Task Force on Research Specific to Pregnant Women and Lactating Women

Meeting

August 22 – 23, 2019

The Task Force on Research Specific to Pregnant Women and Lactating Women (Task Force or PRGLAC) convened the second meeting since its charter extension on August 22 and 23, 2019, at the National Institutes of Health (NIH), 6710B Rockledge Drive, Bethesda, MD. 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=34424&bhcp=1 and for Day 2 at: https://videocast.nih.gov/summary.asp?live=33386&bhcp=1.

Task Force members present:

- Diana Bianchi, M.D. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Chair
- Shelli Avenevoli, Ph.D., National Institute of Mental Health (NIMH)
- Karin Bok, Ph.D., M.S., National Institute of Allergy and Infectious Diseases (NIAID)
- Andrew Bremer, M.D., Ph.D., NICHD
- Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation
- Camille Fabiyi, Ph.D., Agency for Healthcare Research and Quality (AHRQ)
- Dorothy Fink, M.D., Office of Women's Health, Department of Health and Human Services (HHS)
- Steven Foley, M.D., FACOG, Prowers Medical Center
- Susan Givens, R.N., M.P.H., March of Dimes
- Melissa Gorman, M.S.N., RN-BC, CCRN, Shriners Hospital for Children
- Elena Gorodetsky, M.D., Ph.D., Office of Research on Women's Health, NIH
- Bridgette Jones, M.D., University of Missouri-Kansas City
- Kristi Lengyel, M.B.A., UCB Inc.
- Linda Lipson, M.A., Department of Veterans Affairs (VA)
- Aaron Lopata, M.D., M.P.P., Health Research and Services Administration (HRSA)
- Joan Nagel, M.D., M.P.H., National Center for Advancing Translational Sciences (NCATS)
- Voula Osganian, M.D., Sc.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Victoria Pemberton, M.S., RNC, CCRC, National Heart, Lung, and Blood Institute (NHLBI)
- Jeanna Piper, M.D., NIAID
- Jennita Reefhuis, Ph.D., Centers for Disease Control and Prevention (CDC)
- Jeanne Sheffield, M.D., Johns Hopkins University
- Diane Spatz, Ph.D., University of Pennsylvania

- Robert Ternik, Ph.D., Eli Lilly and Company
- Kaveeta Vasisht, M.D., Pharm.D., Food and Drug Administration (FDA)
- Wendy Weber, M.D., Ph.D., M.P.H., National Institute of Complementary and Alternative Health (NCCIH)

Executive Secretary, Lisa Kaeser, J.D., NICHD also was present.

Task Force members absent:

- Terry Adirim, M.D., M.P.H., Department of Defense (DoD)
- Lois Tschetter, Ed.D., RN, IBCLC, South Dakota State University

Day 1

Opening Remarks

Dr. Diana Bianchi welcomed the Task Force to the second meeting since its charter was renewed in March 2019. She also welcomed the five new members of the Task Force, who replaced members who have changed positions. Dr. Bianchi expressed appreciation for the service of the previous members.

Review and Approval of Minutes

The Task Force unanimously approved the minutes from the May 2019 meeting, with no changes.

Charge and Goals for the Meeting

Dr. Bianchi reviewed the goals for this meeting, including the establishment of four working groups that will consider the steps needed for implementation of the recommendations included in the report sent to the HHS Secretary and to Congress in September 2018. Both current PRGLAC members and ad hoc experts are represented in each of these working groups: Research and Training, Regulatory, Communications, and Discovery. For efficiency, each working group will focus on a subset of the recommendations, determining what agencies and stakeholders should be involved in implementation, whether any programs need to be established or expanded, and potential costs and timelines. Two of the 15 recommendations will not be addressed at this time. One, to extend the charter of the Task Force, has been accomplished. The last recommendation, to establish an additional advisory committee to monitor implementation, is premature until the implementation plans have been developed.

Additional PRGLAC-related Activities

Three presenters provided updates on additional activities related to therapeutics used by pregnant and lactating women.

Dr. Leyla Sahin, FDA, updated the Task Force on recent guidances issued by the FDA related to pregnancy, including post-approval pregnancy safety studies, study design considerations for clinical lactation studies, issues to consider when a study participant becomes pregnant during a trial, and ethical and scientific considerations for conducting clinical trials that include pregnant

women. These guidances represent the FDA's current thinking on a particular subject and are open to public comment. For example, considerations could include collecting pharmacokinetic data to help inform dosing during pregnancy and conducting opportunistic studies on drugs used during lactation if no risk is posed to the infant. The FDA follows the HHS framework of human subject protection regulations; all regulatory requirements of 45 CFR 46 Subpart B need to be met.

Dr. Bucci-Rechtweg, Novartis, updated the Task Force on ConcePTION – **C**ontinuum of Evidence from **P**regnancy Exposures, Reproductive **T**oxicology and Breastfeeding to **I**mprove **O**utcomes **N**ow, a project of the Innovative Medicines Initiative (IMI). This initiative is a public-private partnership between the European Union and the European pharmaceutical industry that funds health research aimed at developing next generation vaccines, medicines and treatments, such as new antibiotics.

ConcePTION (https://www.imi.europa.eu/projects-results/project-factsheets/conception), led by Novartis and the University Medical Center Utrecht, will create a biomedical pan-European system capable of providing evidence-based information on the safety of medications during pregnancy and breastfeeding in an efficient, systematic and ethically responsible way. The information generated will be provided in a form that is usable by both healthcare providers and patients. Among its aims are to create the first EU-wide breast milk biobank for research purposes, and to develop tools to predict which drugs are likely to be transferred to breast milk. The project, which will use both public and private funding, was launched in April 2019 and is slated to end March 2024.

Lisa Kaeser, NICHD, reported on a discussion with Drs. John Clements and Jane Wooley of the Medicines and Healthcare Products Regulatory Agency, UK, about their Safer Medicines initiative. Situated similarly to the U.S., many of the UK's 700,000 pregnant women use prescription medications that have not been tested for their use. The project has three overarching goals: supporting the development of safer, more effective medicines in pregnancy, facilitating more rapid identification of harm from medicines in pregnancy using the best available evidence, and enabling informed decision-making through provision of consistent, up-to-date information to women and their health care providers.

Public Comment Period

Six members of the public provided comments about implementation of the Task Force's recommendations. These, along with an additional white paper, will be posted on the PRGLAC website.

The open session of the meeting adjourned to allow the four working groups to meet for the rest of the day.

Day 2

Opening Remarks

Dr. Bianchi welcomed everyone back, thanking them for their work. The plan for the day is to hear from each of the working groups regarding their initial thoughts on implementation, allowing for ample discussion.

Working Group Presentations

Working Group 1: Research and Training – Drs. Bremer and Pemberton

At this initial meeting, Working Group 1 focused on two recommendations:

Recommendation 2 - to increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women. Dr. Bremer noted that far more detailed knowledge is needed to help agencies, industry, and academic researchers understand the impact of untreated disease on pregnant women and their offspring, and that without this knowledge, the risk and responsibility largely rests with women who are using the medications. All levels of research are still needed, including mechanistic, pharmacokinetic and pharmacodynamic, dosing formulations, and testing in clinical trials. Among the initial approaches suggested were increasing funding for this research, developing the necessary framework to allow for prioritization of the drugs needing to be tested, increasing data and biospecimen sharing to allow for wider researcher involvement, considering a range of public-private partnerships to leverage funding, looking for incentives to encourage enrollment of pregnant women as research participants, and facilitating access by early stage investigators to government-funded research networks.

During the discussion, several PRGLAC members noted that the role of research in eventual clinical care is not often well understood by health care providers. This is an area where public private partnerships, such as through the Foundation for the NIH, may help bridge the gap.

Dr. Bremer led a discussion around alternative study designs that may help facilitate gathering information to inform dosing decisions, such as comparative effectiveness research, pragmatic study designs, using common data elements and harmonizing methods and outcome measures. Determining in advance what adaptive research designs are acceptable for future labeling would be helpful. To achieve larger cohorts, participants could be added to clinical registries by pulling data from electronic health records. Investigators who wish to expand their research to include pregnant and lactating women should take advantage of established infrastructure, such as the Clinical and Translational Science Awards (CTSAs); its Trial Innovation Network provides consultation on study design.

Several Task Force members raised the issue of follow up with infants born to women who use therapeutic products during pregnancy or lactation. With so little consistent follow up, linking a woman's data to her child's could be beneficial. Large datasets and research registries, including data from electronic health records, would provide the necessary power.

Recommendation 3 – expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics. Some barriers were identified, including availability of research populations, salary limitations, the need for protected research time, and expensive malpractice insurance. The group made several

suggestions about how to leverage current expertise to encourage young investigators to conduct research in this field, including that of the maternal fetal medicine community, existing T32 programs, and industry mentors. Existing training programs could be adapted to target researchers who are willing to work with pregnant and lactating women, and loan repayment programs and internships can be created or expanded to encompass obstetric and perinatal research. Professional societies may be helpful in educating health care providers about participation in clinical research.

During the discussion, participants pointed out that other disciplines may be critical players in research efforts involving pregnant and lactating women, such as nurses, pharmacoepidemiologists, and nonclinical researchers such as developmental toxicologists. Additional discussion considered the question of whether there should be a dedicated center for pregnancy and lactation research, or whether these areas should be woven into existing research infrastructure.

Working Group 2: Regulatory – Drs. Avenevoli and Bok

Dr. Bok outlined the working group's discussion around the changes made to federal regulations regarding research involving human subjects (the so-called "Common Rule," which most federal health agencies follow). In the revised regulations that went into effect in January 2019, pregnant women were removed from the list of examples of vulnerable populations that require extra scrutiny by Institutional Review Boards when considering research studies. She noted that the FDA is harmonizing their guidance with the revised Common Rule regulations. However, parts B and D have not yet been modified. This is the culture change envisioned in the 2018 PRGLAC Report.

The group also discussed how the overall PRGLAC effort could benefit from ongoing programs, specifically the programs established in response to the Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA), both of which were created by Congress to address the dearth of information about pediatric drug dosing. The group suggested that a separate office within HHS could lead these efforts for pregnant and lactating women across agencies but noted that additional resources would be required.

Liability concerns are the other large obstacle to moving research forward involving pregnant and lactating women. Many health care providers and researchers have not acknowledged the risk of not using medications. To help think about possible options, several people suggested that experts in law/malpractice be included in future discussions.

Dr. Bok stated that the group recommends more studies to look specifically at the impact of the current regulatory requirement for two-parent consent on research. Other suggestions made by Task Force members during the discussion included joining the IMI-ConcePTION project and/or sharing data with the international efforts, leveraging milk banks to analyze donated breastmilk (possibly using a tissue on a chip model), and exploring ways of doing PK studies in investigational drugs. Task Force members who represent industry cautioned that as much preclinical data needs to be collected as possible (several animal models were mentioned) before requiring a drug sponsor to do a pregnancy study plan for including pregnant/lactating women.

The Task Force and members of the public had an extensive discussion about liability issues, including when is the likely time that injury/liability may occur (not as often during the research phase), and extending current studies to include pregnant/lactating women. The Vaccine Injury Compensation program was raised as a possible model, but it may not apply exactly to this population. Another approach is to switch current registries from drug-specific to disease-based.

Working Group 3: Communications – Drs. Vasisht and Fabiyi

Working Group 3 also discussed the changes to the Common Rule, noting that this information needs to be disseminated widely to encourage the inclusion of more pregnant and lactating women in research. The group's initial suggestions included the development of a written communications strategy to reach a wide variety of stakeholders and offered several examples of successful education campaigns/programs. Obstacles include some of the same obstacles that face participation by other groups in research: misinformation on potential harm, mistrust of the health care system, and lack of training on how to recruit pregnant or lactating women to participate in research studies. The Task Force noted that individualized messaging may be needed to reach underserved populations who don't have a history of participation, and research may be required to determine reasons for hesitation.

Another suggestion is to reach out to social media and organizations that are popular sources for pregnant and lactating women. Dr. Pemberton noted that NHLBI has developed such a site for children and their families about participating in research, suggesting that something similar could be created for pregnant and lactating women. However, another suggestion was made to consider a bottom up approach, involving stakeholders from the beginning.

Several specific evidence-based communications strategies were offered:

- FDA Guidance documents
- FDA pregnancy registries webpage
- Benefit: free access to information for pregnant/lactating women
- Benefit for providers: continuing education credits
- Additional licensing or certification requirements
- Partnering with a prominent journal

All agreed that a centralized repository of potential resources/strategies/messages would be helpful.

Moving to Recommendation 13 (optimizing registries), Drs. Vasisht and Fabiyi listed several suggestions, including NICHD's PregSource® registry, and AHRQ's and FDA's registries, asking if there has been any effort to align the information contained in them. The group thought that having a centralized source would increase awareness and improve recruitment into research studies. Regarding misinformation about participation in research studies, it was suggested that the current efforts to correct misimpressions about vaccines might serve as a good model. Basic information on what registries/sites women are currently using would be helpful.

Working Group 4: Discovery – Drs. Lopata and Gorodetsky

The primary charge to this working group is to discuss the development of programs to drive discovery of therapeutics that can be used by pregnant and lactating women. To accomplish this, the group suggested developing a formal needs assessment that would list conditions experienced by pregnant and lactating women that lack therapies or data on current therapies, potential congressional actions to authorize new programs, and creation of a center of excellence. Existing models and programs may help point the way, such as BARDA, the Vaccine Injury Research program, and others. As with the other working groups, critical issues involve liability concerns that may be obstructing research, and the need to address health disparities in participation in research studies. For some of these projects, the Foundation for the NIH may be helpful.

The working group also began the discussion of study designs that would include pregnant and lactating women, but noted that to obtain real participation, congressional action may be required that would ask researchers to justify an exclusion of these groups. A vibrant, but not conclusive, discussion followed about what incentives might encourage private industry to include pregnant and lactating women in the studies they sponsor, such as increased patent protection. The group again encouraged Task Force members to look at the BPCA and PREA laws as possible models.

Even before clinical studies begin, a scan of existing resources for data was suggested, including existing registries and population-based datasets. However, current resources may have some limitations, such as the lack of a mother-baby link, privacy issues, and lack of accessibility of these data to the public. Several programs may provide useful models, such as the OTIS project, the national strategy for HIV/AIDS research, and NIH's Maternal Fetal Medicine Units and Rare Disease networks. One member noted that a scan or overall data effort may require action at the HHS level.

Recap and Next Steps – Dr. Bianchi

Dr. Bianchi noted several common themes around early steps for implementation that emerged from the working groups' presentations and discussion. She heard multiple comments regarding the importance of communications to the full range of stakeholders and their roles in prospective research involving pregnant and lactating women. IRBs and health care providers need further education about the participation of these populations in research and the revision of the Common Rule regulations. Partnerships may be useful in accomplishing improved participation in research, including federal agencies, industry, and foundations.

Several working groups brought up the need for basic, fundamental research in pharmacology, and the development of preclinical models for research. Dr. Bianchi also noted that training of new investigators from the beginning may be useful. At the same time, liability concerns continue to concern researchers inside and outside industry, and health care providers, and the Task Force needs to look for more expertise in that area. Finally, a scan/list of existing data sources and registries to prevent duplication of effort would be helpful.

Dr. Bianchi then reviewed the action steps for each of the working groups, including webinars to be held throughout the fall to expand on these initial thoughts. Groups are encouraged to work

with NICHD staff on additional presentations they would find helpful. Ms. Lengyel noted an upcoming congressional briefing on September 25 that will involve several Task Force members.

Dr. Bianchi thanked everyone for a productive meeting, and adjourned.