

Task Force on Research Specific to Pregnant Women and Lactating Women
Meeting

February 26-27, 2018

The Task Force on Research Specific to Pregnant Women and Lactating Women (Task Force or PRGLAC) convened the third of four two-day meetings on February 26 and 27, 2018, 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=26827&bhcp=1> and for Day 2 at:
<https://videocast.nih.gov/summary.asp?live=26831&bhcp=1>

Task Force members present:

- Catherine Spong, M.D. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Chair
- Shelli Avenevoli, Ph.D., Deputy Director, National Institute of Mental Health (NIMH)
- Diana Bianchi, M.D., Director, NICHD
- Karin Bok, Ph.D., M.S., Department of Health and Human Services (HHS)
- Andrew Bremer, M.D., Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation
- Steven Foley, M.D., FACOG, Prowers Medical Center
- Susan Givens, RN, Mount Carmel St. Ann's
- 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
- Marjorie Jenkins, M.D., M.Ed.H.P., Food and Drug Administration (FDA)
- Bridgette Jones, M.D., University of Missouri-Kansas City
- Athena Kourtis, M.D., Ph.D., Centers for Disease Control and Prevention (CDC)
- Kristi Lengyel, M.B.A., UCB, Inc.
- Linda Lipson, M.A., Department of Veterans Affairs (VA)
- Joan Nagel, M.D., M.P.H., National Center for Advancing Translational Sciences (NCATS)
- Victoria Pemberton, M.S., RNC, CCRC, National Heart, Lung, and Blood Institute (NHLBI)
- Jeanna Piper, M.D., National Institute of Allergy and Infectious Diseases (NIAID)
- Jeanne Sheffield, M.D., Johns Hopkins University
- Diane Spatz, Ph.D., University of Pennsylvania
- Robert Ternik, Ph.D., Eli Lilly and Company

- Sayeedha Uddin, M.D., M.P.H., HHS
- Lee Andrew Wilson, M.S., Health Resources and Services Administration (HRSA)

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

Task Force members absent:

- Terry A. Adirim, M.D., Department of Defense (DoD)
- Camille Fabiyi, Ph.D., Agency of Healthcare Research and Quality (AHRQ)
- Lois Tschetter, Ed.D., RN, IBCLC, South Dakota State University

Review and Approval of Minutes

Dr. Catherine Spong welcomed the Task Force to its third meeting. The Task Force unanimously approved the minutes from the November 2017 meeting.

NIH Research Related to the Task Force on Research Specific to Pregnant Women and Lactating Women

Dr. Spong announced that new codes related to pregnancy and lactation have been established for the NIH Research, Condition, and Disease Categorization (RCDC) listing, allowing the public to see how much NIH funding is being directed to those areas of research.

Taisa Coleman, M.S., presented a new analysis of NIH funding for these three new categories for FY 2017:

- 683 projects were related to pregnancy, totaling \$319 million
- 567 projects were related to maternal health, totaling \$249 million
- 159 projects were related to breastfeeding, breast milk, and lactation, totaling \$91.7 million

Ms. Coleman also presented information on projects in each category as well as projects in overlapping categories. Among the NIH Institutes and Centers, NICHD funded the largest number of projects in each category, most often using a R01 mechanism. Ms. Coleman also showed that while many of these research projects were broadly relevant to the Task Force discussions, only a small number were closely focused on the same topics that the Task Force is considering. Dr. Sarah Glavin explained that "maternal health" includes projects that are focused on the pregnant woman/mother, not the infant.

Summary and Discussion of Work Products from Meetings 1, 2, and 3

Dr. Spong reviewed the history of the Task Force and congressional origin, noting that all Task Force members are now official. She reminded the Task Force of its charge and noted that the final scheduled meeting will take place in May 2018. All Task Force meetings are open to the public; information can be found on the Task Force website:

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

Dr. Spong also noted that to obtain as much public input as possible, the Task Force has issued a Request for Information, which is open for comment until April 2, 2018. She reminded Task Force members that its report is due to the Secretary by September 2018; he then has until December 2018 to act on the recommendations in the report.

Dr. Spong noted that work on the report has begun, including useful appendices such as the summary of comments submitted in response to the Request for Information. The May meeting will focus on the recommendations. She noted that the report will be sent to both the HHS Secretary and to Congress, as required by the legislation, and encouraged Task Force members to offer suggestions and corrections.

Dr. Spong reviewed the recommendations made during previous meetings, which included expanding the workforce, incentivizing the established research infrastructure, increasing opportunities for research, and addressing regulatory, legal, and policy issues, and the Task Force discussed each of these categories. Suggestions were made by Task Force members about the wording of the recommendations, which will be refined at the May 2018 meeting. The recommendations represent a mix of those that may be achieved in the short-term, as well as some aspirational goals.

Public Comment

Six members of the public provided comments for the Task Force members' consideration. These will be posted on the PRGLAC website.

Lessons Learned from Pediatric Research and the Best Pharmaceuticals for Children Act

Task Force members reviewed a document prepared by NICHD staff that compared the state of pediatric research versus the current state of obstetrics and lactation (e.g., numbers of NIH-funded researchers in each area).

Anne Zajicek, M.D., Pharm.D., NIH, provided the Task Force with a history of pediatric drug regulation, and the FDA's efforts to add appropriate pediatric labeling to drugs. Congressional intervention occurred at several points, notably the Best Pharmaceuticals for Children Act (BPCA), which was first passed in 2002, and the Pediatric Research Equity Act, passed in 2003. Dr. Zajicek noted that there is a need for basic science to be conducted on the disease mechanisms of pregnancy and breast milk drug transport, with appropriate safety and efficacy testing of drugs that may be used in pregnancy and lactation.

Perdita Taylor-Zapata, M.D., NICHD, discussed NIH's role in carrying out the BPCA, noting that the NIH has developed innovative methods to do this research, including the use of opportunistic studies. The NIH has established a Pediatric Trials Network and works with stakeholders to determine which drugs should be prioritized for study. She pointed out that epidemiological data are needed. NIH Institutes and Centers provide the funding for BPCA activities.

Lynne Yao, M.D., FDA, discussed the FDA's role in carrying out the BPCA and PREA, which together increase the number of approved therapies for use in children. Since 1998, the FDA has approved 709 products with pediatric specific labeling. Like adult products, pediatric products are held to the same evidentiary standard of substantial evidence of effectiveness and clinical benefit. She pointed out that the approval pathway for pediatric drugs and drugs used in pregnancy are different; when a product is approved for adults, it is approved for all adults, including pregnant women, unless there is a specific contraindication. Dr. Yao recommended that the Task Force identify gaps in knowledge and research on safe and effective therapies for pregnant and lactating women. In discussion with Task Force members, Dr. Yao noted that while a FDA rule requires pregnancy and lactation information on vaccine labels, there is often little information to share. There is also little known about the long-term effects of drugs taken during critical fetal and child development periods.

Susan Nicholson, M.D., Johnson & Johnson, provided the Task Force with the industry perspective on pediatric drug testing. She pointed out that a culture change has been necessary among health care professionals and the general population to allow for such testing, despite the American Academy of Pediatrics statement that "it is unethical to deny children appropriate access to existing and new therapeutic agents." Misperceptions about the safety of drug trials has been perpetuated in the media. Consequently, it has fallen to NIH and FDA to conduct such testing under BPCA and PREA. Since maternal mortality remains a significant challenge, Dr. Nicholson called for "disruptive innovation" to speed up the effort to address it.

Task Force members discussed these presentations, focusing on what incentives might be helpful to increase testing of therapies for pregnant and lactating women. Suggestions included de-risking liability (for industry and health care practitioners), multi-level re-education, and establishing priorities and infrastructure for testing these therapies by medical need. To avoid duplication of effort, it would help to become better aware of research going on globally in this area, including sharing available data. Some participants questioned the value of existing pregnancy registries to track women's experiences in using new therapies. While Phase I trials are unlikely to enroll pregnant women, collecting data from opportunistic studies could provide valuable dosing information. Dr. Spong pointed out that pregnant women will participate in studies.

Effective Communication Strategies with Health Care Providers on Information Relevant to Pregnant Women and Lactating Women

Lorena Kaplan, M.P.H., NICHD, provided a case example for a communication strategy, using NICHD's Safe to Sleep® campaign (STS). After defining its goals, the STS campaign strategies included activities aimed at helping to fill the knowledge gap, anticipating questions, and providing accurate knowledge to help infant caregivers overcome previous perceptions and other barriers. Because knowledge is necessary but not sufficient to ensure behavior change, different strategies were used for infant caregivers, health care providers, and the public, also tailoring these strategies for particular subgroups of the population when research showed particular need for education. The STS campaign used several methods to evaluate its success, including examining changes in the

surveillance data on mortality, household surveys, and more recently, social media. Ms. Kaplan pointed out that throughout the campaign, having key partners to help disseminate the messages has been critical.

In the panel discussion that followed, several approaches to effective communications were offered. John Whyte, M.D., M.P.H., FDA described various channels the FDA uses to communicate with health care professionals who prescribe medications. The agency is studying how physicians consume drug safety information, what format they prefer, and what effect the type of messenger may have, finding that a uniform format that provides human data, ordered information by species, and divided information by trimester is preferred. Consequently, the FDA now publishes a more complete assessment of known risks, including an explicit statement when no data are available. A March 2018 meeting will be held to discuss the impact of this new approach on pregnancy and lactation labeling information.

Kerri Wade, M.P.A., representing the Society of Maternal Fetal Medicine (SMFM), discussed how professional organizations communicate with their clinician members. According to a recent survey, 60% of SMFM members receive updated clinical information from their professional associations, while about 40% receive information from trade publications. SMFM uses a variety of tools to communicate, including its website (making slide decks available for communication with additional audiences), online newsletter, and social media (Facebook, Twitter). An important challenge is determining whether these communication efforts change clinical practice.

Susan Kindig, M.D., J.D., Eli Lilly and Company, stated that she is responsible for communicating the company's data about drugs, largely to physicians through the product label (which is rarely read) and through company representatives. On the other hand, physicians often turn to apps, such as Medscape, to pull product information up on their phones, and participate in continuing medical education.

Susan Givens, M.P.H., RN, Mount Carmel St. Ann's, provided a health care provider perspective, stating that continuing education is a trusted source of information on pregnancy and childbirth. Interactive formats such as conferences are favored to allow for networking but can be costly. Webinars allow professionals to access information at their convenience. While many professionals may not have time to fully read journals, messages from thought leaders published in journals receive attention. Social media is popular among younger professionals, and YouTube is helpful for visual learners.

Several communications priorities were identified during the following discussion, including conducting research to determine whether the strategies are reaching the intended audience and fostering behavior change. Social media is emerging as the favored mode of communication among younger professionals, and repeated messaging using different modalities reaches the broadest audience. One person noted that industry messaging is highly regulated, so that Twitter may be inadequate to meet the requirements. Continuing education credits and recertification are important incentives. To the extent possible, similar messages should be received from different sources (i.e.

pharmaceutical company, physician, nurse, professional society). Some of the organizations are involving women consumers at early stages to help determine what messaging reaches them.

Effective Communication Strategies with the Public on Information Relevant to Pregnant Women and Lactating Women

Jackie Rosenthal, M.P.A., CDC, described CDC's health communications approach, beginning with formative research, moving on to message development and testing, production, and implementation, and ending with evaluation and refinement. She offered a case study of CDC's emergency communications that were targeted to Puerto Rico as the Zika virus outbreak grew, with the primary aim being to prevent unintended pregnancy to reduce adverse birth outcomes. Focus groups and community engagement efforts demonstrated the need for further education on the risks and benefits of contraceptives, particularly long-term contraceptives. Social media successfully drove women who needed information to their website and counseling services.

Bridgette Jones, M.D., University of Missouri, Kansas City, said that the American Academy of Pediatrics (AAP), a professional society, takes a multifaceted approach to communicating with the public, including through its website, social and traditional media, emails, blogs and podcasts, webinars, and direct conversations between pediatricians and parents. They have found that the most trusted messengers are the pediatricians. AAP also publishes reference books.

Diane Spatz, Ph.D., University of Pennsylvania School of Nursing, discussed communication strategies used by the United States Breastfeeding Committee (USBC), a coalition of 50 national nonprofit organizations and coalitions. This large network allows distribution of information on a large scale. The USBC uses its website to educate the public and health care professionals, including establishing 20 learning communities whose aim is to support women's breastfeeding goals.

Kristi Lengyel, M.B.A., UCB, Inc., discussed how industry may communicate with pregnant and lactating women, who find that there is poor information available on the benefits and risks of medicines they may be using. She stated that most often, women turn to social media and online forums to learn about others' pregnancy experiences. She recommended that messages be harmonized across audiences and communication channels, first doing the research to define the problem, aligning the objectives, developing a creative message, then testing it with focus groups. That message should be evaluated at the end of the first and second years of a campaign.

Susan Benjamin Feingold, Psy.D., Illinois School of Professional Psychology at Argosy University, described the results of an opinion survey she created for her patients to find out what information gaps there are about pregnancy, postpartum, and lactation. She found that responses fell into three main categories: myths about motherhood, perinatal mental health issues, and breastfeeding difficulties. Many new mothers reported needing physical and emotional support. Women of color, teen mothers, and lower income women are less likely to be screened for mental health needs. Dr. Feingold recommended training health care professionals to screen for these issues, using social

media to educate the public, making use of online news sources (WebMD), and advertising in popular magazines that reach a wide audience.

The discussion that followed highlighted some of the major themes from the panel's presentations, with the importance of consistent messaging across information sources being the most important. Since social media has become ubiquitous, seeking out thought leaders and influencers to convey these messages can make a difference in whether the target audience accepts them. Conveying accurate information about what is known and what is not known also engenders trust.

Dr. Spong closed the first day after reviewing some of the key points made during the day.

Day 2

Recap and Goals for Day 2

Dr. Spong provided a recap of the previous day's discussions, including that the Task Force can learn from the pediatric drug testing experience (BPCA), that communications plans must be multifaceted and targeted to different audiences, and that metrics are needed to ensure that messages reach their audiences and to evaluate their effectiveness.

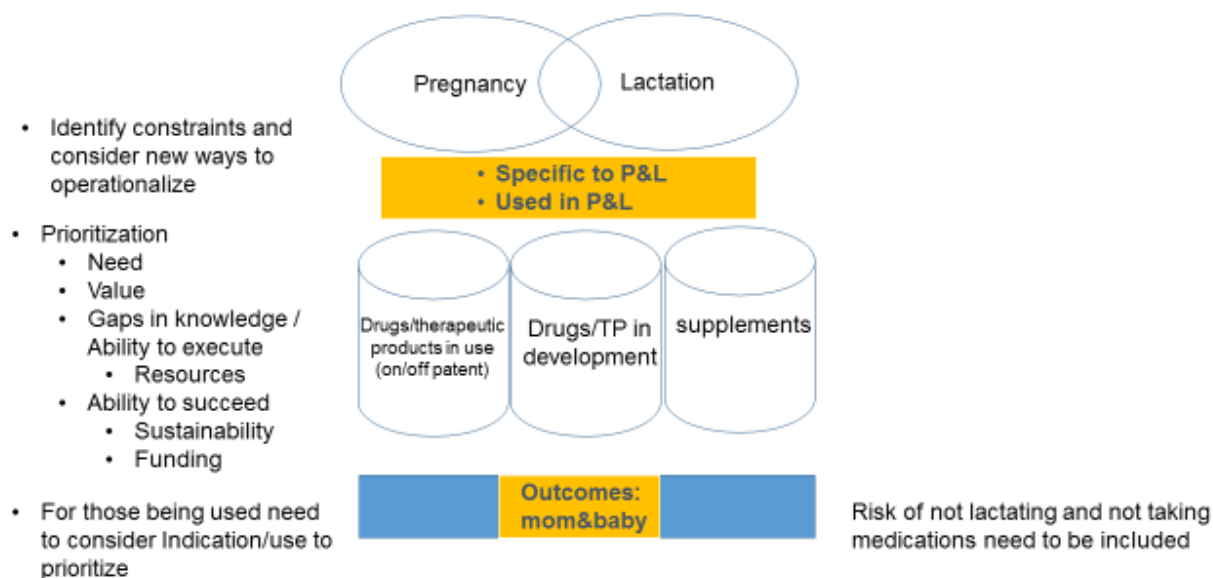
A Plan to Identify and Address Gaps in Knowledge and Research Regarding Safe and Effective Therapies for Pregnant Women and Lactating Women

The legislative mandate for the Task Force includes development of a plan regarding therapies for pregnant and lactating women. Shelli Avenevoli, Ph.D., NIMH, led the discussion.

Several Task Force members commented on the different approaches that may be needed for therapies that are already on the market and medications that are still being developed (prior to approval). A further difference to help structure a plan would be to differentiate between drugs used by pregnant women versus drugs used by lactating women. For each of these categories, the plan could identify priority needs. Another suggested approach to help with prioritization would be to focus on common conditions for which pregnant and lactating women are treated. A further refinement could be indication, need, value, and the ability to execute.

Neonatal outcomes should be included, but in a separate category. Infants who are healthy should be categorized differently from infants who are hospitalized, and the risks of not breastfeeding should be included. One suggestion for further research is to look at breastmilk that cannot be donated to a milk bank because the mother was using a medication.

The Task Force also discussed whether supplements should comprise a third category (beyond new drugs and existing drugs), although very little data exist on many of them. Those used in pregnancy should be separated from those used in lactation. Dr. Spong developed the graphic pictured below that provides an overarching view of these discussions. Dr. Avenevoli noted that this helps convey that there are several points at which the prioritization must occur.



Task Force members discussed *infrastructure, training, and workforce* needs. Over the last 20 years, a pediatric research infrastructure has been developed; there is no such infrastructure for research on therapies for pregnant and lactating women. Several models for achieving this were suggested, including the International Neonatal Consortium, NICHD's Pediatric Trials Network, and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network. Collaborations with some of these existing groups may be a good beginning, and more formal public-private partnerships could be considered.

Among the highest areas for *prioritization* recommended by Task Force members were to focus on medications commonly used in pregnancy (dosing information), medications to increase milk supply, information on the transfer of medications to breast milk, research on the safety of vaccines used in pregnancy, therapeutic agents to treat conditions leading to maternal or infant mortality, and specific medications (e.g. antidepressants, new drugs to treat hepatitis C). The Task Force report could include a list of conditions and their mortality factors. Other considerations related to prioritization were identified as the “ability to succeed,” in addition to the ability to execute, if possible using or maximizing resources that already exist.

Task Force members were reminded that although the goal is to develop evidence-based *standards of clinical care*, there is a lack of basic foundational knowledge about the physiologic changes in pregnancy and lactation, and the course of disease and differing effectiveness of therapies during those periods. Several people pointed out that there are also research resource needs, such as the development of additional animal models that are specifically targeted to pregnancy or placenta-on-a-chip.

Several Task Force members commented on the need to follow *health outcomes* of both woman and infant over both the short and long terms to truly establish risks and benefits of therapies taken during pregnancy or lactation. Pregnancy registries can be helpful in this regard, particularly if pharmacoepidemiologists are available to analyze the data; later, electronic health records could be used to collect and standardize the data if common data elements have been developed so that data from different systems can be combined.

Many suggestions were made concerning the *key players* who should be involved, including pregnant and lactating women; allied health professionals; fathers, partners, and families; tort lawyers, ethics committees, and IRBs; additional industry, pharmacists, and federal representatives; and communication science experts.

The Task Force agreed that *metrics* must be established to allow it to measure whether it has accomplished the goals set by the legislation, including improving content and data, increasing a trained workforce, clinical outcomes, infrastructure goals, and dissemination of its message to target audiences. For example, an overarching goal might be that women have access to therapies that have been evaluated and labeled for efficacy and safety in pregnancy and lactation.

Discussion of Key Points and Review of Recommendations

Dr. Spong continued to refine the main points heard to date by the Task Force on a plan and communications activities. Meeting attendees made numerous suggestions about the wording of specific recommendations, discussing prioritization, training, use of “big” data and animal models, and infrastructure. The incentives and liability discussions were deferred until the May meeting.

Adjournment

Dr. Spong said that the next meeting will take place May 14-15, 2018, at 6710B Rockledge Drive in Rockville, Maryland.

After thanking the Task Force members and participants for their hard work, and encouraging everyone to respond to the RFI, Dr. Spong adjourned the meeting on February 27, at 2:54 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