrollment.

#### *Discussion*

Dr. Bridgette Jones noted that the Task Force could learn from pediatric and geriatric research. Others said that adult and pediatric studies are often conducted separately, and questioned whether it made sense to include pregnant women in studies of the general population. If only a few pregnant women are included (underpowered), then generalizing its findings may be scientifically invalid and unethical if any risk is involved.

Participants also noted that industry is reluctant to study off-patent drugs, especially in pregnant women, so NIH may have to support those studies. Foundational knowledge is critical, including PK and dosing information. Overall, participants agreed that studies could be better designed to meet the needs of pregnant and lactating women. The NICHD’s Obstetric-Fetal Pharmacology Research Centers have experience doing clinical pharmacological trials. Opportunistic studies may have promise in terms of both funding and time involved in participation. Placenta perfusion models, and placenta-on-a-chip may provide unique opportunities to further research on these populations.

#### *Panel: Researcher, Industry, and Research Participant Perspectives*

##### *Research in Pregnancy: The Physician Scientist Perspective*

George Saade, M.D., University of Texas Medical Branch

Dr. Saade stated that teratogenicity is not the only safety concern regarding research with pregnant women; lack of dosage data can be highly problematic. There is little evidence to guide

clinical practice, and research on obstetrical complications can yield a high return on investment in terms of health. Because IRBs may not have expertise in pregnancy, a single IRB approach may help. Another research need is a good *in vivo* model of the placenta or of pregnancy. Without efforts to encourage young scientists to enter this field, maternal morbidity and mortality may continue to rise.

#### *Large Industry Perspective on Ethics and Inclusion*

Robert Ternik, Ph.D., Eli Lilly and Company

Dr. Ternik encouraged the Task Force to consider pregnancy and lactation studies separately, since different types of studies may be used for each. He stated that pregnant women should almost always be excluded from investigational drug studies, except when the drug is being specifically tested for them. The sponsor's responsibility in clinical research is to characterize the risk-benefit profile of the product in the indicated population. Industry considers the risk-benefit analysis, the mechanisms of action, what stage of drug development, and the feasibility of the trial. Industry can play a role in developing best practices for post-market studies.

#### *Small Industry Perspective*

Kristi Lengyel, UCB

Ms. Lengyel said that today's health care system is volatile due to its complexity, volatility, and pressure on costs. She noted the challenges faced by pregnant and lactating women with chronic conditions requiring treatment, such as autoimmune conditions, and described how UCB has worked with patient advocacy organizations to provide up to date information about medications. She recommended a harmonized approach to collecting data, more studies specifically focused on pregnant and lactating women, and partnering with milk banks.

#### *Participant Perspective*

Melissa Gorman, M.S.N., RN-BC, CCRN, Shriners Hospital for Children

Ms. Gorman, a pediatric nurse, described her experience as a research participant who was diagnosed with epilepsy when pregnant. Finding little research on the drug recommended, she enrolled in a pregnancy registry, and later, two studies. Ms. Gorman discussed efforts made by the investigators to make her participation easier, and shared results as they received them.

#### *Discussion*

Linda Lipson said that the discussion highlights the need for public-private partnerships, including professional associations, patients, industry, and physician scientists. One suggestion was made to partner with industry on foundational research, and to use simulations and pharmacometrics in partnership with experts in pregnancy and lactation. Several people noted the need to reduce liability in conducting research, and the expense of clinical trials. It may be helpful to emphasize the long-term health benefits of research on pregnancy and lactation. If considering an incentive program, such as BPCA, there must be clear objectives; should the focus be on drugs already on the market or development of new drugs? All agreed that involving research participants is critical, and that they often want to know about long-term outcomes.

#### *Key Points and Wrap Up*

Dr. Spong summarized the findings from the meeting, including:

- Shift the presumption to inclusion of pregnant and lactating women in research
- Modify Subpart B to require only maternal consent to participation

- Encourage more lactation research – breast milk changes over time
- Incentivize participants and investigators
- Explore liability issues – fear limits industry participation
- Inclusion must be part of study design
- Data collected must be usable
- Blood samples may be ethically obtained from a baby
- Funding still a key issue
- Industry has different skill sets than academia
- Foundational research is critical
- Leverage opportunistic and intentional research
- Universal consent, including minors, would be helpful

Each Task Force member was given an opportunity to identify an important point made during the meeting. Several members agreed to share further information about their activities.

Dr. Spong said that the next meeting will take place February 26-27, 2018, at 6710B Rockledge Drive in Rockville, Maryland.

The meeting was adjourned on November 7, 2017, at 4:35 p.m.

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

Lisa Kaeser, J.D.  
Executive Secretary, Task Force on Research Specific to Pregnant Women and Lactating Women

Attachment A: Participant List