

**TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN
AND LACTATING WOMEN**

**Report to
Secretary, Health and Human Services
Congress**

September 2018

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Executive Summary

The Task Force on Research Specific to Pregnant Women and Lactating Women (“Task Force” or “PRGLAC”) was established by section 2041 of the 21st Century Cures Act, P.L. 114-255 (report, Section 6: Appendix I) and convened in accordance with the Federal Advisory Committee Act (5 U.S.C. App.) with membership as outlined in the Act (report, Section 6: Appendix II). The Task Force was charged with providing advice and guidance to the Secretary of Health and Human Services (HHS) on activities related to identifying and addressing gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities. In addition to advising the Secretary, the Task Force was charged with preparing and submitting to the Secretary and Congress a report that includes five elements (Executive Summary, Box 1).

The Task Force developed 15 recommendations (report, Section 5) based on information gleaned during four open meetings and a public comment period (report, Section 6: Appendices III, IV, V, IX). This Executive Summary provides context for the recommendations (Executive Summary, Box 2). A central theme resonated throughout the recommendations—the need to alter cultural assumptions that have significantly limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for pregnant and lactating women. The cultural shift is necessary to emphasize the importance and public health significance of building a knowledge base to inform medical decision-making for these populations.

| Executive Summary, Box 1. Statutory charge to the Task Force on Research Specific to Pregnant Women and Lactating Women, as established by the 21st Century Cures Act. | |
|---|--|
| ...Provide advice and guidance to the Secretary of the Department of Health and Human Services and prepare a report, for the Secretary to transmit to Congress, that includes the following: | |
| (1) A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies. | |
| (2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research. | |
| (3) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women. | |
| (4) Identification of Federal activities, including | |
| | <p>(a) the state of research on pregnancy and lactation;</p> <p>(b) recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;</p> <p>(c) dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public; and</p> <p>(d) existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities.</p> |
| (5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women. | |

Consequently, research on therapies for these populations must be facilitated and greatly augmented.

Over six million women are pregnant in the United States each year. Of these women, more than 90 percent take at least one medication during pregnancy and lactation (report, Section 6: Appendix VI). However, pregnant women and lactating women are often excluded from clinical research that could ultimately help these populations. The Task Force recommends that this trajectory of exclusion be altered to include and integrate pregnant women and lactating women in the clinical research agenda (**Recommendation 1**). To date, their exclusion may be motivated by concern about possible harms of medication use during pregnancy or lactation. Although the potential harms of unmedicated disease for both the woman and the developing fetus or breast-fed newborn usually elicit less study, they are nonetheless important. A comprehensive review of research in recent years conducted for the Task Force deliberations clearly showed the extremely limited information available on medication use in pregnancy and lactation (report, Section 6: Appendix VI).

Anecdotal reports state that many pregnant women and lactating women also use herbal and dietary supplements, but there are limited to no data to inform their use, dosing, or therapeutic levels. Since these dietary supplements are regulated differently than drugs by the United States Food and Drug Administration (FDA) and do not require pre-market approval, our ability to understand the safety and efficacy of what women consume during pregnancy and lactation is limited.

Evidence-based answers are required for women and their clinicians to make fully informed choices based on the risks and benefits of medicating or not medicating conditions during pregnancy and lactation. The provision of clinical data is essential to increasing the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women (**Recommendation 2**). Furthermore, expansion of this

| Executive Summary, Box 2: Task Force on Research Specific to Pregnant Women and Lactating Women Recommendations |
|---|
| 1. Include and integrate pregnant women and lactating women in the clinical research agenda |
| 2. Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women |
| 3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics |
| 4. Remove regulatory barriers to research in pregnant women |
| 5. Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women |
| 6. Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women |
| 7. Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the National Institute of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model |
| 8. Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are or may become pregnant and by lactating women |
| 9. Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research |
| 10. Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women |
| 11. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women |
| 12. Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women |
| 13. Optimize registries for pregnancy and lactation |
| 14. The Department of Health and Human Services Secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019 |
| 15. Establish an Advisory Committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research |

research requires the training and career development of a workforce with expertise in obstetric and lactation pharmacology and therapeutics (**Recommendation 3**).

The unique relationship between a pregnant woman and her fetus, or a lactating woman and her child, have resulted in federal regulations, guidance, and rules aimed at protecting the woman, fetus, and/or child (report, Section 2). A universal consent for pregnancy and lactation studies might be preferable given state law differences (including those affecting minors). Subpart B of the Common Rule regulations (Sec. 46.204(e)) currently requires both maternal and paternal consent for a pregnant woman to take part in a study that benefits only the fetus. Changing this to a requirement for maternal consent only would facilitate participation in research, more consistent with the requirements for pediatrics, under Subpart D 50.51 and 50.52, where single parent consent is acceptable. 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.

The Task Force recommends removal of unnecessarily burdensome regulatory barriers to research involving pregnant women (**Recommendation 4**).

For any cultural shift to occur, behavior change requires targeted communication strategies. When communicating information relevant to treating disorders in pregnant women and lactating women, messages must be concise, consistent, tailored, and actionable for health care providers and the public (report, Section 3). The Task Force recommends a focused public awareness campaign that highlights the importance of research on therapeutic products in pregnant women and lactating women, the impact of not taking needed medications during pregnancy and lactation, and the effects of not breastfeeding on the mother and child (**Recommendation 5**). In addition, evidence-based communication strategies with health care providers are needed to increase their knowledge and engagement (**Recommendation 6**).

The Task Force recognized that different approaches for subsets of therapeutic products (drugs, vaccines, and dietary supplements) may be required to make significant progress. These include: 1) therapeutics that are already in use and off-patent, 2) those already in use and on-patent, and 3) those in development for conditions not specific to pregnancy or lactation (e.g., antihypertensive agents, antibiotics, and vaccines) and for conditions specific to pregnancy (e.g., hyperemesis) or lactation (e.g., low milk supply). Also, different strategies may be needed to obtain regulatory approval and labeling for therapeutic products for use in pregnant women and in lactating women, with separate processes for prioritization. The Task Force outlined the parameters for moving forward (report, Section 1, Figure 1).

A major impediment to obtaining data on therapeutic products that are used by pregnant women and lactating women is the concern about liability (report, Section 1, Box 3). Without processes to mitigate liability, it is unlikely that incentives or regulations will provide traction to facilitate the development of an evidence base for therapeutic products that may be used by lactating women or by women who are or may become pregnant. The Task Force recommends implementing a liability- mitigation strategy (**Recommendation 7**). One example is the Vaccine Injury Compensation Program, but for this scenario, the mitigation would need to cover liability regardless of whether the therapeutic product receives marketing

approval or not. In addition, targeted programs and/or strengthening the FDA's authority to require, as part of applications for approval of new therapeutics, clinically relevant data for pregnant women and lactating women in study designs could expand the evidence base.

Many therapeutic products are already in use by pregnant women and lactating women. These products are commonly off-patent, thus there is no incentive to pharmaceutical manufacturers to obtain safety and efficacy data in pregnant and lactating populations. The National Institutes of Health's (NIH) Best Pharmaceuticals in Children Act (BPCA) program is a successful model for studying off-patent use of therapies in children (report, Section 6: Appendix XI). This model provides specific funding and has a prioritization process to study off-patent therapies that have public health benefit in children but have not been adequately studied. Using elements of this model, the Task Force recommends developing separate programs, one for pregnant women and one for lactating women, with specific funding and prioritization processes to obtain critically needed data (**Recommendation 8**). The Task Force felt it is essential to have separate programs to ensure the appropriate focus on these distinct patient populations and to mitigate concerns of competition between the needs for pregnant women and lactating women if a single program were developed.

Several conditions are specific to pregnancy; however, the pipeline for products to treat these conditions is minimal at best. The first impediment is liability, requiring the aforementioned liability-mitigation strategy (**Recommendation 7**). The second impediment is limited interest in the development of these products despite significant unmet needs. In lactating women, for example, therapeutic products for low milk supply are virtually nonexistent. Pregnant women urgently need therapeutic products for the treatment of preterm labor, hyperemesis, and cholestasis. Because these needs are distinct, separate prioritization processes for products for pregnant women and lactating women are essential. Research programs should be developed to drive discovery and development of new therapeutic products for conditions specific to pregnant women and lactating women (**Recommendation 9**). These programs could include a variety of models, including incentives, requirements, or other methods to stimulate discovery and development. Examples of targeted programs include the Biomedical Advanced Research and Development Authority (BARDA), which aims to secure the United States from pandemic influenza and other emerging infectious diseases by moving medical countermeasures, such as vaccines, drugs, and diagnostics, from research through advanced development and consideration for FDA approval. Another example is the NIH vaccine development program, which advances experimental vaccines up to phase II clinical trials.

To support Recommendation 1, the inclusion and integration of pregnant women and lactating women in the clinical research agenda, a proactive approach is needed for protocol development and study design (**Recommendation 10**). Specifically, investigators and sponsors should be required to justify the exclusion of pregnant women and lactating women in their study designs and to develop studies to capture the physiologic changes that occur over time in these populations. To achieve these goals, guidance needs to be developed for both investigators and institutional review boards. Also, the Task Force recommends leveraging and supporting both new and established research networks (report, Section 4 and Section 6: Appendix VII) and collaborations through financial support and incentives to perform this work

(Recommendation 11). The Task Force also recommends strengthening existing data resources to inform the evidence base and provide a foundation for research on pregnant women and lactating women **(Recommendation 12).** This includes designing health record systems that link mother and infant records, leveraging large databases and data systems, and utilizing innovative methods for analytics.

To date, one of the major methods for obtaining information on pregnant women has been through the use of registries (report, Section 6: Appendix VII). Registries have not been utilized for obtaining data in lactating women. Registries are typically operated by the pharmaceutical industry, often at the request of the FDA. The Task Force recommends optimizing registries for pregnancy and lactation to include the creation of a user-friendly website for registry listing, developing registry standards with common data elements, and facilitating transparency and access to the data **(Recommendation 13).** Rather than product-specific registries, the Task Force recommends developing disease- or condition-focused registries. The ideal would be a single registry for all therapeutic products. However, establishment of such registries for all relevant conditions will require substantial coordination, collaboration, and funding mechanisms.

Per the 21st Century Cures Act, the charter of the Task Force will expire in March 2019 (Appendix I). Given the large amount of work that remains to fully research therapeutic products used by pregnant women and lactating women, the Task Force recommends that the HHS Secretary consider exercising the authority provided in law to extend the Task Force when its charter expires **(Recommendation 14).** Based on the decisions of the Secretary, a continuation of the Task Force may provide more detail on the implementation of the recommendations made to date and address other pertinent areas related to these initial recommendations. Also, the Task Force recommends that the Secretary establish a Federal Advisory Committee to monitor and report on the implementation of recommendations and on updates to regulations and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research **(Recommendation 15).**

The work of the Task Force augments and extends prior efforts (Appendix X) that recommended the inclusion of pregnant women and lactating women in research. Without research and the establishment of an evidence base, practitioners care for pregnant women and lactating women without adequate data on the safety, efficacy, or appropriate dosing of therapeutic products. Pregnant women and lactating women and their health care providers are left with undesirable options—either taking a therapeutic product without high-quality dosing or safety information or not treating a condition adequately. In the case of lactation, women may be choosing to discontinue breastfeeding to take the therapy based on limited information, which then deprives the mother and infant of the benefits of lactation. Pregnant women, lactating women, their offspring, and families deserve to have this essential information. The Task Force urges the Secretary to take action on these recommendations.

Introduction

Pregnant women and lactating women with acute or chronic medical conditions face difficult decisions about medical management of their health. However, scientific evidence on the safety, efficacy, and dosing of medicinal therapies in pregnant women and lactating women is severely lacking (report, Section 6: Appendix VI). On a daily basis, pregnant women and lactating women and their clinicians are forced to make decisions about whether to therapeutically treat pre-existing or emerging medical conditions such as epilepsy, chronic hypertension, asthma, mastitis, and cholestasis without adequate scientific knowledge of the safety and efficacy of these treatments in this population. Decisions not to treat or inadequate treatment options pose significant risks for the health and survival of pregnant women and their offspring. Consequently, patients and clinicians cannot make appropriate and informed risk-benefit decisions.

Historically, there have been highly publicized cases of prescription drug use by pregnant women that ended with tragic results, such as thalidomide and diethylstilbestrol (DES). These cases illustrated gaps in safety assessment concerns, codified in part in federal regulations, that effectively excluded pregnant women from clinical drug studies. Fundamental ethical principles of justice and equity have prompted professional societies, women's health organizations, and experts in research ethics to recommend that federal policy be revised to require inclusion or a scientific justification for exclusion of pregnant women and lactating women in clinical research, absent compelling reasons for their exclusion (report, Section 2). When a drug is approved by the United States Food and Drug Administration (FDA) for use in adults, the approval includes all adult populations, unless specifically excluded or noted (e.g. approval only in post-menopausal women). Therefore, medicines approved by the FDA for adults includes women of reproductive age and pregnant women. However, at the time of approval of most drugs, there are rarely human data available for pregnant women or lactating women. Because dynamic physiologic changes occur throughout pregnancy and lactation that affect drug levels and action in the body, inclusion of pregnant women and lactating women in clinical trials is essential, unless there are compelling scientific reasons for their exclusion.

Recognizing the urgent public health problem and ethical concerns posed by the lack of information on medications used to treat conditions affecting pregnant women and lactating women, Congress enacted the 21st Century Cures Act (P.L. 114-255), which was signed into law in late 2016 (report, Section 6: Appendix I). Section 2041 of the Act directs the Secretary of the Department of Health and Human Services (HHS) to establish a "Task Force on Research Specific to Pregnant Women and Lactating Women" ("Task Force" or "PRGLAC"). The mandated purpose of the new Task Force is to identify and make recommendations to address gaps in knowledge and research about safe and effective therapies for use during pregnancy and for lactating women, and to explore ethical issues of including pregnant women and lactating women in clinical research. The Act charged the Task Force with reporting its findings and recommendations to the HHS Secretary and to Congress by September 2018; the Secretary then has until December 2018 to decide whether changes to regulations or other actions to increase knowledge in this area may be warranted. The Task Force expires two years from the date of its establishment, but it may be extended by the Secretary.

The authority to establish the Task Force was delegated from the HHS Secretary to the National Institutes of Health (NIH) Director on January 19, 2017. A federal charter establishing the Task Force was filed on March 13, 2017, within the 90-day time frame required by the law, and a notice of the Task Force's establishment was published in the *Federal Register*. Four public meetings were scheduled during 2017-18 to obtain input from the patient, clinician, and research communities (report, Section 6: Appendices II, III, IV, V, IX).

This report fulfills the congressional mandate by providing Task Force findings on the gaps in knowledge and research on medicinal therapies for pregnant women and lactating women, ethical and related regulatory issues surrounding the inclusion of these women in clinical research, the Task Force's proposed plan to identify and address research and knowledge gaps, and recommendations to improve the development of safe and effective therapies for pregnant women and lactating women. The report's appendices provide further information on the legislation, Task Force membership and procedures, the federal "Common Rule" (as it relates to research with pregnant participants), relevant ethics and research literature, federal agency activities, communications and public health campaigns, federal collaborative activities, and acronyms used in the report.

As the Task force focused on the mandate, they deliberated on the wording of "therapy," recognizing that although medicine/therapeutic product was likely the intended meaning, the wording is broad and could include behavioral interventions, devices, medicines, therapeutic products, over-the-counter medicines, and vitamins or dietary supplements. Recognizing that the scope needed to be defined, the Task Force voted at its first meeting to focus on drugs, vaccines, and dietary supplements due to their prevalent use by pregnant women and lactating women.

Gaps in Knowledge Regarding Medicinal Therapies for Pregnant Women and Lactating Women

No comprehensive data collection efforts are taking place in the United States that would enable researchers to determine all the disorders for which pregnant women and lactating women use medicinal therapies, what therapies they use, and what outcomes for themselves and their offspring can be attributed to such drug exposures. However, datasets from large United States electronic health record and health care claims databases, registries, surveys, and other sources indicate that such exposures are extensive.

In the United States, approximately 10 percent (more than six million) of women become pregnant each year, and four million births occur annually (Wang [PMID 28510297](https://pubmed.ncbi.nlm.nih.gov/28510297/)¹). Use of medications by pregnant

¹ <https://pubmed.ncbi.nlm.nih.gov/28510297/>

women or lactating women is widespread and growing, notwithstanding the dearth of information that exists specific to medication use by these populations. A 2011 study using data from two large birth defects studies found that about 90 percent of women took at least one medication during pregnancy, with 70 percent taking at least one prescription medication. Between 1976 and 2008, prescription medication use in the first trimester of pregnancy increased by over 60 percent in the United States, and the use of four or more medications at any time during pregnancy more than doubled (Mitchell [PMID 21514558²](https://pubmed.ncbi.nlm.nih.gov/21514558/)).

Disorders for which pregnant women commonly take medications include those caused by pregnancy and conditions not known to be associated with pregnancy. Among the former are pregnancy-induced hypertension, preeclampsia, preterm labor, gestational diabetes mellitus, pregnancy-related or postpartum depression, infections, pain, and nausea and vomiting of pregnancy (including hyperemesis gravidarum). The latter include, but are not limited to, chronic hypertension, seizure disorders, type 1 and type 2 diabetes mellitus, depression, cancer, endocrine disorders, autoimmune disorders, and substance use disorder (Andrade [PMID 15343213³](https://pubmed.ncbi.nlm.nih.gov/15343213/), Palmsten [PMID 26244530⁴](https://pubmed.ncbi.nlm.nih.gov/26244530/)). A more extensive overview of the state of therapies in pregnant women and lactating women can be found in the report, Section 6: Appendix VI.

A large majority of women in the United States (81.1 percent) begin breastfeeding their newborns, with yet only 51.8 percent still breastfeeding after six months and less than a third (30.7 percent) by the end of the first year (<https://www.cdc.gov/breastfeeding/pdf/2016breastfeedingreportcard.pdf>). Of the sparse literature on postpartum medication use, a majority of articles report that about 50 percent of women during this period—whether breastfeeding or not—take at least one medication (Saha [PMID 26516340⁵](https://pubmed.ncbi.nlm.nih.gov/26516340/)). A small study found that, on average, pregnant women and lactating women took four different medications (excluding vitamins, dietary supplements, and minerals) and that breastfeeding women took

² <https://www.ncbi.nlm.nih.gov/pubmed/?term=21514558>

³ <https://www.ncbi.nlm.nih.gov/pubmed/15343213>

⁴ <https://www.ncbi.nlm.nih.gov/pubmed/26244530>

⁵ <https://www.ncbi.nlm.nih.gov/pubmed/?term=26516340>

significantly more medications than pregnant women, many with unknown safety for the breastfed infant (Stultz, [PMID 17903100](https://pubmed.ncbi.nlm.nih.gov/term=17903100)⁶).

Furthermore, both pregnant women and lactating women use dietary supplements which have an even more limited evidence base. Dietary supplements are not intended to treat, diagnose, or cure a disease; the FDA regulates these under different regulations than drugs or biologic products such as vaccines. Multiple social factors contribute to declining rates of breastfeeding in the year after birth, but studies suggest that postpartum use of specific medicines reduces initiation and/or duration of lactation (Saha [PMID 26516340](https://pubmed.ncbi.nlm.nih.gov/term=26516340)⁷), depriving infants of the significant immediate and long-term health and developmental benefits of breastfeeding. The general absence of data on the extent of the transfer of specific drugs into human milk, and other factors, make health care providers cautious when advising on medication use while breastfeeding (Sachs [PMID 23979084](https://pubmed.ncbi.nlm.nih.gov/term=23979084)⁸). At the same time, there is a lack of research on medications that might be used to stimulate breast milk production in mothers who do not produce enough milk.

Research-based answers are required for women and their clinicians to make fully informed choices between the risks and benefits of medicating or not medicating conditions during pregnancy and lactation. Questions about medication use during pregnancy include what is known of a drug's exposure profile during pregnancy, transport across the placenta, fetal exposure, and the short- and long-term effects of such exposure; how a drug's safety and dosing might differ between non-pregnant/non-lactating adults (for which there may be data) and pregnant or lactating adults; how and why might drug safety, efficacy, and dosing data differ between humans and experimental animal models of specific disorders; and how the baseline rate of birth defects in pregnant women with and without a specific disorder compares with reported rates associated with fetal exposure to a drug for the disorder. Fundamental questions about medications use during lactation similarly include what is the level of infant exposure and what are the short- and long-term consequences of this drug exposure; if the mother does not breastfeed because of concern about infant exposure, what are the short- and long-term consequences; and if a mother breastfeeds but does not take medication for her medical condition, what are the short- and long-term consequences for the mother and the child.

⁶ <https://www.ncbi.nlm.nih.gov/pubmed/?term=17903100>

⁷ <https://www.ncbi.nlm.nih.gov/pubmed/?term=26516340>

⁸ <https://www.ncbi.nlm.nih.gov/pubmed/?term=23979084>

Research needs to include basic science investigations to understand transport of drugs into breast milk, studies of mechanisms and pre-clinical toxicology, and studies of differences between experimental animal and human results of medications.

Approaches to Filling the Knowledge Gaps

Before developing clinical trials to test drugs used by pregnant or lactating women, a sufficient evidence base in both basic and translational research is needed. These elements, largely lacking in obstetrics research, are central to increasing the number of randomized controlled trials (RCTs). For instance, is preeclampsia similar at a cellular level to hypertension? Is gestational diabetes mellitus (GDM) similar to type 2 diabetes mellitus? And what are the effects on the offspring of glucose-lowering medications used to treat GDM? Answers to these questions may lead researchers toward repurposing existing medications for pregnancy-related conditions. Recently, because preeclampsia shares similar pathological characteristics with cardiovascular disease (CVD), researchers from a NIH-supported clinical research network, working in collaboration with the FDA, conducted a phase I randomized, placebo-controlled clinical trial in pregnant women at high risk of preeclampsia. The trial drug, pravastatin, is widely used to reduce CVD risk in other populations. No maternal-fetal safety risks were observed and none of the women taking the drug developed preeclampsia, compared to 40 percent of the control group (Costantine [PMID 26723196⁹](https://pubmed.ncbi.nlm.nih.gov/26723196/)).

RCTs, long considered the “gold standard” of research for safety and efficacy data on medicinal therapies, so rarely yield data specific to pregnant women or lactating women that these women are considered “drug orphans” (Scaffadi [PMID 27297096¹⁰](https://pubmed.ncbi.nlm.nih.gov/27297096/)). A recent review of 338 phase III and post-market trials funded by NIH found that 68 percent of the trials explicitly excluded pregnant women; 47.3 percent excluded lactating women (Spong [PMID 29285540¹¹](https://pubmed.ncbi.nlm.nih.gov/29285540/)). Another review of 558 pharmaceutical industry-sponsored phase IV trials registered at ClinicalTrials.gov found that one percent of these trials were designed

⁹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=26723196>

¹⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=27297096>

¹¹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=29285540>

specifically for pregnant women. Of interest, 95 percent of these trials excluded pregnancy in their criteria for participation (Shields [PMID 24104789](https://www.ncbi.nlm.nih.gov/pubmed/24104789)¹²).

The dearth of RCT data on medications specifically for pregnant women and lactating women reflects shortfalls in other types of research that would inform clinical trial protocols aimed at improving clinical decisions for these populations. Pharmacokinetic (PK) research (how the body absorbs, distributes, and eliminates the drug) is essential for determining dosing of medications among specific patient populations such as pregnant women. Because of physiologic changes associated with pregnancy, even a clinical trial that includes pregnant women may yield questionable data for that group if it only tests the “standard” medication dose for non-pregnant populations. PK modeling has found, for instance, that the recommended preventive dose of ampicillin after anthrax exposure would not prevent infection of pregnant women because of increased metabolism. Given a higher drug clearance rate, a therapeutically effective dose for a non-pregnant adult might not be possible for pregnant women (Andrew [PMID 17329990](https://www.ncbi.nlm.nih.gov/pubmed/17329990)¹³).

Nonetheless, the proportion of human PK trials involving pregnant women was 1.29 percent of the total number of registered trials from the 1960s to 2013 (Illamola [PMID 28925019](https://www.ncbi.nlm.nih.gov/pubmed/28925019)¹⁴). While observational studies generally provide less vigorous evidence than RCTs, they can yield data to inform both clinical research and practice. For example, a case control study of the pharmacogenetics of codeine, prescribed commonly for pain from episiotomy or cesarean delivery, found that rapid metabolism in a subset of nursing women with a specific genetic makeup converted doses considered safe for infants to high, neurotoxic, and potentially fatal amounts of the pain medication in their breast milk (Madadi [PMID 18719619](https://www.ncbi.nlm.nih.gov/pubmed/18719619)¹⁵).

Furthermore, “big data” studies of information on large cohorts of pregnant patients can yield findings of potential use for testing in RCTs or, ultimately, for making treatment decisions. Pregnant patients with severe depression may decide not to use certain antidepressants because of concerns that that may be associated with low birth weight and preterm delivery, although the mechanisms of such outcomes are not

¹² <https://www.ncbi.nlm.nih.gov/pubmed/?term=24104789>

¹³ <https://www.ncbi.nlm.nih.gov/pubmed/?term=17329990>

¹⁴ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28925019>

¹⁵ <https://www.ncbi.nlm.nih.gov/pubmed/?term=18719619>

well understood. However, a recent study of more than 395,000 births in a regional Italian health care utilization database suggests that the risks may be associated with *not* medicating depression in pregnancy. Comparing maternal use of various classes of antidepressants before and during pregnancy, the researchers found that untreated depression in pregnancy may be implicated in the causal pathway of preterm birth and low birthweight (Cantarutti [PMID 27977749](https://pubmed.ncbi.nlm.nih.gov/27977749/)¹⁶).

¹⁶ <https://www.ncbi.nlm.nih.gov/pubmed/?term=27977749>

Section 1. A Plan to Identify and Address Gaps in Knowledge and Research Regarding Safe and Effective Therapies for Pregnant Women and Lactating Women, including the Development of Therapies

Developing a plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women is especially challenging in the current environment, where research capacity and the existing scientific literature are limited. The overarching vision for this plan is **to establish a strong evidence base to guide informed decisions about the use of therapeutic products during pregnancy and lactation in order to improve health outcomes for mothers, children, and families**. The objectives to achieve this goal are summarized in Section 1, Box 1.

Increasing research expertise in obstetrics and lactation will be essential to power the expansion of scientific knowledge in this area. Due to the limited number of individuals with expertise in obstetric and lactation pharmacology, there is a significant need for training programs that provide instruction in obstetric and lactation pharmacokinetics, pharmacodynamics (PD), pharmacogenomics, and pharmacoepidemiology. Although obstetricians have infrastructure and expertise in clinical research, further training specific to pregnancy and lactation pharmacology is needed to conduct research in this area. Given that pediatricians are closely involved in lactation discussions with women who have recently given birth, encouraging the development of pediatric pharmacology expertise specific to lactation may also help move the field forward. Training and expertise are needed across all sectors: industry, academia, institutional review boards, ethics committees, and the federal workforce. Increased engagement and participation in research from pregnant women and lactating women—

Section 1, Box 1: Objectives

- Increase expertise in obstetric/lactation research, especially pharmacology
- Increase engagement and participation of pregnant women and lactating women in clinical research
- Prioritize data collection on therapeutic products used by pregnant women and lactating women
- Increase the quantity and quality of research studies on therapeutic products for pregnant women and lactating women, including basic science, PK/PD, pharmacoepidemiology, and randomized controlled clinical trials
- Increase the availability of clinically meaningful information about therapies used by pregnant women and lactating women for providers and women
- Increase the number of therapeutic products with adequate and useful information for use in pregnant women and lactating women
- Augment the dissemination of current, accurate information on therapeutic products for pregnant women and lactating women
- Enhance collaboration among stakeholders (public, industry, government, etc.) to establish the evidence base and disseminate data related to therapies for pregnant women and lactating women

including lowering perceived and actual regulatory barriers—will be required to accelerate clinical research progress.

Because the research gaps related to pregnancy and lactation are extensive, prioritization will be needed. To support prioritization, additional data on the use of medications during pregnancy and lactation must be obtained and analyzed. The level of detail required for this information exceeds what is available currently—data on user characteristics, indication, dosing, duration of treatment, and timing of use during pregnancy and lactation are especially important to developing priorities and facilitating intervention studies. Such data, in conjunction with information on potential risks and scientific opportunities, can inform prioritization to make the most productive use of limited research resources. Prioritization should be informed by considering barriers to the use of particular therapies, impact on preventive health, potential for emerging threats, prevalence or severity of the conditions, and the prevalence of use of a particular medication or class of medications. The ability (funds, resources, etc.) to execute is an essential aspect of prioritization, as this will translate directly to the viability of the plan. In addition, leveraging scientific opportunities for drugs already in the developmental pipeline, to obtain information about their effects on pregnant or lactating women, would help to facilitate changes in clinical guidelines and practice when these drugs are approved.

A substantially higher number of rigorous research studies will be needed to address the wide research gaps apparent in the literature on pregnant women and lactating women. This body of new research should include:

- Conducting PK/PD studies in pregnant women and lactating women, including methods to support their participation in such research
- Expanding access to pregnancy registries, large-scale administrative and other databases, and completed studies/trials to support pharmacoepidemiological, case-control, and other studies to increase knowledge and inform prioritization
- Strengthening the evidence base of basic research on how common conditions differentially affect women during pregnancy and lactation, and how medications affect the composition and flow of breast milk
- Increasing the number of rigorous controlled trials to provide sound information about the relative risks of using or foregoing medication during pregnancy or lactation for both pregnancy and non-pregnancy related conditions

Building on the extensive network of current collaborations among many stakeholders will be helpful in improving the evidence base and disseminating the information. Trans-federal collaborations have been particularly helpful in increasing the availability of clinically meaningful information about therapies used by pregnant women and lactating women. Including such information on approved product labeling would be especially valuable for women and clinicians.

Key Considerations for a Research Plan

A plan to address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women will require several parallel and intersecting strategies that account for differences in indication (i.e., pregnancy versus lactation), types of therapeutic products, drug development status, whether a drug is on- or off-patent, and maternal and child outcomes (Section 1, Figure 1).

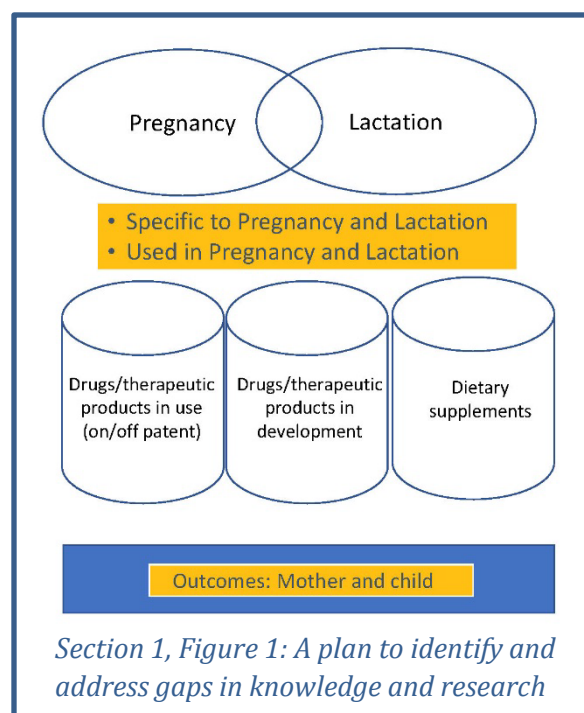
Different research pathways will be needed for pregnant women and lactating women, and for women who are both pregnant and lactating. There are two general uses of medications: those specific to pregnancy and lactation, such as therapies to treat gestational diabetes, cholestasis of pregnancy, or lack of milk production, and those for general conditions (not specific to pregnancy or lactation), such as therapies to treat chronic hypertension or depression, that are used by pregnant or lactating women. The risk-benefit assessment is different for pregnant women and lactating women, driving these separate approaches, although there are some common elements. In addition, research involving lactating women may be more amenable to faster progress.

Medications that are approved for conditions specific to pregnancy or lactation must be shown to be safe and effective in pregnant or lactating women. In contrast, medications approved to treat general conditions (e.g., hypertension) have gone through the FDA approval process for determining safety and effectiveness in non-pregnant or non-lactating adults. When pregnant or lactating women use these medications for the approved use, these drugs are not considered to be used “off-label.” This means that the efficacy dosing and safety of the drugs are considered the same in pregnant or lactating women as they are in non-pregnant/non-lactating adults. However, dosing and PK/PD information specific to pregnancy and lactation is frequently unavailable or inadequate, despite the many physiologic changes women experience during these periods, pointing to the need to enroll pregnant and lactating women in clinical studies. Examples of differences in metabolism and physiology in pregnancy and lactation are described in detail in Section 6: Appendix VI.

Therapeutic products currently in use may be on- or off-patent, which may require different strategies to obtain data. Dietary supplements are regulated under a different set of regulations by the FDA

(<https://www.fda.gov/Food/DietarySupplements/>), thus quality control of these products is limited to post-market inspection and required good manufacturing practices, and assessment of safety and efficacy may be limited.

Vitally important to the plan is that the outcomes include the pregnant or lactating woman and the fetus or infant. Given these complexities and diverse processes for approval, a research plan will need to consider the broad categories outlined in Section 1, Box 2.



Because so many therapies have not been tested in pregnant or lactating women, a prioritization process is needed to gather the necessary data for appropriate dosing. When prioritizing therapies, factors to be considered include the need, value, gaps in knowledge, ability to execute (resources), ability to succeed (sustainability, funding, etc.), and prevalence and incidence of the condition. In addition, the prioritization process must consider risks to the expectant mother, fetus, and pregnancy of not taking a medication and the risk to infant health of not breastfeeding.

Section 1, Box 2: Broad categories for the Plan

| |
|--|
| Therapeutic products for pregnancy-indication currently in use, off patent |
| Therapeutic products for lactation indication currently in use, off patent |
| Therapeutic products for non-pregnancy indication currently in use, off patent |
| Therapeutic products for non-lactation indication currently in use, off patent |
| Therapeutic products for pregnancy-indication currently in use, on patent |
| Therapeutic products for lactation indication currently in use, on patent |
| Therapeutic products for non-pregnancy indication currently in use, on patent |
| Therapeutic products for lactation indication currently in use, on patent |
| Therapeutic products in development for pregnancy-indication |
| Therapeutic products in development for non-pregnancy or lactation-indication |
| Therapeutic products in development for lactation-indication |
| Supplements used in pregnancy |
| Supplements used in lactation |

Critical to the plan is the ability to obtain dosing information that will be aided by the development and use of PK/PD models for therapeutic dosing. When appropriate, this should be feasible even for products still under pre-market development. Given the long-term requirements for safety evaluations, novel methods to assess safety as well as post-market methods, including electronic health records and registries, will need to be utilized.

Assessing Progress and Outcomes

A variety of measures will need to be created, collected, analyzed, and monitored to assess progress in implementing the plan and to track outcomes. This includes monitoring the number of investigators with expertise in obstetric or lactation pharmacology and the number of training programs with this emphasis. Increasing participation in research can be assessed by the number of studies and trials that include pregnant women and lactating women, as well as the numbers of pregnant women and lactating women who are research participants.

Stimulation of research on therapeutic products in pregnant women and lactating women is vital to accomplish the plan. This metric can be monitored through the number of studies, funding levels, the number of grants and investigators, and the level of infrastructure for research related to pregnant women and lactating women. In addition, it is important to ensure the capture of consistent data using common data elements and the presence of pregnancy and lactation information variables in large datasets.

Metrics to assess the availability of clinically meaningful information about therapies used by pregnant women and lactating women include the following:

- Number of therapeutic products with data on dosing, PK/PD endpoints, and safety data specific to pregnant women and lactating women;

- Number of products with adequate and meaningful information for use in pregnant women and lactating women;
- Number of clinical guidelines that reference these products; and
- The time to establish an evidence base for new products.

Increasing the amount and dissemination of information on therapeutic products for pregnant women and lactating women requires monitoring clinical guidelines and new strategies to ensure the data are accessible to providers, women, and their families. This may require targeting specific groups with consistent messaging.

Incentives and mitigation of liability

To facilitate the creation of the desired evidence base for pregnant women and lactating women, mitigating the issues of liability and identifying incentives is essential. The different sectors that conduct research needed for therapeutic products used in pregnant women and lactating women may react differently to different incentives, such as grant funding, publications, profit, public image, and protection from liability. Examples of some approaches are in Section 1, Box 3.

Section 1, Box 3. Examples of Incentives and Mitigation of Liability

| Methods | Objectives of the program | Potential Model |
|--|--|--|
| Additional Patent/Intellectual Property/Data Exclusivity | Provides financial incentive for companies to study or invest in therapies on patent and used by pregnant women or lactating women | Best Pharmaceuticals for Children Act (provides an additional 6 months of market exclusivity for successful completion of requested studies) |
| New Drug or Biologics License Applications (BLAs) | Legislatively require data on use by pregnant women or lactating women | Pediatric Research Equity Act (requiring that studies be conducted in children) |
| NIH-Supported Research | Have specific funding opportunities focused on pregnant women or lactating women for therapies on- and off-patent | |
| Prize Authority | Provide a prize for additional data on specific therapies in pregnancy or lactation | |
| Compensation for Unintentional Injuries | Offset liability concerns related to requirements for testing investigational therapies used by pregnant women and lactating women | Vaccine Injury Compensation Act |

| Methods | Objectives of the program | Potential Model |
|---|---|---|
| R&D Tax Credits | Provide tax incentive for companies to invest in investigational therapies used by pregnant women and lactating women | Orphan Drug Act (provides financial incentives, including tax credits, for conducting studies for drugs to treat orphan diseases) |
| Loan Repayment | To incentivize basic science and clinical researchers into research related to therapies used by pregnant women or lactating women | |
| Priority Review Vouchers | Provide for incentives by shortening review timelines for companies to invest in development of novel therapies or new indications for existing medicines used by pregnant women or lactating women | Drugs to treat tropical diseases and rare pediatric diseases (receipt of a voucher allows the holder to obtain a priority review for a subsequent application for a non-rare or non-tropical disease) |
| Formulary Prioritization/Reimbursement Above Unstudied Generics | Provides incentive for companies to invest in therapies off-patent for pregnant women or lactating women | |

Section 2. Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research

The shift in approach over the last two decades to expect inclusion of children and women in research leaves the presumption of exclusion of pregnant women in clinical research isolated among research populations. Other populations, such as those with intellectual disabilities, routinely are not included in research, but that is more a matter of practice than explicit direction.¹⁷ At the same time, the differing physiologic processes among lactating women and breastfed infants are rarely even considered. Yet more than two decades ago (1994), the Institute of Medicine recommended that pregnant women be presumed to be eligible to participate in clinical studies and that lactating women not be excluded from such studies. (Mastroianni [PMID 25144026](#)¹⁸). More recently, a Committee Opinion of the American College of Obstetricians and Gynecologists (ACOG) (issued in 2007 and re-issued in 2015) stated that “All women should be presumed to be eligible for participation in clinical studies,” ([PMID 17766625](#)¹⁹). And in 2009, a number of academic institutions formed the *Second Wave Initiative* (<http://secondwaveinitiative.org/>), whose mission is to end “the knowledge gap on treating illness in pregnant women.”

Current Metrics of Inclusion/Exclusion

A search of current clinical studies listed in ClinicalTrials.gov²⁰ shows that pregnancy is rarely mentioned unless the study is directly related to pregnancy. Of the 4,408 United States-based studies that recruited women or girls between January and November 2017, 59 studies included “pregnancy” or “pregnant.” Of these, 51 studies were pregnancy-related, and six specifically excluded pregnant women (with only one justifying the exclusion).

Similarly, breastfeeding and/or lactation are usually not mentioned in clinical studies unless a study aim is specifically targeted to lactation. Of the same 4,408 studies reported in 2017, a search for “breastfeeding” or “lactation” yielded 26 studies, 22 of which were infant/breastfeeding studies. Of the four remaining studies that

¹⁷ Spong, et al. 2017. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. <https://jamanetwork.com/journals/jama/fullarticle/2667821>.

¹⁸ <https://www.ncbi.nlm.nih.gov/pubmed/25144026>

¹⁹ <https://www.ncbi.nlm.nih.gov/pubmed/17766625>

²⁰ <https://clinicaltrials.gov/ct2/home>

were not infant/breastfeeding-related, three specifically excluded breastfeeding women, but without clear justification.

The overall finding is clear: Most current studies do not provide for inclusion of pregnant or lactating women in their protocols.

Costs of Exclusion without Justification

The ethical principles of justice and equity require that pregnant women and lactating women be provided safe and effective therapies, just like any other group of individuals. Participation in research benefits the populations represented, particularly if the study is sufficiently powered to draw conclusions for each of those populations. Nonetheless, pregnant women and lactating women are populations not only routinely unrepresented in clinical studies, but often are formally excluded without justification, leading to a disparity.

Additionally, the use of untested or inadequately tested therapies pose risks to maternal and/or fetal health. Less than 10 percent of medications approved by the FDA since 1980 have sufficient information to determine their risk for causing birth defects.²¹ Without conducting appropriate PK studies in pregnancy, it remains unknown whether the dosing will be adequate for therapeutic effect or impact pregnancy outcomes. According to one review of the dearth of information upon which to make prescribing decisions, “A major difficulty in establishing PK information in pregnancy is due to a lack of well-controlled clinical trials...Often, safety information is acquired from clinical reports of atypical drug reactions...” meaning that information is gathered largely from pregnant women experiencing an atypical drug experience and only after a drug is on the market. The ethics of this process are questionable, as pregnant women are theoretically required to undergo an atypical drug experience before clinicians are alerted.²²

Balancing Risks and Benefits

At the same time, exposing both women and fetuses/infants to medication risks without benefit is ethically problematic. Used for decades in pregnant women, selective serotonin reuptake inhibitors (SSRIs) demonstrated a slightly increased risk of fetal anomalies in a study of adequate power.²³ Without sufficient information about fetal safety, clinicians may be reluctant to treat maternal health conditions. Pregnant women, due to concern for

²¹ Adam et al. 2011; <https://www.cdc.gov/pregnancy/meds/index.html#ref>

²² Anger, G.J. and Piquette-Miller, M. (2008), Pharmacokinetic Studies in Pregnant Women, *Clinical Pharmacology & Therapeutics*, 83: 184-187. Doi:10. 1038/sj.clpt.6100377

²³ Chambers et al. 2008, Reefhuis et al. 2015

fetal health and pregnancy outcomes, may choose to stop taking medications needed for their own health. However, this may have untoward implications as the risk of not taking these medications may outweigh the risk of fetal anomalies.

Until proposed revisions become effective²⁴, Federal regulations (the so-called “Common Rule”) designate pregnant women as a “vulnerable population,” along with children, prisoners, and intellectually disabled individuals, largely due to concern for fetal exposure to harm. While the revised regulations would remove pregnant women as an example of a vulnerable population, the requirements of Subpart B still apply. Yet, the benefits of participation in research studies often are overlooked. With the focus on fetal risk, other factors may not be adequately considered, such as use in pregnant women of untested drugs and the consequences of sub-therapeutic treatment. A closely monitored clinical trial may be as safe or safer than variable dosing through usual practice.

To achieve a favorable risk/benefit ratio for conducting research on therapeutics for use by pregnant women and lactating women, some trade-offs may be acceptable. For pregnant women, if maternal benefit can be demonstrated, a marginal increase in fetal risk may be acceptable. If the fetus stands to benefit, some maternal risk may be reasonable (altruism). For lactating women, if the infant may benefit from continued breastfeeding from a mother who is receiving drug treatment, some infant risk may be acceptable. However, research that provides no maternal or fetal benefit should pose no more than minimal fetal risk. In one survey, the majority of women said they would participate in research if the research were likely to benefit the fetus; fewer would participate only for personal benefit.²⁵

Ethical Issues: Discussion

Inclusion, or a Scientific Justification for Exclusion

The Task Force discussed numerous approaches to increasing the range of studies that include pregnant women and lactating women in their study designs, while taking safety and ethical issues into account. For example, removing pregnant women as a “vulnerable population” from the Common Rule regulations and other policy changes would help to shift research assumptions toward inclusion of these populations, signaling to the institutional review boards that oversee human subjects research, research sponsors, academia, and industry that research involving pregnant women and lactating women is both appropriate and necessary. Instead, investigators should be asked to justify exclusion of pregnant women and lactating women in their study designs. This should also be considered based on the amount of information that is known about the drug

²⁴ The revised Common Rule was supposed to go into effect July 19, 2018, but implementation has been delayed until January 20, 2019, to allow institutions time to prepare for compliance.

²⁵ Rodger, et al., Participation of Pregnant Women in Clinical Trials, *American Journal of Perinatology* 2003; 20(2):69-76.

intended to be studied. For example, investigational new drugs may pose very different risks than drugs already on the market.

Consent

The panel also discussed issues around consent, noting that the timing of obtaining consent is important. A universal consent for pregnancy and lactation studies might be preferable given state law differences (including those affecting minors). Subpart B of the Common Rule regulations (Sec. 46.204(e)) currently requires both maternal and paternal consent for a pregnant woman to take part in a study that benefits only the fetus. Changing this to a requirement for maternal consent only would facilitate participation in research, more consistent with the requirements for pediatrics, under Subpart D 50.51 and 50.52, where single parent consent is acceptable. 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.

Alternative Study Designs

Many clinical trials involving pregnant and lactating women could meet the minimal risk standard set by the regulations. Another option would be to add a new subsection for “Minor increase over minimal risk” to Subpart B of the Common Rule regulations (Sec. 46.204). However, scientists can use other available data, such as data from inadvertent exposure, opportunistic prospective studies (in which pregnant women are receiving medication as part of routine patient care), incident pregnancies (that occur after a woman is enrolled in clinical research), comparative effectiveness, or physiological modeling. For example, the current practice of not giving pregnant women live vaccines is now being challenged because evidence from incidental pregnancies does not indicate higher risks.

Each type of study may have benefits and drawbacks. PK studies may require different strategies, such as population pharmacokinetics, in cases where prolonged periods of blood collection would be required. Opportunistic studies may send false safety signals if an adequate number of participants are not enrolled in the study that are representative of the general population of pregnant women. Animal data are helpful to inform trial designs, but animals may not transfer the drug across the placenta or in breast milk the same way that humans do. However, new research efforts to study the placenta in real time, or “on-a-chip,” may provide opportunities not available previously. Women of reproductive age are likely to be digitally savvy, which offers another possible path for participation. New data sharing policies and platforms can provide unprecedented transparency and a way to pool datasets.

Industry Considerations

For decades, the pharmaceutical industry has been reluctant to include pregnant women and lactating women in their research studies on therapeutics because their physiologic changes often affect drug metabolism and increase the complexity of trial design. Industry also has concerns about potential fetal risk (history of thalidomide-induced birth defects) and the critical lack of information about whether drugs cross the placenta or are passed through breast milk. Ethical considerations and the legal consequences of injury to children who

were exposed to medical therapies *in utero* have often led companies to limit the evaluation of new drug research to preclinical assessments of safety in animal models of disease.

Consequently, industry has limited its investment in research in obstetrics, and there is a limited pipeline of researchers and FDA/regulatory reviewers who are expert in this area. To promote new drug development for pregnant and/or lactating women who require therapeutic intervention, incentives should be considered to drive research investment that is both more attractive and better protects scientists and study participants.

Moving Ahead

Despite the challenges to conducting research with pregnant women and lactating women, many women are interested in participating in studies that could benefit their health, their children's health, and other women's health. A requirement for inclusion or scientific justification of exclusion of pregnant women and lactating women in research studies would send positive signals to the research community. Foundational knowledge, such as basic scientific understanding of the cause of pregnancy-induced conditions, such as preeclampsia, is critical. Use of a network (such as NICHD's Obstetric-Fetal Pharmacology Research Centers) might allow studies to be appropriately powered, develop research capacity, and be a cost-effective way of conducting these studies. For extensive details of the federal networks, see Section 6: Appendix VII.

Several strategies could be considered to ensure the conduct of needed research studies. Public-private partnerships, which would include professional associations, patients, industry, and physician scientists, could be one approach. Reducing liability in conducting research and sharing the expense of clinical trials also may provide incentives to the research community to more fully engage in this field. The effort is more likely to achieve success if research participants are involved from the beginning. Researchers in obstetrics and lactation could learn from how the pediatrics field addressed similar issues in the past (see Section 2, Table 1 and Section 6: Appendix XI and Section 6: Appendix XI Table 1).

Section 2, Table 1 NIH Infrastructure Needs for Research on Pregnancy and Lactation Compared with Pediatrics: Current Status

| Infrastructure Need | Measure | Pregnancy and Lactation | Pediatrics |
|---|--|-------------------------|-----------------|
| Workforce – Current (FY 2017) NIH PIs | NIH Primary Investigators (PIs) in relevant research categories ²⁶ | 783 | 8,444 |
| | NIH PIs with projects related to pharmacology within relevant research categories | 79 | 967 |
| | NIH PIs in relevant research categories with appointment (joint or single) in pharmacology-related departments OR with a PharmD degree | 12 | 162 |
| Workforce – Recent (2013-2017) NIH training and career development awardees | K12 scholars with pharmacology background or research, 2012-2017 | 2 | ~24 (estimated) |
| | Individual K awardees with pharmacology related projects, FY 2017 | 4 | ~31 (estimated) |
| | T32 pharmacology programs with specialty focus | 2 | 11 |
| | T32 postdoc trainees from pharmacology programs with specialty focus | 4 | 60 |
| | T32 postdoc trainees with pharmacology background | 62 | |

²⁶ For pregnancy and lactation, relevant NIH categories include Pregnancy; Breastfeeding, Lactation and Breast Milk; and Maternal Health. For pediatrics, the NIH Pediatrics category was used.

| Infrastructure Need | Measure | Pregnancy and Lactation | Pediatrics |
|----------------------------|---|---|---|
| Clinical Research Networks | NIH Clinical Research Networks with specialty focus, and their funding levels | Obstetric-Fetal Pediatric Research Centers (OPRC): \$2.6 M Maternal Fetal Medicine Units Network (MFMU): \$16.8 M Global Network for Women's and Children's Health Research (GN): \$6.4 M | ~53 pediatric clinical networks (estimated) |
| | Number of ongoing open CT.gov registered studies related to pharmacological therapies within these networks, 2017 ²⁷ | OPRC: 9 MFMU: 4 GN: 2 | ~221 (estimated) |
| Inclusion of Population | Policies or requirements for inclusion of target population | No policies or requirements | NIH policy requires inclusion, with allowed exceptions |
| | Percent of phase III NIH funded open clinical trials including relevant population, 2017 | 12 | 29 |
| Industry involvement | Incentives available to industry | None | Additional exclusivity period available under BPCA; Pediatric rare disease priority review voucher program; Orphan Drug Act |
| | Liability concerns | Often cited as a barrier to research | A barrier to early phase research |
| | Legislative and regulatory requirements | No pre-approval human pregnancy or lactation data required | BPCA and Pediatric Research Equity Act (PREA) may require some pediatric data |

²⁷ Note: Not all network studies are related to the use of therapies in pregnancy and lactation; some observational studies, for example, are focused on identifying risk factors for certain conditions.

Section 3. Effective Communication Strategies with Health Care Providers and the Public on Information Relevant to Pregnant Women and Lactating Women

Behavior change is often a goal of targeted communication strategies, particularly those related to public health. When communicating information relevant to pregnant women and lactating women, it is imperative that messages be concise, consistent, tailored, and actionable for health care providers and the public. Each audience has its own needs and preferences, so those must be considered when creating a communications plan.

It is also important to contemplate how to reach these audiences “where they live,” whether it is in an online forum, in a professional journal, in the doctor’s office, or around the dinner table.

Case Study: NIH Safe to Sleep® Campaign

Several federal agencies fund and develop public health campaigns related to pregnant women and lactating women. The NIH, for example, supports the Safe to Sleep® campaign, to increase public awareness about safe infant sleep practices to help reduce the risk of Sudden Infant Death Syndrome (SIDS) and other sleep-related causes of infant death. The campaign also includes information on breastfeeding.

Safe to Sleep® launched as Back to Sleep® in 1994 in response to a recommendation²⁸ from the American Academy of Pediatrics (AAP) that all babies be placed on their backs or sides to sleep to help reduce the risk of SIDS. (In 2005, this recommendation was modified to back-sleeping only.²⁹) To raise awareness of the recommendation, the campaign focused on three primary audiences:

- Infant caregivers and public at-large
- Health care providers
- Maternal and infant service providers

²⁸ American Academy of Pediatrics, Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. (1992). Infant positioning and SIDS. *Pediatrics*, 89, 1120–1126

²⁹ American Academy of Pediatrics, Task Force on Sudden Infant Death Syndrome. (2005). The changing concept of sudden infant death syndrome: Diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. *Pediatrics*, 116(5), 1245–1255

The campaign used the following strategies to help spread the message of safe infant sleep among these priority audiences. Many of the strategies have proved successful and perhaps could be applied to efforts regarding pregnant women and lactating women.

Strategy 1: Increase awareness

These activities intended to promote back-sleeping to the public as the “new normal.” They included the development and widespread dissemination of brochures and other educational materials, public service announcements on radio and television, and partnerships with the manufacturers of baby products (e.g., back-sleeping messages on cereal boxes).

Strategy 2: Engage influencers

This effort intended to increase awareness among health care and maternal and infant service providers of the new AAP recommendations and to update provider practices. It included enlisting the Surgeon General to reinforce the AAP recommendations. It also included the dissemination of campaign materials to the membership of AAP and the American College of Obstetrics and Gynecology; to all hospitals in the United States with newborn nurseries; to clinics of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); and to childcare and licensed home care providers.

Importantly, this communications strategy led to the development of continuing education programs, self-study courses that teach nurses about SIDS, SIDS risk reduction, and easy ways to model and communicate safe sleep messages to caregivers. This approach has been successful in updating provider knowledge and practices and is still used today.

Strategy 3: Tailor the message

This communications strategy came about after research showed that back-sleep messages were being met with resistance among certain audiences. For example, African-American mothers were found to be less likely to put their babies on their backs to sleep³⁰. In response, the campaign again enlisted the Surgeon General’s help in reaching out to racially and ethnically diverse communities via public service announcements. The campaign also conducted meetings with African-American organizations to better understand barriers to action and to identify, discuss, and plan strategies for spreading safe sleep messages within their communities. Because of these meetings, a key sub-audience was identified—African-American grandmothers—for whom the campaign also tailored messaging and outreach strategies.

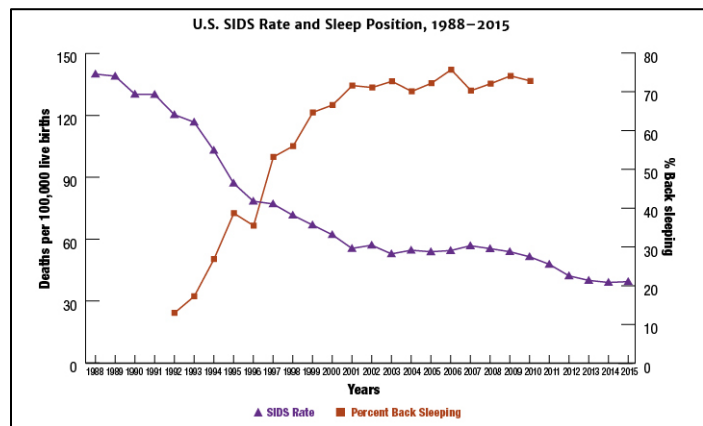
³⁰ Willinger M, Hoffman HJ, Wu K, Hou J, Kessler RC, Ward SL, Keens TG, Corwin MJ. Factors Associated with the Transition to Nonprone Sleep Positions of Infants in the United States. The National Infant Sleep Position Study. *JAMA*. 1998;280(4):329–335. doi:10.1001/jama.280.4.329

Based on these inputs, the campaign sought to train influencers to spread the message of safe infant sleep and address barriers in a culturally sensitive way. It developed and disseminated *Babies Sleep Safest on Their Backs: A Resource Kit for Reducing the Risk of SIDS in African American Communities*. It also conducted national training workshops on SIDS risk reduction with partner organizations, including Alpha Kappa Alpha Sorority, Inc., Women in the National Association for the Advancement of Colored People, and the National Coalition of 100 Black Women.

Strategy 4: Evaluate, evaluate, evaluate

Metrics are critical for evaluating the impact of public health awareness initiatives. To measure its success, the Safe to Sleep® campaign tracks data from the Centers for Disease Control and Prevention (CDC), such as progress on caregiver adoption of safe infant sleep practices³¹; the number of orders of campaign materials; and other sources, including national and regional surveys.

For example, the National Infant Sleep Position Study found that from 1993, the year before Back to Sleep's inception, to 2010, the proportion of infants placed on their backs to sleep increased from 17 percent to 73 percent.³² At the same time, the United States SIDS rate declined by more than 50 percent.³³ (Section 3, Figure 1)



Section 3, Figure 1: Outcomes Driven Communication: Safe to Sleep Campaign

Strategy 5: Partner for success

Finally, a core tenet of Safe to Sleep's communications strategy is partnership with stakeholder agencies and organizations to support message fidelity, information sharing, and technical assistance. Today, Safe to Sleep® co-chairs the Federal Sudden Unexplained Infant Death (SUID)-SIDS Workgroup, which includes CDC, the Health Resources and Services Administration (HRSA), FDA, and others to efficiently coordinate efforts to reduce infant mortality from SUID and SIDS. It also partners with major national organizations, including the following:

³¹ [Pregnancy Risk Assessment Monitoring System](#). CDC Reproductive Health. Centers for Disease Control and Prevention

³² Slone Epidemiology Center (n.d.). [The usual position in which mothers place their babies to sleep: data from the national NISP telephone survey for years 1992 – 2010](#). Retrieved March 2018

³³ National Center for Health Statistics, CDC

- AAP (Task Force on SIDS)
- Association of Women’s Health, Obstetric and Neonatal Nurses (Nurses’ CE activity)
- Kappa Alpha Psi Fraternity, Inc. (Fatherhood initiative on safe infant sleep)
- U.S. Breastfeeding Committee (Information sharing, bridged messaging)

Safe to Sleep® has also found success in partnering at the local level, particularly with states that have high SUID rates. For example, from 2012 to 2015, the campaign conducted state-specific outreach in Arkansas, which in 2013 had the highest sleep-related infant mortality rate in the United States. More than 100 mini-grantees within the state completed awareness-raising and educational events dedicated to safe infant sleep. In 2014, Arkansas dropped to the fourth-highest sleep-related infant mortality rate. While overall rates of SUID and infant mortality in Arkansas remain high, a recent report by the Arkansas Department of Human Services (DHS) found that SUID deaths fell by 62 percent among a subgroup of children who were under DHS supervision.³⁴

Tactics for disseminating information to health care providers and to pregnant women and lactating women

A common thread to communications strategies across government agencies, pharmaceutical companies, and professional societies is the use of formative research to determine how best to reach intended audiences. These approaches include surveys, focus groups, and other means to understand not only the needs of these audiences, but also their valued sources of information.

For example, a 2013 survey found that maternity care providers and childbirth education classes are the most trusted sources of information for first-time and experienced mothers,³⁵ suggesting that to deliver messaging to pregnant women and lactating women, it is important to reach providers and childbirth educators. The following are some possible tactics for reaching that goal:

Offer continuing education

Continuing education (CE) courses can be a valuable tactic for disseminating messaging and practice updates to the provider community. These courses motivate and incentivize providers by offering credits necessary to maintain licensure and certifications.

³⁴ Child Death and Near Fatality Multidisciplinary Review Committee. [Annual Report fo SFY2016 and SFY2017](#)

³⁵ Declercq ER, Sakala C, Corry MP, Applebaum S, Herrlich A. Listening to MothersSM III: Pregnancy and Birth (May 2013), *New York: Childbirth Connection*

CE courses come in several different formats, including in-person sessions, live or archived webinars, and self-paced education modules. There is some evidence that maternal care providers prefer live, in-person courses, compared to online options, but the extra expense and time requirements of these sessions may make them less feasible.³⁶ Live webinars are attractive because they allow for interactive discussion, but again, time constraints of the provider may hamper their ability to attend. Archived webinars and self-paced online modules allow for 24-hour accessibility, which may make it easier for providers to fit training into their busy schedules.

These approaches can, however, present additional challenges (e.g., inability to ask questions in real-time, skimming to find answers to post-test, etc.).

Informative drug labeling

The labeling that accompanies a drug is the principal document used by manufacturers and the FDA to disseminate information to prescribers on a drug's safety and efficacy. The labeling is written for health care providers and communicates all FDA-approved uses of the drug.

FDA is actively working to improve use of the labeling by conducting formative research with physicians. Based on input received at a recent FDA Risk Communication Advisory Committee meeting (March 5 and 6, 2018), prescribers prefer, among other things, consistent labeling language describing human data, if available, and the “bottom line”—the most important information—at the top of the document.

Drug labeling information for pregnant women and lactating women has changed over the last few years as FDA has been implementing the Pregnancy and Lactation Labeling Rule (PLLR - effective June 30, 2015), which removes the letter categories A, B, C, D, and X. The pregnancy letter categories were found to be overly simplistic and often misinterpreted as a grading system. In its place, the FDA replaced these categories with an integrated risk summary that provides the following details:

- More complete assessment of the known risks
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

Today, the FDA labeling includes prescribing information for pregnant and lactating women in (under Section 8, USE IN SPECIFIC POPULATIONS). FDA's efforts to improve providers' awareness of the labeling promise to make this document an effective means of communicating with prescribers. The PLLR provides a framework for inclusion of pregnancy and lactation data; however, data are needed to populate these sections of labeling.

³⁶ Lamaze International, 2015 Lamaze and ICEA Conference Evaluation. Unpublished

FDA staff identified a total of 575 prescription drug and biological product labeling changes (including labeling for new products) approved in PLLR format between June 30, 2015-September 30, 2017. Of these, 129 (22.4 percent) included human data about pregnancy, and 86 (15.0 percent) included human data about lactation. Labeling in 50 products (8.7 percent) included human data about both pregnancy and lactation, but 414 products (72 percent) had neither human data about pregnancy nor human data about lactation. The types of human pregnancy data found in PLLR labeling included information from RCTs, cohort studies, case-control studies, and case reports. Human lactation data found in PLLR labeling included some quantitative data (e.g., breast milk levels of drug). All drugs and biological products approved since June 2015 are required to be compliant with PLLR formatting.

Of these, approximately 575 prescription drug and biological products with labeling approved in the PLLR format between June 30, 2015, and September 30, 2017, 129 (22.4 percent) included descriptions of human data about pregnancy, and 86 (15.0 percent) included descriptions of human data about lactation. (Note: labeling in 50 products of the above-mentioned 215 products included descriptions of human data about both pregnancy and lactation, these products are included in the above numbers.) Almost all labeling currently contains animal reproduction data; the labeling (sometimes referred to as the package insert) is available on FDA's website.³⁷

Within the data review above, FDA identified a total of 67 prescription drug and biological product labelings with pregnancy related post-marketing studies and 11 products with lactation related post-marketing studies. Post-marketing pregnancy studies included pregnancy registry studies, enhanced pharmacovigilance programs, and other complementary studies (e.g., case-control studies). Based on information provided in the study reports submitted to FDA, approximately 7,889 women were enrolled in the 67 post-marketing pregnancy studies, and approximately 27 women were enrolled in the 11 post-marketing lactation studies.

Section 6: Appendix XII represents more detailed PLLR labeling data for new drugs and biological applications approved between June 30, 2015, and September 30, 2017, and includes a list of new molecular entities (NMEs) approved by FDA, which includes some biological products. The information on this chart was obtained from the "snapshots" for each product provided on FDA's website, which includes human and animal data provided, if any, for each product.

The spreadsheet regarding these products includes the specific drug name and detailed information on the percentage of women participants in the pivotal clinical trials that were utilized to obtain FDA approval. In

³⁷ This information was obtained from <https://labels.fda.gov> U.S. Food & Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993.

addition, the source of pregnancy and lactation data in the labeling for each approved NME is listed. The spreadsheet also includes a description of the animal data reported in the PLLR labeling, which includes animal reproduction studies, including embryo-fetal development studies, embryo-fetal toxicology studies, pre- and post-natal toxicology studies, and animal lactation data noting whether the drug was present in the milk and whether it affected the nursing offspring.

The spreadsheet regarding certain Biologics Licensing Applications (BLA) includes the specific name and detailed information on available study data (e.g. human and animal pregnancy studies, available registries, and human lactation studies) from the labeling for each Novel Drug at <https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm483775.htm>.³⁸ This information can also be found on FDA's website.³⁹

Leverage the reach of professional societies

Professional societies whose membership includes maternal care providers can play a significant role in disseminating information relevant to pregnant women and lactating women. For example, membership of the Society for Maternal-Fetal Medicine (SMFM) includes MFM subspecialists, fellows, physicians in related disciplines, nurse practitioners, registered nurses, genetics counselors, ultrasound technicians, medical students, residents, and others. SMFM reaches these audiences through its website, monthly e-newsletter, email blasts, online forums, educational programs, media outreach, direct mail, and social media (including a private Facebook group where members interact to answer practice questions, keep current on the latest protocols and procedures, etc.).

Professional societies like SMFM, the ACOG, the AAP, the Association of Women's Health, Obstetric and Neonatal Nurses, and other organizations that provide family or emergency medical care have built information-sharing communities that could help amplify messaging directed toward maternal care providers and their patients.

³⁸ <https://www.fda.gov/drugs/informationondrugs/ucm412998.htm> Click on the drug name for approval dates, history, and labels; click on Drug Trials Snapshot which highlights who participated in the clinical trials and whether there were differences among sex, race, and age groups. As noted on the website, there are limitations to use of these snapshots.

³⁹ For example, see <http://wayback.archive-it.org/7993/20170111093319/http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/ucm482392.htm>

Use traditional and non-traditional platforms

Traditional means of communicating with providers include publishing manuscripts and thought-leader articles in academic journals, pitching expert interviews with targeted members of the trade press, developing or contributing to web resources, and disseminating information via newsletters, listservs, and email blasts.

Apps for smartphones and tablets can be another route to reach providers, particularly those such as Epocrates and Medscape that specifically target health care professionals with distilled medical information.

Social media can be a powerful tool for reaching not only health care providers, but also directly communicating with pregnant women and lactating women. According to the 2016 Nielsen Social Media Report, people from Generation X (ages 35 to 49) spend an average of seven hours per week on social media, followed by Millennials (ages 18 to 34) at six hours, and Baby Boomers (ages 51 to 69) at four hours.⁴⁰ This exposure represents a huge opportunity to reach target audiences with consistent messaging through evidence-based and patient-centered blogs, organizational and private-group pages on Facebook (such as the SMFM example mentioned above), Twitter chats and live tweeting from conferences, and awareness-raising hashtags on various social media sites.

LinkedIn, a social networking site for professionals, enables users to write posts and share articles with their colleagues, while YouTube and Instagram allow for the sharing of visual content, which could include instructional videos, scientific talks, animations, and infographics.

There are also social media sites that target more specialized audiences. Doximity, for example, is a social network of more than a million health care providers in the United States. It allows users to connect, interact, and share information with colleagues in a professional context, enabling physicians, et al., to get just-in-time information that they can apply to their practices.

⁴⁰ 2016 Nielsen Social Media Report. <http://www.nielsen.com/us/en/insights/reports/2017/2016-nielsen-social-media-report.html>

Section 4. Identification of Federal Activities

Existing Federal Activities Related to Pregnancy and Lactation

An array of federal agencies support research, health care and clinical practice, communications, and collaborative efforts that are directly applicable to the Task Force on Research Specific to Pregnant Women and Lactating Women. Section 4, Figure 1 lists federal agencies included in this report. Federal activities were identified by Task Force agencies, supplemented by systematic searches of agency databases, websites, and publications.

Research Activities

Each of the featured federal agencies offer unique contributions to research related to pregnancy and lactation (Report, Section 6: Appendix VII). Agencies with a strong foundation in toxicology, maternal and fetal medicine, teratology, and epidemiology often collaborate to assess how prenatal exposures can affect risks to the offspring.

Biomedical research and regulatory agencies have taken a lead role in studying the safety and effectiveness of interventions for pregnant women and lactating women and their children. Health care services agencies, along with their medical research counterparts, support efforts to measure and improve the utilization, quality, and impact of health care services and interventions.

Agencies often emphasize different aspects of pregnancy, lactation, and maternal health and focus on these issues to varying degrees. For example, CDC supports a wide range of research that includes the effects of environmental exposures on pregnant women and their children, vaccine use in pregnant women and lactating women, and behavioral and educational interventions for these populations.

NIH funds research projects that involve pregnancy, breastfeeding and lactation, and/or maternal health. These projects are reported in three overlapping categories, ranging from 159 projects in the breastfeeding category to 683 projects in the pregnancy category. The number of research projects in each category and the number of projects that overlap categories was evaluated (See report, Section 6: Appendix VII, Figure 1). A small number of studies can be found overlapping all three categories. For example, one NIH study is examining the long-term safety and durability of antiretroviral therapy for pregnant women and lactating women with HIV and their infants. Other NIH-funded studies relevant to the Task Force may address only maternal and not child outcomes—and therefore are reported only in the maternal health category—or are focused on infant

Section 4, Figure 1: Federal Agencies

- Agency for Healthcare Research and Quality (AHRQ)
- Centers for Disease Control and Prevention (CDC)
- Department of Agriculture (USDA)
- Department of Defense (DoD)
- Department of Veterans' Affairs (VA)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)
- National Institutes of Health (NIH)
- National Vaccine Program Office (NVPO)
- Office of the Assistant Secretary for Health (OASH)
- Substance Abuse and Mental Health Services Administration (SAMHSA)

outcomes and breastfeeding and are reported only in the breastfeeding category. Each of these categories includes grants from at least 19 of NIH's 27 Institutes and Centers. For more details, see Section 6: Appendix VII.

Prenatal Exposures

Identifying the impact of prenatal exposures is a shared research interest of several federal agencies. The National Toxicology Program (NTP) is an interagency program, involving NIH, EPA and others, that provides scientific information about hazardous substances in the environment and serves as a central resource for activities, programs, and policies that advocate for health and disease prevention. For example, one NTP-supported study examined developmental effects and pregnancy outcomes associated with cancer chemotherapy use in pregnant women. At the

FDA, researchers are evaluating prenatal exposure to hand-held metal detectors and magnetic resonance imaging. Through its epidemiological research, CDC addresses the impact of occupational and environmental exposures that affect the health of pregnant women and their offspring. Section 4, Figure 2 lists examples of studies of prenatal exposure in military personnel and veterans.

Section 4, Figure 2: Prenatal Exposure and the Military

Military personnel and veterans may be exposed to stresses and toxins not typically found in civilian life.

Examples of DoD and VA studies include:

- Effect of maternal PTSD on preterm birth (VA)
- Environmental exposures for women who served in the Gulf War (DoD)
- Procedures for counseling female veterans about the teratogenic risks of prescription medications (VA)

CDC and NIH support a range of structured cohort and case-control studies to help assess whether prenatal exposures—including prenatal exposure to medications—are related to specific structural birth defects. For example, the National Birth Defects Prevention Study (NBDPS) and the Birth Defects Study To Evaluate Pregnancy Exposures (BD-STEPS) have provided insight into antibiotic and asthma medications taken by pregnant women and possible links to birth defects.

Safety and Efficacy of Medicinal Therapies in Pregnant Women and Lactating Women

Several federal agencies support research on the safety and efficacy of medications, therapies, vaccines, and other pharmaceutical drugs in pregnant women and lactating women. As the federal regulatory agency with responsibility for approval of drugs, devices, and biologics, FDA supports research to advance knowledge about the safety and efficacy of these products. Research areas that involve pregnant women and lactating women include basic research into mechanisms of therapies in pregnancy and lactation; medication use, safety, and efficacy in pregnant women and lactating women; PK and PD; exposure to medical devices; preclinical studies in toxicity; and the effects of tobacco product use in pregnant and lactating populations. For example, FDA established the Medication Exposure in Pregnancy Risk Evaluation Program—a collaborative, multi-site research program that conducts studies of medication use and outcomes in pregnancy. USDA supports studies on the safety and effectiveness of vitamin supplementation in pregnant women and young children. As shown in Section 4, Figure 3, NIH has established state-of-the-art clinical research networks with specialized expertise in studies involving pregnant women.

A range of CDC programs, including the Center for Global Health, conduct research to improve pregnancy outcomes around the world. Research topic areas include antiretroviral therapies for HIV-positive pregnant women, influenza vaccines for pregnant women, and safety and efficacy of antiretroviral therapies in hepatitis B virus (HBV) and HBV-HIV infected women. The NVPO, part of the HHS Office of the Assistant Secretary for Health, directs clinical studies that focus on immunization of pregnant women. Examples include: 1) Tetanus Toxoid, Reduced Diphtheria Toxoid, and

Acellular pertussis vaccine (Tdap) Safety in Pregnant Women and 2) Safety of Simultaneous Administration of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) and Inactivated Influenza Vaccine in Pregnant women. In each study, reaction symptoms are observed and analyzed to determine maternal and fetal outcomes. With the most recent Zika outbreak, several federal agencies collaborated to develop and fund studies about maternal immunization and Zika infection in pregnant women.

Section 4, Figure 3: Examples of NIH Clinical Research Networks

- The Obstetric-Fetal Pharmacology Research Units (OFRU) network provides expert infrastructure to conduct safe, technically sophisticated, complex studies in pharmacology, placental transfer, and testing of therapeutic drugs during pregnancy.
- The Maternal-Fetal Medicine Units Network (MFMU) conducts clinical trials to decrease maternal complications, fetal growth abnormality, and preterm birth; and to provide the basis for cost-effective, evidence-based obstetric practice.
- The International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network evaluates potential therapies for HIV and HIV related symptoms in infants, children, adolescents, and pregnant women both domestically and internationally.

Utilization and Quality of Care for Pregnant Women and Lactating Women

Some federal agencies are directly involved in providing medical care for pregnant women and lactating women, and conduct research on utilization and quality of care as it relates to their programs. Other agencies do not provide health care services themselves, but as part of their research mission they collect data or conduct broad-based studies on the utilization and quality of care.

Although HRSA is not primarily a research agency, it supports research related to clinical care. HRSA research projects often focus on health care utilization, dissemination of evidence-based practices in the community, and the impact of HRSA's programs. For example, one HRSA study looked at the efficacy of an exercise intervention to prevent perinatal depression in women who attended federally qualified health centers. HRSA also supports the Maternal and Child Health Research Network on Pregnancy Related Care (also known as the CARN Network), a group of practicing obstetrician-gynecologists affiliated with the ACOG. CARN conducts a range of provider surveys to inform clinical practice.

Several agencies support research on the utilization, acceptance, and benefits of maternal immunization. For example, CDC is currently funding a study on immunization delivery in obstetrics and gynecology settings to promote vaccination of women before and during pregnancy. CDC's Internet Panel Survey on Pregnant Women is conducted in November and April of each year to monitor vaccination trends in pregnant women and includes topical questions on areas of special interest, such as Zika virus. The NVPO's efforts to enhance maternal

immunization research include developing a maternal-neonatal database and validating vaccine safety definitions in research involving pregnant women and newborns.

Researchers funded by the VA are assessing the coordination of pregnancy care received by women veterans. To evaluate these health services, researchers are examining health care utilization data and conducting interviews from women veterans and their health care providers.

FDA, NIH, and AHRQ support research on medication use among pregnant women and lactating women with various medical conditions, including asthma, seizure disorders, mental health disorders, diabetes, and bacterial and viral infections. AHRQ's largest research portfolio relevant to pregnancy and lactation is devoted to the cost and quality of maternal and obstetric care. AHRQ conducts research on a range of topics like the risks and benefits of labor induction and cesarean delivery, implementation of recommended therapies, and differences across hospitals and providers in obstetric practice. CDC and AHRQ also provide funding for large databases with information about the use of medication and other interventions by pregnant women, as shown in Section 4, Figure 4.

Section 4, Figure 4: Examples of Large Databases

- **Medical Expenditure Panel Survey (MEPS)** – includes data on health services, costs, and how services are paid. (AHRQ)
- **Healthcare Cost and Utilization Project (HCUP)** – provides data on hospital stays, emergency room, and other visits. (AHRQ)
- **Pregnancy Risk Assessment Monitoring System (PRAMS)** – collects data on maternal attitudes and experiences before, during, and shortly after pregnancy. (CDC)
- **Maternity Practices in Infant Nutrition and Care (mPINC)** – collects data on breastfeeding practices from maternity care service facilities. (CDC)

Health Care and Clinical Practice

Beyond supporting research efforts related to pregnancy and lactation, federal agencies contribute to health care and clinical practice in the forms of recommendations, guidance, and/or direct provision of clinical care. NIH, AHRQ, NVPO, OASH, CDC, and FDA do not directly support clinical care; however, each agency's research helps shape the scientific evidence base for clinical practice recommendations and efforts to inform both health professionals and the public.

In addition to their own research and clinical care activities, federal agencies advise other entities about the research and topic areas that each agency supports. NIH works with ACOG to ensure that clinical practice guidelines that rely upon scientific evidence from NIH-funded studies are effectively translated for use in clinical practice. NVPO, through the National Vaccine Advisory Committee, helps develop recommendations for

Section 4, Figure 5: U.S. Preventive Services Task Force (USPSTF)

Led by AHRQ, USPSTF is a voluntary panel of experts who convene to provide evidence-based recommendations about clinical preventive services like medications, vaccines, screenings, and counseling services. NIH and other federal agencies work with AHRQ on USPSTF recommendations. Eighteen of the current USPSTF recommendations are directly focused on pregnancy and/or lactation, and 26 recommendations are related to pregnancy and/or lactation.

vaccine research priorities and ways to promote adequate availability of safe and effective vaccines. AHRQ and OASH, among others, create initiatives and recommendations to address the importance of healthy lifestyles while pregnant and breastfeeding. AHRQ works with OASH, HRSA, SAMHSA, and Ohio State University on the Healthier Pregnancy Initiative to increase screening and referral for preventive services for tobacco use, alcohol use, depression, intimate partner violence, obesity, and breastfeeding in pre- and perinatal care settings. AHRQ also sponsors the Evidence-Based Practice Reports, which provide science-based information on costly, yet common, medical conditions and novel health care strategies and technologies. These reports, along with information provided by other federal agencies, help to form the basis of recommendations for USPSTF (see Section 4, Figure 5).

FDA provides regulations and recommendations to ensure safety and effectiveness of therapies, prescription drugs, biologics, and medical devices for pregnant women and lactating women. For example, FDA offers vital information about the toxicity potential of infectious disease therapies for women of childbearing age and pregnant women in the guidance *Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications*. FDA is also involved in training activities for health care providers to teach them about safety and effectiveness of certain drugs in pregnant women.

HRSA, DoD, and VA directly support clinical care through programs and health care services. HRSA's Health Center Program provides comprehensive primary care services to over 24 million people nationwide through a national network of health centers. HRSA also supports several programs that benefit pregnant women, infants, and children: Title V Maternal and Child Health Block Grant, Healthy Start, Maternal, Infant, and Early Childhood Home Visiting Program, the Ryan White HIV/AIDS program, and Healthy Tomorrows Partnership for Children program. HRSA also offers training programs related to pregnancy and lactation for health care professionals.

The DoD provides health care services to pregnant women and lactating women through TRICARE—the health care system for active duty military, dependents, and retirees. The DoD also offers special programs related to pregnancy and lactation like the Family Advocacy Program and the New Parent Support Program. The VA offers health care services directly to pregnant women and lactating women veterans through the Veteran's Health Administration and in the community. In addition to primary care services, the VA offers guidance for pregnant women and lactating women and their physicians about medication use during pregnancy and lactation. Two examples of how the VA provides guidance about medication use during pregnancy and lactation include the VA's Pharmacy Benefit program, which bases decision aids on information from the FDA, the National Library of Medicine's LactMed®, and the VA's Teratogenic Drugs Project.

Federal Communication Strategies

As shown in Section 4, Figure 6, several federal agencies fund and develop public health campaigns related to pregnant women and lactating women. NIH supports the Mom's Mental Health Matters campaign, which targets depression and anxiety around pregnancy. NIH also supports the Safe to Sleep campaign, which focuses on SIDS and other sleep-related causes of infant death, and includes information on breastfeeding.

Treating for Two is an initiative by the CDC, in collaboration with federal and non-federal partners, to improve the health of women and infants by working to find the safest treatment for common conditions before and during pregnancy. It intends to fill knowledge gaps and provide reliable guidance. The NIH-funded LactMed® database is a unique resource for lactating women and their health care providers. It is a searchable database to provide information on drugs and other chemicals to which breastfeeding mothers may be exposed. The Text4baby campaign, a public-private partnership involving several agencies, provides a free text messaging service with health information specifically designed for pregnant women and new mothers.

Each federal agency develops and provides health communications related to pregnancy, breastfeeding, and lactation. Most of these tools are designed to increase awareness and educate health professionals, pregnant women, mothers, and their loved ones. Many NIH institutes provide resources to the public about pregnancy and breastfeeding as it pertains to pre-existing medical conditions. VA offers information about medication use by pregnant women and lactating women. The Office on Women's Health within OASH also provides resources for the public about medications in pregnancy, Zika and pregnancy, tobacco and pregnancy, nursing moms in the workforce, and breastfeeding and lactation.

In addition to providing resources for pregnant women or lactating women, several agencies create communication tools for health care providers. AHRQ gears most communication tools toward providers and health service organizations; however, it also offers fact sheets and infographics for the public about topics like substance abuse and effects on pregnant women and their offspring. DoD and CDC websites provide resources for pregnant women and lactating women, their health care providers, and public health professionals. CDC develops messaging to address several medical conditions and health issues as related to pregnancy. Examples include gestational diabetes, Zika, infections, folic acid, preventing birth defects, safe medication in pregnancy, pregnancy and opioid pain medication, international travel, listeriosis, blood pressure, and breastfeeding.

FDA and NVPO also provide materials about medications and vaccines during pregnancy. FDA creates print, digital, and web-based material that provides safety information about biologics, medications, and medical devices for pregnant women and lactating women and their health care providers. NVPO supports social media efforts, administers the www.vaccines.org website that provides materials about vaccinations during pregnancy, and held a webinar about vaccine safety in 2016.

Section 4, Figure 6: Public Health Campaigns



Trans-Federal Collaborative Efforts

Federal agencies frequently join forces and work together on research, clinical guidelines and recommendations, clinical care, and communications to advance the development and appropriate use of medicinal therapies for pregnant women and lactating women (see Section 4, Figure 7).

Examples include—but are certainly not limited to—the Federal Interagency Forum on Child and Family Statistics (NIH, HRSA, AHRQ, CDC, DoD, etc.), Treating for Two initiative (CDC and NIH), Text4Baby (NIH, HRSA, CDC, and others), antiretroviral pregnancy registry (NIH, CDC, FDA, HRSA), Zika Experimental Science Team (ZEST) (NIH, FDA, HRSA), the Immunization Safety Task Force (CDC, NIH, DOD, IHS, VA, FDA, and DoD), a conference to address opioid misuse and pregnancy (FDA, NIH, DoD, CDC, and SAMHSA), a scientific conference about children exposed to ZIKV in the womb (NIH, HRSA, EPA, USAID, and other HHS divisions), and collaborations on clinical practice guidelines (VA and DoD).

Section 4, Figure 7: Trans-federal Collaboration



The Zika Pregnancy and Birth Defects Task Force, created by CDC in collaboration with other agencies, conducts research to reduce the impact and risk of Zika in pregnant women, infants, and children and produces data to inform stakeholders in clinical care settings.

Section 5. Recommendations to Improve the Development of Safe and Effective Therapies for Pregnant Women and Lactating Women

The Task Force submits the following recommendations to the Secretary of HHS regarding research and the development of safe and effective therapies specific to pregnant women and lactating women based on information gleaned during four meetings and a public comment period. The Task Force developed these recommendations in open, public sessions and voted on each recommendation at the May 2018 meeting (report, Section 6: Appendices III, IV). All recommendations received a majority vote, with occasional abstentions as noted below.

The central theme of all recommendations is the need to alter cultural assumptions that have significantly limited scientific knowledge of therapeutic safety, effectiveness, and dosing for pregnant and lactating women. It is critical to facilitate and augment research on therapies for these populations.

1. Include and integrate pregnant women and lactating women in the clinical research agenda

- Remove pregnant women as an example of a vulnerable population in the Common Rule
- The Food and Drug Administration (FDA) should harmonize with the Common Rule and remove pregnant women as a vulnerable population
- The Department of Health and Human Services (HHS)⁴¹ should develop guidance to facilitate the conduct of research in pregnant women and lactating women

2. Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women

- Provide additional resources and funding for research to obtain clinically meaningful and relevant data for specific and co-existing conditions in pregnant women and lactating women, including but not limited to:
 - Develop preclinical models
 - Expand basic science research to inform drug development
 - Develop new tools and methods to assay therapeutic products, such as those that utilize small volumes and are sensitive to detect minute quantities in human milk
 - Develop new tools to assess pharmacodynamic response in pregnant women, lactating women, and children
 - Fund clinically relevant research and studies to inform therapeutic product use in pregnant women and lactating women
 - Design trials to capture long-term maternal, obstetric, and child outcomes

⁴¹ The Secretary could delegate this responsibility to one of its operational divisions.

- Utilize longer award periods by government funders (beyond the typical 5-year award), when needed, for study design and data collection

3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics

- Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
- Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
- Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics

4. Remove regulatory barriers to research in pregnant women⁴²

- Modify subpart B of the Common Rule
 - Change 46.204(e) in subpart B to maternal consent alone
 - Given the recognized autonomy of a pregnant woman, the evolution of family structure, that for a child only one parental signature is required for research to benefit the child and to align with parental consent for pediatrics
 - Add in the option of “Minor increase over minimal risk” from subpart D to 36.046

5. Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women

- Highlight the importance of research on therapeutic products in pregnant women and lactating women, including the impact of not taking the medication during pregnancy and lactation as well as the impact of not breastfeeding on mother and child
- Engage stakeholders such as Department of Health and Human Services (HHS), professional societies, industry, advocacy groups, and public and global partners

⁴² One member abstained due to a concern that the word “barrier” was too strong.

6. Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women

- Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs
- Increase the engagement of health care providers to disseminate information from research findings to their patients
- Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries
- Develop appropriate strategies for sharing and interpreting research findings and risk

7. Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are or may become pregnant and by lactating women⁴³

- Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women
 - Using the Vaccine Injury Compensation Program (VICP) as a model, however include mitigation whether or not the therapeutic product achieves marketing approval
- If liability mitigation is insufficient, consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data (such as pharmacologic and clinical data) on pregnant women and lactating women to inform dosing and safety

8. Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the National Institute of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model

- Provide specific funding
- Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women

9. Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women⁴⁴

- Create separate prioritization processes for pregnant women and lactating women
 - Unmet need examples in lactation: low milk supply, mastitis
 - Unmet need examples in pregnancy: preterm labor, hyperemesis

⁴³ One member abstained due to conflict of interest.

⁴⁴ One member abstained due to conflict of interest.

- Consider a Biomedical Advanced Research and Development Authority (BARDA)-like model and the NIH vaccine model that takes clinical development up to phase II

10. Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research

- Investigators/sponsors must specifically justify exclusion in study design
- Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation
- Develop a systematic plan on how data for pregnant women and lactating women will be obtained in a timely fashion to include pharmacokinetics/pharmacodynamics and safety
- Develop guidance for institutional review boards and investigators about the inclusion of pregnant women and lactating women in research
- Develop a systematic plan for if a woman becomes pregnant in a study to include whether product should continue, if un-blinding is necessary, how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information

11. Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women

- Provide financial support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, and methodologies.
- Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women
- Encourage networks/collaborations to engage in public-private partnerships to facilitate research

12. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women

- Design health record systems to link mother and infant records
- Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries
- Use novel data resources
- Use innovative methods of data analytics
- Require common data elements to facilitate collaboration and use

13. Optimize registries for pregnancy and lactation

- Create a user-friendly website for registry listing
- Develop registry standards and common data elements that facilitate input of pertinent data with easy, transparent access to obtain information in real time
 - Include maternal, obstetric, and child outcomes, along with birth defects

- Facilitate access to data and transparency of information in registries
 - Use the ART registry as a model
- Develop disease/condition-focused registries
 - Move toward a single registry for all therapeutic products with input from stakeholders

14. The Department of Health and Human Services Secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019

15. Establish an Advisory Committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research⁴⁵

⁴⁵ One member abstained due to consideration that this committee may have a different scope.

Section 6. Appendices

Appendix I – Legislation

Appendix II – Task Force Membership

Appendix III – Meeting Agendas

Appendix IV – Meeting Minutes

Appendix V – Public Comments

Appendix VI – Research on Therapies in Pregnant Women and Lactating Women

Appendix VII – Federal Activities Related to Pregnancy and Lactation, by Agency

Appendix VIII – Pregnancy Registries

Appendix IX – Request for Information (RFI) and RFI Summary

Appendix X – Historical Recommendations Regarding Testing of Therapies Used by Pregnant Women and Lactating Women

Appendix XI – Lessons Learned from Implementing the Best Pharmaceuticals for Children Act: Implications for PRGLAC

Appendix XII – List of Acronyms

Appendix I – Legislation

SEC. 2041. <<NOTE: 42 USC 289a-2 note.>> TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN.

(a) Task Force on Research Specific to Pregnant Women and Lactating Women

(1) Establishment.--Not later than 90 days after the date of enactment of this Act, the Secretary of Health and Human Services (referred to in this section as the "Secretary") shall establish a task force, in accordance with the Federal Advisory Committee Act (5 U.S.C. App.), to be known as the "Task Force on Research Specific to Pregnant Women and Lactating Women" (in this section referred to as the "Task Force").

(2) Duties.--The Task Force shall provide advice and guidance to the Secretary regarding Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.

(3) Membership.--

(A) Federal members.--The Task Force shall be composed of each of the following Federal members, or the designees of such members:

(i) The Director of the Centers for Disease Control and Prevention.

(ii) The Director of the National Institutes of Health, the Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the directors of such other appropriate national research institutes.

(iii) The Commissioner of Food and Drugs.

(iv) The Director of the Office on Women's Health.

(v) The Director of the National Vaccine Program Office.

(vi) The head of any other research-related agency or department not described in clauses (i) through (v) that the Secretary determines appropriate, which may include the Department of Veterans Affairs and the Department of Defense.

(B) Non-federal members.--The Task Force shall be composed of each of the following non-Federal members, including--

(i) representatives from relevant medical societies with subject matter expertise on pregnant women, lactating women, or children;

- (ii) nonprofit organizations with expertise related to the health of women and children;
- (iii) relevant industry representatives; and
- (iv) other representatives, as appropriate.

(C) Limitations.--The non-Federal members described in subparagraph (B) shall--

- (i) compose not more than one-half, and not less than one-third, of the total membership of the Task Force; and
- (ii) be appointed by the Secretary.

(4) Termination.--

(A) In general.--Subject to subparagraph (B), the Task Force shall terminate on the date that is 2 years after the date on which the Task Force is established under paragraph (1).

(B) Extension.--The Secretary may extend the operation of the Task Force for one additional 2-year period following the 2-year period described in subparagraph (A), if the Secretary determines that the extension is appropriate for carrying out the purpose of this section.

(5) Meetings.--The Task Force shall meet not less than 2 times each year and shall convene public meetings, as appropriate, to fulfill its duties under paragraph (2).

(6) Task force report to congress.--Not later than 18 months after the date on which the Task Force is established under paragraph (1), the Task Force shall prepare and submit to the Secretary, the Committee on Health, Education, Labor, and Pensions of the Senate, and the Committee on Energy and Commerce of the House of Representatives a report that includes each of the following:

- (A) A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies.
- (B) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research.
- (C) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women.
- (D) Identification of Federal activities, including--
 - (i) the state of research on pregnancy and lactation;
 - (ii) recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;

(iii) dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public; and

(iv) existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities.

(E) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

(b) Confidentiality.--Nothing in this section shall authorize the Secretary of Health and Human Services to disclose any information that is a trade secret, or other privileged or confidential information, described in section 552(b)(4) of title 5, United States Code, or section 1905 of title 18, United States Code.

(c) Updating Protections for Pregnant Women and Lactating Women in Research.—

(1) In general.--Not later than 2 years after the date of enactment of this Act, the Secretary, considering any recommendations of the Task Force available at such time and in consultation with the heads of relevant agencies of the Department of Health and Human Services, shall, as appropriate, update regulations and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research.

(2) Criteria for excluding pregnant or lactating women.--In updating any regulations or guidance described in paragraph (1), the Secretary shall consider any appropriate criteria to be used by institutional review boards and individuals reviewing grant proposals for excluding pregnant women or lactating women as a study population requiring additional protections from participating in human subject research.

Appendix II - Task Force Membership

CHAIRPERSON

Catherine Y. Spong, M.D.
Deputy Director
Eunice Kennedy Shriver National Institute of Child
Health and Human Development
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

MEMBERS

Terry A. Adirim, M.D.
Deputy Assistant Secretary of Defense
Defense Health Agency
U.S. Department of Defense
Falls Church, VA 22042

Shelli A. Avenevoli, Ph.D.
Deputy Director
National Institute of Mental Health
National Institutes of Health
U.S. Department of Health and Human Services
Rockville, MD 20892

Diana W. Bianchi, M.D.
Director
Eunice Kennedy Shriver National Institute of Child
Health and Human Development
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Karin Bok, Ph.D.
Senior Vaccine Science Advisor
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Washington, DC 20201

Andrew A. Bremer, M.D., Ph.D.
Program Director
National Institute of Diabetes and Digestive and
Kidney Diseases
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Christina Bucci-Rechtweg, M.D.
Global Head, Pediatric and Maternal Health Policy
Clinical Development and Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Camille Fabiyi, Ph.D.
Senior Advisor for Women's Health
Office of Extramural Research, Education, and
Priority
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
Rockville, MD 20857

Steven A. Foley, M.D.
OB/GYN
Prowers Medical Center
Lamar, CO 81052

Susan R. Givens, RN
Lamaze Certified Childbirth Educator
Mount Carmel St. Ann's
Westerville, OH 43081

Melissa J. Gorman, M.S.N., RN-BC, CCRN
Education Coordinator
Shriners Hospitals for Children
Boston, MA 02114

Elena K. Gorodetsky, M.D., Ph.D.
Research Program Officer
Office of Research on Women's Health
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Marjorie R. Jenkins, M.D.
Director of Medical Initiatives
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
Silver Spring, MD 20993

Bridgette L. Jones, M.D.
Associate Professor of Pediatrics
Children's Mercy Hospital and University of
Missouri–Kansas City School of Medicine
Kansas City, MO 64113

Athena P. Kourtis, M.D., Ph.D.
Lead Medical Officer
HIV Section
Division of Reproductive Health
National Center for Chronic Disease Prevention and
Health Promotion
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services
Atlanta, GA 30341

Kristi L. Lengyel, M.B.A.
Director of Patient Advocacy
UCB, Inc.
Washington, DC 20002

Linda R. Lipson, M.A.
Scientific Review Administrator
Health Services Research & Development Service
Office of Research and Development
Veterans' Health Administration
U.S. Department of Veterans Affairs
Washington, DC 20420

Joan Nagel, M.D., M.P.H.
Program Director
Division of Clinical Innovation
National Center for Advancing Translational
Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Victoria Pemberton, RNC, M.S.
Clinical Trials Specialist
National Heart, Lung, and Blood Institute
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Jeanna M. Piper, M.D.
Senior Medical Officer
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Jeanne S. Sheffield, M.D.
Director
Department of Gynecology and Obstetrics Division
of Maternal-Fetal Medicine
Johns Hopkins University School of Medicine
Baltimore, MD 21287

Diane L. Spatz, Ph.D.
Helen M. Shearer Professor of Nutrition University
of Pennsylvania School of Nursing
Philadelphia, PA 19104

Robert L. Ternik, Ph.D.
Senior Research Advisor
Lilly Corporate Center
Eli Lilly and Company
Indianapolis, IN 46285

Lois Tschetter, Ed.D., RN
Assistant Dean for Undergraduate Nursing
South Dakota State University College of Nursing
Brookings, SD 57006

Sayeedha G. Uddin, M.D.
Senior Public Health Analyst
Office on Women's Health
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Hyattsville, MD 20201

Lee A. Wilson, M.S.
Senior Advisor
Health Resources and Services Administration
U.S. Department of Health and Human Services
Rockville, MD 20857

EXECUTIVE SECRETARY

Lisa Kaeser, J.D. Director, Office of Legislation and
Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, MD 20892

Appendix III - Meeting Agendas

- August 21-22, 2017
- November 6-7, 2017
- February 26-27, 2018
- May 14-15, 2018

Task Force on Research Specific to Pregnant Women and Lactating Women

August 21–22, 2017

Location: National Institutes of Health, 31 Center Drive, Building 31, Room 6C6,
Bethesda, MD 20892

Day 1

Monday, August 21, 2017

| | |
|------------|---|
| 8:30 a.m. | Welcome and Opening Remarks Lawrence Tabak, DDS, PhD |
| 8:40 a.m. | Introductions |
| 9:00 a.m. | Background, Timeline, Goals, and Report Catherine Spong, MD |
| 9:30 a.m. | Scope of the Task Force |
| 9:30 a.m. | Scope from Development and Legislation Kathryn Schubert, MPP |
| 9:45 a.m. | Discussion <ul style="list-style-type: none">• Population: pregnant women, lactating women• Therapies: drugs (prescription, over-the-counter), vaccines, alternative therapies, non-drug interventions• Feasibility |
| 10:45 a.m. | BREAK |
| 11:00 a.m. | State of Research on Pregnancy and Lactation Anne Zajicek, MD, PharmD |
| 11:45 a.m. | Q&A |
| 12:00 p.m. | LUNCH |
| 12:45 p.m. | Identification of Federal Activities |
| 12:45 p.m. | Overview of Federal Activities Catherine Spong, MD |



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of Child Health and Human Development

| | |
|------------------|---|
| 12:50 p.m. | National Institutes of Health Diana Bianchi, MD |
| 1:00 p.m. | Centers for Disease Control and Prevention Athena P. Kourtis, MD, PhD |
| 1:10 p.m. | Food and Drug Administration Marjorie R. Jenkins, MD, MEdHP, FACP |
| 1:20 p.m. | Q&A and Discussion |
| 1:30 p.m. | HHS Office of the Assistant Secretary for Health Sayeedha Uddin, MD, MPH |
| 1:40 p.m. | Agency for Healthcare Research and Quality Camille Fabiyi, PhD, MPH |
| 1:50 p.m. | Health Resources and Services Administration Lee Andrew Wilson, MS |
| 2:00 p.m. | Department of Defense Terry Adirim, MD, MPH |
| 2:10 p.m. | Q&A and Open Public Discussion |
| 2:15 p.m. | BREAK – Eclipse viewing time Bring your own protective eyewear |
| 3:00 p.m. | National Vaccine Program Karin Bok, PhD, MS |
| 3:10 p.m. | Veterans Affairs Laurie Zephyrin, MD, MPH, MBA |
| 3:20 p.m. | Q&A and Open Public Discussion |
| 3:30 p.m. | Other Federal Efforts Sarah Glavin, PhD |
| 3:40 p.m. | Open Public Discussion and Identification of Additional Activities |
| 4:35 p.m. | Recap of Day 1 and Charge for Day 2 Catherine Spong, MD |
| 5:00 p.m. | END OF DAY 1 |

Day 2

Tuesday, August 22, 2017

- 8:30 a.m.** **Recap of Day 1 and Outline and Goals for Day 2**
Catherine Spong, MD
- 8:45 a.m.** **Panel Discussion: Recommendations for coordination of and collaboration on research related to pregnant women and lactating women**
- 8:45 a.m. Brief overview presentations outlining current and opportunities for coordination/collaboration
- 8:45 a.m. NIH Perspective
Diana Bianchi, MD
 - 8:55 a.m. FDA Perspective
Marjorie R. Jenkins, MD, MEdHP, FACP
 - 9:05 a.m. Industry Perspective
Christina Bucci-Rechtweg, MD
- 9:15 a.m. Panel Discussion
Panelists: Diana Bianchi, MD; Christina Bucci-Rechtweg, MD; Marjorie R. Jenkins, MD, MEdHP, FACP; Susan Givens, RN; Jeanne Sheffield, MD; Sayeedha Uddin, MD, MPH; Kristi Lengyel
- Current coordination and collaboration
 - Opportunities for coordination and collaboration
 - Challenges to coordination and collaboration
- 9:45 a.m. Q&A and Open Public Discussion
- 10:30 a.m.** **BREAK**
- 10:45 a.m.** **Public Comment Period**
- 11:30 a.m.** **LUNCH**
- 12:30 p.m.** **Panel presentation and discussion: Dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public**

| | |
|------------------|---|
| 12:30 p.m. | <p>Overview Presentations Outlining Current Efforts on Dissemination of Research and Information</p> <ul style="list-style-type: none"> • 12:30 p.m. Professional Society Perspective Michael Greene, MD • 12:40 p.m. Patient Perspective Jamie Zahlaway Belsito • 12:50 p.m. CDC Perspective Athena P. Kourtis, MD, PhD |
| 1:00 p.m. | <p>Panel Discussion</p> <p>Panelists: Michael Greene, MD; Jamie Zahlaway Belsito; Athena P. Kourtis, MD, PhD; Siobhan Dolan, MD; Tekoa King, MPH; Lee Andrew Wilson, MS</p> <ul style="list-style-type: none"> • Current Dissemination of Research and Information • Opportunities for Dissemination of Research and Information • Challenges to Dissemination of Research and Information |
| 1:30 p.m. | Q&A, and Discussion |
| 2:15 p.m. | Open Public Discussion |
| 2:45 p.m. | BREAK |
| 3:00 p.m. | <p>Outline of Overarching Recommendations from Panels</p> <p>Panelists: Bridgette Jones, MD; Diane Spatz, PhD; Robert Ternik, PhD; Linda Lipson, MA</p> |
| 4:15 p.m. | <p>Recap of Meeting, Action Items, and Charge to Group</p> <p>Catherine Spong, MD</p> |
| 4:30 p.m. | END OF DAY 2, ADJOURN MEETING |

Task Force on Research Specific to Pregnant Women and Lactating Women

November 6–7, 2017

Location: 6001 Executive Boulevard, Conference Room C/D, Rockville, MD 20852

Day 1

Monday, November 6, 2017

- | | |
|-------------------|--|
| 8:30 a.m. | Welcome and Opening Remarks Catherine Spong, MD |
| 8:35 a.m. | Review and Approval of Minutes from August Catherine Spong, MD |
| 8:40 a.m. | Introduction of Task Force Members |
| 9:15 a.m. | Summary and Discussion of Work Products from Meeting 1 <ul style="list-style-type: none">• Identification of federal activities• Recommendations for coordination of and collaboration on research related to pregnant women and lactating women• Dissemination of research findings and information relevant to pregnant and lactating women to providers and the public |
| 9:15 a.m. | Scientific Research and Federal Activities on Drugs, Vaccines, Vitamins, and Other Supplements for Pregnant and Lactating Women Sarah Glavin, PhD |
| 9:45 a.m. | Discussion |
| 10:00 a.m. | Overview of Draft Section of Federal Activities for Secretary's Report Catherine Spong, MD |
| 10:45 a.m. | Discussion |
| 11:15 a.m. | BREAK |
| 11:30 a.m. | Public Comment Period |
| 12:15 p.m. | LUNCH |
| 1:30 p.m. | Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research |

Updated October 26, 2017



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

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| 1:30 p.m. | Overview of Pregnant Women in Research and Ethical Issues Amina White, MD |
| 2:15 p.m. | Discussion |
| 2:30 p.m. | BREAK |
| 3:00 p.m. | Panel: Federal and Local Requirements Related to Pregnant and Lactating Women Participating in Clinical Research |
| 3:00 p.m. | <p>Brief Overview of Presentations</p> <ul style="list-style-type: none"> • 3:00 p.m. Overview of 45 CFR 46 Subpart B and implications of the revised Common Rule proposal • Lisa Buchanan, MAOM, CIP • 3:10 p.m. Consent requirements for both mother and father Anne Drapkin Lyerly, MD, MA • 3:20 p.m. IRB interpretation of 45 CFR 46 Subpart B Karim Calis, PharmD, MPH, FASHP, FCCP • 3:30 p.m. IRB interpretation of definition of “minimal risk” to the fetus Maggie Little, PhD • 3:40 p.m. Regulatory perspective • Tamara Johnson, MD, MS • 3:50 p.m. Applicability to lactating women Victoria Pemberton, RNC, MS, CCRC |
| 4:00 p.m. | <p>Panel Discussion</p> <p>Moderator: Ruth Faden, PhD, MPH</p> <ul style="list-style-type: none"> • Would the removal of pregnant women as a “vulnerable population” change research in this population? • Many comments on the proposed Common Rule revisions recommend that pregnant women not be considered a “vulnerable population” but instead be considered “medically complex.” Should NIH or others supporting research in these populations impose additional ethical restrictions beyond the Common Rule? • How should the therapeutic benefit for the pregnant woman be weighed against risk to the fetus? • What is the role of spousal/paternal consent? • How do the ethics of conducting research with pregnant women change for lactating women, if at all? |
| 4:30 p.m. | Q&A and Open Public Discussion |
| 4:50 p.m. | Recap of Meeting, Action Items, and Charge to Group Catherine Spong, MD |
| 5:00 p.m. | END OF DAY 1 |

Day 2

Tuesday, November 7, 2017

- 8:30 a.m.** **Recap of Day 1 and Outline and Goals for Day 2**
Catherine Spong, MD
- 8:45 a.m.** **Panel: Inclusion of Pregnant Women and Lactating Women in Research**
- 8:45 a.m. Brief Overview of Presentations
- 8:45 a.m. Reluctance to include pregnant women in clinical research to include physiologic changes and complexity
David Haas, MD, MS
 - 8:55 a.m. Reluctance related to liability
Michael Greene, MD
 - 9:05 a.m. Reluctance in vaccine research
Carleigh Krubiner, PhD
 - 9:15 a.m. Impact on lactating women
Diane Spatz, PhD
- 9:25 a.m. Panel Discussion
Moderator: Marjorie Jenkins, MD, MEdHP, FACP
- What methods may alleviate or alter this reluctance to include pregnant women in research?
 - How does lactation affect research?
 - How would full inclusion affect research?
- 10:00 a.m. Q&A and Open Public Discussion
- 10:30 a.m.** **BREAK**
- 10:45 a.m.** **Panel: Ethical Issues of Specific Clinical Research Designs**
- 10:45 a.m. Brief Overview of Presentations
- 10:45 a.m. Observational studies and clinical trials
Jeanne Sheffield, MD
 - 10:55 a.m. PK/PD studies
Steve Caritis, MD
 - 11:05 a.m. Convenience studies
Amina White, MD
 - 11:15 a.m. Issues of inclusion in clinical research
James Griffin, PhD

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|---------------------------------|--|---------------------------------|------------------|------------------------------|--------------------|------------------------------|----------------|-------------------------|----------------------------------|
| 11:25 a.m. | <p>Panel Discussion</p> <p>Moderator: Andrew Bremer, MD, PhD</p> <ul style="list-style-type: none"> • How has inclusion of other groups (pediatric, older populations) affected research design or study outcomes? • Do specific study designs have less ethical impact for pregnant or lactating women? • Does pregnancy or lactation provide new opportunities for research designs? | | | | | | | | |
| 11:55 a.m. | Q&A and Open Public Discussion | | | | | | | | |
| 12:15 p.m. | LUNCH | | | | | | | | |
| 1:30 p.m. | Panel: Researcher, Industry, and Research Participant Perspectives | | | | | | | | |
| 1:30 p.m. | <p>Brief Overview of Presentations</p> <table> <tr> <td>• 1:30 p.m. Physician scientist</td><td>George Saade, MD</td></tr> <tr> <td>• 1:40 p.m. Industry (large)</td><td>Robert Ternik, PhD</td></tr> <tr> <td>• 1:50 p.m. Industry (small)</td><td>Kristi Lengyel</td></tr> <tr> <td>• 2:00 p.m. Participant</td><td>Melissa Gorman, MSN, RN-BC, CCRN</td></tr> </table> | • 1:30 p.m. Physician scientist | George Saade, MD | • 1:40 p.m. Industry (large) | Robert Ternik, PhD | • 1:50 p.m. Industry (small) | Kristi Lengyel | • 2:00 p.m. Participant | Melissa Gorman, MSN, RN-BC, CCRN |
| • 1:30 p.m. Physician scientist | George Saade, MD | | | | | | | | |
| • 1:40 p.m. Industry (large) | Robert Ternik, PhD | | | | | | | | |
| • 1:50 p.m. Industry (small) | Kristi Lengyel | | | | | | | | |
| • 2:00 p.m. Participant | Melissa Gorman, MSN, RN-BC, CCRN | | | | | | | | |
| 2:10 p.m. | <p>Panel Discussion</p> <p>Moderator: Linda Lipson, MA</p> <ul style="list-style-type: none"> • Are there different approaches and/or concerns for research in pregnancy and lactation from the physician/scientist/researcher viewpoint, as compared with industry's? • How does the participant play a role in research for pregnant or lactating women? • Does the size or scope of industry affect interest in research for pregnant women and lactating women? | | | | | | | | |
| 2:40 p.m. | Q&A and Open Public Discussion | | | | | | | | |
| 3:15 p.m. | BREAK | | | | | | | | |
| 3:30 p.m. | Discussion of Key Points Related to Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research | | | | | | | | |
| 4:30 p.m. | <p>Recap of Meeting, Action Items, and Charge to Group</p> <p>Catherine Spong, MD</p> | | | | | | | | |
| 5:00 p.m. | END OF DAY 2, ADJOURN MEETING | | | | | | | | |

Task Force on Research Specific to Pregnant Women and Lactating Women

February 26–27, 2018

Location: 6710B Rockledge Drive, Room 1425/1427 (1st Floor), Bethesda, MD 20817

Day 1

Monday, February 26, 2018

- 8:30 a.m.** **Welcome and Opening Remarks**
Catherine Spong, M.D.
- 8:35 a.m.** **Introduction of Task Force Members**
- 8:40 a.m.** **Review and Approval of Minutes from November's Meeting**
Catherine Spong, M.D.
- 8:45 a.m.** **Summary and Discussion of Work Products from Meetings 1 and 2**
- 8:45 a.m. Review of Work Products and Recommendations from Meetings 1 and 2
Catherine Spong, M.D.
- 9:15 a.m. Discussion
- 9:45 a.m.** **BREAK**
- 10:00 a.m.** **Public Comment Period**
- 10:45 a.m.** **Panel: Lessons Learned from Pediatric Research**
- Brief Overview of Presentations
- 10:45 Community involvement/groundswell
Mark Del Monte, J.D.
- 10:55 Best Pharmaceuticals for Children Act (BPCA) overview
Anne Zajicek, M.D., Pharm.D., FAAP
- 11:05 NIH and BPCA
Perdita Taylor-Zapata, M.D.
- 11:15 FDA and BPCA
Lynne Yao, M.D., FAAP
- 11:25 Industry perspective
Samuel Maldonado, M.D., M.P.H., FAAP
- 11:35 a.m. Discussion
Moderator: Andrew Bremer, M.D., Ph.D.



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

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|-------------------|--|
| 12:15 p.m. | LUNCH |
| 1:15 p.m. | Effective Communication Strategies with Health Care Providers and the Public on Information Relevant to Pregnant Women and Lactating Women |
| 1:15 p.m. | Communication Strategy Case Example: NICHD Safe to Sleep® Campaign <i>Lorena Kaplan, M.P.H., CHES</i> |
| 1:50 p.m. | Panel: Effective Communication Strategies with Health Care Providers on Information Relevant to Pregnant Women and Lactating Women |
| | Brief Overview of Presentations |
| 1:50 | Federal perspective <i>John Whyte, M.D., M.P.H.</i> |
| 2:00 | Professional society perspective <i>Kerri Wade, M.P.A.</i> |
| 2:10 | Industry perspective <i>Susan Kindig, M.D., J.D.</i> |
| 2:20 | Health care provider perspective <i>Susan Givens, RNC-OB, M.P.H., LCCE</i> |
| 2:30 p.m. | Discussion <i>Moderator: Jeanna Piper, M.D.</i> <i>Additional panelists: Jeanne Sheffield, M.D., and Victoria Pemberton, RNC, M.S., CCRC</i> |
| 3:15 p.m. | BREAK |
| 3:30 p.m. | Panel: Effective Communication Strategies with the Public on Information Relevant to Pregnant Women and Lactating Women |
| | Brief overview of presentations |
| 3:30 | Federal perspective <i>Jackie Rosenthal, M.P.A.</i> |
| 3:40 | Professional society perspective <i>Bridgette Jones, M.D.</i> |
| 3:50 | Professional organization perspective <i>Diane Spatz, Ph.D.</i> |
| 4:00 | Industry perspective <i>Kristi Lengyel, M.B.A.</i> |
| 4:10 | Patient perspectives <i>Susan Benjamin Feingold, Psy.D.</i> |

- 4:20 p.m. Discussion
Moderator: Karin Bok, M.S., Ph.D.
Additional panelists: Melissa Gorman, M.S.N., RN-BC, CCRN-K, and Lois Tschetter, Ed.D., RN, IBCLC, CNE
- 4:50 p.m. **Recap of Meeting, Action Items, and Charge to Group**
Catherine Spong, M.D.
- 5:00 p.m. **END OF DAY 1**

Day 2

Tuesday, February 27, 2018

- 8:00 a.m.** **Recap of Day 1 and Outline and Goals for Day 2**
Catherine Spong, M.D.
- 8:15 a.m.** **A Plan to Identify and Address Gaps in Knowledge and Research Regarding Safe and Effective Therapies for Pregnant Women and Lactating Women, Including the Development of Such Therapies**
- 8:15 a.m. Discussion: Options for a Plan or Plans
Moderator: Shelli Avenevoli, Ph.D.
- 10:00 a.m.** **BREAK**
- 10:15 a.m. Discussion Continues
Moderator: Shelli Avenevoli, Ph.D.
- 11:45 p.m.** **LUNCH**
- 12:45 p.m.** **Discussion of Key Points and Review of Recommendations**
- 12:45 p.m. Discussion of Key Points for Effective Communication Strategies with Health Care Providers and the Public on Information Relevant to Pregnant Women and Lactating Women
Catherine Spong, M.D.
- 1:30 p.m. Discussion of Key Points for a Plan to Identify and Address Gaps in Knowledge and Research Regarding Safe and Effective Therapies for Pregnant Women and Lactating Women, Including the Development of Such Therapies
Catherine Spong, M.D.
- 2:15 p.m. Review of Recommendations from Meetings 1, 2, and 3
Catherine Spong, M.D.
- 2:45 p.m.** **Recap of Meeting, Action Items, and Charge to Group**
Catherine Spong, M.D.
- 3:00 p.m.** **END OF DAY 2, ADJOURN MEETING**

Task Force on Research Specific to Pregnant Women and Lactating Women

May 14–15, 2018

Location: 6710B Rockledge Drive, Room 1425/1427 (1st Floor), Bethesda, MD 20817

Day 1

Monday, May 14, 2018

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| 8:30 a.m. | Welcome and Opening Remarks <i>Catherine Spong, M.D.</i> |
| 8:35 a.m. | Review and Approval of Minutes from February's Meeting <i>Catherine Spong, M.D.</i> |
| 8:40 a.m. | Introduction of Task Force Members |
| 8:45 a.m. | Summary and Discussion of Work Products from Meetings 1–3 <i>Catherine Spong, M.D.</i> |
| 9:15 a.m. | Open Discussion |
| 9:45 a.m. | BREAK |
| 10:00 a.m. | Public Comment Period |
| 10:45 a.m. | Summary of Request for Information <i>Lisa Kaeser, J.D.</i> |
| 11:15 a.m. | FDA Presentation on Risk Communication Advisory Committee Meeting on the Pregnancy and Lactation Labeling Rule and New Guidance for Industry on Pregnant Women <i>Lynne Yao, M.D.</i> |
| 11:35 a.m. | Review of Historical Recommendations in Pregnancy and Lactation <i>Elizabeth Wehr, J.D.</i> |
| 11:50 a.m. | Open Discussion |
| 12:15 p.m. | LUNCH |



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

| | |
|-----------|---|
| 1:15 p.m. | Incentives and Liability Discussion Panelists: <i>Christina Bucci-Rechtweg, M.D.; Kristi Lengyel, M.B.A.; Jeanne Sheffield, M.D.; Robert Ternik, Ph.D.; Kathleen Miller, Ph.D.; and Lynne Yao, M.D.</i> Moderator: <i>Karin Bok, Ph.D., M.S.</i> |
| 2:00 p.m. | Recommendations to Improve the Development of Safe and Effective Therapies for Pregnant Women and Lactating Women, Including Topics Covered from Meetings 1–3* |
| 2:00 p.m. | Discussion on Strategy and Structure for Recommendations <i>Catherine Spong, M.D.</i> |
| 2:15 p.m. | A Plan to Identify and Address Gaps in Knowledge and Research Regarding Safe and Effective Therapies for Pregnant Women and Lactating Women, Including the Development of Such Therapies <i>Catherine Spong, M.D.</i> Moderator: <i>Shelli Avenevoli, Ph.D.</i> |
| 2:45 p.m. | Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research <i>Catherine Spong, M.D.</i> Moderator: <i>Shelli Avenevoli, Ph.D.</i> |
| 3:15 p.m. | Open Discussion |
| 3:45 p.m. | BREAK |
| 4:00 p.m. | Effective Communication Strategies with Health Care Providers and the Public on Information Relevant to Pregnant Women and Lactating Women <i>Catherine Spong, M.D.</i> Moderator: <i>Jeanna Piper, M.D.</i> |
| 4:20 p.m. | Federal Activities: State of Research, Coordination and Collaboration on Research, Dissemination of Research Findings, and Existing Federal Efforts <i>Catherine Spong, M.D.</i> Moderator: <i>Jeanna Piper, M.D.</i> |
| 4:45 p.m. | Open Discussion |

5:00 p.m. **Recap of Meeting, Action Items, and Charge to the Group**
Catherine Spong, M.D.

5:00 p.m. **END OF DAY 1**

*Time will be adjusted for these topics, and there is open discussion on day 2 from 8:00 a.m. to 11:45 a.m. that is available if the scheduled time is not sufficient.

Day 2

Tuesday, May 15, 2018

- 8:00 a.m.** **Recap of Day 1 and Outline and Goals for Day 2**
Catherine Spong, M.D.
- 8:15 a.m.** **Open Discussion: Recommendations to Improve the Development of Safe and Effective Therapies for Pregnant Women and Lactating Women**
- Moderator:** *Andrew Bremer, M.D., Ph.D.*
- 10:00 a.m.** **BREAK**
- 10:15 a.m. Open Discussion, continued
- 11:45 p.m.** **LUNCH**
- 12:45 p.m.** **Review of Recommendations with Voting**
Catherine Spong, M.D.
- 2:00 p.m.** **Recap of Meeting, Action Items, and Charge to the Group**
Catherine Spong, M.D.
- 2:30 p.m.** **END OF DAY 2, ADJOURN MEETING**

Appendix IV – Meeting Minutes

- August 21-22, 2017
- November 6-7, 2017
- February 26-27, 2018
- May 14-15, 2018

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 https://www.nichd.nih.gov/sites/default/files/2017-11/Post_Meeting_Participant_List.pdf

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

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.

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 https://www.nichd.nih.gov/sites/default/files/2017-11/Post_Meeting_Participant_List_0.pdf

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 21st 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 21st 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

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

Other members of the public present:

See https://www.nichd.nih.gov/sites/default/files/2018-03/PRGLAC_PostMeetingParticipants.pdf

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.

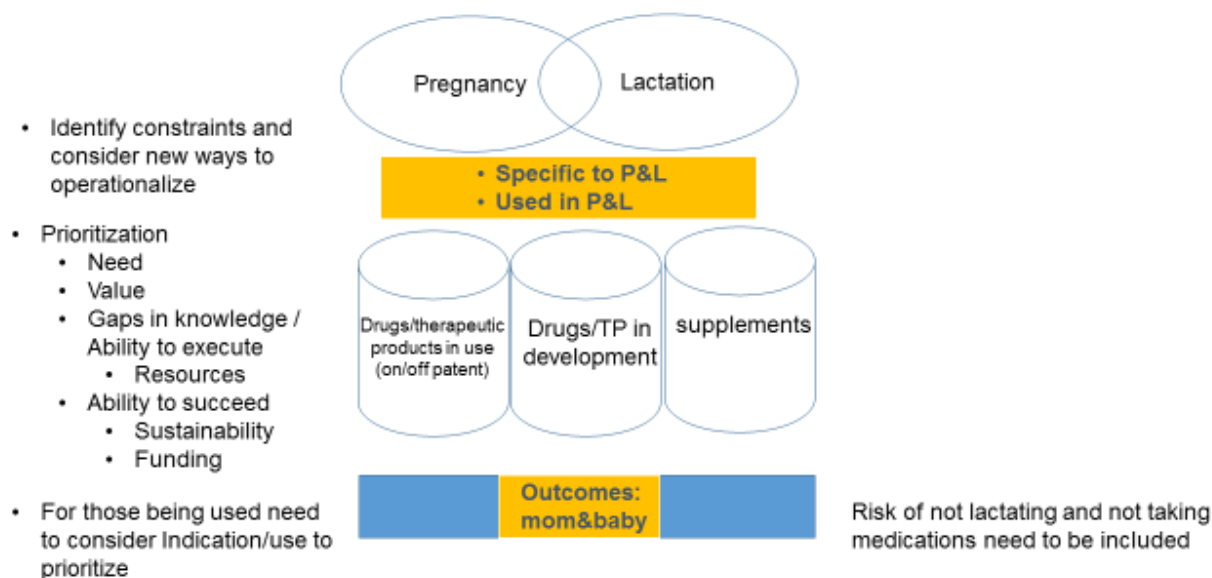
A Plan to Identify and Address Gaps in Knowledge and Research Regarding Safe and Effective Therapies for Pregnant Women and Lactating Women

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

Task Force on Research Specific to Pregnant Women and Lactating

Women Meeting

May 14 - 15, 2018

The Task Force on Research Specific to Pregnant Women and Lactating Women (Task Force or PRGLAC) convened the fourth of four two-day meetings on May 14 and 15, 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=27386&bhcp=1> and for Day 2 at:

<https://videocast.nih.gov/summary.asp?live=27390&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., 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
- Camille Fabiyi, Ph.D., Agency of Healthcare Research and Quality (AHRQ)
- Steven Foley, M.D., FACOG, Prowers Medical Center
- 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

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

Task Force members absent:

- Terry A. Adirim, M.D., MPH, Department of Defense (DoD)
- Susan Givens, RN, Mount Carmel St. Ann's
- Lois Tschetter, Ed.D., RN, IBCLC, South Dakota State University
- Lee Andrew Wilson, M.S., Health Resources and Services Administration (HRSA)

Review and Approval of Minutes

Dr. Catherine Spong welcomed the Task Force to its fourth meeting. The Task Force unanimously approved the minutes from the February 2018 meeting, after correcting the list of attendees to clarify Dr. Avenevoli was in attendance.

Summary and Discussion of Work Products from Meetings 1 - 3

Dr. Spong reviewed the legislative history behind the PRGLAC Task Force and reminded the group about pending deadlines. The Task Force report is due to the Secretary of HHS by September 2018 but must begin the clearance process by July 6, 2018. The Secretary has until December 2018 to decide whether and how to act on the PRGLAC recommendations. The Task Force's charter will expire in March 2019, unless the Secretary chooses to extend it.

Dr. Spong noted that the draft report was sent out to Task Force members for review, including all components of the report (covered in the first three meetings) except for the recommendations, which are the goal of this meeting. Task Force members made suggestions, and Dr. Spong requested that everyone with specific comments submit them by the end of the week.

Public Comment Period

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

Summary of Request for Information

Lisa Kaeser, J.D., NICHD, provided a summary of the responses to the Request for Information (RFI), which was open for public input between February and April 2018. The RFI received a robust response of 34 comments on a range of topics related to pregnancy and lactation.

Study design issues received the most comments, focusing on how to design studies that would include pregnant and/or lactating women (e.g., opportunistic studies), with some respondents stating that there should be a presumption of inclusion of pregnant and lactating women in research studies. While most concentrated on clinical studies and inclusion of these populations,

several also noted the need for basic research. Ethical issues also received attention, with most commenters stating that federal regulations should not continue to designate pregnant women as a “vulnerable” population. Eight of the submissions were similar, each calling for more research on therapeutics to address maternal milk supply. Respondents also called for better communication with pregnant and lactating women about research, recommending health care providers as a good avenue for sharing this information. Ten respondents mentioned that herbal supplements are widely used by pregnant and lactating women but have not been rigorously tested.

The full RFI summary will be posted on the PRGLAC website.

Task Force members continued discussion of the points raised by respondents to the RFI, particularly the study design and ethical issues posed by conducting research on therapeutics that include pregnant and lactating women. The point was raised that “inclusion” does not necessarily mean that every clinical trial includes these populations, but that their exclusion should be justified. However, if pregnant or lactating women will be key end users of a therapeutic, they should be included in the research unless fetal safety data have not been established. The suggestion was made to make federal regulatory requirements for pregnant women similar to those governing pediatric research.

FDA Presentation on Risk Communication Advisory Committee Meeting on the Pregnancy and Lactation Labeling Rule and new Guidance for Industry on Pregnant Women

Lynne Yao, M.D., FDA, updated Task Force members on FDA’s new draft guidance for industry on pregnant women, which had been published after the last PRGLAC meeting. She reviewed the history of regulatory ethics requirements regarding participation of women of reproductive age in clinical studies. The new guidance discusses integration of pregnant women into clinical research, both in premarket and postmarket settings. It also covers the situation when a woman participating in a study becomes pregnant. The comment period on this draft closes June 8, 2018.

Dr. Yao also discussed the Pregnancy and Lactation Labeling Rule (PLLR), which is intended to provide health care providers with information to help with decision making related to pregnancy and lactation, who often have the responsibility to make those decisions in the absence of information, in conjunction with the end user. Task Force members continued their discussion of the ethical issues involved with conducting the studies needed to provide data specific to pregnant and lactating women, which will be the subject of many of the PRGLAC recommendations.

Review of Historical Recommendations in Pregnancy and Lactation

Elizabeth Wehr, J.D., NICHD, described her review of publications since the 1990s that made recommendations regarding the inclusion of pregnant women in research studies. More specifically, these recommendations covered research strategies, methods, topics, trial infrastructure, and resources. Over time, the recommendations have become increasingly

specific, such as the type of trials that would be feasible, the use of large databases, and emphasis on preclinical topics. Only recently has recognition of the need for research on lactation increased, which includes the impact of not breastfeeding if medications are being used. A number of these recommendations distinguished between research on new medications versus research on approved therapeutics in pregnant women.

Dr. Spong pointed out that the Task Force recommendations would be building on this earlier work. The need for tracking pregnant women's use of therapeutics through electronic health records was raised as one approach.

Open Discussion

Dr. Spong set the stage for the Task Force's discussions on its recommendations by reviewing the recommendations made during the first three meetings in several major categories, including expanding the workforce expert in this area, providing incentives to conduct research that includes pregnant and lactating women, data needs, optimal study designs, modifying regulatory or legal requirements, and increasing awareness and communications. Task Force members agreed that it is important to keep the number of recommendations manageable, to encourage action on them.

Incentives and Liability Discussion

A panel of experts, Christina Bucci-Rechtweg, M.D., Kristi Lengyel, MBA, Jeanne Sheffield, M.D., Robert Ternik, Ph.D., Kathleen Miller, Ph.D., Lynne Yao, M.D., and Karin Bok, Ph.D., M.S. (moderator) discussed potential approaches to reducing liability and creating incentives for industry to engage in research that includes pregnant and lactating women. Among existing programs (e.g., Orphan Drug Act, vaccine injury compensation program), the Best Pharmaceuticals for Children program (FDA, NIH), which provides incentives for industry to conduct research to inform pediatric drug labeling, was offered as a possible model, although several discussants cautioned against merging pregnant and lactating women into that program. The panel urged the Task Force to distinguish between incentives for testing drugs that are already on the market versus new drug development, to try to match incentives to address market failures (drugs to promote milk supply), and to recognize the need for foundational research. Resource limitations may require prioritization of the drugs to be studied. There is also a dearth of expertise that will require training in pharmacology related to obstetrics and lactation.

DISCUSSION: Recommendations to Improve the Development of Safe and Effective Therapies for Pregnant Women and Lactating Women

Dr. Spong outlined the plan for the Task Force's deliberations on PRGLAC's recommendations to the Secretary in its final report. The recommendations will be grouped and discussed according to the four major topic areas requested by Congress.

Dr. Avenevoli moderated the discussion on recommendations pertaining to the *development of a*

plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women. The Task Force was urged to recommend research that is conducted in a timely fashion. Another suggestion was to include metrics and/or timelines for each recommendation to be able to judge whether progress is being made. The group discussed how to identify the gaps in research, find funding for addressing those gaps, and how to prioritize which gaps need to be addressed first. Some discussants wanted the recommendations to be targeted toward preclinical and clinical research, while others emphasized the need for basic pharmacokinetic and pharmacodynamic research. To conduct this research, it was pointed out again that training programs in lactation and obstetric pharmacology need to be developed for health professionals.

Dr. Avenevoli also moderated the discussion on *ethical issues* surrounding the inclusion of pregnant women and lactating women in clinical research. Task Force members reached consensus on modifying subpart B of the Federal Regulations on the Protection of Human Subjects (Common Rule), changing the requirement for both maternal and paternal consent for participation of a pregnant woman in research to one of maternal consent alone (consistent with the requirement for pediatric research). The group also discussed adding an option of “minor increase over minimal risk” to subpart D 36.046, to help create a presumption of inclusion of pregnant and lactating women in research.

Dr. Piper moderated the discussion on the recommendations within the category of *effective communication strategies* with health care providers and the public on information relevant to pregnant women and lactating women. Task Force members commented on the idea of creating a public awareness campaign about the importance of pregnant and lactating women’s participation in research, suggesting that health care providers and their professional organizations would be key conduits for the information. Such communications efforts should be evidence based. They also discussed tailoring the messages for different audiences and whether this could become a global effort.

Dr. Piper also moderated the discussion on *federal activities and the state of research*, coordination and collaboration on research, and dissemination of research findings. In addition to each federal participant agency’s description of its activities relevant to pregnant and lactating women that will be included in the final report, Task Force members discussed how to leverage currently existing networks and collaborations to include more research and data collection on these populations, and to consider engaging in public-private partnerships. The group also discussed the role that industry registries could play, recommending that health care providers refer their patients for registry participation (prioritizing disease-focused registries) so that data on the effects of therapeutics can be gathered. Development of Common Data Elements would facilitate harmonization of these data. It was also noted that the new PregSource® research registry, sponsored by NICHD, would be adding a medications tracker as of September 2018.

Dr. Spong noted that Congress has asked whether the Task Force will recommend that it be extended.

Day 2

Recap and Goals for Day 2

Dr. Spong provided a recap of the previous day's discussions. She outlined some of the central points made during the earlier discussions, such as the need to address the issues around therapeutics used by lactating women separately from those used by pregnant women, and even women of reproductive age. The discussion on incentives and liability mitigation includes potential models to use for research on therapeutics used by pregnant and lactating women (BPCA, vaccine injury compensation). Regarding some of the ethical issues raised by research with these populations, both basic research and a change in culture may be required so that clinical research may proceed. By gathering evidence early (even in small studies), with the potential for following women to determine longer term outcomes, safety and efficacy data can be generated. However, there should also be a prioritization process, particularly at the beginning. Potential partners in this effort include agencies, industry, professional societies and nonprofit organizations.

Review of Recommendations with Voting

Dr. Spong reviewed the procedures for discussion, amendment, and voting on each of the PRGLAC recommendations. Ms. Kaeser recorded the votes on each of the following; each received a majority of votes:

1. Include and integrate pregnant women and lactating women in the clinical research agenda

- Remove pregnant women as an example of a vulnerable population in the Common Rule
- FDA should harmonize with the Common Rule and remove pregnant women as a vulnerable population
- Develop HHS Guidance to facilitate the conduct of research in pregnant women and lactating women

2. Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women

- Provide additional resources and funding for research to obtain clinically meaningful and relevant data for both specific and co-existing conditions in pregnant women and lactating women
Including but not limited to:
 - Develop preclinical models
 - Expand basic science research to inform drug development
 - Develop new tools and methods to assay therapeutic products such as those that utilize small volumes and are sensitive to detect minute quantities including in human milk

- Develop new tools to assess pharmacodynamic response in pregnant women, lactating women, and children
- Fund clinically relevant research and studies to inform therapeutic product use in pregnant women and lactating women
- Design trials to capture long-term maternal, obstetric, and child outcomes
- Utilize longer award periods by government funders (beyond the typical 5-year award) when needed for study design and data collection

3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics

- Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
- Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
- Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics

4. Remove regulatory barriers to research in pregnant women

- Modify subpart B of the Common Rule
 - Change 46.204(e) in subpart B to maternal consent alone
 - Given the recognized autonomy of a pregnant woman, the evolution of family structure, that for a child only one parental signature is required for research to benefit the child and to align with parental consent for pediatrics
 - Add in the option of “Minor increase over minimal risk” from subpart D to 36.046

5. Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women

- Highlight the importance of research on therapeutic products in pregnant women and lactating women, including the impact of not taking the medication during pregnancy and lactation as well as the impact of not breastfeeding on mother and child
- Engage stakeholders such as Department of Health and Human Services (HHS), professional societies, industry, advocacy groups, and public and global partners

6. Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women

- Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs

- Increase the engagement of health care providers to disseminate information from research findings to their patients
- Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries
- Develop appropriate strategies for sharing and interpreting research findings and risk

7. Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are or may become pregnant and by lactating women

- Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women
 - Using the Vaccine Injury Compensation Program (VICP) as a model, however include mitigation whether or not the therapeutic product achieves marketing approval
- If liability mitigation is insufficient, consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data (such as pharmacologic and clinical data) on pregnant women and lactating women to inform dosing and safety

8. Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the National Institute of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model

- Provide specific funding
- Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women

9. Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women

- Create separate prioritization processes for pregnant women and lactating women
 - Unmet need examples in lactation: low milk supply, mastitis
 - Unmet need examples in pregnancy: preterm labor, hyperemesis
- Consider a Biomedical Advanced Research and Development Authority (BARDA)-like model and the NIH vaccine model that takes clinical development up to Phase II

10. Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research

- Investigators/sponsors must specifically justify exclusion in study design
- Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation

- Develop a systematic plan on how data for pregnant women and lactating women will be obtained in a timely fashion to include pharmacokinetics/pharmacodynamics and safety
- Develop guidance for institutional review boards and investigators about the inclusion of pregnant women and lactating women in research
- Develop a systematic plan for if a woman becomes pregnant in a study to include whether product should continue, if un-blinding is necessary, how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information

11. Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women

- Provide financial support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, and methodologies.
- Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women
- Encourage networks/collaborations to engage in public-private partnerships to facilitate research

12. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women

- Design health record systems to link mother and infant records
- Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries
- Use novel data resources
- Use innovative methods of data analytics
- Require common data elements to facilitate collaboration and use

13. Optimize registries for pregnancy and lactation

- Create a user-friendly website for registry listing
- Develop registry standards and common data elements that facilitate input of pertinent data with easy, transparent access to obtain information in real time
 - Include maternal, obstetric, and child outcomes, along with birth defects
- Facilitate access to data and transparency of information in registries
 - Use the ART registry as a model
- Develop disease/condition-focused registries
 - Move toward a single registry for all therapeutic products with input from stakeholders

14. The Department of Health and Human Services Secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019

15. Establish an Advisory Committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research

Adjournment

Dr. Spong said that the draft PRGLAC report would be sent to the Task Force members for final review prior to its submission for clearance at the end of June 2018. The final report will be sent to the Secretary, HHS, and to Congress, in September 2018.

After thanking the Task Force members and participants for their hard work, Dr. Spong adjourned the meeting.

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

Appendix V - Public Comments

- August 21-22, 2017
- November 6-7, 2017
- February 26-27, 2018
- May 14-15, 2018

Remarks Made at the Task Force on Research Specific to Pregnant Women and Lactating Women in Bethesda, MD on August 22nd, 2017

My name is Jonathan Bortz. I am an endocrinologist and was in practice for about 14 years and have been working in the pharmaceutical and ingredient industry for the last 14 years, where I have been responsible for developing products for women's health like prescriptive prenatal vitamins and iron replacement products.

Because these were all for the prescriptive market, I had to make sure that they would be prescribed by physicians and that each product would offer unique and valuable attributes in order for physicians to prescribe them rather than recommending OTC alternatives. This automatically set a very high bar for us to clear to ensure that the what was being promoted to doctors was backed up with great science and a good (and often novel) rationale.

This forced us to scour the world for unique and high quality ingredients that brought meaningful differentiation to the product. The right form of ingredient and the right dose needed to meet the therapeutic goals of the product. Each and every ingredient had to earn its way into the formulation. We were never interested in just putting a composition together with 15 different vitamins and minerals just to make label claims.

This process also led us to seek and exploit emerging science and develop concepts that would never have come to being if we relied only on conventional knowledge of vitamins and minerals. We subjected the nutrient ingredients to the same scientific scrutiny and rigor that is accepted for small molecule pharmaceuticals and essentially developed a method of creating new product concepts by properly exploiting little known or poorly understood facts about each nutrient ingredient. In other words, we treated nutrients like the Agency would like us to treat small molecules.

Here is an example of what I mean. Folic acid is the backbone of all prenatal vitamins because it is well understood to play a significant role in reducing birth defects. This is a main reason that it is part of the mandated food fortification program in the US. Well, supplementing folate a very successful strategy for reducing Neural Tube Defects, but is just the tip of the iceberg in terms of the sort of positive impact nutritional intervention can have on the outcome of the pregnancy. You see, folate, vitamin B12 and choline are responsible for a key metabolic system called Single Carbon Metabolism that plays a critical role in a variety of important neurodevelopmental, metabolic and genetic functions. Adequate supply of all three of these nutrients has been shown to reduce Neural Tube defects like spina bifida and anencephaly as well as significantly impact neurodevelopmental milestones – and yet doctors and patients don't know about these other two players. They only know about folic acid.

Folic acid is also the synthetic form of the vitamin and behaves differently to the natural form, folate. Supplemented folic acid lands up in mother's milk, binding to the protein Folate Receptor α (FR α) that ordinarily binds to the natural folate. But the folic acid binds more avidly and therefore displaces or prevents folate from binding to these proteins and hence this may reduce the bioavailability of folate to the nursing infant. Nobody knows that and yet doctors and consumers think that all vitamins and minerals are the same. They are not. The attitude that folic is folic, or iron is iron is iron is just not true, and it is we in industry that are motivated to tease out the differences and develop products that have true benefits and teach the marketplace about ones that don't or may in fact be potentially problematic or have unintended consequences.

This also puts industry in a place where conventional science can't go – looking for science that can teach us, not dated science that just maintains the status quo. We can bridge the gap that academia and policy makers can't readily access, and we are motivated to show that these innovations are truly different from the pedestrian approach seen in most OTC products. Prescription products are NOT the same as OTCs and the prescriptive companies are promoting this message – backed up by science and appropriate messaging, because by treating all vitamins and all minerals the same, as low tech ingredients is literally a case of 'throwing the baby out with the bathwater.'

Thank you.

Comments for Federal Task Force August 23, 2017 by Amita Gupta, MD, MHS

Good Morning. My name is Amita Gupta and I am an infectious diseases physician and clinical researcher at Johns Hopkins University who conducts studies on HIV and TB in pregnant and lactating women internationally. Active tuberculosis (TB) is a leading cause of maternal mortality, including in HIV-infected women. Infants born to mothers with TB have a higher rate of prematurity, low birth weight and stillbirth. Maternal TB more than doubles the risk of mother-to-child transmission of HIV, and significantly increases the risk of mortality for the newborn and other young children living in the household. Women of childbearing age are more likely than men to progress from latent TB infection (LTBI) to active TB, possibly owing to immune changes associated with pregnancy. In fact, the risk of developing TB is the highest within the first 90 days postpartum than any other time in a woman's life.

However, TB prevention and treatment during pregnancy pose challenges. Physiologic adaptations occur throughout pregnancy and peak in the third trimester. These changes are dynamic and can significantly affect drug disposition. The safety and efficacy of individual or multidrug regimens for pregnant women cannot be adequately predicted without clinical trials, yet safety and pharmacokinetic (PK) data during pregnancy are lacking for most TB drugs, including first line drugs that we have been using since the 1950s. Because of the lack of data regarding safety, tolerability, and the pharmacokinetics of TB drugs during pregnancy, inconsistencies in national and international treatment guidelines exist. The World Health Organization, for example, recommends the use of pyrazinamide during pregnancy in first-line TB treatment, but the US CDC does not, owing to inadequate data on potential adverse fetal effects. Thus, the type and duration of regimen that a pregnant woman with TB receives literally depends on what country she is in and what guidelines her doctor chooses to follow.

Multidrug-resistant (MDR) TB presents a bigger challenge, because treatment options remain extremely limited during pregnancy. Most aminoglycosides, key in MDR TB treatment, are potentially ototoxic and nephrotoxic for the fetus. Reproductive toxicity studies suggest that other second-line drugs for MDR TB, such as ethionamide-prothionamide, may also have teratogenic potential. Although new compounds are in development and new oral drugs have been recently approved such as bedaquiline and delamanid, lack of safety or PK data during pregnancy severely limits their use in this population.

Guidelines for prevention of TB progression has also suffered from lack of adequate data in pregnancy. The standard regimen (daily isoniazid for ≥ 6 months) has never been systematically assessed for safety and PK data in pregnancy, and there are some data to suggest there is increased risk of drug-induced liver injury. After exclusion from 13 trials of LTBI treatment in HIV-infected adults and the critical need to advance prevention for HIV-infected pregnant women, a NIH-funded Phase IV clinical trial was designed to study INH in pregnancy and is near completion. Why did it take so long to study a drug used since the 1950s in pregnant women? Furthermore, newer, shorter preventive regimens (e.g., 12 once-weekly doses of isoniazid plus rifapentine; 1 month of daily isoniazid plus rifapentine) are now available or under study in non-pregnant populations, but again pregnant women have been excluded from clinical trials of these regimens. Pregnant women should be allowed access to and benefit from advances in TB treatment. Pregnancy provides an important healthcare system entry point, at which women can be screened and treated for both TB and LTBI. But we urgently need the development of evidence-based treatment standards for pregnant women, which will require inclusion of this special population into studies of newly approved and investigational drugs for MDR TB or dedicated studies of these drugs in pregnant and lactating women.

Potential benefit of research on TB drugs would be significant, and consideration must also be given to the consequences of off-label use in the absence of evidence-based guidance. It is safer to administer TB drugs during pregnancy in a research setting, given the rigorous safety monitoring, requisite informed consent requirements, and ability to confirm correct dosing. Access to the benefits of research is an essential component of the ethical principle of justice in clinical research, and pregnant women have not benefited fairly from research given their under-representation in past trials.

Based on a NIH convened expert consensus meeting, we have outlined a set of recommendations for earlier inclusion of pregnant and lactating women in clinical trials and published these in *Clinical Infectious Diseases* in 2016. In summary, despite substantial TB-related morbidity and mortality in pregnant/lactating women and their infants, drug-sensitive TB, MDR TB and LTBI care is currently being provided without sufficient clinical trial data on drug safety and dosing. Studies in pregnant or lactating women with TB are needed to provide accurate data to improve clinical treatment decisions.



Federal Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

HESI DART written statement for August 21-22, 2017 Meeting

The ILSI Health and Environmental Sciences Institute (HESI) Technical Committee for Development and Reproductive Toxicology (DART) respectfully submits the following comments on how nonclinical research can improve the clinical development of safe and effective therapies for pregnant and lactating women.

HESI DART is a tripartite organization comprising scientists from academia, government and industry. Our core mission centers around building consensus on optimal nonclinical testing strategies and how to translate developmental and reproductive hazards identified in nonclinical studies into meaningful human risk assessments.

The thalidomide tragedy of the early 1960s magnified the importance of identifying potential risks to the developing fetus and newborn infant during the drug development process. There have been considerable advances in our scientific understanding of the biology of pregnancy and lactation, especially around the transport mechanisms responsible for enabling drug exposure to the developing conceptus and breastfed infant. This increased knowledge has informed the design of comprehensive nonclinical testing strategies aimed at identifying developmental hazards. Implementation of these testing paradigms coupled to clinical trial exclusion criteria and/or stringent contraception requirements have helped mitigate a possible repeat of the thalidomide tragedy. But significant gaps remain. The most fundamental one is that the above diligence means that the very population we are trying to protect (pregnant women) are largely excluded from clinical trials. It has been estimated by the CDC, that <10% of drugs that come to market have sufficient information to inform the human risk for birth defects. In addition to the challenges this presents to healthcare professionals trying to treat certain conditions during pregnancy, tragically, the unknown level of risk can also lead to the termination of wanted pregnancies through fear. And for women who wish to breastfeed but need medications, the lack of adequate risk information is even more acute, leading to the painful choice to discontinue nursing their child.

So what can we do about this? Prior to marketing approval, the main avenue that enables hazard identification during pregnancy and lactation is via nonclinical testing, using animals as well as an extensive array of *in vitro* and other alternative systems. Our continued reliance on these systems underscores the importance of being able to translate what these nonclinical data mean for humans. The work of HESI DART and other organizations such as the Teratology Society, have contributed significant progress against this goal.

While the core framework of nonclinical testing has remained largely unchanged for over 50 years, there have been significant modifications to meet the needs of the ever-changing drug development landscape. So while the overarching paradigm remains focused on identifying hazards to the three fundamental components of the reproductive cycle; fertility, embryo-fetal development and postnatal development, testing protocols have evolved to accommodate the introduction of new drug modalities, such as biopharmaceuticals. For these molecules, secretion into breast milk and the ability to cross the placental barrier are generally much more limited than



for traditional small molecule drugs. In addition, due to their more targeted nature, many biopharmaceuticals only cross react with nonhuman primates (and not rat and rabbit, the more traditional species for these studies) which creates some advantages in terms of informing human risk, such as species similarities in the placental transfer of Fc-containing biotherapeutics. Integrating these advantages with our continued drive to reduce use of nonhuman primates however, is not without challenge. For example, to ensure the unnecessary use of nonhuman primates, dosing of drug candidates to assess effects on embryo-fetal development does not begin until pregnancy has been confirmed, which means that the earliest stages of pregnancy, such as implantation, are not fully assessed. And based on lower group sizes together with substantially longer gestation and maturation periods, mating studies become quite impractical.

As well as evolving testing strategies to cater for changes in drug modalities, significant advances have been made in our scientific understanding of normal vs abnormal development e.g. through identification of adverse outcome pathways. These achievements have been complemented by the development of a wide array of alternative models aimed at enhancing our ability to interrogate mechanisms of abnormal development (and their relevance to humans) and improving the efficiency of drug development. For example, models such as embryonic stem cells and Zebrafish have enabled us to identify developmental hazards sooner and further refine the chemistry of new drug candidates before they are tested in humans.

In summary, nonclinical testing will continue to remain the bastion for identifying developmental hazards. And while significant progress has been made to help inform the human risk of developmental hazards identified in nonclinical systems, continued nonclinical research is needed. This is especially true for effects on lactation (which is often only indirectly assessed via pup survival) and for effects in early pregnancy. This latter point is perhaps of greatest clinical relevance given that often, women taking medications may not realize they are pregnant until organogenesis is well underway.

We thank the Task Force for the opportunity to highlight the importance of nonclinical research for the development of safe and effective therapies for pregnant women and lactating women and encourage you to include these considerations in your final report.

HESI DART PRGLAC Subcommittee:

Anthony Scialli (Georgetown University, Scialli Consulting)
Belen Tornesi (AbbVie)
Connie Chen (HESI)
Graeme Moffat (Amgen)
Mary Ellen McNerney (Bristol-Myers Squibb)
Melissa Tassinari (Retired)
Susan Makris (US EPA)

TAG

Treatment Action Group

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August 17, 2017

Ms. Lisa Kaeser, Executive Secretary
Eunice Kennedy Shriver National Institute of Child Health and Human Development
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892

Treatment Action Group's Comments for the Task Force on Research Specific to Pregnant and Lactating Women

Dear Ms. Kaeser,

Thank you to you and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) for organizing this meeting.

Below, please find a hard copy of the comments I will present to the Task Force on Research Specific to Pregnant and Lactating Women on Tuesday, 21 August 2017.

Sincerely,

/Lindsay McKenna/

Lindsay McKenna, MPH
Senior TB/HIV Project Officer
Treatment Action Group

Treatment Action Group's Comments to the Task Force on Research Specific to Pregnant and Lactating Women

Thank you to the the Eunice Kennedy Shriver National Institute of Child Health and Human Development for organizing this meeting and to the Task Force for its commitment to finding solutions for pregnant women and the clinicians charged with their care, and for allowing this opportunity for the public to offer our perspectives. I will be focusing my comments on research for pregnant women with tuberculosis (TB).

I'm Lindsay McKenna and I work at Treatment Action Group (TAG), an independent, activist and community-based research and policy think tank that has been fighting for better treatment, prevention, diagnosis, a vaccine, and a cure for HIV for 25 years, and for TB, and hepatitis C virus for over 10 years.

TAG first became engaged in issues related to pregnancy and research while reviewing clinical trials protocols for TB drugs and regimens. We noticed over and over again identical language used to exclude pregnant women from research, even when the ratio of potential benefit to harm favored their inclusion in trials.

Recognizing that in the absence of evidence, clinicians are put in the difficult position of treating pregnant women with medicines without adequate guidance on dose adjustments, safety, or efficacy; and the risks and burden of anxiety this creates for women who require treatment while pregnant, we have been working to challenge this assumption that pregnant women cannot be safely and ethically included in research.¹

TAG is a nonprofit, tax-exempt
501(c)(3) organization.
E.I.N. 13-3624785

The International Maternal Pediatric Adolescent AIDS Clinical Trials network (IMPAACT), which is funded by the U.S. National Institutes of Health (NIH), is a great example of how this can be done. You will hear more about the IMPAACT network in Dr. Nachman's remarks.

IMPAACT, along with the four other clinical research networks (the AIDS Clinical Trials Group [ACTG], HIV Prevention Trials Network [HPTN], HIV Vaccines Trials Network [HVTN], and Microbicide Trials Network [MTN]) under the NIH Division of AIDS (DAIDS), will be up for re-competition in 2020. DAIDS is soliciting feedback now for how these networks should be structured and what scientific questions they should aspire to answer. I encourage the Task Force to engage with DAIDS leadership on this subject to reinforce the importance of the IMPAACT network and the infrastructure and expertise it has built to facilitating future research in pregnant and postpartum women.

TAG's efforts and thinking around research and pregnancy have been focused in the context of TB and HIV, but the ideas we have for how to close data gaps for pregnant women have potential to benefit women with or at risk of other diseases and infections as well.

We'd like to appeal to the Task Force to further investigate and consider including the following among its recommendations to the U.S. Secretary of Health and Human Services (HHS) for how the federal government can help address gaps in research and knowledge for pregnant and postpartum women:

1. Develop an international registry to collect data on the incidence of adverse events among pregnant women treated for TB and other indications. It can be modeled after the Antiretroviral Pregnancy Registry (APR) created in 1989 to address data issues among pregnant women with HIV;
2. Establish a mandate for research networks, institutions, and investigators that receive funding from the U.S. government to put in place a standing protocol to, where appropriate, allow for the enrollment of pregnant women in the studies they conduct; and
3. Work with regulatory authorities and legislators to craft regulatory policy or legislation as necessary to codify the assessment of new therapies in pregnant and postpartum women, which can be enforced by regulatory authorities.

Prioritization of diseases on which the task force and the federal government will focus efforts and investments is inevitable. In closing, I encourage the Task Force to ensure that its priorities are not determined solely by the burden of disease in the U.S., which would leave out diseases like Zika, Ebola, and tuberculosis, but also in terms of existing and emerging threats to global health security, which will inevitably affect U.S. citizens, including antimicrobial resistance (AMR).

¹ McKenna L, Frick M, Lee C, et al. A community perspective on the inclusion of pregnant women in TB drugs trials. Clin Infect Dis. 2017 June 16. doi: <https://doi.org/10.1093/cid/cix533>.

Medication and Vaccination Data from the Healthy Pregnancy Study

Jennifer Radin is an epidemiologist at Scripps Translational Science Institute (STSI) in La Jolla, CA and the principal investigator of the Healthy Pregnancy Study. She will talk about medication and vaccination data collected through this app-based research study. STSI aims to replace the *status-quo* of one-size-fits-all-medicine with individualized health care that is based on the known genetic factors influencing health and disease and that takes advantage of advances in digital technology for real-time health monitoring.

This Healthy Pregnancy Study is a prospective, long-term, multi-year ResearchKit app created in collaboration between STSI and WebMD. The study aims to improve understanding of pregnancy through the collection of both survey and connected device data. The app collects medication (prescribed and over-the-counter) and vaccination data through an initial health history questionnaire and weekly surveys (see Figure). This data can be linked with outcome variables, such as pregnancy complications and diagnoses, symptoms, physiological measurements, activity, sleep, birth outcomes and more. Since the study is run entirely online, new questions can quickly and easily be added to the app at any time. The app is available for download from the iTunes store: <https://itunes.apple.com/us/app/webmd-pregnancy/id600535431?mt=8>.

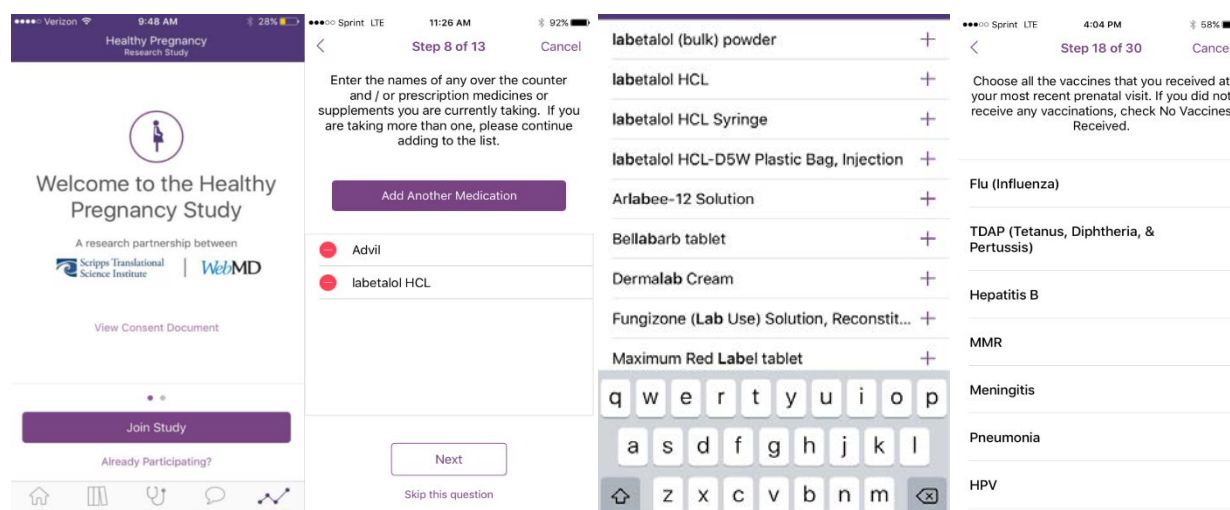


Figure. Healthy pregnancy app screen shots. Left to right: (a) Welcome screen (b) Medications during pregnancy question- health history questionnaire (c) Drop down list of prescribed and over-the-counter medications (d) Vaccinations during pregnancy question- health history questionnaire.

All pregnant women living in the United States, who own an iPhone and are comfortable reading and writing on it in English are eligible to join. However, in the near future, there are plans to expand to the study to Android phones, other languages and countries, and even postpartum women and their babies. As the availability of an increasing array of wireless, connected sensors grows, we also anticipate including a greater amount of automated daily (or even more frequent) collection of multiple parameters such as blood pressure, heart rate, activity, sleep, stress, glucose and more.

Currently, 6 out of the top ten prescribed medications and 2 of the top ten over the counter medications taken by women in the study are FDA category C, meaning animal studies show potential harm and adequate and well controlled human studies don't exist (see Table). The

high prevalence of category C drug use highlights the incredible need to provide women with better evidence based information about drug safety and effectiveness during pregnancy. By crowd-sourcing data from hundreds of thousands of pregnant women through a popular pregnancy app, the Healthy Pregnancy Study intends to fill in important research gaps regarding vaccine and drug safety, interactions, and effectiveness during pregnancy, even for less commonly taken medications.

Table. List of the top ten most prescribed and over-the-counter medications during pregnancy, drug indication, FDA pregnancy category, and percentage of participants taking the drug. Data is from the health history questionnaire, n=1,123.

| Prescribed Medications | Over-the-counter |
|---|---|
| 1. Antidepressants (8%) | 1. Prenatal Vitamins (93%) |
| a. Zoloft, C (3%) | 2. Allergy (7%) |
| b. Prozac, C (1%) | a. Zyrtec, B (4%) |
| c. Bupropion, C (1%) | b. Benadryl B, (2%) |
| d. Lexapro, C (1%) | c. Claritin, B, (1%) |
| e. Celexa (1%) | 3. Acetaminophen (Analgesic), B (5%) |
| 2. Levothyroxine (Thyroid Deficiency), C (5%) | 4. Aspirin (NSAID/Analgesic), C/D, (4%) |
| 3. Progesterone (Infertility/Prevent Miscarriage), A (2%) | 5. Zantac (Nausea/Heartburn), B (2%) |
| 4. Metformin (Type 2 Diabetes), B (1%) | 6. Tums (Antacid), C (2%) |
| 5. Diclegis (Morning Sickness), A, (1%) | 7. Probiotic (Healthy Gut), Not Assigned (2%) |
| 6. Adderall (ADHD/Narcolepsy), C (1%) | 8. Unisom (Sleep), B (1%) |



Oral Comments for Meeting of the Task Force on Research Specific to Pregnant and Lactating Women

Sharon Nachman, MD, Chair, International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network.

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network is a global collaboration of investigators, institutions, community representatives and other partners organized for the purpose of evaluating interventions to treat and prevent HIV infection and its consequences in pregnant/postpartum women, infants, children, and adolescents through the conduct of high quality clinical trials. The Network is funded by the National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH).

The Network's mission is population-oriented and focused specifically on pregnant and postpartum women, infants, children and youth. Our research agenda includes evaluation of:

- new and existing anti-HIV drugs and formulations;
- novel approaches for addressing tuberculosis (TB) in HIV-infected or at-risk populations;
- therapeutic interventions for achieving HIV "cure" (sustained viral remission);
- biomedical and behavioral interventions to prevent HIV acquisition and transmission;
- immunogenicity, safety and efficacy of high priority vaccines; and
- methods to prevent and manage comorbidities and complications of HIV infection and its treatment.

The Network has over two decades of experience conducting clinical trials in pregnant and postpartum women and a strong US domestic and international presence. We currently work with 52 NIAID- and NICHD-funded sites located in US (22) and 13 other countries (30). These sites bring extensive clinical trials capacity and a wealth of experience for implementation of the Network's scientific agenda. The IMPAACT Network has an excellent track record of productivity, with data from our studies informing and shaping public health policy and guidelines in the US and worldwide. Our research agenda draws upon the expertise and experience of leading scientists and investigators from around the world and benefits from strong collaborative partnerships with other research organizations, private industry and other groups. In pursuit of the highest priority science for our key populations, we invite investigators from inside and outside of the network to submit new study proposals at any time, and our work is guided and supported by a strong and active Community Advisory Board.

While the network is well known for studying how to prevent mother-to-child transmission (PMTCT) of HIV, our research agenda and expertise stretch far beyond PMTCT. We are experienced clinical researchers with a passion for solving problems in our specific populations of interest. We have learned from our experiences in these studies that, when properly informed, pregnant and breast-feeding women are more than willing to participate clinical research and can successfully be enrolled and followed in studies with a range of designs.

An example of the Network's contributions is our master study for evaluation of pharmacokinetics (PK) and safety of licensed ARVs for HIV and TB drugs in pregnant and postpartum women. This trial has evaluated over 15 agents to date and provided essential and previously non-existent information on appropriate dosing of these therapies across the trimesters and post-partum. Incorrect dosing of TB therapies during pregnancy puts both mothers and infants at risk of dying from TB, hence the evaluation of these drugs as well. This unique trial also includes the opportunity to study the "wash-out" and post-delivery PK of these HIV and TB therapies in newborn infants, recognizing that both mothers and infants are persons in their own right - not simply extensions of each other. This templated study, led by experts in obstetrics, pharmacokinetics and pharmacodynamics, has broad applicability to other licensed treatments that are commonly used in pregnant/postpartum women despite the absence of PK data and knowledge of appropriate dosing levels in these populations.

We also have enormous strength in emerging infections. For example, at the height of the H1N1 epidemic, our Network developed, fielded and completely enrolled a study of a novel H1N1 vaccine in HIV+ pregnant women within three months. This study evaluated both a novel type and dose of influenza vaccine and demonstrated both safety and immunogenicity, making it the reference for all new influenza vaccines in pregnant (and HIV+) women.

The Network knows when to challenge 'status quo' as seen with our nearly completed study of isoniazid (INH) in pregnant women at high risk for TB. The existing guidelines recommend administering a standard adult dose of INH to pregnant women at risk for TB, despite a paucity of data on safety and effectiveness of this approach in this population. To address this gap, the IMPAACT Network developed a study into which over 900 pregnant women at risk for TB were rapidly enrolled (ahead of schedule). The results will be presented soon after the study and analysis are completed next year.

Investigators, funding agencies and even ethics committees/institutional review boards must let go of the mind-set that pregnant women or even women who could become pregnant should automatically be excluded from studies of novel therapies. The IMPAACT Network's track record demonstrates that such studies - designed specifically for pregnant and postpartum women - can be implemented in a safe, timely and effective manner.

The IMPAACT Network is an existing, unique and valuable resource for which funding should be continued. In fact, our expertise and infrastructure for studies in pregnant and postpartum women and their children can and should be utilized to study other pathogens in these important but often neglected populations.

Comments on research for pregnant women with tuberculosis to the PRGLAC Task Force

Written by: Kate O'Brien

Submitted: August 17, 2017

I would like to thank the Task Force for giving me the opportunity to comment on research needs facing pregnant women. I am Kate O'Brien – a mother, an advocate and a TB survivor. I'll be focusing my comments to reflect the experience of having TB while pregnant, and the vital need to expand research to meet the critical treatment needs of all pregnant women that have TB.

When I became pregnant with my second baby in 2015 I was overjoyed. That wonderful feeling abruptly changed when I almost immediately started feeling terrible. After months of confusion and misdiagnosis after misdiagnosis, I landed in a hospital ICU and learned I had active tuberculosis. I was kept in isolation for 75 days in total, away from my toddler son.

While everyone around me knew how to treat tuberculosis, and I had a drug-susceptible strain that has been "cureable" for many years, my pregnancy seemed to throw a wrench into everything. Despite my correct understanding that pregnant women have been treated for TB for decades, that pregnant women were being treated for TB all over the world, I felt like an outlier, a "special case". I was given the typical first-line drugs for the illness, which pass through the liver. I woke up scratching myself at night, wondering if the negative pressure air in my isolation room made things dry. I secretly hoped my skin was stretching from the pregnancy and the baby was gaining weight despite my inability to do the same. I cheerfully reported this symptom to my doctor the next day, and was gently shown a skyrocketing liver chart. The liver is more sensitive during pregnancy, so the first-line antibiotics used to treat TB gave me hepatitis. Even though I was showing progress on fighting the illness and was eating more and coughing less - we had to wait a week without medication for my liver to "cool down". I stopped eating. I started feeling awful. Then I would start a new drug. We repeated this cycle several times. I was unable to take pyrazinamide and rifampin, two of the four drugs used to routinely treat TB.

This cycle resulted in extra weeks away from my child and unnecessary medications for my baby. Why was I taking them? Was this typically how a pregnant woman with TB reacts or was my liver extra-EXTRA sensitive? If so many women had taken and were taking the EXACT same antibiotics, why couldn't anyone tell me?

We started on second line drugs, drugs typically used to treat resistant strains, drugs that have less information and more side effects. We had no idea if they would work, if I could tolerate them. I had no idea when I would be able to leave the hospital and my family was totally upended, living week to week by my liver. Despite having a common strain of a common illness that has been around for centuries, my baby and I were an experiment.

They wondered if we would have to deliver early in order to treat me. Everyone was concerned with killing the TB, but as you can all imagine, the overriding thought for me was "What is going to happen to my baby?" My baby was the only one with me in many of those hours spent in isolation. I loved my baby, and the feeling of guilt was only outmatched by anxiety. Was it going to be alright? What was I doing to it? This drug causes hearing loss, will my baby be deaf? Should I breastfeed? If women in poor countries get this disease so much, their babies must be breastfeeding, right? I had question after question with no concrete answer. This made the anxious thoughts and fears worse, this made the guilt worse, it made everything worse. Eventually I kept asking "why isn't anyone writing down what happens to pregnant women when they take these medications? Don't TB patients get followed for months? Doesn't anyone care about their babies?" The answer I was getting by not getting an answer was 'No'. No one cared

about their babies enough to record anything, and no one was going to take note of mine, either. There wasn't a place to put the information. There wasn't anyone interested.

Earlier today a registry was mentioned, to collect this sort of data on pregnant women with tuberculosis. This would have had a profound impact on my situation in every aspect. I would have been treated better, faster, with much less insecurity and fear. The length of treatment and uncertainty was so difficult not just for me but for my toddler son, for my husband, for our parents and our finances. The information is available, but it's not being collected in a way that can help us answer these questions! These patients are under DOT and are already being monitored to some extent. The data is out there ready to help someone, and to CONTINUE helping people for years and years.

Pregnancy isn't a "complication" or a "condition" - and it certainly shouldn't be an *exclusion* criterion for studies of medicines that women may need to take *while pregnant*. Most women are able to conceive from 16-40. We are of "childbearing age" for much of our lives. A drug isn't truly safe for women unless it is safe for pregnant women, and if the goal we keep seeing of having women equally represented in medical research is ever going to be fully realized, we have to stop pretending that pregnancy isn't some sort of a discrepancy and acknowledge that living with the chance of pregnancy is half of female adulthood. This is especially true of women around the world who don't have the same agency to pick when they conceive, as perhaps many of us do. We aren't "special women". We are women.

I gave birth in April 2015 to a beautiful baby boy. Jimmy is affectionate, funny, climbs on everything and appears to be healthy but I still worry all the time. He doesn't really talk yet, and well meaning people tell me not to be concerned. In the absence of information, what else can I be? I urge you to end the neglect of pregnant women in research and their exclusion from clinical trials, especially those designed to evaluate treatments for new and frightening drug resistant strains of TB. I can tell you from first hand experience - pregnant women will be forced to take these treatments anyway. Give them the support of doing so under careful observation in the context of a supervised clinical trial, that has the potential to inform the safe treatment of pregnant women in the future. Give them the knowledge that their situation, their children are worth a few notes. This WILL make things easier for patient and doctor down the road and it's the right way to do things.

I thank you for your interest and work in maternal health from the bottom of my heart today, and on behalf of my children.

- Kate O'Brien, "We Are TB"

Statement of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) to the Task Force on Research Specific to Pregnant and Lactating Women

August 21, 2017

Good morning. I am Sheila Heitzig with the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), a national pregnancy outcome public-private research model that is coordinated by the American Academy of Asthma, Allergy, and Immunology and is designed to conduct observational studies about medication and vaccine safety in pregnancy.

On behalf of the VAMPSS investigators, we applaud the goals of the Task Force in identifying existing sources of relevant data, proposing methods for bringing together these existing data sources to facilitate amalgamated review, and identifying gaps in research in this topic area. However, we wish to emphasize, as has been well established in more than one comprehensive review, that more than 80% of the prescription medications currently on the market in the U.S. have **no or inadequate** pregnancy safety data. When we consider over-the-counter and herbal products, which are more commonly used by pregnant women than prescription medicine, the number of products with **no or inadequate** pregnancy safety data is likely closer to 100%.

While VAMPSS is one of the national research groups that provides an important source of relevant data on pregnancy safety for both prescription AND over the counter medications and vaccines, we want to make clear that we believe the overarching and overwhelming challenge of the Task Force is going to be in addressing the lack of safety data. There is no existing single or combined set of research programs in this field that is anywhere near sufficiently supported to address this research gap that affects every mother and child in this country.

Thank you.

The Vaccines and Medications in Pregnancy Surveillance System is a collaboration among the American Academy of Allergy, Asthma, & Immunology (AAAAI); the Organization of Teratology Information Specialists Research Center at the University of California-San Diego (OTIS); the Slone Epidemiology Center at Boston University (SEC); and the Harvard Pregnancy Research Group. For more information on VAMPSS, please contact Sheila Heitzig at sheitzig@aaaai.org, or call (414)-272-6071 or visit www.aaaai.org/vampss.

THE PATIENT PERSPECTIVE:
Jamie Zahlaway Belsito
August 20, 2017

***Excerpts from Moms around the United States who
took meds while pregnant and/or Breastfeeding***

I was on Prozac after having my first child due to postpartum depression and depression. Was told it was ok to be on this medication while pregnant. At 34 and half weeks I went into labor with my second child. The doctors tried to stop the labor but she was coming and I delivered her via c-section 5 1/2 weeks early. She was 6lbs 9 oz but her lungs weren't fully developed and she was in ICU for 3-4 days. She was shaky and had tremors when I asked why she was like that they said she was withdrawing from the anti depressant. She only spent one more day in the hospital than I did. She was healthy and spent the next five weeks sleeping (doctors said she will sleep like in the womb until her due date came) Emily is a healthy and happy 12 yr old despite how she came in the world. It came out several months later that women shouldn't be on Prozac while pregnant (go figure) wish I came off the meds while I was pregnant but what was done was done. I'm just grateful that she was ok! Hope this helps you!

SHERI, Nashua, NH

*

I'd love to get together and chat about how many of my moms struggle with PPD and self medicate themselves into an addiction. I'd also like to chat about who I need to beg to listen to me about how desperately I need funds to help the ridiculous number of pregnant women and moms in Mass who have NO access to treatment.

JULIE, Quincy, MA; ED of Sober Mommies

*

I went on Zoloft when I was still breastfeeding my son 7 years ago, but it was only a few weeks of that since I stopped breastfeeding for other reasons.

I went back on meds for a few years before I got pregnant with my daughter. I stopped all psych meds for the entire pregnancy. I did this with my Psychologist and with the understanding that if I needed meds during the pregnancy we would find what would work and be ok with pregnancy. I didn't have to go on anything until after she was born. I only breastfed her for a few days and then probably 2 weeks or so after she was born, I went back on my psych meds.

SAMANTHA, Bellingham, WA

*

I was diagnosed with PPD at my 6 week postpartum checkup in December of 2006. When I didn't pass the Edinburgh, the Dr. told me that there was a therapist onsite who could see me in an hour. She was covered by a grant, so I saw her for 18 months free of charge. She referred me to a psychiatrist at the Gifford Clinic, which is part of UCSD's maternal mental health program. I was put on several different medications for depression and anxiety, but none helped, and one day when I was home alone with my baby, I saw "movies" playing of myself throwing my baby through the entertainment center. I could feel the adrenalin and my body starting to follow through, so I ran into the bedroom, put him in his crib and closed the door. I immediately called my therapist and told her about the episode. We talked for a while and the psychiatrist called me and we talked as well. Someone came home, so I turned off my phone and pretended to be asleep so I wouldn't have to deal with people. Apparently turning your phone off when you're in crisis is not a good thing because the police ended up at my door telling my then husband that they were responding to a call that a woman was going to throw her baby out the window. All I kept thinking was that it wasn't the window, it

was the entertainment center. My husband had no idea how bad things were for me, so until they mentioned Jacob and me by name, he insisted they had the wrong house. They didn't take the baby or me, but I saw my therapist the next morning, and she and my husband convinced me to go inpatient.

When I was inpatient at UCSD, the doctors tried to convince me to stop breastfeeding so I could get on stronger meds. I refused, and had already tried everything that was safe for breastfeeding, so they let me go home after a few days. I kept getting worse, so I ended up at Grossmont Hospital's Psych Ward, where I was finally convinced that the stress hormones in my breastmilk were also harmful for my baby and that the best thing I could do was give my baby a happy mom. I conceded and gave up breastfeeding, which was the only thing that made me feel safe around my baby. They tried med after med, and nothing seemed to work. I was hospitalized 4 times that year and tried pretty much every depression and anxiety med available.

All that being said, the "anxiety" that caused my "movies" could have been the beginnings of psychosis, as several years later I was diagnosed with schizoaffective disorder. That may be why none of the meds worked. The jury is still out on that. I likely will never know for sure. If you have any other questions, feel free to ask. There's a lot more to my story, but I was trying to stick to meds and breastfeeding.

MARCIE, San Diego, CA

*

My first two pregnancies, i did not take any meds. the first pregnancy was my twin miscarriage. I took lorazepam for a week or so afterwards. After Theodore's birth, i took nothing (and suffered greatly with crippling anxiety) until he was 7 mos old. i was diagnosed with depression at that point

and began taking prozac which i have been on since. I was on meds for Darby's pregnancy, breastfeeding and beyond.

MARYANNE, Boston, MA

*

I've also been thinking that women should be required to see their midwife or doctor that they saw most often during their pregnancy at their postpartum visit. I was unable to see my primary midwife at my 6 week postpartum and she's the one who knew me and my moods the best. It should be a priority.

Amberly, Mother of 3, Danvers, MA

*

A psychiatrist told me there was NO med I could take while breastfeeding. I left feeling broken and even more hopeless.

Becky, Mom of 2, Milwaukee, WI

*

From speaking to moms at my groups...most go off meds without the knowledge of the doctor(s). ALSO- when asked about medication history on intake forms it ONLY asks about Current Meds, not PAST MEDS and this is something that needs to change.

Jennifer, Group Leader of a New Mom group in Southern Florida

*

I got conflicting info from my OB and Psychiatrist. Finally turned to LactMed and went with the info there. I recommend that website to pregnant/new mamas all the time.

Graeme, Mom of 2, Charleston, South Carolina

*

On anafranil and med monitored by a psych during two pregnancies and 3yrs bf with one and currently bf now. Went off during first tri of 2nd pregnancy on my own....BAD idea. My psych was very pro mom med during both....risk vs benefit and as long as i was monitored by her my obs were fine...thankfully. I was given the possible negative outcome during birth...which happened...but nothing horribly serious although glad i was told.

Samantha, Mom of 2, Alexandria, Virginia

*

I started Lexapro when my third (and last) son was 3 months old. My family practice physician (and myself) consulted Dr Thomas Hale and his InfantRisk resource, as well as LactMed, and were satisfied with this as a safe medication for me. Im thankful for those evidence-based resources for breastfeeding mothers, and that my Dr knew of them. I wish more providers did.

Carrie, Mom of 3, Anchorage, Alaska

*

IBCLC's are the best resource to check meds and breastfeeding. I was lucky to have one; many moms are not. Doctors need to know when it's time to refer their patient to an IBCLC for safe breastfeeding while medicating. It can be done. Sadly, few doctors relay accurate information.

Julie, Mom, Phoenix, Arizona

*

I don't think I was on anything during pregnancy but I was postpartum, while breastfeeding. I had extremely low platelets and had to take Prednisone and some other stuff to

raise them. Didn't have much monitoring. I felt pretty much on my own.

Carly, Mom, Philadelphia, PA

*

I took Zantac during my first and Prilosec during my second for AWFUL reflux. My midwife encouraged it because she wanted me to be able to eat enough

Lindsay, Mom of 3, Beverly, Massachusetts

*

I was on Zoloft for many years before I became pregnant with my first. Both my psychiatrist and OB/GYN would not give me an answer about if I should continue to take it. They both kept on passing the buck to the other provider. I always wonder if they would have given me a straight answer if I wasn't a lawyer. Anyways, I interpreted this action to mean that I should stop taking the meds. I went down slowly, under supervision of both providers. Without the medication I spiraled into a deep depression that resulted in me having to go on short-term disability from my lawfirm job. I couldn't drive, walk, it was awful! I went back to the psychiatrist and said, this can't be good for the baby either and I went back on the medication for the pregnancy and then nursed for 2 years. I never went off when I had the next two and again, continued nursing each for 2 years while on Zoloft. There were NO issues. Boys were healthy, great apgars, and nursed and gained weight.

Lillian, Mom of 2, Topsfield, Massachusetts

*

We see conflicting messages from OBs, nurses, lactation consultants and pharmacists given to our moms ALL THE TIME...even providers working in the same office. Wrong information is consistently given.

Sarah, Founder of Moms Mental Health Initiative, Wisconsin
*

I was not on meds during or after my pregnancies, but I recently attended the Alaska Psychiatric Association conference, and one of the presenters offered the view that the choice around taking meds perinatal is often framed as risking exposure to meds vs no risk (refraining from meds). This is not an accurate view as exposing a fetus or infant to depression or bipolar or other diagnoses carries its own significant risk. Many prescribers do not take this into account when making their recommendations.

Allison, Mom, Anchorage, Alaska
*

I was not on meds during or after my pregnancies, but I recently attended the Alaska Psychiatric Association conference, and one of the presenters offered the view that the choice around taking meds perinatal is often framed as risking exposure to meds vs no risk (refraining from meds). This is not an accurate view as exposing a fetus or infant to depression or bipolar or other diagnoses carries its own significant risk. Many prescribers do not take this into account when making their recommendations.

Vanessa, Mom of 3, pregnant with #4, Los Angeles, California
*

This. I hate this. I have women come in daily - with a different message from every single health provider they see - about meds and breastfeeding. It is so unfair to do this - repeatedly - to a pregnant or new mom who is already struggling with her mental health. we need one message. The risk benefit ration of taking mom off meds and feeling that makes breastfeeding safe is a lie. how about we get our

acts together and let them know they can do both. and they are the best mom for doing so.

Lisa, Mom of triplets, Director, Center for Perinatal Mood and Anxiety Disorders at [Monmouth Medical Center](#)

*

I was on blood pressure meds but was taken off after finding out I was pregnant

Leanne, 9 mos Pregnant Mom, Woburn, Massachusetts

*

In my experience the majority of providers don't want to take the time to research what meds are incompatible with Breastfeeding (which are very few) and air way to far on the side of caution and tell them to stop or pump and dump. It's shocking to me that obstetricians and pediatricians graduate from med school with little to no education on Breastfeeding.

Cheryl, Mom of 2, Labor and Delivery Nurse at Catholic Medical Center, Manchester, New Hampshire

*

I had a plan in place with my psychiatrist - we chose meds deemed safe for pregnancy. My OB immediately stated I should stop them when I came for my initial visit - so I requested an appointment with a neonatal specialist. I brought my plan to him and he said "this is exactly what I would have put you on. This is a fantastic plan and perfectly safe. Anxiety and depression can actually have a much bigger impact on your baby than these medications have." We did develop a plan for my anti-anxiety medicine where I would attempt to stop using it past the 37 week mark to ensure she wasn't born with any in her system.

I was mentally stable throughout the pregnancy and was able to care for my family well during my pregnancy. My daughter was born perfectly healthy, on time and is now 1

and thriving still. My postpartum period was much more easily handled because I had a plan in place and I felt confident. If I had listened to my OB I don't know what would have happened - but we have to self advocate. A lot of them don't know psychiatric meds - they aren't trained enough to even understand what is safe and what isn't. They tend to nix them all because it's safer for them since they don't know. It doesn't have to be that way...

Meaghan, Mom, Rochester, New York

PRGLAC NIH-led Federal Task Force to Consider Perinatal Mood and Anxiety Disorders (PMAD) in Pregnant and Lactating Women

It has been repeatedly substantiated that Perinatal Mood and Anxiety Disorders is the most common complication surrounding childbirth, yet all too often it goes unrecognized and untreated.

Perinatal mood disorders (PMAD), or pregnancy and postpartum depression are the names most commonly used for the psychiatric syndrome surrounding childbirth that includes a variety of moderate to severe mood and anxiety symptoms that require professional mental health treatment.

The clinical presentation often includes many of the following distressing and overwhelming symptoms: depressed mood, severe anxiety, panic attacks, insomnia and/or sleep disturbances, appetite loss, feelings of hopelessness and worthlessness, suicidal thoughts, loss of pleasure or joy, lack of energy and motivation, difficulty functioning at one's usual level, inability to cope with normal life demands, rumination, and/or obsessive and disturbing thoughts.

Far less common is symptoms of mania and psychosis (1 to 2 out of 1000 childbearing women) that research has linked to bipolar disorder and is considered the single strongest predictor of a postpartum psychosis.

According to the World Health Organization, depression affects 13% of women worldwide within a year of delivery (Bulletin of the World Health Organization 2012;90:139-149). In the United States and worldwide, the prevalence and incidence rates of PMAD has been estimated at 10 to 15% of women experiencing significant symptoms of depression and/or anxiety during their pregnancy or the postpartum period (Gavin et al, Obstet Gynecol.2005;106(5 Pt 1):1071-1083; O'Hara M. & Swain A., Int Rev Psychiatry. 1996;8:37-54).

While the PRGLAC NIH-led Federal Task Force has been assigned the mammoth task of identifying gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women, it is essential to consider perinatal depression and anxiety disorders along with other health and medical concerns. PMAD has enormous implications for the mental health, physical health and the overall well-being of women and their children.

Meltzer-Brody, S. (2011) reports that perinatal depression can have devastating consequences for the affected women, their children, and family, (Feldman et al. *J Am Acad Child Adolesc Psychiatry*.2009;48:919–927), and has been associated with serious adverse consequences for the developing neonate (premature birth, low birth weight, and future behavioral disturbances).

In addition, maternal depression has been linked to detrimental effects on maternal sensitivity and attachment in the postpartum period; mothers are more likely to exhibit impaired parenting and have infants with colic. Those children exposed to maternal depression have been found to have higher levels of cortisol than infants of mothers who were not depressed. Even nursing can be affected, as Meltzer-Brody reports that curtailed breastfeeding is associated with maternal depression (Meltzer-Brody S., *Dialogues Clin Neurosci*. 2011 Mar; 13(1): 89–100).

There are numerous research studies corroborating the negative outcomes on children and families of depressed mothers, yet the incredible toll that PMAD takes on the private life of mothers, children and families is not easily measured. Many are unaware of the chaos and havoc caused by PMAD, which results in excessive personal suffering, and the loss of joy in becoming a mother that often accompanies this debilitating mental health syndrome when it is not recognized early and treated promptly.

In the past few years we have made progress toward understanding various aspects surrounding perinatal mood and anxiety disorders: incidence and prevalence rates; development of new assessment and screening tools; predictors and risk factors; clinical symptom presentation; the effect on infant attachment and the couple/family relationship; and the efficacy of some evidence-based psychotherapeutic treatment methods.

Yet, there still remains many gaps and much to be learned about the pathogenesis of PMAD, the effect and exposure of various psychotropic medications on the fetus, on infants and in breast milk, the efficacy of evidence-based psychotherapeutic approaches alone or in combination with medication, as well as the usefulness of incorporating complementary and alternative methods in treatment.

From a perinatal psychiatry perspective, Meltzer-Brody (2011, *Dialogues Clin Neurosci.* 13(1):89-100) states that more research is needed to address gaps in the literature in the following: prospective studies that further our understanding of the safety of antidepressant exposure in pregnancy and lactation; longitudinal neurodevelopmental studies of children exposed to maternal mental illness, with or without psychotropics during pregnancy; translational research that clarifies the pathophysiology of PMAD with the long-term goal of ensuring the best possible clinical outcomes for mother and child.

In conclusion, there is a need for increased awareness of PMAD in both the public sector and with health care professionals. Despite encouraging steps in that direction, we have only just begun to address many significant gaps in knowledge and treatment. We need further efforts to investigate issues of prevention, to identify and promptly refer women at heightened risk, and to research safe and effective treatments for those with PMAD. There needs to be a willingness to explore an interdisciplinary treatment approach incorporating a combination of alternative and traditional therapies. These treatment approaches should consider the risk-benefits of using psychotropic medications when necessary, along with safe, effective evidence-based psychotherapies (2014, <http://apa.org/health/briefs/perinatal-depression>), such as cognitive-behavioral, interpersonal, mindfulness-based therapy, couple/family, EMD-R, and integrative approaches), and various alternative methods (acupuncture, nutritional and supplemental approaches, yoga, movement therapy, hypnosis, Transcranial Magnetic Stimulation, etc.) for women's optimal mental health.

Frank J. Nice, RPh, DPA, CPHP

www.nicebreastfeeding.com

First set of comments:

I have been consulting on medications and breastfeeding (and occasionally on pregnancy) for over 40 years.

Please check out my website for further information that is available.

Insufficient milk supply as addressed several times by Diane Spatz. Along with medication use, insufficient milk supply (aka, hypoprolactinemia), is one of the three most common reasons why women do not breastfeed or discontinue breastfeeding. She also mentioned domperidone and also the information that is available from Dr. Tom Hale, who is at Texas Tech University. In fact, Tom Hale will be running two clinical trials as part of the Orphan Drug Status given to the FDA to domperidone, which should fit in perfectly with your Task Forces' objectives. Also, please check out his Medications and Mothers' Milk and his website as valuable breastfeeding resources, as mentioned by Diane Spatz.

"Extremely limited literature in lactation women": More data exists on medications and breastfeeding than you may realize. Please again check out Dr. Tom Hale and my website. I have also attached two of my articles (<https://nicebreastfeeding.com/wp-content/uploads/2016/09/Medications-and-Breastfeeding-Current-Concepts.pdf> and [https://nicebreastfeeding.com/wp-content/uploads/2016/09/Selection and Use of Galactogogues.pdf](https://nicebreastfeeding.com/wp-content/uploads/2016/09/Selection_and_Use_of_Galactogogues.pdf)). As an aside, I spent many years at the NINDS as Assistant Director of the Clinical Neurosciences Program.

"Limited Assays": Please see above regarding breastfeeding and lactation

"Benefits of breastfeeding vs medications in women": It is really: Benefits of breastfeeding and benefits of the medication vs risks of not breastfeeding (aka, risks of artificial formula) vs risks of the medication.

Please see my article: Medications and Breastfeeding: Current Concepts (<https://nicebreastfeeding.com/wp-content/uploads/2016/09/Medications-and-Breastfeeding-Current-Concepts.pdf>)

Inclusion of OTCs and supplements and supplements and "complimentary" (it is really "complementary") medications: As for breastfeeding women, OTCs and herbal medications, especially herbal galactogogues (see both articles) appear to be used much more widely than prescription drugs.

PS: It was hard to hear some speakers who did not speak directly into their microphones. Also, I regret that as an offline participant that I could not actively participate in your discussion. Therefore, thank you for considering the information in my email.

Second set of comments:

I believe that in the past two days, I did not hear anyone discuss or mention Lactation Consultants.

I have found that in my experience that Lactation Consultants appear to be the most knowledgeable healthcare professionals (yes, even more than doctors and pharmacists) concerning medication (including galactagogues) use in breastfeeding mothers. Medication use is part of their board certification (a very rigorous program) as Lactation Consultants (yes, most are nurses). Some of them have excellent websites that discuss medication use, among many other issues. KellyMom does provide an excellent service, despite what Diane Spatz said today, and does reach a large population of the breastfeeding community.

I believe your Task Force should collaborate with the International Lactation Consultant Association (ILCA) and the United States Lactation Consultant Association (USLCA) and even with LaLeche League International (LLLI).

Once again, I believe there are more evidence based medications and breastfeeding studies out there than was stated yesterday and then repeated today. I use this data every day in counseling breastfeeding mothers on medication use. Yes; I admit that they are not all controlled clinical trials, but stating that a paucity of information and data exists, results in medication use being one of the three most common reasons why women do not breastfeed or discontinue breastfeeding. In my 40 years of practice, I have had to advise less than a dozen women to discontinue breastfeeding because of a drug they had to take. I discuss all the tools and techniques and data that I use to help women that are breastfeeding and must take a medication to continue to breastfeed. That is all covered in my seminal article, "Medications and Breastfeeding: Current Concepts" that I forwarded to you yesterday and on my website.

In all these cases, I collaborate with Lactation Consultants to obtain our positive outcomes.

Please do not make the current breastfeeding situation as dire as you do but also keep up your Task Force work on breastfeeding because both healthcare providers and breastfeeding mothers, babies, and families need all the support they can get, especially concerning medication use.

Once again, thank you for all that you do.

PS: Concerning recreational drug use, I have also just published my book: "Recreational Drugs and Drugs Used To Treat Addicted Mothers: Impact on Pregnancy and Breastfeeding" that you can also find on my website.

Katherine L. Wisner, M.D., M.S.
Norman and Helen Asher Professor of Psychiatry and Behavioral Sciences and Obstetrics and Gynecology
Director, Asher Center for the Study and Treatment of Depressive Disorders
Northwestern University Feinberg School of Medicine
676 North Saint Clair St.
Suite 1000
Chicago, IL 60611
312 695 8441 Barbara Sutcliffe, administrative assistant
Katherine.Wisner@northwestern.edu

It was nice to meet with you and participate in this meeting, which gave me new energy to tackle research with pregnant women!

Another thought about gaps ---**the workforce gap is huge!** We need more research, but who will do the research as we move forward?

A benefit of the NICHD networks that we did not talk about is stimulating new investigators. A benefit of our NICHD OPRC network (Northwestern, Pittsburgh, UTMB) is that funds are set aside for training, and we excite new researchers and show them that work with pregnant women is possible and rewarding.

At Northwestern:

My former research coordinator of our OPRC site is a young woman who was accepted to Northwestern's MD/PhD program, to pursue her PhD in pharmacology.

My junior faculty member just received a K23 to study pharmacokinetics of atypical antipsychotics in pregnant women, and submitted an R21 to define PK of lithium in pregnancy.

My MFM BIRCWH scholar submitted an R21 to conduct a pilot study to inform a comparative effectiveness trial of antiemetic agents, and a novel agent, mirtazapine, for nausea/vomiting/hyperemesis.

My genetic epidemiology junior faculty member (PI for pilot for OPRC) just submitted an R01 to study neonatal adaptation problems associated with SSRI exposure.

And we just expanded our studies with Young Jeong, PhD, our colleague at University of Illinois – Chicago, to study nifedipine in pregnancy and mechanisms through which CYP enzymes are stimulated in pregnant women.

The rewarding work is contagious through these networks!! Workforce development is a BIG GAP! We need a plan for investigator development. The BIRCWH program has supported some scholars, as has the WRHR, but these funds have been cut recently.

Thanks again for this meeting!!

Ms. Lisa Kaeser, Executive Secretary
Eunice Kennedy Shriver National Institute of Child Health and Human Development
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892

17 August 2017

Public Comment Re: Federal activities necessary to address gaps in knowledge about how to safely and effectively treat tuberculosis infection and disease in pregnant and postpartum women.

Dear Ms. Kaeser,

As a community of advocates, researchers, and clinicians concerned by the paucity of data available to guide the safe and effective treatment of pregnant and postpartum women with tuberculosis (TB) infection and disease, we submit the following public comment for consideration by the Task Force on Research Specific to Pregnant Women and Lactating Women (the Task Force).

TB affects both mother and the existing pregnancy. It increases the likelihood of poor birth outcomes, including spontaneous abortion, suboptimal weight gain, preterm labor, transmission of congenital TB, neonatal and perinatal mortality, low birth weight, and postnatal TB.^{1,2} If left untreated, TB in pregnancy can result in maternal mortality rates up to 40 percent.³ Despite substantial clinical need for TB prevention and treatment, pregnant women remain neglected by research initiatives.

Researchers, regulatory authorities, and communities have reached consensus about the need to include pregnant women in TB research.⁴ Yet, systematic exclusion of pregnant women from research persists, even when the ratio of potential benefit to harm favors their inclusion.⁵ Despite their exclusion from research, pregnant women get TB and clinicians have to treat them. In the absence of evidence, clinicians are put in the difficult position of treating TB in pregnant women using regimens of both old and newer TB drugs without adequate guidance on dose adjustments, safety, or efficacy.

To improve the availability of information critically important to guiding the safe prevention and treatment of TB in pregnant and postpartum women, we appeal to the Task Force to investigate and recommend to the Secretary of Health and Human Services to:

1. Develop a registry to collect data on the incidence of adverse events among pregnant women treated for TB infection and disease and other indications. It can be modeled after the Antiretroviral Pregnancy Registry (APR) created in 1989 to address data issues among pregnant women with HIV and overseen by an Interagency Advisory Committee with members from the U.S. Centers for Disease Control and Prevention, Food and Drug Administration, and National Institutes of Health;
2. Work with regulatory authorities and legislators to craft regulatory policy or legislation as necessary to codify the assessment of new therapies in pregnant and postpartum women, which can be enforced by regulatory authorities; and
3. Establish a mandate for research networks and institutions that receive funding from the U.S. government to put in place a standing protocol to, where appropriate, allow for the enrollment of pregnant women in the studies they conduct.

Respectfully submitted,

Organizations:

ACREOD
ACTION Global Health Advocacy Partnership
AIDS-Free World
American Thoracic Society (ATS)
Asian & Pacific Islander American Health Forum
Children's Hospital of Philadelphia
Eurasian Key Population Health Network (EKHN)
Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)
European AIDS Treatment Group (EATG)
Genesis Educational Trust
Global Coalition of TB Activists (GCTA)
Infectious Diseases Society of America (IDSA)
International Community of Women living with HIV Eastern Africa
International Health Consultancy, LLC
Jhpiego
JOPPA CENTRE
Kenya AIDS NGOs Consortium (KANCO)
Kigali Hope Association
Meera Foundation
National TB Controllers Association (NTCA)
New Jersey Association on Corrections
Pakistan Institute of Medical Sciences
Positive Women's Network - USA
Red Ribbon Istanbul
RESULTS
RESULTS International Australia
Socios En Salud (SES)
TB Proof
Treatment Action Group (TAG)
World Foundation for Medical Research and Prevention

Individuals:

Abderramane Abdelrahim, Programme, Tuberculose National, Ndjamen, Chad
Adjei Simon, Ghana Health Service, Bawku, Ghana
Alena Skrahina, The Republican Research and Practical Centre for Pulmonology and TB, Minsk, Belarus
Aliaksandr Skrahin, Belarusian State Medical University, Minsk, Belarus
Amita Gupta, Johns Hopkins University, Baltimore, MD, United States
Annette Gaudino, New York City, NY, United States
Arnaud Riat, Geneva, Switzerland
Ataulhaq Sanaie, ACREOD, London, United Kingdom
Bankole Peter Kuti, Obafemi Awolowo University Ile-Ife Nigeria, Ile-Ife, Osun, Nigeria
Barbara J Seaworth, University of Texas Health North East, San Antonio, TX, United States
Bavesh D. Kana, Johannesburg, Gauteng, South Africa
Bonnie Richardson, Chicago, IL, United States
Brian Citro, University of Chicago Law School, Chicago, IL, United States
Brian McKenna, Contemporary Women's Care, Northwell Health, St. James, NY, United States
Carrie Fritschy, We Are TB, Colorado Springs, CO, United States
Chloé dagress D'artagnan, Glen Ridge, NJ, United States

Christa Gallego, Escondido, CA, United States
Claire Dagress, Marina Del Rey, CA, United States
Colleen Daniels, New York City, NY, United States
Dalene von Delft, TB Proof, Cape Town, South Africa
Daniel Chiarilli, Columbia University, New York City, NY, United States
Dean Lewis, GCTA, Mumbai, Maharashtra, India
Debashish Das, Kolkata, India
Deniz Uyank, Istanbul, Turkey
Diana Nilsen, Long Island City, NY, United States
Doroty Namutamba, International Community of Women Living with HIV Eastern Africa, Kampala, Uganda
Dr. Arne von Delft, TB Proof and School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa
Dr. C.S. Jamunanantha, Jaffna, Sri Lanka
Dr. Joyce Sauk, Port Moresby, Papua New Guinea
Dr. Sarah Lespérance, Iqaluit, Nunavut, Canada
Dr. Vivian Cox, DR-TB STAT Task Force, Global Drug Resistant Tuberculosis Initiative, Chattanooga, TN, United States
E. Alice Christensen Majid, Dar Es Salaam, Tanzania
Edward Lomotey, Accra, Ghana
Erica Lessem, New York City, NY, United States
Faustin Kitetele Ndolumingu, Kalembelembe Pediatric Hospital, Kinshasa, Congo
Filiz Duyar, Ankara, Turkey
Giordono Uchofen, Arzobispado de Lima – Centro Medico Parroquial San Jose, Lima, Peru
Grace Montepiedra, Harvard School of Public Health, Boston, MA, United States
Gugu Dhlom, Cape Town, South Africa
Helen Cox, Cape Town, South Africa
Ihsan Ullah, Bannu, Pakistan
Iveta Ozere, Riga Eastern Clinical University Hospital Centre for Tuberculosis and Lung Diseases, Upeslejas, p.o.Cekule, Riga region, Latvia
James Aquino, New York City, New York, United States
Jeffrey R. Starke, Houston, TX, United States
Jessica Hale, Jersey City, NJ, United States
Jill Saanders, Maseru, Lesotho
Jum'atil Fajar, RSUD dr. H. Soemarno Sosroatmodjo, Kuala Kapuas, Kalimantan Tengah, Indonesia
Jyoti Mathad, Weill Cornell Medicine, NY, United States
Kate O'Brien, We Are TB, Rumson, NJ, United States
Kathryn Snow, Melbourne, Australia
Kelly Dooley, Baltimore, MD, United States
Kenyon Farrow, Baltimore, MD, United States
Keri Lijinsky, USAID, Washington D.C., United States
Khairunisa Suleiman, Nairobi, Kenya
Lafay Michelle, Paris, France
Laura A Peterson, Minneapolis, MN, United States
Lerato Legoabe, Johannesburg, South Africa
Lindsay McKenna, Brooklyn, NY, United States
Lisa V. Adams, Dartmouth's Geisel School of Medicine, Norwich, VT, United States
Lisa Marie Cranmer, Atlanta, GA, United States
Lisa Pannek, New York City, NY, United States
Lourdes Cruzado, GCTA, Lima, Peru
Marie Elizabeth Theunissen Famcru, Stellenbosch University, Cape Town, Western Cape, South Africa

Marije Van Schalkwyk, Stellenbosch University, Cape Town, Western Cape, South Africa
 Maryam Bibi Rumaney, Stellenbosch University Cape Town, Western Cape, South Africa
 Mike Frick, Brooklyn, NY, United States
 Mbumba Ngimbi Richard, Kinshasa, Congo
 Michael Odey Odo, Lilongwe, Malawi
 Navya Dasari, Philadelphia, PA, United States
 Nimer Ortuno-Gutierrez, Damien Foundation, Brussels, Belgium
 Nyamdulam Batjargal, National Center for Communicable Diseases, Ulaanbaatar, Mongolia
 Ogar Charles, Calabar, Nigeria
 Patricia Vasseur, Ermont Val d'oise, France
 Patricia Morgan, FHI360, Denver, CO, United States
 Pete Dupree, Denver, CO, United States
 Peter Gumboots, Bindura, Zimbabwe
 Rachael Crockett, RESULTS UK, London, United Kingdom
 Raj Vatsa, Stop TB Partnership, Geneva, Switzerland
 Rashmi Sharma, New Delhi, Delhi, India
 Raymond J Egolf, Palm Harbor, FL, United States
 Richard Jefferys, New York City, NY, United States
 Rinn Song, Boston, MA, United States
 Roberto Luiz Targa Ferreira, Grupo Hospitalar CONCEIÇÃO, Porto Alegre, Brazil
 Sandra M. Pallega, Bridgewater, NJ, United States
 Sarang Thaker, University of Illinois – School of Medicine, Chicago, IL, United States
 Sharon Wilson, New York City, NY, United States
 Shilpa N. Naik, BJ Government Medical College, Pune, Maharashtra. India
 Shivani Thaker, Chicago, IL, United States
 Stacie C. Stender, Cape Town, South Africa
 Suraj Madoori, Arlington, VA, United States
 Svetlana Doltu, Chisinau, Moldova
 Tania Thomas, University of Virginia, Charlottesville, VA, United States
 Tariro Kutadza, DAPP, Harare, Zimbabwe
 Taye Balcha, Armauer Hansen Research Institute, Addis Ababa, Ethiopia
 Tim Horn, Asbury Park, NJ, United States
 Timothy Sterling, M.D., Vanderbilt University Medical Center, Nashville, TN, United States
 Tushar Nair, Global Coalition of TB Activists, New Delhi, Delhi, India
 Wim Vandevelde, GNP+, Cape Town, South Africa
 Yael Hirsch-Moverman, ICAP, Columbia University's Mailman School of Public Health, New York City, NY, United States
 Zeaur Rahim, International Centre for Diarrheal Disease Research, Dhaka, Bangladesh

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PUBLIC COMMENTS PRGLAC
NOVEMBER 6-7, 2017
COALITION TO ADVANCE MATERNAL THERAPEUTICS
Kathryn G. Schubert, Society for Maternal-Fetal Medicine
kschubert@smfm.org

I am Katie Schubert, Chief Advocacy Officer at the Society for Maternal-Fetal Medicine. I am providing comment today on behalf of the Coalition to Advance Maternal Therapeutics, an advocacy coalition whose steering committee includes the American Congress of Obstetricians and Gynecologists, American Academy of Pediatrics, March of Dimes, and SMFM. The Coalition's members represent organizations in the maternal and child health community, as well as organizations who care about the safety and efficacy of medications used in pregnancy and breastfeeding.

We began discussing this issue in 2013, when we realized that our members – healthcare providers and consumers – pregnant and lactating women – simply didn't know enough about the medications they were prescribing or being prescribed. This is largely in part because pregnant women are not only not included in clinical trials, but often are actively excluded. Women taking medications get pregnant and pregnant and lactating women take medications. We came together with the idea that more guidance and data are essential to improving the care and treatment of this population.

Speaking on behalf of CAMT - we believe that it is unethical to not include pregnant and lactating women in trials where it is appropriate. There are mechanisms in place already to do this – IRBs are equipped to consider the risks and make expert recommendations on trial design. We recognize that research in pregnancy and lactation is multi-faceted – that is, that to have the broader picture, the answers may include randomized controlled trials, prospective and retrospective studies, pregnancy exposure registries and the use of existing models such as LactMed and VAMPSS. We encourage PRGLAC to ensure that studies will be conducted and identify the areas of most importance and urgency to encourage such research.

Public Comment of Sarah Mancoll, M.Sc., Public Policy Professional and Mother to Three Children, Ages 4.5, 2.5, and 5 months, in Response to a Call for Public Comments Issued by the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) on October 2, 2017

WRITTEN COMMENT

Since the late summer of 2012, I have not been able to receive treatment for an autoimmune disorder that adversely affects my quality of life. The autoimmune disorder, alopecia areata, is a disease that attacks hair follicles, causing hair to fall out in patches. I chose to stop treatment in 2012—treatment which I had been regularly receiving since the fall of 2003—after consulting with my obstetrician and my dermatologist (and later, my child’s pediatrician) about the possible negative effects of treatment on a developing baby during gestation, and/or while receiving breast milk. As my doctors explained, we simply don’t know enough about how treatment for alopecia areata *might* affect a developing baby—we don’t have enough research to confidently say, “Yes, you can continue with treatment, full stop,” or “Yes, you can continue with treatment, after the first trimester.” To play it safe, my doctors told me, it would be best to end treatment before conception and to begin treatment again only after weaning.¹

Between the time that I stopped receiving treatment and the time that I returned to work after my first maternity leave—a period of 12 months—I went from having an almost full head of hair to having full-blown alopecia universalis, the complete loss of hair on the scalp and body. For more than four years now, this has been the state of things.

There is no known cure for autoimmune-related alopecia, and there is no clear understanding of why some people develop the disease and others do not.² Research suggests that genes and environment both play a role.³ Oddly, autoimmune-related alopecia can come and go over the course of a lifetime. Some people lose hair and then regrow it, some people lose hair that never returns, and some people go through a seemingly endless cycle of losing and re-growing hair.

Fortunately, there are some known methods for treating—although not curing—autoimmune-related alopecia. Many of these treatments are thought to suppress, alter, or “trick” the immune response.⁴ One of the most common treatments—the treatment that I received from 2003 through 2012 and that worked for me—is the injection of corticosteroids at the affected site (intralesional corticosteroids), which act to suppress the immune response locally. Injections are typically given every month or so by a dermatologist. The injections are quite painful, and for even relatively small bald patches (e.g., the size of a quarter), you might need ten or more needle insertions. If you have several bald patches, you might need several dozen needle insertions in one sitting. The injection of corticosteroids also causes atrophy of the skin, which can appear as “dents” on the head, especially when bald patches are located near the hairline.⁵ In a nutshell, this and other forms of treatment are unpleasant, but I chose to pursue treatment because I badly wanted to keep my hair.

Although autoimmune-related alopecia only affects hair follicles and has no adverse effects on other parts of the body, the disease can still exact a big toll. It should not be discounted as *just* a cosmetic

¹ <https://jamanetwork.com/journals/jamadermatology/fullarticle/1735120>

² <https://www.niams.nih.gov/health-topics/alopecia-areata#tab-overview>

³ According to comments provided by Frederick W. Miller, M.D., Ph.D., Senior Investigator, Clinical Research Branch / Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, during a congressional briefing held on October 12, 2017 entitled “Individually Rare, Collectively Common: How Environmental Health Science Helps Us Understand and Prevent Autoimmune Disease.”

⁴ <https://www.aad.org/public/diseases/hair-and-scalp-problems/alopecia-areata#treatment>

⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3002419/>

Public Comment of Sarah Mancoll, M.Sc., Public Policy Professional and Mother to Three Children, Ages 4.5, 2.5, and 5 months, in Response to a Call for Public Comments Issued by the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) on October 2, 2017

concern. Alopecia in its various forms can be devastating emotionally and psychologically and is associated with depression and anxiety; it's not "*just hair*." ^{6 7}

I speak from experience. From 2003, when I was first diagnosed, to 2012, when I received my last injection of corticosteroids, I lived with constant worry that more and more hair would fall out and that I would no longer be able to hide my alopecia areata. Every few years, I would go through a period of great hair loss, when clumps and clumps of hair would come out in my hairbrush, in the shower, and in my hands. In 2013, when I finally lost the last bit of remaining hair, I struggled to present myself in public and sometimes avoided social gatherings altogether. Itchy wigs were uncomfortable to wear in hot and humid D.C., and I wasn't comfortable wearing my baldness out in public. As a result, I chose to wear head wraps. Unfortunately, head wraps come with complications, too: Head wraps can be uncomfortable in hot and humid weather, they can cause headaches, and they can lead to awkward social interactions. (For example, strangers come up and ask me if I have cancer, and old acquaintances will sometimes not recognize me unless I reintroduce myself.) Since I no longer have eyebrows or eyelashes, my eyes sting with dust when I walk outside and I hide whenever someone's taking a picture. To be honest, I still don't recognize myself in the mirror—even today, more than four years after I lost the last of my hair.

My husband and I have considered having a fourth child. Since I'm now 36, we would need to do that sooner rather than later. I hesitate not only because I worry about the effect of a fourth child on our careers (and sanity); I hesitate because I hate being bald. I'm afraid that the longer I forgo treatment, the more likely I am to never regrow hair. (Follicles die if they are fallow for too long.⁸)

When I went to my very first obstetrics appointment back in 2012, I came home with a list of medications that I was allowed to take while pregnant. It was not an especially long list. I joked with my family that the only drugs I could take were acetaminophen and antacids. For every condition that couldn't be addressed with acetaminophen or antacids, I was out of luck. Several months later, when I forgot to take that list of medications on vacation with me and came down with a cold, I sweated bullets trying to recall whether medicated cough drops had been on the list.

The reality for many pregnant and/or lactating women is that our treatment options are limited as compared to the general population—either because treatments have been shown to be unsafe, or because there simply isn't enough research to make an educated decision. For many women—especially women of my generation who waited until their 30s to start families and so try to have their children in rapid succession—having children can mean several years in a row of limited treatment options. For me, with alopecia universalis, it's a pain. For other women with more serious conditions, it can be much more than a pain.

In closing, I want to thank the Task Force on Research Specific to Pregnant Women and Lactating Women for exploring how pregnant and lactating women might better benefit from knowledge produced by research. Equity in research and healthcare matters. Just as we demand today that research reflects and benefits people of different genders, ethnicities, and life stages, we must also make sure that pregnant and lactating women are both represented in and benefit from research.

⁶ <https://www.yalemedicine.org/stories/alopecia-doctors-reverse-hair-loss/>

⁷ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1261195/>

⁸ <https://www.yalemedicine.org/stories/a-mom-struggles-with-hair-loss/>

PUBLIC COMMENT
PRGLAC
November 6, 2017

Nathan D. Nelson
Senior Director of Licensing. Special Counsel
BALCHEM Corporation

My name is Nathan Nelson, I work for Balchem Corporation. I am here today on behalf of a Prescription Prenatal Vitamin Coalition. As many of you know, prenatal vitamins are widely used in the pregnant population and are perhaps the most commonly prescribed therapy for this segment. What you may not know is that there are still some major barriers for pregnant women to gain access to prenatal vitamins. I'd like to highlight just four of these barriers: clinical research gaps, economic gaps, regulatory gaps and logistical gaps.

Clinical Research Gaps. As with other drug and non-drug therapies for our pregnant and lactating population, there is little to no clinical research that supports the benefits of prescription prenatal vitamin therapies. We need to change that. The coalition I represent asks the PRGLAC committee to emphasize in its report to Congress that not only are there major gaps in clinical research to support prescription drugs addressing conditions that patients may suffer from during their pregnancy, there are also major gaps in clinical research related to the condition of pregnancy itself. We need to close these gaps.

Economic Gaps. Prescription prenatal supplements that are manufactured to drug standards and promoted with extensive detailing to prescribing physicians sometimes differ in quality and certainly in cost to their over-the-counter cousins. The higher costs may have to do with the research, development, and promotion of these higher quality supplements. Unless patients have some type of insurance coverage for such prenatal supplements, they may be forced to purchase lower quality over-the-counter vitamins that may be manufactured merely to food or dietary supplement standards.

Regulatory Gaps. Prenatal vitamins are not "approved drugs" in accordance with FDA regulation. However, the FDA has informally stated that due to the longstanding safe and effective use of prenatal vitamins, it chooses to take no enforcement action against these drugs as a class. Because they are not approved "drugs" but rather prescription dietary supplements properly bearing a prescriptive legend, we hope that the Task Force will include in the scope of its report to Congress a review of prescription dietary supplements in addition to its review of prescription drugs. But there is a more worrying gap related to economics and to regulation, which I refer to as a "logistical gap."

Logistical Gaps. We have heard that some major payers have pressured a prescription compendium company to reclassify prenatal vitamins from their current reimbursable status to a non-reimbursable status. These intermediaries act as blockades in the logistics of manufacturing high quality prescription prenatal vitamins and getting them to end-users. We believe that any effort to limit patient access to this prescriptive category is contrary to the Secretary's work

ensuring the health of this population. We believe these third-party payers attempt to increase their own profits at the expense of expecting mothers and their babies and are putting many women and their babies at risk. They argue that expecting mothers should simply pay for over-the-counter vitamins out of their own pocket. But what of Medicaid patients who can't afford to do that? Do they just go without a prenatal supplement? The risk of neural tube defects rises significantly when pregnant women are not adequately supplemented. Expecting mothers need to supplement iron, folate, choline, vitamin B12 and DHA. The cost of ensuring that pregnant women continue to have coverage is negligible, especially compared to the costs on our health care systems to care for children born with neural tube defects.

These gaps are real and the risks they bring are too great to overlook. Thank you for your time and attention. Please let our Coalition know if we can help the Task Force in any way to ensure that it meets its goal to guide and advise the Secretary in protecting the health and well-being of pregnant and lactating Americans.



PRESIDENT:

Stephen R. Braddock, M.D.

February 15, 2018

PRESIDENT-ELECT:

Christina D. Chambers, Ph.D., M.P.H.

Ms. Lisa Kaeser

Executive Secretary

PAST PRESIDENT:

Robert Felix

Eunice Kennedy Shriver National Institute of Child Health and Human Development
31 Center Drive

TREASURER:

Beth Kiernan, M.P.H.

Room 2A03

MSC 2425

SECRETARY:

Marsha Leen-Mitchell

Bethesda, MD 20892

(301) 496-0536

MEMBERS-AT-LARGE:

Patricia Cole, M.P.H.

Sharon Lavigne, M.S., LGC

Anna Pupco, M.D.

RE: PRGLAC Public Comments

Dear Ms. Kaeser,

NATIONAL OFFICE:

5034A Thoroughbred Lane
Brentwood, TN 37027

Phone: (615) 649-3082

Fax: (615) 523-1715

www.MotherToBaby.org

(866) 626-6847

I represent the Organization of Teratology Information Specialists (OTIS). We would like to file our comments jointly with the Teratology Society as a written comment and also intend to present public comments during the time allotted for oral comments on Monday, February 26th from 10:00 a.m. – 10:45 a.m. Dr. Katherine Wisner from Northwestern University will be presenting the oral comments from OTIS and the Teratology Society.

Our public comments are as follows:

OTIS (The Organization of Teratology Information Specialists) is the professional organization for North American teratology information service providers. Through our component focusing on the general public, Mother to Baby, we provide an evidence-based information resource for women and men who have questions about exposures prior to and during pregnancy and breastfeeding. We are acutely aware of the limited body of research on the safety of medications used to treat pregnant or breastfeeding women with chronic or acute illness, and have a long history of doing research to improve the available data.

The Teratology Society is an international nonprofit consisting of members including researchers, clinicians, epidemiologists, and public health professionals from academia, government, and industry who study birth defects and disorders of developmental origin. The mission of the Teratology Society is to prevent birth defects and disorders of developmental origin by promoting research and exchange of ideas, communicating information to health professionals and other interested parties, and providing education and training. Our journal, *Birth Defects Research*, publishes original scientific research that

contributes to the understanding of the biology of embryonic development and the prenatal causative factors and mechanisms leading to adverse pregnancy outcomes.

Specifically, OTIS and the Teratology Society are committed to:

1. Rapidly assessing and integrating new information on research results into the information we provide to women, health care providers and the general public.
2. Initiating new research projects that address questions that are of high interest regarding exposures to pregnant and breastfeeding women.
3. Developing and executing strategies to effectively communicate research findings to pregnant women, health care professionals and the general public through publications, fact-sheets, the Mother to Baby website and other methods such as position papers, blogs, and social media campaigns, that aim to broaden awareness of the prevalence of birth defects and developmentally-mediated disorders and the need for continued investigation into the causes and prevention of such.

For more information about OTIS, we invite you to visit us at mothertobaby.org. More information about the Teratology Society may be found on www.teratology.org.

OTIS and the Teratology Society applaud the PRGLAC effort, which aligns well with some of our strategic goals. We welcome alliances with other groups with similar goals, and we offer the PRGLAC project our full support.

On behalf of OTIS and the Teratology Society, I would like to thank you for your consideration.

Sincerely,

/Stephen R. Braddock, M.D./

Stephen R. Braddock, M.D.
OTIS President

SMFM Comments to PRGLAC

February 26-27, 2018

On behalf of the Society for Maternal-Fetal Medicine, I am pleased to provide comments to PRGLAC. My name is Katie Schubert.

SMFM was founded in 1977 and is the medical professional society for high-risk pregnancy physicians. We are the leaders in care for pregnant women, and experts in both maternal and fetal health. Our 2,600 members are dedicated to improving care and outcomes for pregnant women. We have long been interested and advocating for better, safer and more effective information about medications taken during pregnancy and lactation, but also to ensuring that maternal health and research during pregnancy and lactation is prioritized.

SMFM's position on research specific to pregnancy is that there should be a presumption of inclusion – that is, that pregnant and lactating women should be included in clinical trials unless there is an obvious or justified reason for excluding them. We see this as a first step in changing the way that we think about research. NIH should build on their work related to gender as a biologic variable by including pregnant females in research involving animal models, as well as changing the consent requirements so that research involving a pregnant woman and fetus should only require *the mother's consent*. This would better align with the current one-parent consent requirement for pediatric research.

We echo the CAMT comments by encouraging PRGLAC to prioritize disease states in which there is a significant need for data about medications used during pregnancy and lactation. Our members are doing all that they can to properly manage chronic conditions as well as emergent issues in pregnancy, but they could be doing so much more with additional research – for example, potentially pregnant women with hepatitis C could be cured, but currently there is no research to test medications to see if they are safe or effective during pregnancy or lactation, and therefore, we cannot recommend or discourage those medications' use. We could be doing better, and women deserve better than being prescribed older drugs that our members know are safe anecdotally. A prioritized list of disease states would be great first step for further research so that we can make an impact on the areas of greatest need.

We also encourage FDA to release its final pregnancy exposure registry guidance to better assist with communicating risks and benefits to patients and providers. Beyond this, we further encourage these registries to do all they can to make the information transparent and easily available for both patients and providers. We are willing and able to assist with raising awareness about research opportunities and inclusion in clinical trials amongst our members and their patients, as well as drilling more specifically down to information surrounding medications used during pregnancy and lactation.

Finally, SMFM strongly believes that NIH needs additional funding that would allow truly prioritizing research involving pregnant women across Institutes. We must expand current research related to pregnancy and lactation generally, as well as to do all we can to encourage industry to engage in clinical research – we must remove barriers to including pregnant women in their work. We are committed to advocating for initiatives that would make strides in these areas.

Thank you for the opportunity to provide these comments. We look forward to continuing to support the work of PRGLAC and improving the health and wellbeing of women and their children.

From: [Fed Is Best.org](http://FedIsBest.org) [<mailto:christie@fedisbest.org>]

Sent: Wednesday, February 07, 2018 2:15 PM

To: Kaeser, Lisa (NIH/NICHD) [E] <kaeserl@mail.nih.gov>

Subject: Letter of Intent to Speak at the Task Force Meeting on February 26

Dear Ms. Kaeser,

I am writing to request the opportunity to speak at the Task Force meeting on February 26, 2017 at the NIH. I am writing as one of the Co-Founders of the Fed is Best Foundation whose mission is to research and provide education to parents and health professionals on safe infant feeding and safe breastfeeding to prevent the complications of jaundice, dehydration and hypoglycemia and the related brain injury caused by insufficient infant feeding. We would like to provide the U.S. Task Force important information that we have gathered regarding the prevalence of these complications, their pathogenesis, the preventable health care costs and the irreversible long-term consequences to newborns who sustain brain injury from these complications. We wish to address gaps in scientific knowledge, research and public awareness of these preventable complications that is costing the U.S. healthcare system billions of dollars a year. In addition, we wish to raise awareness on the ethical and legal gaps in informed consent and patient education on these feeding complications that occur on a daily basis.

Jaundice from insufficient feeding and dehydration are among the leading causes of newborn extended and repeat hospitalization in the U.S. and across the globe.[1-4] Among the leading risk factors for jaundice and dehydration, a entity called starvation jaundice, is exclusive breastfeeding of a newborn before full breast milk production.[5] This most commonly results from insufficient breast milk supply and secondly, from ineffective latch. According to the Academy of Breastfeeding Medicine, starvation jaundice occurs to 10-18% of U.S. exclusively breastfed newborns in the first month of life.[6] The increased risk of this brain-threatening complication associated with early exclusive breastfeeding and the important role of supplementation to prevent and treat jaundice is not currently shared with mothers. This serious gap in patient education results in approximately 228,000 phototherapy admissions every year in addition to preventable admissions for hypoglycemia (low blood sugar), hypernatremia (high sodium), dehydration and failure to thrive, all known causes of perinatal brain injury and disability. Phototherapy admissions cost the U.S approximately \$3.2 - 4.5 billion dollars annually, the majority of which (approximately 86%) are caused by starvation jaundice (i.e. non-hemolytic jaundice).[7,8] Previously healthy newborns who sustain brain injury from feeding complications can develop subtle to severe declines in attention, motor, sensory, language, behavioral and cognitive development leading to lower academic achievement and even frank global developmental disability and cerebral palsy.[9] The long-term consequences of brain injury from feeding complications can result in millions of dollars in health care costs over the lifetime of a child. A recent malpractice case of jaundice resulting in brain injury of a breastfed newborn resulted in an award of \$46.5 million dollars to a family in Arkansas. The cost to society and the emotional and psychological toll of these injuries are immeasurable.

We need publicly available statistics on the incidence of infant feeding complications in hospitals, a requirement that on its own will drive rates of feeding complications down by encouraging hospitals aggressively prevent complications. While decades of scientific evidence has shown the neurological consequences of jaundice, dehydration and hypoglycemia, we need more data to show the prevalence and the range of specific developmental disabilities in newborns who develop feeding complications. We also need research on the best ways to ensure infant patient safety and prevent feeding complications while supporting a mother's personal infant feeding goals.

Our organization has reviewed almost the entire scientific literature on infant feeding complications and has received thousands of breastfeeding complication stories from mothers directly. We believe that there are major gaps in breastfeeding education, public policy and health professional training regarding safe infant feeding, newborn caloric and fluid requirements and recognition of feeding complications. Given the financial and societal costs of infant feeding complications and their devastating consequences, we believe safe infant feeding is the most pressing issue in maternal-infant health. We would be grateful for the opportunity to assist the Task Force committee to address these issues in order to improve patient care while saving the U.S. healthcare system billions of dollars in preventable costs. In addition to speaking at the meeting, we plan to provide a written submission before the posted deadline in order to give the committee a more complete picture of the issues I have discussed above. We would also like to inquire as to how we can be involved in your Task Force committee as members or advisors beyond the upcoming meeting. We are currently involved in quality improvement research aimed at reducing neonatal feeding complication admissions at a large hospital and would be able to pass on the knowledge and insight gained from our involvement to your committee.

I thank you for this opportunity to participate in the Task Force's meeting.

Sincerely,

Christie del Castillo-Hegy, M.D.

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4. Olusanya, B. Et al Niger J Clin Pract. 2016 Jan-Feb;19(1):1-17. The burden and management of neonatal jaundice in Nigeria
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As a neonatologist I am on the front line of taking care of newborns with problems related to complicated pregnancies, deliveries, and prematurity. Due to advances in obstetric care, maternal-fetal medicine, and reproductive endocrinology, an increasing number of infants are born each year to mothers with problems such as preeclampsia, gestational diabetes, obesity, and autoimmune disease. In addition, about 10% of infants born in the U.S. are premature. It is well-known that pregnancy complications, preterm delivery, and maternal-infant separation, as a result of neonatal intensive care unit (NICU) admission, are associated with delayed lactogenesis II (the onset of copious milk volume) and problems with breastfeeding. In the Infant Feeding Practices II study almost 25% of mothers experienced a significant delay in the onset of lactation.

In recent years U.S. hospitals have strived for high exclusive breastfeeding rates at time of discharge and, in an effort to do so, have implemented the Baby Friendly Hospital Initiative (BFHI). During this same time period my neonatal colleagues and I have witnessed a skyrocketing increase in newborns admitted NICUs for complications related to breastfeeding. The most common medical diagnoses related to exclusive breastfeeding include dehydration, excessive weight loss (>7%), hyperbilirubinemia (jaundice), hyponatremia (elevated sodium level) and hypoglycemia (low blood glucose). In addition, our newborn nurseries have had to adopt protocols for managing newborns who are dropped onto the floor by their fatigued nursing mothers, as this has become a relatively common problem. Sudden unexpected postnatal collapse (SUPC) has also been increasing in incidence, and many of these cases occur within the first two hours of life during unsupervised skin-to-skin contact to facilitate early breastfeeding. These conditions can have lifelong consequences if there is a delay in diagnosis and treatment, including low IQ and neurodevelopmental impairment. The most severe cases of jaundice, electrolyte abnormalities, falls, and SUPC can lead to death.

Research involving pregnant and nursing mothers needs to focus on the critical safety issues associated with policies that aim for high rates of exclusive breastfeeding. Potential research areas include collecting data about the scope of neonatal morbidities related to insufficient milk intake and identifying pregnancy risk factors that are “red flags” for the development of lactation problems. This information can be used to improve the recognition of maternal-infant dyads that are at risk for lactation failure, decrease NICU admissions for the multiple problems related to exclusive breastfeeding, and, in doing so, prevent newborn morbidity and mortality. It can also be used to improve and update current breastfeeding initiatives that are already in place, such as the BFHI, and create additional resources to better support all mothers during pregnancy, in the hospital after delivery, and for the entire postpartum period.

Jessica Madden, MD

Neonatologist, Rainbow Babies and Children's Hospital, Cleveland, Ohio
Member, American Academy of Pediatrics Section on Neonatal-Perinatal Medicine
Member, Academy of Breastfeeding Medicine

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Bass, et al. Trends in the incidence of sudden unexplained infant death in the newborn: 1995-2014. *J Pediatr*. 2018. Published online Feb 5, 2018.

February 19, 2018

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a national pregnancy outcomes, public-private research project, coordinated by the American Academy of Asthma, Allergy, & Immunology (AAAAI), designed to conduct observational studies about medication and vaccine safety in pregnancy. The VAMPSS investigators have focused their efforts on influenza vaccines, antiviral medications, and asthma medications, all of which can significantly affect the health and well-being of pregnant and lactating women and their babies. The system, operational for more than ten years now, is positioned and ready to study other drugs as well.

The VAMPSS team has accomplished important work already. VAMPSS studies of the 2009 pandemic H1N1 influenza vaccine and subsequent seasonal flu vaccines have found reassuring evidence of their safety during pregnancy. Data analysis found that women vaccinated during pregnancy were no more likely to experience miscarriage, have a baby born with a birth defect, or have a baby born smaller than normal compared with those who did not receive a vaccination. However, it is estimated that fewer than 50% of pregnant women follow federal health authorities' recommendation that they receive the influenza vaccine. Increased support for VAMPSS studies would allow us to expand on our findings to support federal efforts to encourage pregnant women to get the flu vaccine.

The results of VAMPSS studies are shared with AAAAI's 6,500 members via a multilayered communications campaign. As allergist/immunologists care for women who are pregnant or capable of becoming pregnant, they are in a position to counsel these patients on the benefits of influenza vaccines. This is particularly important for patients with asthma, who are at higher risk of experiencing severe influenza symptoms. Indeed VAMPSS was established with the support of the AAAAI because of the prevalence of asthma, and the importance of providing appropriate safety information to pregnant moms for the management of their asthma for improved healthcare outcome for themselves and their babies.

Communications to AAAAI members provide information on VAMPSS study findings through email, member newsletters, and the AAAAI's two scientific journals. Patient education materials provided by the Organization of Teratology Information Specialists (OTIS) are distributed to our members and others by the AAAAI and the MotherToBaby team, a service of OTIS. In addition to a workshop at the AAAAI Annual Meeting each year, the VAMPSS team has held educational webinars for many health care provider groups including primary care and other specialty physicians, allied health professionals, and pharmacists.

The VAMPSS Independent Advisory Committee includes representatives from the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the Society for Maternal and Fetal Medicine, and the American Thoracic Society, which significantly expands the impact of our physician outreach efforts.

The VAMPSS team thanks the PRGLAC for the opportunity to submit comments to this meeting. We share your attention and focus on communicating with health care professionals about the importance of research on the impact of drugs and medications in pregnant and lactating women. We have supported the development and implementation of the Pregnancy and Lactation Labeling Rule and continue to reach out to health care providers in other specialties to improve communication between providers and their patients on these important issues. We have a proven track record and would welcome opportunities to participate in further discussions and efforts in our shared goals to improve patient and public information on these issues.

For further information, contact Sheila Heitzig, JD MNM CAE, at sheitzig@aaaai.org, or call 414-918-6071.

On behalf of the Coalition to Advance Maternal Therapeutics (CAMT), I am here providing comments broadly on the topic of research specific to pregnant and breastfeeding women, as well as on the communication piece.

CAMT is comprised of a dozen organizations who care very deeply about the inclusion of pregnant and breastfeeding women in research, and dedicated to ensuring safe and effective information about medications taken during this time are improved and transparent.

Overall, CAMT hopes that PRGLAC will proceed with a presumption of inclusion in research. This shift in perspective would go a long way to ensure inclusion in research. As part of this, animal models must include pregnant females, and the consent for research involving a pregnant woman and fetus should only require *the mother's consent*, to better align with the current one-parent consent requirement for pediatric research.

Beyond this, we encourage HHS, through NIH, to prioritize disease states in which there is a significant need for data about medications used during pregnancy and lactation. Currently, we know women take prescription medications while pregnant and breastfeeding. Anecdotally, we know that women are prescribed medication that we think are safe and are effective, but we could be doing better, and women deserve better. A prioritized list of disease states would be great first step for further research.

The release of final pregnancy exposure registry guidance by FDA would assist with communicating risks and benefits to patients and providers, but more needs to be done to make this information transparent and easily available.

We support the creation of an education and awareness campaign surrounding both medications in pregnancy and lactation as well as surrounding research in pregnancy and lactation. Such a campaign must be geared toward both consumers and health care professionals.

Finally, NIH needs additional funding that would allow truly prioritizing research involving pregnant women across Institutes, but also to expand current research related to pregnancy and lactation generally.

Thank you for the opportunity to provide these comments. We look forward to continuing to support the work of PRGLAC and improving the health and wellbeing of women and their children.

TO: Task Force on Research Specific to Pregnant Women and Lactating Women
February 2018

FROM: Genetic Alliance, Expecting Health
www.ExpectingHealth.org

The below comments serve as recommendations for effective communications strategies with women, families, and other relevant stakeholders on the critical issue of ensuring that medical research addresses questions from women in pregnancy, postpartum, and early childhood. As such we appreciate your considerations of our organizational knowledge and recommendations below.

Background

At Expecting Health, we know that women understand and want to be informed about complex concepts, but it is imperative that we prioritize our use of clear messaging to break down information. With decades of experience in maternal health communications and patient engagement in research, we know how to access women and the issues they care about most. Moms tell us time and time again that they want the best lives for their children, understand that their health greatly impacts outcomes for their children, and therefore are focused on improving behavior and increasing health knowledge during and post-pregnancy. For pregnant and lactating women with medical needs, it becomes all the more important to understand how to increase chances for a healthy pregnancy and empowering breastfeeding experience. There is no population for which more market and behavior data is collected than pregnant women. Because women are changing their behaviors and are interested in improving health behaviors, pregnancy is the ideal time to focus on informed participation, change in knowledge, and messaging to informed decision making.¹ Healthcare and research can capitalize on what the consumer and product market already knows around participation in this population and learn from behavior to build trust, lines of communications for research and clinical trials, and effective feedback gathering.

Recommendations

1. Mechanisms for stakeholder involvement, input, feedback collection, and subsequent iteration should be incorporated throughout the research process. Pregnant and lactating women should be invited to be leaders—from the beginning—to aid in crafting the most valuable research questions, more effective recruitment, and better, faster integration and dissemination of results.

¹ Tierney, M., Odea, A., Danyliv, A., Noctor, E., McGuire, B., Glynn, L., . . . Dunne, F. (2015). Factors influencing lifestyle behaviours during and after a gestational diabetes mellitus pregnancy. *Health Psychology and Behavioral Medicine*, 3(1), 204-216. doi:10.1080/21642850.2015.1073111.

2. Messages need to be consistent across all audiences so that healthcare providers, patients, and communities receive clear messages and multi-pronged communications strategies routinely reach all individuals. Involvement of all players will support efficiency in building a new culture for research in prenatal practice.
3. The expectation for involvement in research should be based in ongoing relationship and mutual trust; not consent and single-use participation. Involving women and their trusted informants is critical for partnership and trust building.
4. The research paradigm must allow for self-reported data, and both respect and trust women's knowledge as part of their medical landscape.
5. In order to see impact on the quality and scope of the population, it is essential that communications, research questions, and research processes are framed from a lens of health equity. Nuanced variables on trust, barriers, and benefits to participation in research for vulnerable populations must be acknowledged fully and throughout the process.

Suma Shah, MD- Public Comment for PRGLAC Task Force

Multiple sclerosis (MS) is a chronic autoimmune condition primarily affecting young adults. Internationally, there is a growing body of evidence to suggest an increasing gender ratio with time to an estimated 3-4:1. As there are numerous uncertainties faced by young women of childbearing age who are living with this chronic condition, it has become critical to define a clear approach to questions of disease management during pregnancy. Currently, there are no disease modifying therapies (DMTs) that are deemed safe (FDA pregnancy class A) during conception and pregnancy. As a result of the limited available data, management decisions for MS patients during pregnancy are made more difficult.

A few weeks ago, I met a 27-year-old woman in consultation for multiple sclerosis. She had been recently diagnosed with MS and wanted to speak to a specialist about how this diagnosis would affect her ability to start a family. As a provider serving patients with multiple sclerosis and neuroimmunologic disease, this was not the first time this subject had been broached. Currently, navigating this conversation not only requires knowledge of the latest breakthroughs in care for our patients but also the expertise in extrapolating that evidence to our young female population. This extrapolation results in an uncertainty that lends itself to an array of answers. Patients are often left confused or questioning the validity of provider recommendations, especially when different MDs are recommending differing advice.

Unfortunately, dedicated research to the pregnant and breastfeeding population is still lacking. During my fellowship year, I've spent the several months reviewing the available literature for therapy options for patients who would like to become pregnant, are pregnant, or are postpartum. The available information is limited. There are fields of medicine (e.g rheumatology, oncology) that seem to be a step ahead of us in gathering information regarding outcomes after treatment with certain disease modifying medications, but even this is not enough. The gold standard of research in medicine is the randomized controlled trial but, as a group, medical researchers have not successfully convinced themselves to do so for the pregnant population.

One of the questions I am frequently asked is: How have other patients in similar circumstances responded to treatment with disease modifying therapies during pregnancy? We could start there. Though this would be more of a retrospective analysis of past experiences, it may help guide where to focus our energies going forward. Additionally, in the last decade the available treatments for multiple sclerosis have nearly doubled. There is a shift towards immunomodulatory therapy as first-line care. As the arsenal of treatments for MS grows, so should our understanding of how it can be used for unique populations.

This morning, I received a message from a patient who has decided to stop breastfeeding so that she may resume therapy. I'll be seeing her this week to discuss options but cannot help but wonder: couldn't there be a way to allow her to breastfeed while still treating her safely? The implications of medication exposure to a nursing child seem to directly conflict with the desire to breastfeed. Reconciling this takes thoughtful, educated reflection on the risks and benefits of management options, but we need data for that.

Ultimately, the care of our patients with MS becomes about doing so with the least risks (both from the treatments themselves and possible disease relapse). The stakes are high: the lack of MS therapy may

result in weakness, sensory changes, overall functional impairment. In contrast, we do not want to expose any future children to medications that may put their health in jeopardy.

From: Emilie Bishop [<mailto:emilie@bishop.be>]
Sent: Thursday, February 01, 2018 5:50 PM
To: Kaeser, Lisa (NIH/NICHD) [E] <kaeserl@mail.nih.gov>
Subject: Written Comments for February 26 PRGLAC Meeting

My name is Emilie Bishop. I am 34 years old and the stay-at-home mom of my three-year-old son, Jonathan. We live in Bellevue, Washington, a suburb of Seattle, and Jonathan was delivered vaginally at full term at Evergreen Hospital Medical Center in neighboring Kirkland, Washington. Evergreen has the distinction of being the first hospital in the country to earn the WHO's "Baby-Friendly" designation, based on their adherence to a ten-step protocol designed to promote breastfeeding among mothers who give birth there. There are many reasons to promote breastfeeding in parts of the world where, very regrettably, clean water and nutritious formula may be hard to come by. I would like to share the story of how such policies hurt me and my son, who are privileged to have a six-figure household income and access to clean water, formula, medical care, and a growing awareness that breastmilk is a food, not the magic elixir our prenatal classes and postpartum care team claimed.

As previously stated, my son was born vaginally and full-term, on January 20, 2015. He was on the small side at 6'12", but with no complications or concerns. He was, however, born to parents who had suffered a miscarriage in September 2010 and were unable to conceive again until April 2014. In that time, I was diagnosed with endometriosis and underwent two laparoscopic surgeries as well as numerous other tests and treatments, sometimes in an attempt to conceive again, sometimes just to try to stop the unrelenting pelvic pain. We conceived naturally after failed fertility treatments and a discouraging attempt at adoption. To say our son was wanted and that I wanted him to have the best of everything was an understatement.

At the time of my pregnancy, Evergreen was our closest hospital and the home of the ob/gyn practice I'd used since 2006. Several local friends had delivered babies at Evergreen and had great things to say. Most of them breastfed at least part-time and were grateful for the extra support they found at Evergreen. I wanted to breastfeed, and our prenatal classes and paperwork made it sound like the only proper way to feed a baby. I knew from preparations we'd made for the possibility of becoming parents through adoption and from my own well-being that formula was fine, but I believed the hospital that breast milk had everything short of actual super powers. Why would I doubt my doctor and hospital staff when they had been to medical school and read scientific papers?

All was not roses and sunshine for us, despite the La Leche League video we watched in prenatal class. Every latch attempt required multiple people to assist us and often resulted in me screaming in pain. Within hours, I had one nipple bruised from my son needing to be pulled off because his nose got covered and he was suffocating, as well as another nipple bleeding from being scratched by his finger nail. My son was very sleepy that first day and had a bout of low body temperature. I was given a nipple shield and cream for comfort, as well as a pump to stimulate milk production. Neither helped. He was down four percent of his body weight in less than twenty-four hours, but because he'd had one wet diaper, we were discharged with a follow-up appointment two days later with a lactation consultant at the hospital's breastfeeding center. We were told to only breastfeed at home. By the time we got to that follow-up appointment, we'd spent two nights on the phone with various nurse lines, asking if 12 hours was too long between wet diapers, if he should still have meconium every few hours, if I should still have such intense pain with every latch. Always the advice was the same: keep breastfeeding. It's normal, he's fine, keep breastfeeding, they'll check him out at the appointment. When we got there, he was down eleven percent (74 hours after birth), weighing only 5'9" and so dehydrated he was peeing

every 23 hours (24 was the cut-off to go to the ER, we'd been told). A weighted feeding showed he was only getting an ounce between both breasts over twenty minutes, even with the LC correcting position. He gagged up his first few swallows of formula. We were readmitted for the night.

That night, we were taught how to "triple-feed," or nurse, bottle-feed with formula, then pump for additional stimulation and/or to add to the formula at the next feeding. It took an hour each time, and we were told to do that every 2-3 hours round the clock to build up my milk supply. I was asked if my breasts had changed during pregnancy. Since I bought extender hooks for my bras, I said, "I think so? A little at least." No one told me that wasn't enough.

The next six weeks are a blur of lactation consultant appointments, pediatrician appointments, exhaustion from the triple-feeding schedule, and self-loathing for not doing the one thing I had been told a "good" mother did for her baby. I felt like a complete failure for not recognizing my son was starving and then for not being able to increase my milk supply. By two months I'd weaned completely and was only feeding him formula from a bottle. I felt horribly guilty, but I couldn't keep up with the schedule that was doing nothing to increase my supply.

I learned later that my breasts have the hallmark features of insufficient glandular tissue, or IGT. They are wide-spaced, tube-shaped, and have changed very little since I was eleven years old, including when I was pregnant. For reasons unknown to me and the larger medical world, my breasts are not equipped to make enough milk and nothing will change that. No one in the entire hospital told me this. When I saw our charts 2.5 years later, though, I saw the very first nurse/LC who visited us wrote "Mom has wide-spaced breasts that is sometimes consistent with low supply (I will not discuss this with mom at this time)." In other words, better to boost our breastfeeding numbers than to prevent a newborn's starvation and a mom's mental breakdown.

The Baby-Friendly Hospital Initiative makes actions like this nurse's justifiable. One of their ten steps is to give no food or drink other than breastmilk except when medically indicated. Another is that hospitals will track the number of mother/infant dyads who have exclusively breastfed during their hospital stay. At my particular hospital, we were told that if we chose to formula-feed from the start, we would need to bring our own formula and bottles, and that we were responsible for preparation and cleaning. But as a first-time mother who wanted the best for my long-awaited baby, I had no reason to think I would need formula, so I didn't bring it. Hospital staff are taught that newborns don't need much to eat in the first few days, that weight loss is expected, and that medical indicators are things like unresponsiveness or seizures, not the more subtle steps leading to such a crisis. And if the only number that the BFHI tracks to ensure its program's "success" is the rate of exclusively breastfed babies at discharge, what's to stop women like my first nurse from lying to a clueless new mom so that she meets this arbitrary standard long enough to check the right box? No one cares about what comes later.

The NIH needs to start taking stories like this one seriously, because it isn't an anomaly. Data from a major hospital system in Utah and a national study recently published in *Academic Pediatrics* both found that newborns who are readmitted to the hospital are much more likely to be exclusively breastfed than formula- or combo-fed. The WHO, which created the BFHI, has admitted to a world-wide rise in newborn jaundice due to exclusive breastfeeding practices. All of these are preventable by being honest with mothers about general risk factors and their own personal risk factors associated with exclusive breastfeeding, closer monitoring to ensure babies aren't losing excessive amounts of weight, and making formula available without shame or additional hoops for an exhausted new mother to jump through. No family should have to suffer because ideologically-based lies when alternative and perfectly

adequate food is readily available. If the BFHI won't allow for that, then it's time to let it go. Ireland has banned it entirely, citing it as an unnecessary expense that doesn't live up to its promises. The US could do the same, or at least add humanity and common sense back into the equation.

Thank you for your concern.

Sincerely,

Emilie Bishop

THE TERATOLOGY SOCIETY

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www.teratology.org**

February 27, 2018

To: Federal Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

via email to Lisa Kaeser, JD, Executive Secretary, kaeserl@mail.nih.gov

The Teratology Society respectfully submits the following comments to the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) for consideration and in fulfilling its task to identify gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women.

The Teratology Society is an international, nonprofit organization consisting of researchers, clinicians, epidemiologists, and public health professionals from academia, government, and industry. Together, our mission is to prevent birth defects and disorders of developmental origin by promoting research and exchange of ideas, communicating information to health professionals and other interested parties, and providing education and training. We are committed to supporting new research initiatives that address questions regarding exposures to pregnant and breastfeeding women and defining associated risks; rapidly assessing and integrating new information on research results into the information we provide to women, health care providers and the general public; and communicating with these populations through our website (www.teratology.org), publications, position papers, blogs, and social media campaigns. Our journal, *Birth Defects Research*, publishes original scientific research that contributes to the understanding of the biology of embryonic development and the causative factors and mechanisms leading to adverse pregnancy outcomes.

As noted in the statement presented by Kathy Wisner, M.D., the Teratology Society joins with OTIS (Organization of Teratology Informational Services/ Mother to Baby) in applauding the PRGLAC effort, which aligns well with our mission and strategic goals. Here, we are providing additional comment, reflecting the breadth and depth of experience of our members, who include leaders in the fields relevant to the topics being addressed by the Task Force. The Teratology Society fully endorses the concept that pregnant or breastfeeding

women need access to translatable information on medications in order to be able to make informed choices regarding their health and the health of their child.

The evaluation of potential developmental and reproductive risks of new drugs continues to rely on nonclinical testing in animals, as it is the only integrated model for pregnancy that takes into account both maternal and fetal environments. While these studies have proven invaluable to informing health care providers, policy makers/regulators, and patients of potential risks, there remains a critical need for improved nonclinical models (e.g., lactation) and basic developmental, mechanistic and computational research to improve translational understanding. The Teratology Society endorses the statement previously provided by the ILSI Health and Environmental Sciences Institute (HESI) Developmental and Reproductive Toxicology (DART) Technical Committee regarding the importance of robust nonclinical research to support improved clinical development of safe and effective therapies for pregnant and lactating women. Advances in nonclinical research and translation to clinical outcomes is a prominent theme of the Teratology Society annual meeting, position papers, and other communications, where the diverse perspectives of our multidisciplinary membership provide a robust and comprehensive evaluation of these topics.

The need for systematic research on the safety of medicines used during pregnancy and lactation to provide relevant data to women for making informed health care decisions is clear. Yet, as highlighted in the November 6 - 7, 2017 PRGLAC meeting, the inclusion of pregnant and lactating women in clinical trials continues to present numerous ethical challenges, including the need for maternal treatment in the face of potential fetal/infant risk, and thus faces ongoing general reluctance. The Teratology Society commends the PRGLAC for their much-needed attention to this topic and supports ongoing discussion and consideration of approaches for the safe and meaningful study of drugs in pregnancy and lactation. We believe that the Teratology Society, as a multidisciplinary organization, is in a unique position to contribute to this discussion.

Central to the mission of the Teratology Society is the communication of information to health professionals, investigators, policy makers and other interested parties. We recognize that the development of an effective communication strategy designed to provide information to various audiences with differing interests, backgrounds, and understanding can be challenging. When developing messages related to use of medicines in pregnancy and lactation, it is critical that considerations for the therapeutic benefit of the medicine, the potential risk of the untreated maternal disease state to the woman and/or child, as well as for potential risks of the medicine, are balanced. Messages must be uniquely crafted and disseminated through a variety of channels to reach and inform health care providers, patients, and the general public, as well as policy makers, to enable their ability to make informed decisions. Language, cultural aspects, socio-economic status, and level of education must be considered in outreach efforts. Redundant delivery of the message in multiple formats can help ensure dissemination, comprehension, and impact. The use of communication partnerships, such as the collaboration that the Teratology Society has with OTIS, can be instrumental in effective implementation of communication strategies, and in maintaining their relevance in a rapidly evolving scientific and social environment.

The success of communication efforts also needs to be reassessed and adjusted regularly. The FDA Pregnancy and Lactation Labelling Rule (PLLR; <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>) is a prime example of such communication adjustment. The PLLR requires changes to the content and format of information presented in prescription drug labeling in order 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, thereby allowing them to make informed and educated decisions for themselves and their children.

Finally, with regard to research needs to advance clinical knowledge for pregnant and lactating women, it is clear that no single approach will solve this issue. Continued advances in nonclinical research to improve our mechanistic understanding of development, and translation of animal studies will continue to strengthen our confidence in predicting and communicating potential risks associated with use of drugs in pregnancy and lactation. Of particular note is a need for improved nonclinical models for lactation. In addition, concern for fetal risk has largely focused on structural outcomes resulting from early pregnancy exposure. A greater understanding of risk throughout pregnancy, as exemplified by divergent outcomes associated with Zika virus, is a critical need. A judicious approach is needed for the conduct of clinical trials in pregnant and lactating women to provide meaningful data for the appropriate use of therapies in pregnancy and lactation. Effective approaches for identification, collation, and communication of data from other available sources (e.g., post-marketing reports, case studies) are needed, and consideration should also be given to post-approval observational studies.

The Teratology Society endorses continuous and rigorous support for the scientific and methodological research that underpins the availability of safe and effective therapies in pregnant women and lactating women, as well as health and risk communication efforts. The multidisciplinary nature of such research is embedded in the Teratology Society mission and strategic goals.

We again thank the PRGLAC Task Force for the opportunity to provide comments and encourage the Task Force to take these points into consideration in your final report.

Sincerely,

Teratology Society

The Coalition to Advance Maternal Therapeutics (CAMT), appreciates this opportunity to provide public comments on the PRGLAC task force's recommendations to the Secretary.

CAMT is comprised of a dozen organizations who care deeply about the inclusion of pregnant and breastfeeding women in research and are dedicated to ensuring medications taken during this time are safe and effective and the information about these medications is transparent and comprehensive. We are supportive of the work that PRGLAC has taken on over the last year, and appreciate the amount of thoughtful consideration the task force has engaged in with regards to maternal and infant health.

CAMT requests that the task force make further recommendations in several areas of need: Workforce; Infrastructure; Data; Opportunities; Regulation; and Education. Within each of these areas of focus, our concern is rooted in the belief that there should be a presumption of inclusion in research for pregnant and lactating women. With this shift in perspective, the research community, industry, health care providers and consumers will be better able to work together to close the gaps in knowledge and research on safe and effective therapies for this population.

CAMT first recommends that PRGLAC extend its work for another year to further implement and examine additional issues related to research in pregnancy and lactation.

We continue to urge HHS, through NIH, to prioritize disease states in which there is a significant need for data about medications used during pregnancy and lactation. Inclusion of pregnant and lactating women in clinical trials is necessary to provide the best evidence-based care for women and research in pregnant women requires thoughtful study design. Currently, we know 7 in 10 women take prescription medications while pregnant and breastfeeding.¹ More data is needed related to what conditions women use medications for during pregnancy and while breastfeeding. A prioritized list of disease states would be a great first step for further research.

Additional efforts are also needed to ensure that research is designed to include representation of all potentially affected individuals, including those in diverse and underserved populations who often are not fully represented in current study designs. Underserved women are typically in need of more health services because of high rates of chronic conditions and unmet reproductive health care needs. PRGLAC should take the necessary steps to address obstacles to participation that may be experienced disproportionately by underserved women, such as the lack of child care during time spent as a research participant.

Workforce. Specific to workforce, we urge PRGLAC to support investments in development and training of investigators with obstetrical, lactation and pharmacology expertise.

Infrastructure. On the topic of infrastructure, we continue to advocate for supplemental, prioritized funding for research in pregnancy and lactation.

Data. Regarding data, CAMT supports the PRGLAC determination that there is insufficient available data related to medications in pregnancy and lactation. We support recommendations that would require research studies to have plans for incident pregnancies so that outcomes could be captured, to leverage

¹ Mitchell AA, Gilboa SM, Werler MM, et al. Medication Use During Pregnancy, With Particular Focus on Prescription Drugs: 1976-2008. *American journal of obstetrics and gynecology*. 2011;205(1): 51.e1-51.e8. doi:10.1016/j.ajog.2011.02.029.

existing registries to capture data, and to create a plan to allow data sharing among this population for further study.

Opportunities. CAMT also supports recommendations that would improve opportunities to encourage innovative trial designs, and that provide robust ways in which to collect data from existing and new models of study.

Regulation. We appreciated the ongoing PRGLAC discussions around the implications of potential regulatory or policy fixes. CAMT continues to support the need for a regulatory framework that ensures investigators can begin with a presumption of inclusion when evaluating the use of medication in pregnant and lactating women. It will be important to consider that there may be separate pathways for medications that are currently being used in pregnancy and lactation versus those that are in development or slated for future development.

Education. Finally, CAMT supports recommendations that would highlight the importance of education and advocacy efforts around research on therapies in pregnancy and lactation. We urge PRGLAC to support the development of public-facing information to help the public understand the new package insert format for pharmaceuticals, the meaning of the data described on the new pregnancy and lactation label, and clinical trial opportunities and inclusion in research.

Thank you for the opportunity to provide these comments. We look forward to continuing to support the work of PRGLAC and improving the health and wellbeing of women and their children.



May 7, 2018

Lisa Kaeser, JD
Executive Secretary, NICHD

RE: Task Force on Research Specific to Pregnant Women and Lactating Women

Dear Dr. Kaeser,

This letter of intent is being submitted to confirm the participation of PATH at the May 14–15 meeting of the Task Force on Research Related to Pregnant Women and Lactating Women (PRGLAC). PATH is a global health non-profit organization dedicated to the health of women and children and focused on driving transformative innovation to save lives. PATH has headquarters in Seattle, WA and an office in Washington D.C., as well as presence in over 50 countries around the world. One PATH representative, Carrie Hubbell Melgarejo, will attend this PRGLAC meeting in person to present oral comments.

Ms. Melgarejo's oral presentation will include requests for enhanced research in the following areas:

- **To identify lactating women's barriers to optimal breastfeeding of children.**

Optimal breastfeeding, including early initiation of breastfeeding within one hour of birth, exclusive breastfeeding through six months, and continued breastfeeding until the infant is two years old and beyond, has been shown to be one of the most effective interventions to save children's lives.¹ However, barriers to these optimal practices—whether at the facility, at work, at home, or in the community—are not well understood; further research to identify practices that break down these barriers is greatly needed.

- **To determine feasible and effective mechanisms of support for pregnant and lactating women to ensure optimal infant feeding.**

Innovation and research are needed to identify effective mechanisms of support for all pregnant and lactating women. This includes improvements in counseling and skill building among pregnant women in preparation for lactation and identifying innovative ways to reach all mothers, not just those that seek support during pregnancy. Further research is needed to understand barriers to seeking skilled support for lactation, especially in the first weeks of life while lactation is being established. This research will also provide insight on effective initiatives to ensure all women have access to cost-effective, skilled support for any issues that arise in lactation and infant feeding. When feeding at the breast is not an option, further research and design is needed to understand optimal lactation processes to ensure adequate supply, and equally important, optimal infant feeding mechanisms for providing mother's own milk for growth, development, and optimal health, with the eventual goal of advancing to feeding at the breast.

- **To identify and address determinants of inequity for pregnant and lactating women to receive counseling and support for optimal infant feeding.**

Given the disparities found in the use of human milk in the neonatal intensive care units in the United States,² further research is needed to identify determinants of optimal use of human milk for all infants. Additionally, formative research is needed to determine facilitators and barriers to accessing community resources for

¹ Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *The Lancet*. 382;(9890):427–451. doi: 10.1016/S0140-6736(13)60937-X.

² Boundy EO, Perrine, CG, Nelson, JM, Hamner HC. Disparities in hospital-reported breast milk use in neonatal intensive care unit —United States, 2015. *Morbidity and Mortality Weekly Report*. 2017; 66(48). Available at: <https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6648a1-H.pdf>.

human milk, in rare cases where the mother is unable to provide her own milk to her child. In general, formative research is needed to identify socio-cultural factors linking optimal care-seeking behaviors and research to identify solutions for such inequities.

- **To assess the cost benefit of employers providing paid leave and workplace support for lactating mothers.**

A cost-benefit analysis of paid leave and support for lactation in the workplace provided to mothers is needed to assess the business-related and social benefits to providing optimal nutrition. Further research is needed to determine models that offset the costs to the employers to support mothers, as well as ways to mitigate these costs, given the benefits of optimum nutrition for infants and the impact on the whole of society. The United States is behind many other countries, including other wealthy and low- to middle-income countries, in terms of access and use of paid parental leave. The economic assessment of costs associated with not breastfeeding is needed to detail room for improvement in current workplace policies. Regulations requiring jobsite lactation facilities and accommodations are very important to this effort, and research is needed on how these can be even more effective. Additionally, further research is needed to design effective programs that incentivize employers to support such practices that benefit society.

- **To determine challenges and systems improvements for mothers, including the mothers of sick and small infants who may be in a neonatal intensive care unit, to receive counseling and support and appropriate logistics (i.e., rooming in) for providing their breast milk for their infant.**

The World Health Organization and the American Academy of Pediatrics identify that mother's own milk is optimal for the infant and should be prioritized, and that donor human milk is the next best alternative for premature, low-birthweight infants when mother's own milk is unavailable. Further research is needed to guide systems-strengthening approaches for ensuring all infants and mothers receive support to prioritize the provision of mother's own milk for their infants.

- **To determine equality of eligible neonates to access to donor human milk across socio-demographic, region, and ethnicity.**

Similarly, research is needed to determine factors that limit mothers of vulnerable infants from being able to supply adequate volumes of breast milk to their own infants and the optimal method of using donor human milk as a bridge, while continued lactation is supported to increase supply. It is unknown how many infants require donor human milk in the neonatal intensive care units in the United States, and what percentage of infants in need are receiving donor human milk during this critical time period. Further improvements in data collection during this period are essential to capture the ongoing need and the factors that ensure all infants receive optimal nutrition support.

- **To improve the quality of donor human milk provided from human milk banks through determination of optimal temperature thresholds for pasteurization of human milk, as well as established methods for safety and supply.**

Current methods of pasteurization for donor human milk performed by human milk banks ensure safety, while also ensuring the quality of the milk in terms of retaining immune and other biologically active substances in human milk. Research is needed to determine the optimal pasteurization temperature curve for human milk that maintains the destruction of potentially pathogenic viruses and bacteria, while maximizing the retention of immune components. Additionally, research is needed for improvements in the methods of supplying safe and quality donor human milk, through improved diagnostics, processing devices/systems, and tracking systems that are specialized for human milk. Furthermore, research is needed to better understand the importance of the properties found in human milk and optimal processing techniques to ensure safety in the supply of donor human milk.

- **To assess current feeding practices and health outcomes among vulnerable infants in neonatal intensive care unit settings.**

Current methods of infant feeding are not well understood in neonatal intensive care units around the United States, nor globally. Further data collection and improved methods for data collection are required, especially for better understanding the practices in current neonatal feeding of the most sick and vulnerable infants. Research is needed to understand best practices in supporting mothers of infants in the neonatal intensive care units to provide optimum human milk for their infants, characterizing diets of vulnerable neonates with associated health outcomes to know how best to feed low-birthweight and premature infants.

Please contact us if further information is required.

Sincerely,

/Kiersten Israel-Ballard/

Kiersten Israel-Ballard
Associate Director
Maternal, Newborn and Child Health/Nutrition
kisrael-ballard@path.org
206.285.3500

SMFM Comments to PRGLAC

May 14-15, 2018

On behalf of the Society for Maternal-Fetal Medicine, I am pleased to provide comments to PRGLAC in its final meeting. My name is Katie Schubert.

As you know, SMFM was founded in 1977 and is the medical professional society for high-risk pregnancy physicians. Our 2,600 members are dedicated to improving care and outcomes for pregnant women. We have long been interested and advocating for better, safer and more effective information about medications taken during pregnancy and lactation, but also to ensuring that maternal health and research during pregnancy and lactation is prioritized.

One area of concern that we would ask PRGLAC to consider is the idea that when medications are approved in adults, they are automatically approved for use in pregnant and lactating women. That is, even though there may not be data because pregnant and lactating women were not included in the clinical trials associated with a drug's approval, those medications are still technically approved in this population. We need to ensure that there is data available, that pregnant and lactating women are included in these studies, so that health care providers and patients can make informed, evidence-based decisions when it comes to their health care and treatment. SMFM's position on research specific to pregnancy is that there should be a presumption of inclusion, with appropriate changes to regulatory framework and ethics policy that would support this idea.

We strongly believe that the NIH needs additional funding that would allow it to prioritize research involving pregnant women across Institutes. We must expand current research related to pregnancy and lactation generally, as well as to do all we can to encourage industry to engage in clinical research – we must remove barriers to including pregnant women in their work. We are committed to advocating for initiatives that would make strides in these areas.

In terms of recommendations that we believe the task force should make, the task force's discussion throughout its meetings align with the need for additional workforce by way of investigators with expertise in obstetrics, lactation and pharmacology throughout the spectrum of research opportunities – within industry, academics and the federal workspace.

HHS can certainly leverage existing infrastructure to conduct clinical trials that include pregnant and lactating women, but must be supported to develop new multicenter infrastructures as well. Opportunistic studies utilizing existing NICHD networks would be a good place to start.

It will be imperative that new studies include plans for incident pregnancies so that outcomes can be captured, and that there be a central clearinghouse for such data. Pregnancy exposure registries need to be transparent and easily accessible to both providers and consumers. Additionally, trials must be designed to take into account the physiological changes that occur during pregnancy and lactation.

Data collection efforts may take many forms – we believe that leveraging different study designs including but not limited to randomized control trials, comparative effectiveness trials, retrospective analysis via exposure registries and other programs such as PregSource™ would be helpful. We urge PRGLAC to recognize that there may need to be separate paths for drugs already developed and in use,

as well as for generic drugs, and those that have not yet been approved by FDA. Prioritizing disease states or areas of need will help to focus in on where to start.

Overall, we hope PRGLAC recognizes the need for an appropriate regulatory framework that can evaluate medication use in pregnant and lactating women. We also hope that more research in pregnancy and lactation can move forward as a result of this task force's important work. We support a continuation of the task force to further implement these recommendations and to explore new areas of need.

Finally, a key aspect of these recommendations and the work of the task force and broad community will be to ensure public and provider awareness of it. Encouraging a meaningful dialogue that will highlight the importance of research on therapies during pregnancy and lactation will go a long way to increasing awareness of the issue. Such conversations must include not only the impact on the fetus, but the health and wellbeing of the mother as well – that is, the impact of not taking a medication during pregnancy and lactation along with the impact of not breastfeeding on both mother and child must be considered.

Thank you for the opportunity to provide these comments. We look forward to continuing to support the work of PRGLAC and improving the health and wellbeing of women and their children.

Public comment to members of the Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC), May 14–15, 2018

Thank you to the Task Force for your consideration today. This comment is on behalf of a group of 32 researchers, civil society members, affected community members, and organizations interested in the prioritization of pregnant and lactating women in research. Many of the organizations and individuals who signed on to this comment provided feedback in response to the Request for Information (RFI) released ahead of this meeting, but felt it also important to provide additional emphasis during the public comment time today.

In the last two decades, the research community and private sector have made significant strides in terms of closing critical knowledge and data gaps related to drug safety and efficacy. Yet progress has not been standard across the board, and is particularly lagging as it relates to pregnant and lactating women. Pregnant women continue to be excluded from or de-prioritized in clinical research initiatives due to a multitude of factors, such as the complex physiology of pregnant women, the risk studies may pose to the fetus, and the classification of pregnant women as a vulnerable population, among others. This neglect has left pregnant women and their providers to make decisions without adequate information or guidance regarding the safety and efficacy of necessary treatments.

We understand that there are many factors to weigh when developing a research study, including ethical considerations, liability, risk, research needs and design considerations, as well as existing mandates and incentives. However, these factors should not preclude pregnant and lactating women from participating in meaningful and necessary research. Pregnant and lactating women should be able to reap the same benefits from the development of new therapies as other populations and have a right to the assurance that the therapies they are prescribed have been studied specifically to determine safety, efficacy, and appropriate dosing during pregnancy and the postpartum period.

As the Task Force is considering the recommendations it will include in its report to the US Secretary of Health and Human Services (HHS), we urge you to:

- Address U.S. legal and regulatory deterrents to including pregnant and lactating women in clinical trials through legislation and other amendments.
- Support the need for adequate and prioritized funding for research in pregnant and lactating women, and for expanded infrastructure and capacity of research networks capable of conducting trials in this population.
- Improve and/or establish the mechanisms and resources necessary to ensure that data are collected to inform use of existing medicines in pregnant and lactating women, such as replicating the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) studies conducted under P1026. These studies collect pharmacokinetic and safety data during pregnancy and postpartum, allowing for the comparison of important data points in the 2nd and 3rd trimester with those collected during the postpartum period. These studies also assess drug levels in breast milk, collect neonatal blood samples to look at levels of drug transfer to the infant and the half-life of the drug in the infant, and if breastfeeding, collect infant blood to evaluate the level of the drug in the plasma of the

breastfeeding infant. P1026 evaluates the pharmacokinetics and safety of antiretroviral drugs when used alone and when co-administered with anti-tuberculosis medicines during pregnancy, and when administered with hormonal contraceptives.

- Develop a regulatory framework and guidance to ensure that moving forward, for new therapies under development, safety and other data necessary to inform use in pregnant and lactating women are not left to post-marketing evaluations.
- Allow for the inclusion of pregnant women in phase III trials that are studying drugs for use in treating serious medical conditions that occur in both pregnant and non-pregnant individuals, such as HIV and TB. This includes allowing non-pregnant individuals who become pregnant to continue on investigational therapies with informed consent and careful follow-up in order to collect data on safety and pregnancy outcomes. At the very least, women who are required to cease use of the study drug when pregnancy is recognized should be followed throughout pregnancy to monitor maternal and pregnancy outcomes.
- Implement study and/or data requirements specific to pregnant and lactating women to help shift researcher mindsets from assumed exclusion to presumed inclusion.
- Finally, establish disease-focused registries to complement clinical research initiatives and help capture opportunistic and longer-term data and outcomes for therapies used to treat serious conditions in women who become or are already pregnant, such as the Antiretroviral Pregnancy Registry (APR).

On behalf of the 32 organizations and individuals who signed on to this public comment, we want to thank the Task Force for their work on this issue, and everyone today for their time and consideration.

***This public comment has been endorsed by the following organizations and individuals:**

Organizations

Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), Washington, D.C., USA
Treatment Action Group (TAG), New York, USA
AVAC, New York, USA
Babes Network, YWCA Seattle, Washington, USA
Bailey House, Inc., New York, USA
Blossom Trust, India
Global Media Foundation, West Africa
International AIDS Society (IAS), Switzerland
International Community of Women Living with HIV, East Africa
John Snow Inc., Massachusetts, USA
Kids & Teens Resource Center, Nigeria
TB Proof, South Africa
Tuberculosis and Pregnancy Research Working Group (TBPWG), USA
The Sentinel Project on Pediatric Drug-Resistant TB, Massachusetts, USA
Women and Youth Development Initiative (WOYODEV), Nigeria

Individuals

Alora Gale-Schreck, Babes Network, Washington, USA

Anna Forbes, Independent Consultant, Maryland, USA
Arne von Delft, TB Proof & University of Cape Town School of Public Health and Family
Medicine, South Africa
Dorothy Namutamba, International Community of Women Living with HIV, Uganda
Jennifer Furin, Harvard Medical School, Massachusetts, USA
Jennifer Gayles, Maryland, USA
Lindsay McKenna, Treatment Action Group (TAG), New York, USA
Lisa Rossi, Magee-Womens Research Institute, Pennsylvania, USA
Lynda Marie Emel, HIV Prevention Trials Network (HPTN), Washington, USA
Mark Harrington, Treatment Action Group (TAG), USA
Mercy Annapoorani, Blossom Trust, India
Michelle Galloway, TB Proof, South Africa
Phumeza Tisile, TB Proof, South Africa
Raphael Godlove Ahenu, Global Media Foundation, Ghana
Suraj Madoori, Treatment Action Group (TAG), New York, USA
Tosin Victoria Apiriola Ajayi, Women and Youth Development Initiative, Nigeria
Wieda Human, TB Proof, South Africa

May 7, 2018

Written submission to the Research Specific to Pregnant Women and Lactating Women Task Force
From VAMPSS, the Vaccines and Medications in Pregnancy Surveillance System

Introduction

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a unique nationwide post-marketing surveillance system established to comprehensively monitor the use and safety of vaccines and medications during pregnancy. Spearheaded by the American Academy of Allergy, Asthma & Immunology (AAAAI), VAMPSS provides a coordinated effort involving [prospective registry surveillance](#), [case-control surveillance](#) and [database surveillance](#) to study the safety of exposures in pregnancy.

The [prospective surveillance arm](#) is coordinated by the Organization of Teratology Information Specialists (OTIS) at the University of California-San Diego and involves prospective enrollment and follow-up of pregnant women exposed to selected vaccines or medications during pregnancy. Outcomes among participants exposed to a vaccine or medication under evaluation are compared to outcomes among participants not exposed.

The [case-control surveillance arm](#) is coordinated by Slone Epidemiology Center at Boston University (SEC) and involves enrollment of mothers of infants with congenital malformations and infants without malformations. Among mothers of infants with each specific malformation, the prevalence of antenatal exposure to the vaccines and medications of interest is compared to the corresponding exposure prevalences in comparison groups: mothers of non-malformed infants and mothers of infants with other malformations. SEC ceased data collection activities on November 30, 2015 but continues to provide historical analysis for drugs and medications available prior to that date.

The [database surveillance arm](#) is coordinated by the Harvard Pregnancy Research Group, which utilizes the Medicaid Analytic eXtract (MAX) database as its primary data source. The MAX database includes Medicaid enrollment and healthcare utilization data from more than 1.6 million pregnancies ending in live birth from 2000-2010. A secondary data source of commercially insured women is Truven MarketScan, which includes data from more than 604,000 pregnancies ending in live birth between 2011 and 2015.

The prospective and case control arms of VAMPSS collect information directly from participating mothers, thus obtaining comprehensive data on actual exposures and important confounders such as alcohol and tobacco use. Because the system obtains exposure information directly from the subject, this coordinated effort will provide the ability to address questions regarding the safety of over-the-counter medications, dietary supplements and products not acquired by the pregnant woman in traditional medical settings.

Under the guidance of an Investigative Team that includes representatives from AAAAI, all three research arms, and an independent Advisory Committee, VAMPSS brings together three complementary methods of surveillance, taking advantage of the benefits of all. The Investigative Task Force coordinates all aspects of protocol development, data collection, data analyses, data interpretation, and generation of reports, and meets weekly by teleconference to discuss methodological issues and review progress.

The Advisory Committee includes members from the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), American Thoracic Society (ATS), as well as a biostatistician and a consumer representative. Including these organizations creates significant opportunities to reach out to practitioners and, in turn, their pregnant and lactating patients. This independent Advisory Committee provides advice regarding overall VAMPSS goals, methods, results and reports. It provides independent, scientifically rigorous and confidential peer review of accumulating data and the related analyses.

The major goal of VAMPSS is to provide national systematic post-marketing surveillance system for pharmacologic therapy during pregnancy. With this system, we hope to identify as early as possible the circumstances in which a drug or immunization causes harm. We hope to provide reassuring data in a timely manner to all concerned for those drugs and immunizations (likely the majority) that are safe during pregnancy. To date, VAMPSS has published articles on the safety of the 2009-10 pandemic H1N1 influenza vaccine and 2011-12, 2012-13 and 2013-14 seasonal influenza vaccines in pregnancy.

Feedback regarding specific needs of the scientific community in order to conduct more research on therapies used by pregnant and/or lactating women

Randomized clinical trials are typically powered to be large enough to identify maternal and fetal benefits of a given therapeutic intervention, and they may be large enough to identify relatively common maternal risks and pregnancy complications, but they are yet too small to identify risks of specific birth defects (teratogenesis). Such defects (e.g., neural tube defects, oral clefts) affect approximately 1 in 1000 live births, and many defects are even less common. Typical RCTs may include a few hundred to as many as 1000 or so exposed subjects, and even if all subjects in a given RCT were pregnant women who were exposed in the first trimester (when organogenesis is most vulnerable to teratogenesis), RCTs would have insufficient statistical power to identify important (e.g., up to 20-fold) increases in risks for specific birth defects. Providing meaningful data on a medication's relative safety in pregnancy will require, as it always has, observational (epidemiologic, or "opportunistic") studies that, because of their sample size or design, have sufficient statistical power to identify or rule out large and moderate increases in risk. It is critical that those who propose RCTs involving pregnant women recognize that such trials may advance knowledge in many areas of benefit and risk, but they cannot be relied upon to provide information on teratogenic risks.

VAMPSS believes the inclusion of pregnant women and lactating women in both pre- and post-market studies should be dependent on risk benefit considerations. The likely benefit of the exposure must be considered to outweigh the likely risks, to both the pregnant woman and the fetus, based on available animal or human data. In many cases, the available data are insufficient to define those risks, such that only unique benefit would warrant inclusion of pregnant women in the trial. Some medications should only be studied in pregnant and lactating women in the post-market environment when efficacy in non-pregnant patients has been confirmed and the benefit-risk considerations can be individualized.

For further information, contact Sheila Heitzig, JD MNM CAE, at sheitzig@aaaai.org, or call 414-272-6071.

April 1, 2018

Dear Ms Kaeser:

I am responding to the Request for Information (RFI): **Research Specific to Pregnant Women and Lactating Women**, NOT- HD-18-003 announced Feb 15, 2018.

I perform clinical pregnancy research using non-invasive imaging devices for fetal application under NIH-funding, and I supervise present and past FDA investigational device exemption (IDE) studies on approved biomagnetometer devices being used for fetal heart rhythm diagnosis, and similar experimental devices in development. I participated in the writing group for the 2014 AHA Scientific Statement on Fetal Diagnosis and Treatment (Circulation, 2014), and also supported an application to the AMA for a Category III CPT code for fetal magnetocardiography. I have no conflicts of interest. Here are the areas that I personally feel require more evaluation in research in pregnancy:

Small companies develop pediatric, fetal, or pregnancy devices: Over 60% of the companies developing new technology for pregnancy or pediatrics are very small with limited experience in clinical research, applying for NIH grants, taking products through FDA, establishing subcontracts with universities, and commercializing their products.

I Agree with the American Academy of Pediatrics, they stated: *"In our view, the solution to the lack of pediatric devices lies in a comprehensive approach that includes providing assistance to innovators, streamlining regulatory processes, elevating pediatric device issues at the FDA and NIH, and improving incentives for devices for small markets -- while still preserving the ability to ensure the safety of new products once on the market. We look forward to working with Congress to pass legislation to ensure that when it comes to medical devices, children have access to the very best of what science and medicine have to offer."*

- **The principles listed above by the AAP should be implemented for pregnancy studies and for the fetus.** In addition to this lag in pediatric devices, devices supporting the health of the pregnant patient and her fetus, are also not coming through the pipeline at the same rate as for the adult. As an example, the fetal period is the only time in the human life-cycle when standard cardiac monitoring and electrocardiography are not a routine part of the care of the high risk patient.
- **NIH R grants, SBIR and STTR grants** currently support the technology development that is taking place. A reasonable portion of funding for these granting mechanisms should specifically target pediatric, fetal, and pregnancy research. In addition, I would like to see the NIH have more input from pediatric and pregnancy experts at the grant assignment level and within the review committees. Recently one of these committees, SBIB H82, was permanently closed by CSR. The time to market for pediatric-fetal-pregnancy (P-F-P) devices, about 17-20 years, is longer than for adult devices, and making adjustments in the length of current NIH or FDA funding mechanisms to account for this longer time to market is needed. Just one example of a difference between adult and P-F-P research and FDA IDE's, is the retrieval of medical records (source documents), particularly time consuming. It is necessary to track two subjects/two clinical outcomes, mother's and baby's. New surnames, hospital changes (mother and/or baby) and varying electronic medical records (EMR) formats make it very labor intensive to retrieve charts in order to track outcomes. In addition, many hospitals store parts

of the record, such as ECG's, on other software than the EMR software, and out-source their record requests to 3rd Parties.

- **FDA approval processes:** It is my understanding that external peer medical experts from industry and academics, are convened very late for FDA approval processes, often on the day that a device is proposed for approval before a panel of physicians, and scientists. This is completely different from the NIH where the experts are present from the beginning, to assess the design of the study and provide feedback. FDA could solicit and retain medical experts in each expertise area, and utilize them in the assessment of new pediatric-fetal-pregnancy (P-F-P) technologies.
- **Provide access to advisors within the FDA, NIH, and Universities** that facilitate device-based P-F-P research, especially clinical trials IDE development. To some extent this has been done for pediatrics with the Pediatric Device Consortium, but currently fetal device research is not covered under the pediatric umbrella, even though it is one of the most active areas of device research. A **Pregnancy Device Consortium** could be developed to support both maternal and fetal device development.
- **The current paperwork load for pregnancy clinical trials and for outcomes assessment is enormous** Universal templates and better study design support would help. Post-market surveillance, if made universal, could increase the need to retrieve P-F-P medical records. Many P-F-P studies recruit from around the country due to the rarity of disease. Thus, FDA post-market surveillance would be costly and difficult for companies, and academic investigators, unless a mechanism to support acquisition of source documents is developed.
- **Funding amount and time frames of SBIR/STTR grants:** Because some new devices have no predicate or CPT Code, or only a Category III CPT Billing code, there is little means for device developers to support the early clinical roll-out phase. SBIR and STTR grants can provide needed support for emerging technology. **But to be helpful, it is critical that the NIH remove the requirement of Third-Party investors for Phase IIB SBIR/STTR grant applications.** Eliminating this third-party investor requirement for Phase IIB SBIR/STTR grants would allow additional time and funding for P-F-P device developers to continue multicenter clinical trials and obtain a Category I CPT code.
- **CPT Code III and Payment.** Virtually all emerging devices have a Category III CPT code (T code or 4 digit code), and these are predominantly excluded from payment by insurance companies. As a result, Obstetrical and Children's Hospitals are reluctant to purchase emerging products, further slowing the pipeline to commercialization. Developing a plan with the AMA and stakeholders for evaluating P-F-P devices for possible early transition to Category I, with fewer centers owning the emerging devices, would be helpful.
- **Consenting Practices. Inclusion of minors, rural women, and minority women:** Removing the pregnant woman from the "vulnerable list" is a great step forward, and excluding onerous 2-person consent processes for non-invasive procedures in adult pregnant women may help stimulate research, and facilitate postnatal follow-up, which in turn should improve care and reduce mortality. Allowing women to consent for their infant (up to age 1 year) during the pregnancy, and having a single IRB of record, would also help for studies that involve neonatal follow-up of a condition. Many IRB's currently discourage recruitment of pregnant minors and non-English-speaking women (with a medical interpreter), even though in some cases, they stand to gain the most from results of certain studies. Also, incentives to encourage participation of rural and minority pregnant women, such as transportation re-imbursement or providing transportation should be encouraged.

Thank you for your consideration. And best wishes for supporting this difficult area of research.

Sincerely Yours,

Janette

Janette F. Strasburger, MD
Professor of Pediatrics, Medical College of Wisconsin
Division of Cardiology, Children's Hospital of Wisconsin.
9000 W. Wisconsin Ave, MS 713
Milwaukee, WI 54956
Office - 414-955-5673

From: Graaf, R. van der <R.vanderGraaf@umcutrecht.nl>
Sent: Wednesday, April 25, 2018 7:50 AM
To: Kaeser, Lisa (NIH/NICHD) [E] <kaeserl@mail.nih.gov>
Subject: input PRGLAC 14 May

Dear Lisa Kaeser,

Thank you for the opportunity to send in comments. I have some comments on the timing of the trials in pregnant women. Please see my specific comments below. I have also attached the paper in which I express some of these concerns.

Kind regards,

Rieke van der Graaf PhD
Ass professor Medical Ethics
University Medical Center Utrecht
Julius Center
Netherlands
+31887551347

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2495-9>

Page 9:

Line 351: “if there are limited safety data or other approved treatments are available in this situation it may be more appropriate to complete phase 3 clinical trials in a nonpregnant population”. We agree that safety issues and proper dosing should be addressed before larger groups of (pregnant) women are exposed to a drug. However, by explicitly pointing at phase III trials in nonpregnant population the reader may get the impression that other *design options* are no reasonable alternative. Yet, there are options to earlier include pregnant women in the drug development process while ensuring that sufficient safety and efficacy data are available before more substantial numbers of pregnant women are enrolled. One of these alternatives is the use of an adaptive trial design. Please also see *Roes KCB, van der Zande ISE, van Smeden M, van der Graaf R. [Towards an appropriate framework to facilitate responsible inclusion of pregnant women in drug development programs](#). Trials. 2018 Feb 20;19(1):123.*

Line 355: “if there are limited therapeutic options”. Please add: “and inclusion is a reasonable option”

Line 358: “if there are safety data for a drug that has been studied previously for other indications or populations: in these situations, the risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials”: Please reverse the order : “Pregnant women may be enrolled in earlier phase trials provided that the risk-benefit ratio of inclusion is favorable”

From: jean public <jeanpublic1@gmail.com>

Sent: Tuesday, April 17, 2018 3:13 PM

To: Kaeser, Lisa (NIH/NICHD) [E] <kaeserl@mail.nih.gov>; americanvoices@mail.house.gov; info@njaicv.org

Subject: Re: if pregnant women are urged not to smoke or drink they also should not be taking vaccines

public comment on federal register

to keep babies and pregnant women safe, they should take nothing out of the ordinary when [pregnant.no](#) drinking alcohol, no taking drugs, no taking vaccines, no thing unusual into the body. keep it pure. i believe that keeps the pregnant women best suited for bringing about the healthiest baby she can have. this comment is for the public record. i think you are hurting american women and babies with your preaching vaccines to pregnant women.

vaccines hurt some bodies and they can injure or kill. the baby is developing in the most marvelous way and some influences can mean the development of a brain does not take place properly but is affected by the substance ingested. this comment is for the public record. keep the body pure. jeanpublic1!@[gmail.com](mailto:jeanpublic1@gmail.com)

On Tue, Apr 17, 2018 at 9:35 AM, jean public <jeanpublic1@gmail.com> wrote:
the developing fetus is very easily affected we see that over and over

[Federal Register Volume 83, Number 74 (Tuesday, April 17, 2018)]

[Notices]

[Pages 16893-16894]

From the Federal Register Online via the Government Publishing Office [www.gpo.gov]

[FR Doc No: 2018-07918]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of the Secretary; Notice of Meetings

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended, notice is hereby given of meetings of the Task Force on Research Specific to Pregnant Women and Lactating Women.

The meetings will be open to the public, with attendance limited to space available. Individuals who plan to

[[Page 16894]]

attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: Task Force on Research Specific to Pregnant Women and Lactating Women.

Date: May 14-15, 2018.

Time: May 14, 2018 8:30 a.m. to 5:00 p.m., May 15, 2018 8:00 a.m. to 2:30 p.m.

Agenda: The Task Force is charged with providing advice and guidance to the Secretary of HHS, regarding Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.

Place: 6710B Rockledge Drive, Room 1425/1427 (1st Floor), Bethesda, MD 20817.

Contact Person: Ms. Lisa Kaeser, Executive Secretary, Eunice Kennedy Shriver National Institute of Child Health and Human Development, 31 Center Drive, Room 2A03, MSC 2425, Bethesda, MD 20892, (301) 496-0536, kaeserl@mail.nih.gov.

Public comments are welcome either by filing written comments and/or providing oral comments at the meeting. Oral comments from the public will be scheduled on May 14, 2018, from approximately 10:00 a.m.-10:45 a.m. Any member of the public interested in presenting oral comments on May 14, 2018, should submit a letter of intent, a brief description of the organization represented, and the oral presentation to Ms. Lisa Kaeser (Kaeserl@mail.nih.gov) by 5:00 p.m. on Monday, May 7, 2018. Written comments to be included at the meeting should also be sent to Lisa Kaeser by 5:00 p.m. on Monday, May 7, 2018.

The submitted presentations and any written comments will be formatted to be posted on the PRGLAC website for the record. Only one representative of an organization may be allowed to present oral comments. Presentations will be limited to three to five minutes per speaker depending on the number of speakers to be accommodated within the allotted time. Speakers will be assigned a time to speak in the order of the date and time when their request to speak is received. Both printed and electronic copies are requested for the record.

Details and additional information about these meetings can be found at the NICHD website for the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) <https://www.nichd.nih.gov/about/advisory/PRGLAC/Pages/index.aspx>.

Dated: April 11, 2018.

Michelle D. Trout,
Analyst, Office of Federal Advisory Committee Policy.
[FR Doc. 2018-07918 Filed 4-16-18; 8:45 am]
BILLING CODE 4140-01-P

APPENDIX VI - Research on Therapies in Pregnant Women and Lactating Women

To ensure that pregnant women and lactating women and their children benefit from safe and effective therapies, many different types of research are necessary, and research projects of all types must be designed and implemented with the needs of pregnant women and lactating women specifically in mind. Preclinical, fundamental research discoveries in biology, disease, and behavior are essential so that scientists can understand the underlying basis of a condition and identify potential therapeutic targets. Cell or tissue samples, animal models, and/or computer simulations are critical precursors to the design and testing of new approaches to diagnosis, prevention, and treatment. For pharmaceutical interventions, pharmacokinetics and pharmacodynamics (PK/PD) research—the study of how drugs move through the body and the relationship between drug concentration and the resulting effect—are needed for developing safe and effective formulations and doses. Observational studies in humans—often through case series or cohort studies—shed light on the risk factors associated with a condition and describe prevention and treatment approaches used in the community. Epidemiological research can describe population trends in diseases or conditions and associated risk and resilience factors, giving scientists clues to improving human health. Randomized controlled clinical trials (RCTs) provide rigorous evidence that interventions are safe and effective for human use. Other types of research—such as studies of adherence and surveys to uncover variation in clinical practice—can help inform clinical decisions. Unfortunately, the pace of research progress across all types and methods has not been sufficient to ensure that pregnant women and lactating women and their providers have enough scientific evidence for well-informed clinical decisions.

Objectives, Scope, Methodology, and Limitations

This analysis of published scientific evidence on therapies in pregnant women and lactating women is based on research articles published over the last 10 years. The analysis focuses on research in selected categories, relating to conditions for which pregnant women and lactating women are known to use medicinal therapies (See Appendix VI, Figure 1). For purposes of the analysis, medicinal therapies were defined to include drugs and vaccines, as well as vitamins, minerals, herbal remedies, and other supplements. The objectives were to supplement the expertise of the Task Force members by:

- Quantifying the research literature involving medicinal therapies for pregnant women and lactating women, by category, topic, and research type

Appendix VI, Figure 1: Categories for Analysis (Selected Conditions)

- Asthma
- Autoimmune diseases (excluding diabetes)
- Cancer
- Central nervous system disorders
- Diabetes (all types)
- Endocrine disorders (excluding diabetes)
- Hyperemesis, nausea and vomiting
- Hypertensive disorders
- Infectious diseases
- Kidney disorders
- Low milk supply
- Mental health
- Pain
- Preterm birth
- Substance abuse
- Vaccines

- Identifying substantial research gaps, by category, topic, and research type
- Determining funding sources for the research, with a focus on identifying gaps and potential opportunities for collaborations.

The analysis focuses on distinguishing and reporting the types of research, as opposed to judging the scientific merit or rigor of the design, implementation, and conclusions of each published research project. The analysis provides information on the utilization of research approaches that can expand the scientific evidence base to inform clinical decisions about the use of therapies in pregnant women and lactating women. “Original” research that systematically collects and reports new data, rather than describe individual cases or summarize previous findings, is most important to expand the scientific evidence base. For this analysis, original research was defined to include basic/preclinical research, PK/PD, pop/DB, RCT, case series and cohort studies, and other research. These types of research are described in Appendix VI, Figure 2.

Selection of the categories was based on published reports⁴⁶, the recommendations of Task Force members, presentations by experts, and comments provided to the Task Force. The categories selected include some known to be associated with pregnancy, such as preeclampsia and preterm labor, along with “pre-existing” conditions, such as cancer, that may occur in pregnant or lactating women but are not associated with pregnancy.

Appendix VI, Figure 2: Research Types

- **Basic/fundamental:** preclinical research designed to improve understanding of a condition, identify targets, obtain toxicology data, design interventions, or conduct pre-clinical testing
- **PK/PD:** pharmacokinetic and/or pharmacodynamic research on the time course of drug absorption, distribution, metabolism, and excretion and the relationship between drug concentration and effect
- **Pop/DB:** case-control or epidemiological studies involving large scale or population-representative data
- **RCT:** randomized controlled clinical trials, where human subjects are prospectively and randomly assigned to one or more interventions to evaluate the interventions' safety and/or effectiveness
- **Case series or cohort study:** a study that follows one or more groups of individuals and assesses condition status, outcome, and/or risk
- **Case report:** detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of an individual patient
- **Review:** a summary of previously published work
- **Editorial/commentary:** a statement of opinion about a research study, a scientific body of work, or science or public policy
- **Other:** original research content not described by any of the previous categories. Examples may include methodology papers, non-representative cross-sectional surveys, economic analyses, and others

⁴⁶ Andrade SE, Gurwitz JH, Davis RL et al. Prescription drug use in pregnancy. *Am J Ob & Gyn.* 2004;191:398-407. <https://www.ncbi.nlm.nih.gov/pubmed/15343213>; Andrade se, Raebel MA, Morse AN et al. Use of prescription medications with a potential for fetal harm among pregnant women. *Pharmacopepidemiol Drug Saf* 2006;15:546-554. <https://www.ncbi.nlm.nih.gov/pubmed/16586470>; Mazer-Amirshahi, M, Samiee-Zafarghandy SS, Gray G, van den Anker JN.

For each category, an information specialist, in consultation with the analytic team, developed a detailed PubMed search strategy to identify publications that focused on the research category, the population of pregnant women and lactating women, and medicinal therapies (as defined above). The search was limited to articles published between January 2006 and August 2017. The search was not limited by language. To avoid substantial double counting, two categories—autoimmune disorders and endocrine disorders—were defined to exclude diabetes, although diabetes could have been considered in these categories. Some articles were necessarily included in more than one category. For example, research on pregnant women with HIV and substance abuse disorders was included in both the infectious diseases and substance abuse categories. In the analyses that addressed the literature, each article was counted only once. In analyses by category, each article was counted within each applicable category. About 7 percent of articles were included in more than one category. A total of 25,736 records were retrieved using these searches, and 14,081 unique publications were included in the final combined dataset.

Analysts screened each publication by considering its title and abstract and (where necessary) the full article, to eliminate false positives. The analysts classified the remaining articles by type of research reported and coded whether the research was specifically focused on vitamins, dietary supplements, or herbal remedies. For articles reporting original research, the analysts also recorded all funding sources from the acknowledgement or funding section of the original article.⁴⁷ For non-industry support, the country of the funding organization was also recorded. Because industry support is typically provided through large multinational pharmaceutical companies, it was not feasible to track country of origin for industry support.

For each category, publications were analyzed by subtopics using Medical Subject Headings (MeSH®), the National Library of Medicine's controlled vocabulary thesaurus. MeSH® consists of sets of terms naming descriptors in a hierarchical structure, which facilitates detailed searches. Analysts also applied automated text-searching software to publication abstracts to verify and in some cases supplement the information obtained by analysis of the MeSH® terms. Subtopics of interest included specific conditions (e.g., sites of cancers) within a general category, or such topics as specific substances (e.g., alcohol, opioids, or marijuana) within a general category (substance abuse). The original search terms were used initially in the text searching software, then supplemented by a “like” algorithm that matched

Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. *Am J Obstet Gynecol* 2014;211:690.e1-11. <https://www.ncbi.nlm.nih.gov/pubmed/24912093>.

⁴⁷ The PubMed database does include some funding information, although not at the level of detail required for this analysis; therefore, review and coding by the analysts was required. Text retrieval and analysis software was used to assist with this task, but all information was reviewed and verified by the analysts.

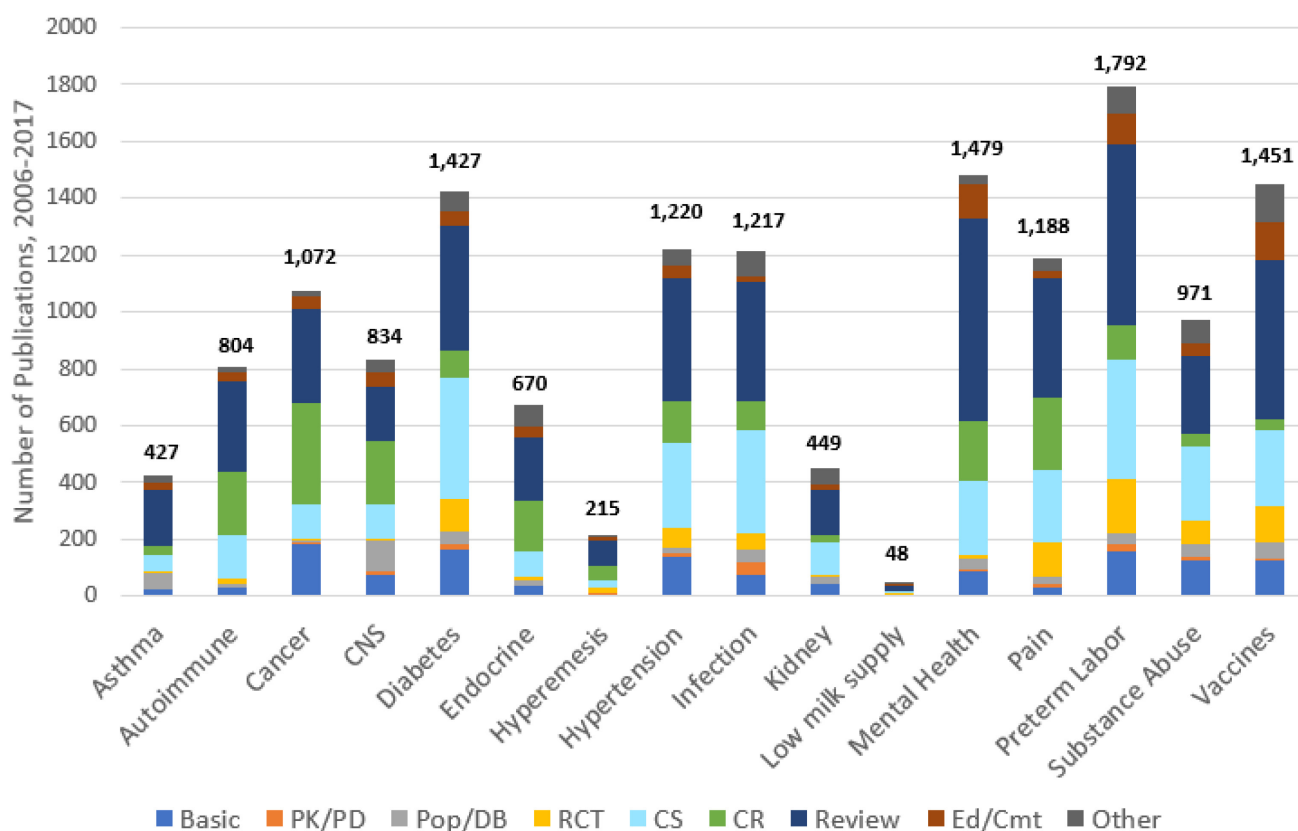
publications based on shared terms. Articles with like terms were reviewed to set the algorithm threshold.

Several limitations affect this analysis. Practical considerations regarding the volume of publications made it necessary to limit the analysis to published research of the last decade that focused on medicinal therapies for pregnant women and lactating women within 16 selected categories. The analysis did not attempt to encompass published research on every medicinal therapy for every disorder that may occur in pregnant or lactating women. Finally, in less than one half of one percent of cases, neither an article nor its abstract were available, and the analysts jointly made judgments about its type, based on its title. In less than 20 other cases, automated translations were used when an article or abstract was available only in a language other than English.

Summary

The number of articles by category and type of research is shown in Appendix VI, Figure 3. Over this period of slightly longer than a decade, preterm labor had the highest number of publications among the categories studied. Some categories that include pregnancy-specific conditions – such as gestational diabetes – had relatively high numbers of publications, but pregnancy-associated nausea and vomiting and low milk supply had relatively fewer. Some conditions that are pre-existing or not directly associated with pregnancy (like infection and vaccines) also had over 1,000 publications, while others (like asthma) had fewer.

Appendix VI, Figure 3: Number of Publications Related to Therapies for Pregnant Women and Lactating Women, by Category and Type, January 2006—August 2017



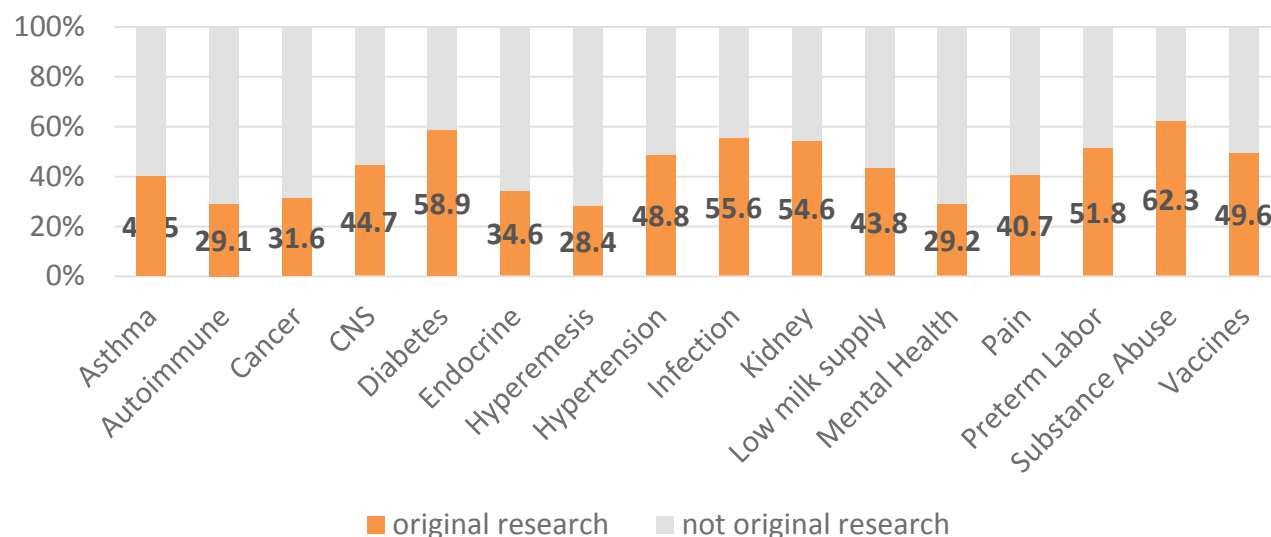
Notes: The Autoimmune and Endocrine categories exclude diabetes. A publication that reported research on multiple conditions and/or medications for the conditions (substance abuse and mental health, for example) may be included in more than one category if appropriate.

The distribution of publications by type of research varied across categories. As shown in Appendix VI, Figure 3, RCTs represented a larger share of the research in the low milk supply, pain, preterm birth, and vaccine categories compared with other categories such as asthma, autoimmune disorders, cancer, CNS disorders, endocrine disorders, and mental health. Population-based and large database studies were most prominent in the CNS disorders category. Basic and preclinical research were a larger share of the research on cancer, diabetes, hypertension, and substance abuse, compared to autoimmune disorders, low milk supply, and pain. PK/PD studies were rare for all categories, although slightly more common in infectious diseases compared to other categories.

As noted, for purposes of the analysis, “original research” publications included articles on basic research, PK/PD, Pop/DB, RCT, case series (CS), and the “other research” category (The “other” category included, for example, surveys of physicians about clinical practice related to treating a condition during pregnancy). Appendix VI, Figure 4, shows the percent of total publications that were original research,

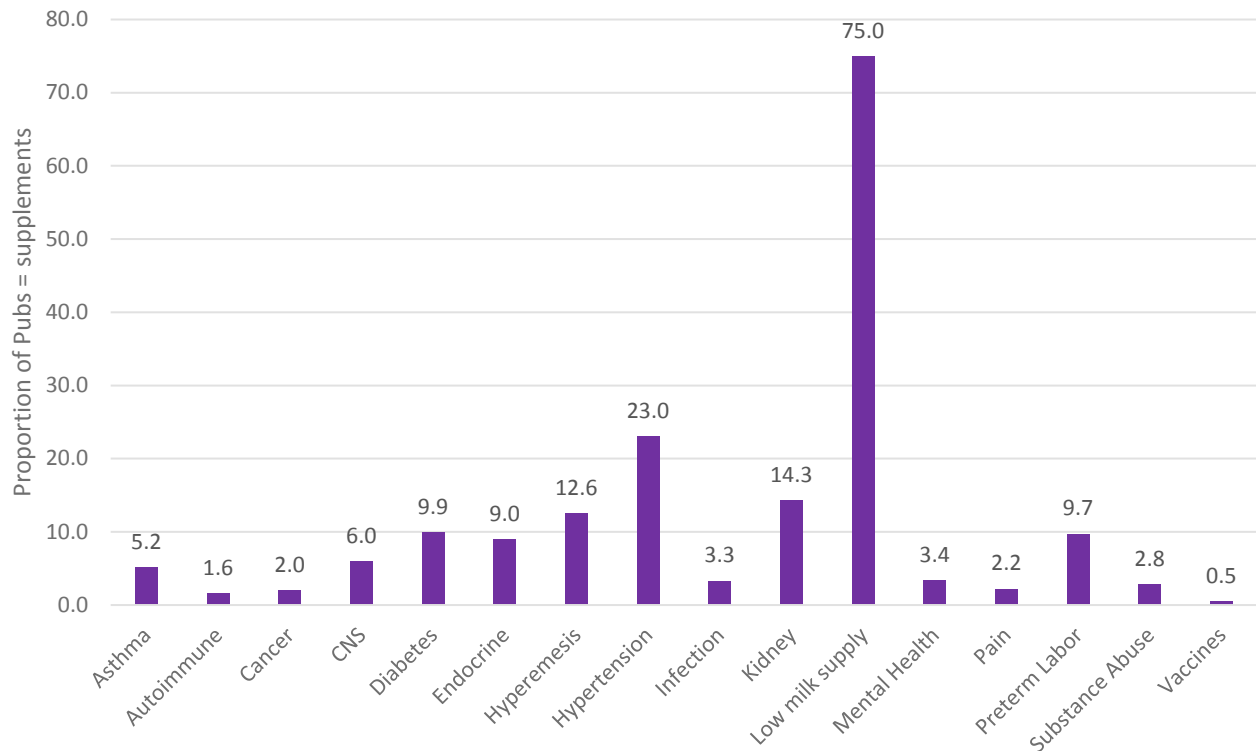
by category. For two-thirds of the categories, the majority of the publications were not original research. Only one category (substance abuse) had the proportion of original research exceeding 60 percent.

Appendix VI, Figure 4: Percent of Original Research Publications Related to Therapies for Pregnant Women and Lactating Women, by Category, January 2006—August 2017



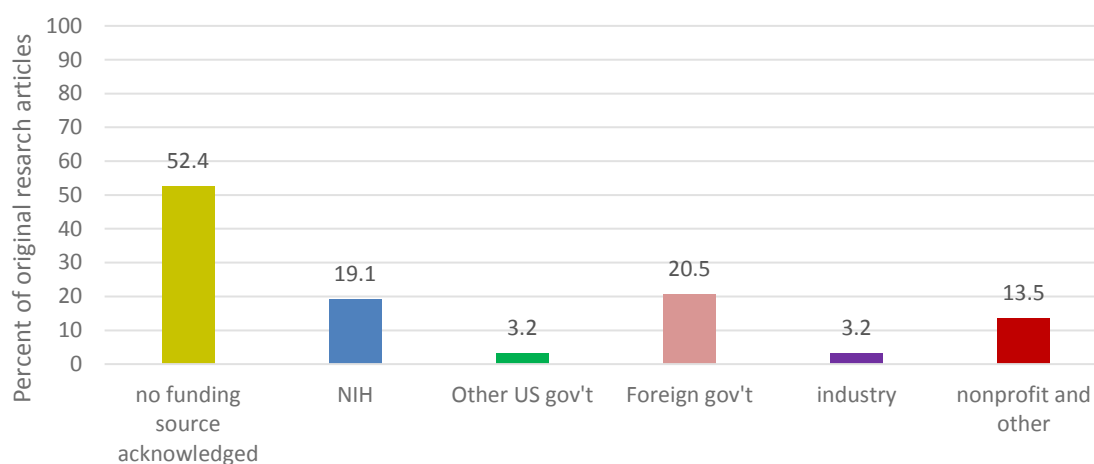
The proportion of research that focused on vitamins, minerals, herbal remedies, and/or other dietary supplements varied widely across categories, as shown in Appendix VI, Figure 5. For autoimmune diseases, cancer, infection, mental health, pain, and substance abuse, these remedies accounted for less than 5 percent of publications on the topic. However, the proportion was much larger for low milk supply, hypertensive disorders, diabetes, and preterm birth. Most of these publications focused on vitamin and mineral supplements, and a substantial number were RCTs. However, because of variability in the composition and other characteristics of unregulated products, there are difficulties in interpreting study results for application to clinical practice.

Appendix VI, Figure 5: Percent of Publications Related to Therapies for Pregnant Women and Lactating Women That Focused on Supplements, by Category, January 2006—August 2017



Many research studies on therapies for pregnant and/or lactating women are funded by national government agencies in the United States and around the world. As is common in published research generally, many publications did not acknowledge a funding source. Industry and nonprofit organizations also support research in this area. Appendix VI, Figure 6 shows the distribution of funding sources across all categories for original research publications only. About half of all publications did not acknowledge any funding source. Eighteen percent of original research publications acknowledged at least one NIH institute, and 20 percent acknowledged funding from a government agency outside the United States. Industry support was acknowledged in 3 percent of publications.

Appendix VI, Figure 6: Funding Sources for Original Research Publications Related to Therapies for Pregnant Women and Lactating Women, January 2006—August 2017



Note: a single article was counted in multiple groups if multiple types of funding sources are acknowledged. As a result, the sum of the percentages exceeds 100.

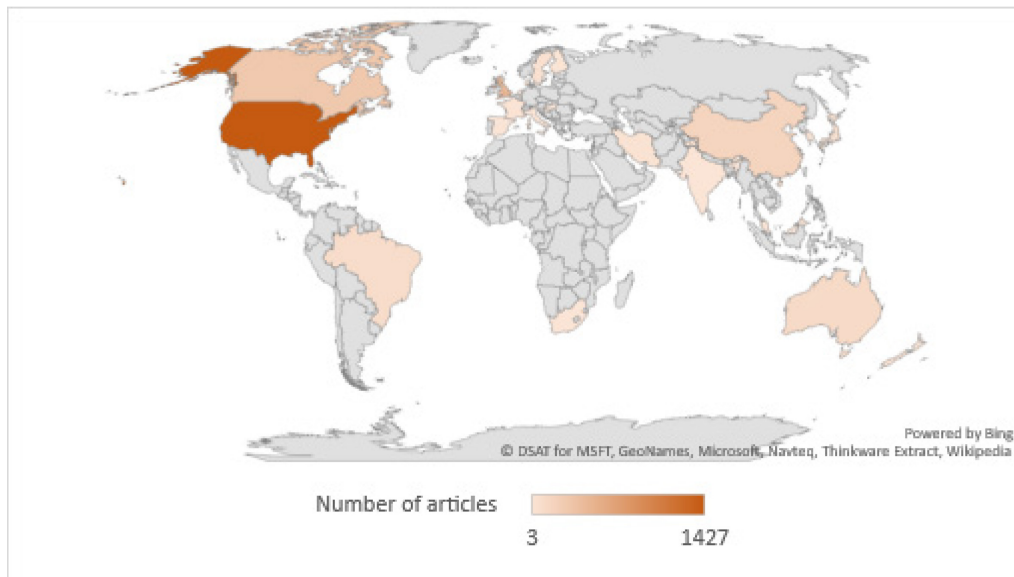
Funding sources varied considerably across the 15 selected categories and by types of research. Vaccine research had the fewest publications with no acknowledged external funding. The proportion of articles supported by NIH funding was highest for preterm birth and substance abuse. Although foreign governments were typically acknowledged at a rate similar to NIH, foreign governments supported relatively fewer research publications on substance abuse and relatively more on infectious diseases.

Across all research types, both United States and foreign government funding was more typically found in publications that reported results from basic/preclinical research and randomized controlled trials. Industry funding was disproportionately represented in the population/database category; in several European countries, industry funding helped to establish, maintain, and analyze data from population databases and registries (See Appendix VIII, for more information about population databases and registries).

The number of articles by country of origin for non-industry funding—government, nonprofit, and other organizations—is shown in Appendix VI, Figure 7. Slightly less than half of the articles that credited government or nonprofit sources were supported by organizations in the United States. The remainder were supported by organizations in other countries. Organizations in the United Kingdom supported the second-largest number of publications in both the government and non-profit sections.

Government agencies in Canada and China supported a relatively large number of publications, but the share of the nonprofit support from those countries was smaller than several European countries, including Sweden, Denmark, and Finland. Both government agencies and nonprofits in Australia supported this research.

Appendix VI, Figure 7: Country of Origin for Funding Sources for Original Research Publications Related to Therapies for Pregnant Women and Lactating Women, Excluding Industry Funding, January 2006—August 2017



Asthma

Introduction

Asthma is a chronic (long-term) lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing. Asthma most often begins during childhood but affects people of all ages. In the United States, more than 25 million people are known to have asthma.⁴⁸ Asthma is one of the most common chronic conditions in pregnant women, and asthma (especially if it is poorly controlled) is associated with risks and adverse outcomes for both mother and baby, including preeclampsia, preterm birth, and low birth weight.⁴⁹

⁴⁸ <https://www.nhlbi.nih.gov/health/health-topics/topics/asthma/>

⁴⁹ <http://emedicine.medscape.com/article/796274-overview>

Scientific Literature

The analysis identified 427 articles, published between January 2006 and July 2017, that are related to medicinal therapies for asthma in pregnant women and lactating women. Appendix VI, Figure 8, shows the distribution of publications by type of research.

Appendix VI, Figure 8: Publications on Medicinal Therapies for Asthma in Pregnant Women and Lactating Women, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Asthma | 24 | 0 | 60 | 4 | 59 | 30 | 195 | 29 | 26 |

There were no publications on PK or PD of asthma-related drugs, and there were few RCTs related to asthma in pregnant women. Most of these studies were conducted in Australia. Two studies determined that pharmacist-led and nurse-led educational interventions can help pregnant women with asthma to control symptoms.⁵⁰ Another study found that asthma episodes during pregnancy could be significantly reduced with a validated treatment algorithm, and follow-up data found that mothers who were randomized to the treatment algorithm had infants with fewer recurrent episodes of bronchiolitis, a lung condition.⁵¹

A substantial number of publications used population-level data or large databases to address research questions related to asthma in pregnancy. Population-level pregnancy registries have been established in a range of countries with national health systems, including Denmark, the United Kingdom, Australia, Norway, and Finland. For some but not all these registries, data on symptoms could be linked with pharmaceutical records. Researchers analyzed these types of data to address several types of questions related to asthma and pregnancy. Studies across a range of countries described physician prescribing patterns for pregnant and/or lactating women with asthma. For example, a recent study in France found that compared to pre-pregnancy prescriptions for the same women, during the pregnancy physicians typically increased prescriptions for inhaled corticosteroids and reduced prescriptions for montelukast (a leukotriene receptor antagonist) and for fixed-combination therapies that combined inhaled

⁵⁰ PMID 24522786 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24522786>); PMID 24401041 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24401041>)

⁵¹ PMID 21907861 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=21907861>); PMID 24068472 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24068472>)

corticosteroids with short-acting or long-acting beta-2 agonists.⁵² A similar study in the Netherlands found that although use of most prescription medications for asthma continued through pregnancy, such use decreased significantly in the first few months of pregnancy, especially for long-acting bronchodilators.⁵³

Most studies of potential effects of antenatal asthma medications on offspring focused on structural birth defects. Over a dozen population-based or registry-based studies assessed associations between fetal exposure to untreated asthma during pregnancy or asthma-related medications during pregnancy. Results of the studies have been mixed, although negative effects reported (if any) have been small. Using data from Canada, the United States and the United Kingdom, several studies found no increased risk of congenital malformations associated either with asthma medications or with the underlying condition.⁵⁴ However, other studies found some increased risks for congenital anomalies among pregnant women with asthma and/or women taking asthma medications while pregnant. For example, a study using data from Sweden found a small increased risk of cardiac defects, cleft palate, and anal atresia associated with antenatal asthma medication.⁵⁵ An analysis of data in a New York state registry also found an increased risk for cardiac anomalies.⁵⁶

Twenty-two publications concerned vitamins and other supplements in the treatment of asthma in pregnant or lactating women. Of these, half were original research articles. Many of these articles focused on potential mechanisms of action, to assess how the active agents could affect inflammation and/or immune function in pregnant women with asthma.

Appendix VI, Figure 9, shows the pregnancy and lactation publications by type, separately. Almost all the pregnancy- and lactation-related research focused on pregnancy only, and not lactation.

⁵² [PMID 27657554 \(https://www.ncbi.nlm.nih.gov/pubmed/27657554\)](https://www.ncbi.nlm.nih.gov/pubmed/27657554)

⁵³ [PMID 23063582 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=23063582\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=23063582)

⁵⁴ For example, see [PMID 23450814 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=23450814\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=23450814), [PMID 17121872 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=17121872\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=17121872), and [PMID 22000568 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=22000568\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=22000568) (among others)

⁵⁵ [PMID 17279357 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=17279357\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=17279357)

⁵⁶ [PMID 19067406 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=19067406\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=19067406)

Appendix VI, Figure 9: Pregnancy and Lactation Publications on Medicinal Therapies for Asthma, Shown Separately, by Publication Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Asthma | 21 | 0 | 60 | 4 | 58 | 29 | 184 | 29 | 26 |
| Lactation | | | | | | | | | |
| Asthma | 3 | 0 | 0 | 0 | 1 | 1 | 11 | 0 | 0 |

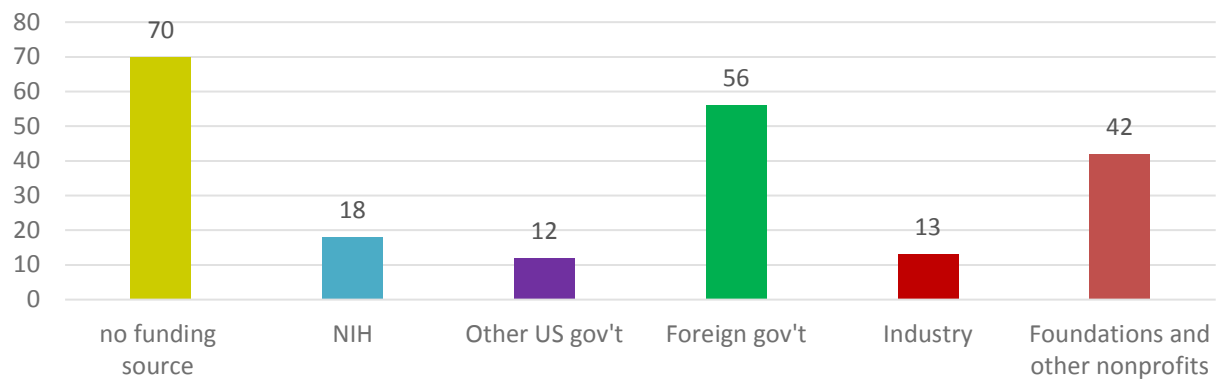
Current Research Activities

NIH is supporting several projects related to asthma in pregnancy⁵⁷. For example, NICHD is funding a study to increase understanding of factors that predict poor asthma control during pregnancy. Researchers are assessing predictors of asthma control variability during pregnancy, including demographic, biologic, genetic, and environmental factors, with particular interest in the role of maternal allergy. Women whose asthma is exacerbated during pregnancy may be at elevated risk from environmental exposures, such as poor air quality.

Appendix VI, Figure 10, shows external funding sources acknowledged by original research articles published from 2006-2017 on medicinal therapies for asthma in pregnant women and lactating women. About 40 percent (70 of 173) did not acknowledge any external funding source. Foreign government agencies supported the largest share of funded research, followed by foundations and other nonprofit organizations.

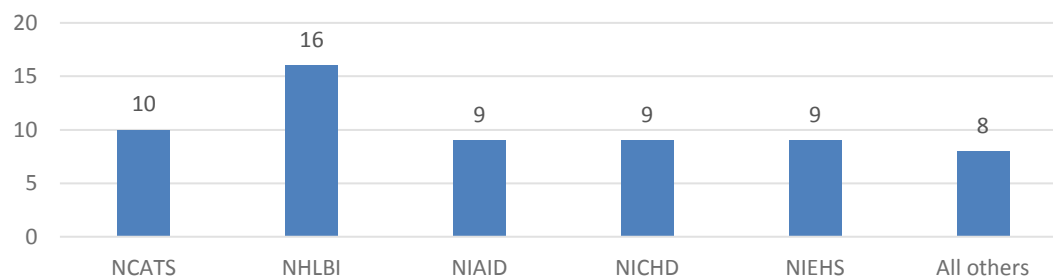
⁵⁷ Figures for NCATS include relevant publications supported in whole or in part by the Clinical and Translational Science Awards (CTSAs). Some CTSAs were previously funded under the National Center for Research Resources (NCRR), and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Appendix VI, Figure 10: Original Research Publications (n=173) for Asthma in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: foreign government agencies included the Canadian Institutes of Health, the Medical Research Council of the UK, and similar health research agencies in 10 countries. A single publication may be reported in multiple categories if multiple funding sources were cited.

Original Research Publications for Asthma in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs⁵⁸ included NCI, NIA, NIDA, NLM, and the NIH OD. A single publication may be reported in multiple categories if multiple funding sources were cited.

⁵⁸ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Research Gaps

The existing research base on medications for asthma in pregnant women and lactating women are severely limited. For pregnant women, for example, no PK/PD studies have been published on asthma medications in the past decade. Existing database research suggests that some asthma drugs may have teratogenic effects, but the results are mixed and when effects have been observed, these effects have been small. More information on potential teratogenic effects and subtle and/or long-term consequences of prenatal exposures is needed. In addition, research on exposures to these therapies through breast milk is needed.

Autoimmune Disorders

Introduction

Autoimmune disorders occur when the immune system mistakenly attacks healthy cells in the body. Women, particularly African-American, Hispanic-American, and Native-American women, are at higher risk than men for certain autoimmune diseases. There are more than 80 types of autoimmune diseases, and some have similar symptoms, which can make diagnosis a challenge.⁵⁹ Rheumatoid arthritis, antiphospholipid antibody syndrome, scleroderma, multiple sclerosis (MS), and systemic lupus erythematosus (SLE) are the autoimmune disorders most frequently reported in pregnant women and lactating women.⁶⁰ Pregnancy may improve symptoms of certain autoimmune disorders, such as rheumatoid arthritis but for others, such as SLE, pregnancy may produce no change or worsen symptoms.⁶¹

Scientific Literature

The analysis identified 804 articles published between January 2006 and July 2017 that related to medicinal therapies for autoimmune disorders in pregnant women and lactating women. Of these, 13 publications (about 1.6 percent) related to research on vitamins, minerals, or other supplements. Appendix VI, Figure 11, shows the literature by publication type.

⁵⁹ <https://medlineplus.gov/autoimmunediseases.html>

⁶⁰ Although diabetes mellitus and some thyroid disorders are often considered autoimmune diseases, these conditions are covered elsewhere in this report

⁶¹ PMID 18716941 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18716941>)

Appendix VI, Figure 11: Publications on Medicinal Therapies for Autoimmune Disorders in Pregnant Women and Lactating Women, by Type of Research, 2006-2017

| | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|-------------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Autoimmune | 29 | 3 | 13 | 16 | 155 | 221 | 321 | 28 | 18 |

Of the articles, 234 (29 percent) reported on original research. The majority of articles were either case reports or reviews, although observational case series were also common. For example, a recent cohort study of SLE assessed the risk of renal flares (an increase in disease activity affecting the kidney) during pregnancy in women with a history this disorder. The researchers found that kidney involvement in SLE was uncommon during pregnancy, especially in women with no history of kidney disease.⁶² Other researchers followed pregnant women with one of six different autoimmune disorders, who were treated with cyclosporin A, an immunosuppressant drug. The scientists found that the rate of adverse pregnancy outcomes for these women was similar to the rate in the general population, and they suggested that discontinuing the drug during pregnancy was not warranted for women who benefit from it.⁶³

There were few reports of RCTs in pregnant women and lactating women with autoimmune disorders. A pilot trial compared bromocriptine and prednisone with prednisone-only treatment for pregnant women with SLE in the third trimester. The researchers found that treatment was well-tolerated and fewer women in the bromocriptine group experienced pregnancy complications such as premature rupture of the membranes or preterm birth.⁶⁴ A larger study, comparing bromocriptine to a control group, suggested that this medication also may help reduce the risk of postpartum SLE relapse.⁶⁵

Of the autoimmune disorders addressed in the articles, the most frequent were rheumatoid arthritis, antiphospholipid antibody syndrome (AA syndrome), MS, and SLE. Other publications addressed autoimmune disorders generally or focused on medications, not a specific disorder. For the most

⁶² [PMID 28400421 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=28400421\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=28400421)

⁶³ [PMID 27145741 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=27145741\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=27145741)

⁶⁴ [PMID 17911444 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=17911444\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=17911444)

⁶⁵ [PMID 25973434 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=25973434\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=25973434)

common disorders in the literature, Appendix VI, Figure 12, shows the distribution of publications by type of research.

Appendix VI, Figure 12: Publications on Medicinal Therapies for Autoimmune Disorders in Pregnant Women and Lactating Women, by Type of Research and Disorder, 2006-2017

| Autoimmune Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Rev | Edit/Comment | Other |
|----------------------|-------|-------|--------|-----|-------------|--------------|-----|--------------|-------|
| AA syndrome | 9 | 1 | 1 | 3 | 24 | 32 | 81 | 4 | 4 |
| SLE | 2 | 1 | 2 | 3 | 42 | 28 | 52 | 4 | 4 |
| MS | 5 | 0 | 2 | 3 | 30 | 21 | 42 | 9 | 3 |
| Rheum. Arthritis | 3 | 0 | 5 | 2 | 55 | 21 | 55 | 3 | 3 |

Appendix VI, Figure 13 shows the pregnancy and lactation publications, by disorder and type of research, separately. Lactation was infrequently the subject of autoimmune-related research.

Appendix VI, Figure 13: Pregnancy and Lactation Publications on Medicinal Therapies for Autoimmune Disorders, Shown Separately, by Disorder and Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| AA syndrome | 9 | 1 | 1 | 3 | 24 | 32 | 80 | 4 | 4 |
| Lupus | 2 | 1 | 2 | 2 | 41 | 26 | 48 | 4 | 4 |
| MS | 4 | 0 | 1 | 2 | 25 | 18 | 32 | 4 | 3 |
| Rheum. Arthritis | 3 | 0 | 5 | 2 | 55 | 19 | 39 | 3 | 3 |
| Lactation | | | | | | | | | |
| AA syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Lupus | 0 | 0 | 0 | 1 | 1 | 2 | 4 | 0 | 0 |
| MS | 1 | 0 | 1 | 1 | 5 | 3 | 10 | 5 | 0 |
| Rheum. Arthritis | 0 | 0 | 0 | 0 | 0 | 2 | 16 | 0 | 0 |

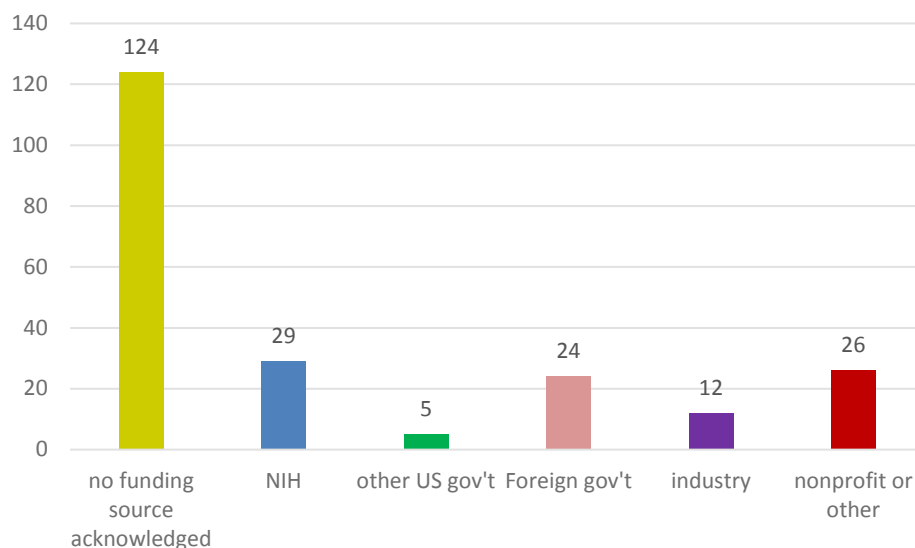
Current Research Activities

NIH supports few projects related to autoimmune disorders in pregnancy, and some are only indirectly related to medication. For example, researchers funded by NIAMS are analyzing gene expression to help

understand the natural amelioration of RA during pregnancy; such mechanistic investigation of disease process can inform pharmaceutical research, however.⁶⁶

Appendix VI, Figure 14, shows external funding sources acknowledged by original research articles, published from 2006-2017, on autoimmune disorders in pregnant women and lactating women. Of the 234 original research publications, slightly fewer than half (47 percent) acknowledged at least one external funding source.

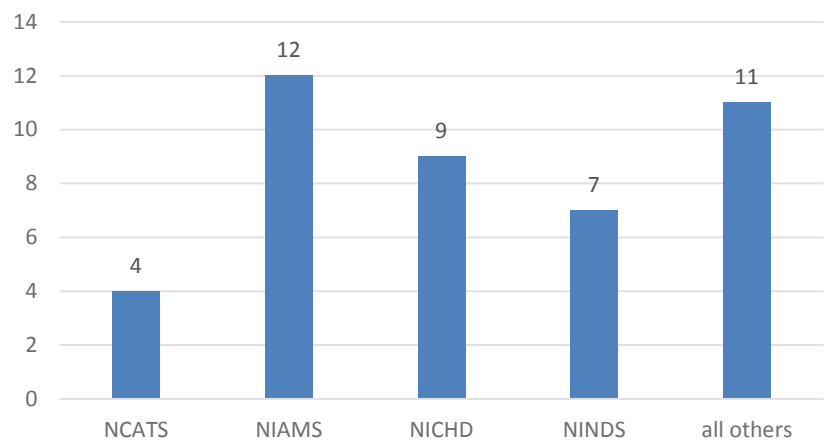
Appendix VI, Figure 14: Original Research Publications (n=234) on Medicinal Therapies for Autoimmune Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other United States government agencies included CDC, DoD, USDA, and AHRQ.

⁶⁶ [R01AR073111](https://projectreporter.nih.gov/project_info_description.cfm?aid=9469350&icde=36320936&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=):
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9469350&icde=36320936&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

Original Research Publications on Medicinal Therapies for Autoimmune Disorders in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs⁶⁷ included NCCIH, NCI, NHLBI, NIA, NIAAA, NIAID, NIDCR, NIEHS, NIGMS, and NIMH. A single publication may be reported in multiple categories if multiple funding sources were cited.

Research Gaps

Research in autoimmune diseases during pregnancy is scattered and some conditions are especially understudied. Few studies are available, in either animals or humans, to describe the PK/PD of commonly used medications for women with an autoimmune disease during pregnancy. Also limited is the number of RCTs, and of the few published, at least half were small pilot trials of fewer than 30 participants. Medicinal therapies in lactating women with autoimmune disorders appear to be especially understudied.

Cancer

Introduction

Cancer can occur during pregnancy or lactation, although it is relatively rare. Breast cancer is the most commonly diagnosed type of malignancy during pregnancy. It affects about 1 in 3,000 women who are

⁶⁷ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

pregnant. Other cancers that affect younger populations, including cervical and lymphatic cancers, may also occur during pregnancy.⁶⁸

Scientific Literature

The analysis identified 1,072 articles, published between January 2006 and July 2017, that related to medicinal therapies for cancer in pregnant women and lactating women. Of these, 21 publications (about 2 percent) related to vitamins, minerals, and other supplements. Appendix VI, Figure 15, shows the literature by publication type.

Appendix VI, Figure 15: Publications on Medicinal Therapies for Cancer in Pregnant Women and Lactating Women, by Research Type, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|--------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Cancer (all) | 181 | 10 | 5 | 4 | 118 | 357 | 333 | 46 | 18 |

The large majority of articles were either case reports or reviews; a more limited number of original research publications focused on disease mechanisms of cancer in pregnant women and on the potential impact of exposure to chemotherapy on fetal development. For example, one animal study showed that a cancer drug (ifosfamide) resulted in changes in placental size and structure and may negatively alter fetal brain, liver, and kidney tissues.⁶⁹ Another animal study showed that Gleevec (imatinib mesylate) therapy for cancer very early in pregnancy resulted in reduction of the mammary gland tumor without reducing the animal's the ability to lactate.⁷⁰

Few RCTs were reported. One publication on outcomes for women who became pregnant during a clinical trial for a breast cancer treatment reported no congenital malformations in offspring exposed antenatally to the experimental treatment.⁷¹

⁶⁸ <http://www.cancer.net/navigating-cancer-care/dating-sex-and-reproduction/cancer-during-pregnancy>

⁶⁹ PMID 27124550 (<https://www.ncbi.nlm.nih.gov/pubmed/27124550>)

⁷⁰ PMID 27550925 (<https://www.ncbi.nlm.nih.gov/pubmed/27550925>)

⁷¹ PMID 22367645 (<https://www.ncbi.nlm.nih.gov/pubmed/22367645>)

In contrast to other conditions affecting pregnant women, there were few studies that used population-level data, registries, or large databases to address research questions related to cancer in pregnancy. Few studies reported on pharmacokinetic and/or pharmacodynamic effects of cancer drugs specifically when taken during pregnancy or lactation. One such study, however, analyzed pooled data on four anti-cancer drugs used in pregnant and non-pregnant women. The researchers found higher rates of renal clearance of the drugs among the pregnant women and suggested that higher dosing for two of the drugs may be needed to achieve therapeutic efficacy, although they cautioned that additional research is needed to confirm their results.⁷²

Appendix VI, Figure 16, shows the distribution of publications by type of article.

Appendix VI, Figure 16: Publications on Medicinal Therapies for Cancer in Pregnant Women and Lactating Women, by Research Type and Cancer Site, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Breast Cancer | 29 | 0 | 0 | 2 | 26 | 69 | 62 | 14 | 7 |
| Lymphatic Cancer | 7 | 1 | 1 | 0 | 11 | 64 | 27 | 6 | 2 |
| Gynecologic Cancer | 10 | 0 | 1 | 0 | 26 | 88 | 23 | 10 | 4 |
| Lung Cancer | 11 | 0 | 0 | 0 | 5 | 38 | 7 | 1 | 0 |

The most common type of cancer in this literature was breast cancer, followed by gynecologic, lymphatic, and lung cancers. Many other publications were either not focused on these types of cancer or did not focus on a specific type. Appendix VI, Figure 17, shows the pregnancy related publications and lactation-related publications, by type, separately. Lactation was only infrequently the subject of cancer-related research.

⁷² PMID 24713311 (<https://www.ncbi.nlm.nih.gov/pubmed/24713311>)

Appendix VI, Figure 17: Pregnancy and Lactation Publications on Medicinal Therapies for Cancer, Shown Separately, by Cancer Type and Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Pregnancy only | | | | | | | | | |
| Breast Cancer | 29 | 0 | 0 | 2 | 23 | 65 | 60 | 14 | 7 |
| Lymphatic Cancer | 7 | 1 | 1 | 0 | 10 | 62 | 26 | 6 | 2 |
| Gynecologic Cancer | 10 | 0 | 1 | 0 | 25 | 86 | 23 | 10 | 4 |
| Lung Cancer | 11 | 0 | 0 | 0 | 5 | 38 | 7 | 1 | 0 |
| Lactation | | | | | | | | | |
| Breast Cancer | 0 | 0 | 0 | 0 | 3 | 4 | 2 | 0 | 0 |
| Lymphatic Cancer | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 | 0 |
| Gynecologic Cancer | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| Lung Cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Current Research Activities

NIH supports several projects related to cancer in pregnancy, including analyses of registry and/or population-based data. For example, NCI funds a large, population-based study of incidence, diagnostic characteristics, and mortality associated with cancers in pregnant and postpartum women. The scientists will use national Swedish medical data to determine if pregnancy is associated with increases in the risk for certain cancers.⁷³ Several NCI-funded grants are focused on possible reasons why pregnancy may increase a woman's long-term cancer risk. For example, one project focuses on invasive

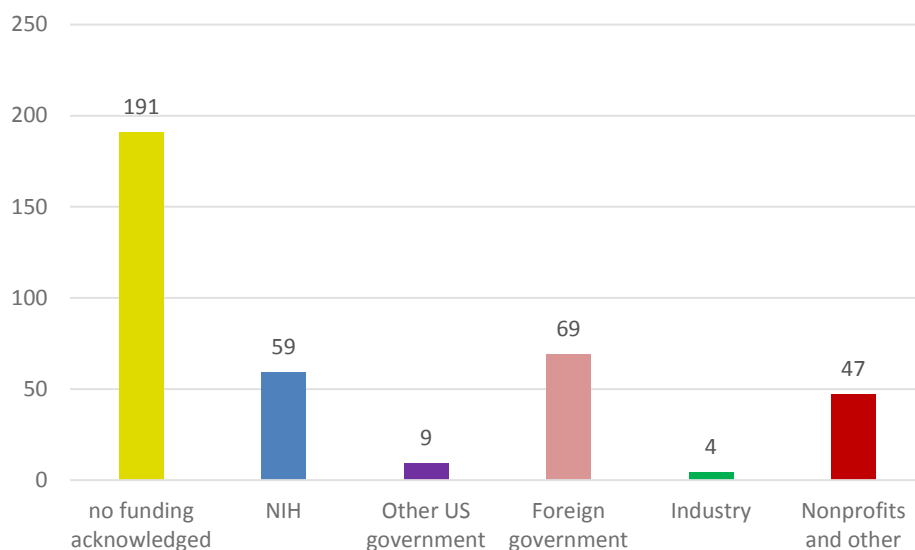
⁷³ [R21CA208793](https://projectreporter.nih.gov/project_info_description.cfm?aid=9330818&icde=36206730&ddparam=&ddvalue=&ddsub=&r=1&csb=default&cs=ASC&pbll=)

(https://projectreporter.nih.gov/project_info_description.cfm?aid=9330818&icde=36206730&ddparam=&ddvalue=&ddsub=&r=1&csb=default&cs=ASC&pbll=)

placentation, an obstetric condition involving lack of control of the maternal/fetal interface that results in cellular invasion of placental tissue into the surrounding tissues.⁷⁴

Appendix VI, Figure 18, shows external funding sources acknowledged by original research articles on medicinal therapies for cancer in pregnant women and lactating women. Of the 357 original research publications, slightly over half (53 percent) acknowledged at least one funding source. Foreign Government agencies supported the largest share of research, followed by the NIH. Among NIH ICs involved in this research, NCI supported the greatest number of research publications by a very wide margin. However, of the 59 publications that acknowledged NIH funding, 42 (71 percent) acknowledged more than one NIH IC. Nonprofit organizations, including professional societies, foundations, and universities in the United States and elsewhere, also supported this research. Little industry support was acknowledged.

Appendix VI, Figure 18: Original Research Publications (n=357) on Medicinal Therapies for Cancer in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017

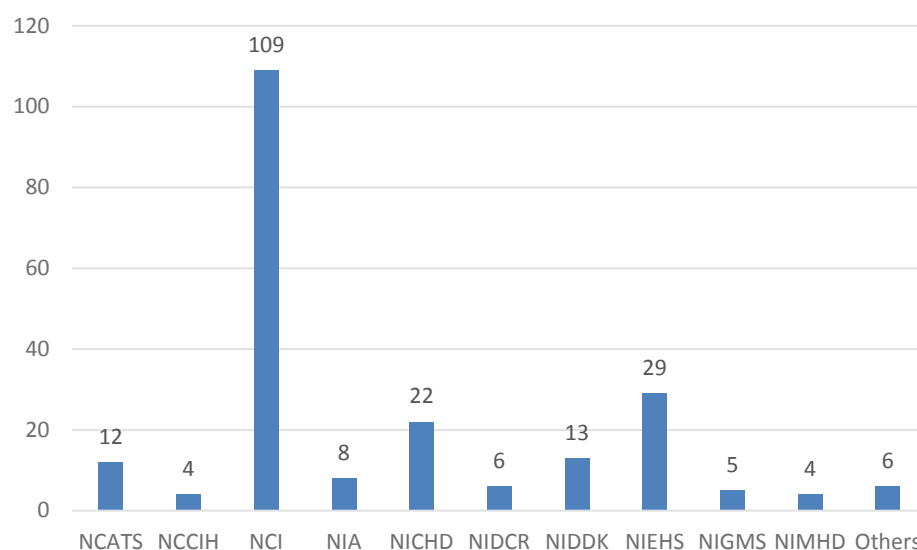


Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other than NIH, U.S. government agencies included CDC, DoD, VA, NSF, USDA, and the Department of Energy.

⁷⁴ [R21CA212429](https://projectreporter.nih.gov/project_info_description.cfm?aid=9387086&icde=36206789&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

(https://projectreporter.nih.gov/project_info_description.cfm?aid=9387086&icde=36206789&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

Original Research Publications on Medicinal Therapies for Cancer in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs⁷⁵ included NIMH, NIAAA, and NHLBI. A single publication may be reported in multiple categories if multiple funding sources were cited.

Research Gaps

Lactation in women with cancer is understudied. In pregnant women, very few PK/PD studies have been published on cancer medications in the past decade, even for the types of cancers that occur in pregnant women with some frequency. Only limited database/registry/population research has been conducted to investigate potential teratogenic or other adverse effects of anti-cancer medications during pregnancy.

⁷⁵ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Central Nervous System Disorders

Introduction

The central nervous system (CNS), consisting of the brain and spinal cord, coordinates and integrates most functions of the body. CNS conditions include epilepsy and other seizure disorders, migraine, and other types of headaches, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and stroke. In the United States, about 3.4 million people have epilepsy, including an estimated 400,000 children under 18 years of age.⁷⁶ According to some reports, anti-seizure medications are commonly used in pregnancy for control of epilepsy (These drugs are also used for certain mental health conditions).⁷⁷ Although the risk of stroke is considerably higher in older individuals, about one-third of individuals hospitalized for stroke are under the age of 65.⁷⁸ Headache disorders, including migraine, may improve during pregnancy. However, because headache disorders are very common, many pregnant women seek to continue treatment during their pregnancies.⁷⁹

Scientific Literature

The analysis identified 834 articles, published between January 2006 and July 2017, that are related to CNS conditions in pregnant women and lactating women. For all CNS conditions combined, about 38 percent of the publications reported original research. Fifty publications, 22 reporting on original research, addressed vitamin, mineral or other supplements in pregnant or lactating women with epilepsy. Most of those articles focused on whether folic acid and/or vitamin K could improve outcomes for pregnant women with epilepsy.

The CNS conditions most commonly addressed in the publications were epilepsy and other seizure disorders, stroke, and headache disorders. For these conditions, Appendix VI, Figure 19, shows the distribution of publications by condition and type of research.

⁷⁶ [PMID 28796763 \(https://pubmed.ncbi.nlm.nih.gov/28796763/\)](https://pubmed.ncbi.nlm.nih.gov/28796763/)

⁷⁷ [PMID 15343213 \(https://pubmed.ncbi.nlm.nih.gov/15343213/\)](https://pubmed.ncbi.nlm.nih.gov/15343213/)

⁷⁸ <https://www.cdc.gov/stroke/facts.htm>

⁷⁹ [PMID 21442333 \(https://pubmed.ncbi.nlm.nih.gov/?term=21442333\)](https://pubmed.ncbi.nlm.nih.gov/?term=21442333)

Appendix VI, Figure 19: Pregnancy- and Lactation-Related Publications on Medicinal Therapies for CNS Disorders, by Condition and Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-------------------|-------|-------|--------|--|-----|-------------|--------------|---------|---------------|-------|
| Seizure disorders | 9 | 8 | 52 | | 2 | 44 | 2 | 19 | 25 | 13 |
| Stroke | 1 | 0 | 4 | | 0 | 7 | 2 | 4 | 3 | 0 |
| Headache/migraine | 0 | 0 | 5 | | 1 | 6 | 13 | 41 | 3 | 0 |

As shown in Appendix VI, Figure 19, for each of these conditions in pregnant or lactating women, there were few publications reporting research on basic science or mechanism of disease, PK/PD, or RCTs. Half of the PK/PD studies in seizure disorders focused on the anti-convulsant drug lamotrigine, with three other drugs addressed in one or two articles each.⁸⁰ These studies reported that pregnant women cleared the anti-seizure drugs from their system relatively quickly and had lower concentrations of a drug in their system, compared to non-pregnant women. A study of multiple anti-seizure drugs found lower concentrations of the medications in the pregnant research participants, along with increased seizure activity, compared to their pre-pregnancy history.⁸¹

For seizure disorders generally, there was a substantial number of publications that analyzed population-level data or large databases. In addition to pregnancy and other registries in foreign countries, there are several large health-related sources of data in the United States, including administrative records and electronic health records. These include the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a collaborative effort between the FDA and researchers from Vanderbilt University, the HMO Research Network, and that of Kaiser Permanente Northern and Southern California, as well as state Medicaid program data. Researchers have analyzed these types of data to address several types of questions related to CNS conditions and pregnancy, both for individual drugs and for the general class of anti-seizure drugs. These types of studies include:

⁸⁰ [PMID 18180176 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=18180176\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=18180176); [PMID 18201913 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=18201913\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=18201913); [PMID 27818298 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=27818298\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=27818298)

⁸¹ [PMID 23911354 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=23911354\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=23911354)

1. Descriptions of physician prescribing patterns for pregnant and/or lactating women⁸²
2. Assessments of the effectiveness of these medications in controlling seizures in pregnant women,⁸³ and (in one study) the effect of untreated disease on seizure incidence in pregnant women with and without seizure disorders⁸⁴
3. Analysis of potential effects of these medications on the offspring

Most of the studies of potential effects on offspring of maternal anti-seizure medications focused on risk of structural birth defects. Studies of subtle or later-emerging outcomes for offspring were relatively rare. One such study of data from an Australian pregnancy registry assessed language ability at 6 to 8 years of age among children exposed to anti-seizure medications during their mothers' pregnancy. The researchers found a negative correlation between medication exposure and language ability for valproate, one specific drug, but no relationship for other drugs in the same class.⁸⁵ Another study, of Danish registry data, assessed behavioral problems at 4 to 5 years of age in children exposed antenatally to maternal anti-seizure medications. The children had higher scores in an assessment for behavioral problems than either children of mothers without epilepsy or those whose mothers had epilepsy but avoided medication while pregnant.⁸⁶

Few clinical trials were published in this area. One study addressed infection-related seizures during pregnancy; another was a secondary analysis of limited relevance to seizure disorders; while a third focused on preventing infection in pregnant women with spinal cord injury.⁸⁷

Although there were multiple review articles on headache and migraine in pregnant women and lactating women, relatively little original research in this area was published.

⁸² PMID 19453723 (<https://www.ncbi.nlm.nih.gov/pubmed/19453723>); PMID 25653296 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25653296%5Buid%5D>); PMID 23061694 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=23061694>)

⁸³ PMID 24995555 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24995555>)

⁸⁴ PMID 25218112 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25218112>)

⁸⁵ PMID 21339499 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=21339499>)

⁸⁶ PMID 24090777 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24090777>)

⁸⁷ PMID 18986822 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18986822>)

Appendix VI, Figure 20, shows the pregnancy and lactation publications, by disorder and type of research, separately. The very large majority of these publications report research on pregnancy, and not lactation. Some of the few lactation publications also involve pregnancy. For example, one PK/PD publication looked at the concentrations of the drug levetiracetam, an anti-seizure medication, in both blood plasma of pregnant women and the breast milk of nursing mothers.⁸⁸

Appendix VI, Figure 20: Pregnancy and Lactation Publications on Medicinal Therapies for CNS Disorders, Shown Separately, by Condition and Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Seizure disorders | 6 | 7 | 50 | 1 | 35 | 1 | 8 | 18 | 7 |
| Stroke | 1 | 0 | 4 | 0 | 7 | 2 | 4 | 3 | 0 |
| Headache/migraine | 0 | 0 | 5 | 1 | 6 | 13 | 36 | 3 | 0 |
| Lactation | | | | | | | | | |
| Seizure disorders | 0 | 1 | 1 | 1 | 3 | 0 | 2 | 3 | 2 |
| Stroke | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache/migraine | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 |

Current Research Activities

NIH supports several projects related to medicinal therapies for CNS in pregnancy. For example, NINDS funds a group of scientists whose long-term goals are to (1) define changes in the brain and cerebral circulation during pregnancy that promote seizure in circumstances other than preeclampsia and (2) describe how preeclampsia can predispose the brain to seizure, leading to eclampsia ([R01NS045940](#)⁸⁹). In some states, CDC's Pregnancy Risk Assessment Monitoring System gathers information about the use of anti-seizure drugs in pregnant women. The North American Antiepileptic Drug Registry

⁸⁸ [PMID 17381438](#) (<https://www.ncbi.nlm.nih.gov/pubmed/?term=17381438>)

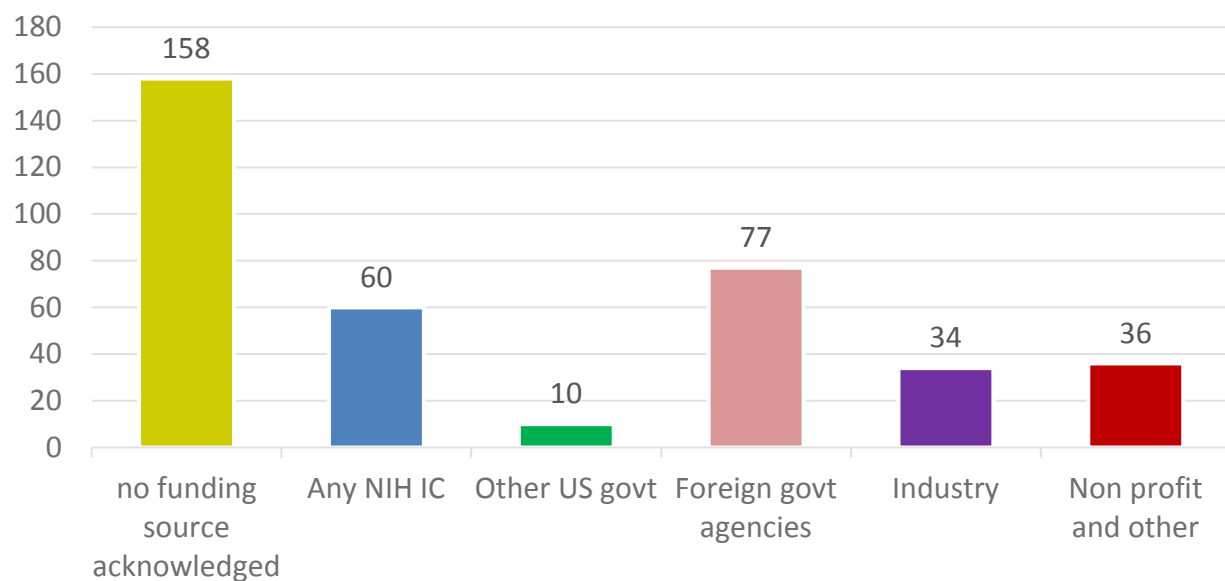
⁸⁹

https://projectreporter.nih.gov/project_info_description.cfm?aid=9449467&icde=40663606&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

(<http://www.aedpregnancyregistry.org/>), affiliated with Harvard Medical School, is a voluntary registry of women exposed to anti-seizure drugs during pregnancy.

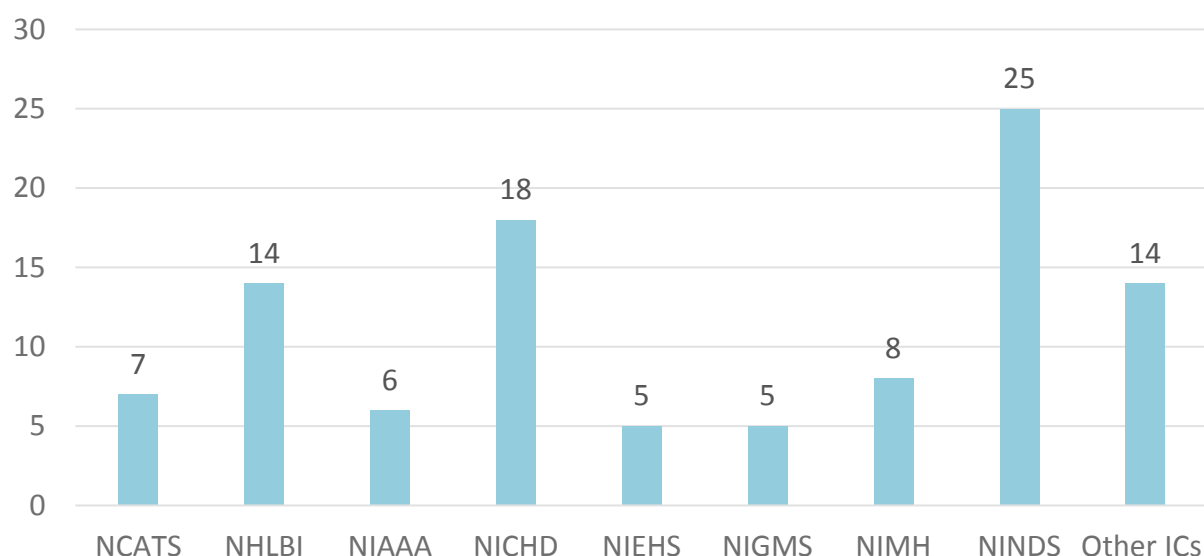
Appendix VI, Figure 21, shows external funding sources acknowledged by original research articles published from 2006-2017 on CNS conditions in pregnant women and lactating women. Over 45 percent of the publications did not acknowledge any external funding source. Government agencies of foreign countries supported the largest share of funded research, followed by the NIH. Among NIH ICs funding this research, NINDS, NICHD, and NHLBI supported research resulting in the greatest number of publications.

Appendix VI, Figure 21: Original Research Publications on Medicinal Therapies for CNS Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Note: Foreign government agencies included the Canadian Institutes of Health Research, the U.K. Medical Research Council and similar health research agencies in 14 other countries.

Original Research Publications on Medicinal Therapies for CNS Disorders in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs⁹⁰ included NIDA, FIC, NCI, NIA, NIAID, NIAMS, NIDCR, NIDDK, and the NIH OD. A single publication may be reported in multiple categories if multiple funding sources were cited.

Research Gaps

Research on medicinal therapies for CNS disorders in pregnant women and lactating women is very limited. Results of PK/PD studies show that pregnant women clear anti-seizure drugs quickly, indicating the need for dosing studies. More information on potential teratogenic effects of medications for CNS disorders is certainly needed, especially studies that address subtle and/or long-term consequences. Clinical trials and/or rigorous comparative effectiveness studies on effectiveness of drugs in controlling seizures in pregnancy have not been conducted to inform prescribing decisions.

⁹⁰ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Diabetes

Introduction

Poor control of diabetes during pregnancy increases the chances both birth defects and other health problems for a child and pregnancy complications with immediate and/or lasting impact on a woman's health. Some women have either type 1 or type 2 diabetes before pregnancy, while others may develop gestational diabetes mellitus (GDM) during pregnancy. Each type of diabetes during pregnancy is a serious concern, and the treatment strategy for each type of diabetes may have its own potential risks to the pregnant woman and fetus. Moreover, although women with pre-existing type 1 diabetes are typically treated with insulin during their pregnancies, the optimal medication management for those women with pre-existing type 2 diabetes, and GDM in particular, remains ill-defined. Although there are gaps in our understanding of the risk factors and management of all forms of diabetes, much less is known about GDM than about type 1 or type 2 diabetes. After the baby is born, many women with diabetes prefer to breastfeed, and available evidence suggests that breastfeeding may help the mother's glycemic control and reduce the risk of diabetes later in life for the newborn. Scientific information to assess the impact of diabetes treatment during lactation on the infant is limited.⁹¹

Scientific Literature

The analysis identified 1,427 articles, published between January 2006 and July 2017, that are related to medicinal therapies for some form of diabetes in pregnant or lactating women. Of these, 141 publications (10 percent) concerned vitamin, mineral, or other supplements. Appendix VI, Figure 22, shows the distribution of publications by type of research.

Appendix VI, Figure 22: Publications on Medicinal Therapies for Diabetes in Pregnant Women and Lactating Women, by Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Diabetes | 164 | 21 | 44 | 114 | 423 | 101 | 437 | 49 | 74 |

Nearly three-fifths (59 percent) of the publications on medications for diabetes in pregnant women and lactating women reported on original research. As shown in Appendix VI, Figure 22, basic science studies, RCTs, and case series or cohort studies were common. The basic science studies typically used

⁹¹ <https://www.cdc.gov/pregnancy/diabetes.html>; PMID 21348815

animal models to investigate the mechanisms of GDM and/or potential therapies for it. One mechanistic study in a mouse model of GDM found that resveratrol, a plant-based compound reported to exhibit beneficial effects in treating type 2 diabetes, relieved GDM in the mice by enhancing activation of the factor known as AMP-activated protein kinase.⁹² Another study isolated a polysaccharide containing the element selenium from lotus leaf and found that this substance had positive effects in a rat model of GDM.⁹³ However, these are just two of many basic science studies focusing on GDM.

Many case series and cohort studies investigated outcomes of women with diabetes during pregnancy and their babies. Most of these studies focused on GDM rather than pre-existing type 1 or type 2 diabetes. Although one cohort study in China found no differences in the rates of macrosomia (significantly larger than average size of newborn), neonatal hypoglycemia, or cesarean delivery for women who were treated for mild GDM, compared to pregnant women with untreated GDM and pregnant women without the disorder,⁹⁴ there is inconsistency in the literature with respect to maternal and fetal outcomes and gaps in knowledge remain. With respect to treatment of GDM, researchers at an Israeli treatment center followed pregnant women with GDM who were initially treated with glyburide (an oral diabetes medicine), then switched to insulin if they failed to achieve glycemic goals. The researchers reported that about three-quarters of the women achieved glycemic control with glyburide, and about half of the remaining women achieved the glycemic control goals with insulin.⁹⁵ Nonetheless, study results regarding the management of GDM have been inconsistent and a lack of consensus about the optimal treatment of GDM remains as evidenced by discrepancies among professional society treatment guidelines.

RCTs in the United States and those elsewhere assessed differing treatments for diabetes in pregnancy. Researchers in Brazil reported that treatment of GDM with metformin or glyburide (two oral diabetes medications) was equivalent for both women and newborns.⁹⁶ In Pakistan, an open-label, randomized trial found that metformin, or metformin with insulin if needed to maintain glycemic control, was

⁹² [PMID 26542478 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=26542478\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=26542478)

⁹³ [PMID 27580896 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=27580896\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=27580896)

⁹⁴ [PMID 25068946 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=25068946\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=25068946)

⁹⁵ [PMID 21067291 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=21067291\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=21067291)

⁹⁶ [PMID 20542272 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=20542272\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=20542272)

effective for treating type 2 diabetes in pregnancy.⁹⁷ In a larger trial, researchers in the United States found that one-third of women with recent GDM experienced delays in lactation and that insulin treatment, maternal obesity, and suboptimal in-hospital breastfeeding were risk factors for such a delay.⁹⁸ However, many scientific gaps remain in our understanding of the treatment and long-term effects of GDM on both the mother and her offspring.

Recent progress in the development of accurate continuous glucose monitoring (CGM) systems has the potential to greatly improve management of diabetes during pregnancy (when either used alone or in combination with an insulin pump), and studies of how best to incorporate new technology into diabetes care during pregnancy may have a high impact on improving therapy and outcomes for pregnant women with all types of diabetes.

Of the 141 articles reporting research on vitamin, mineral, or other supplements, 93 (66 percent) were original research articles and 37 (26 percent) were clinical trials. Nearly all the trials focused on GDM. Researchers tested a number of different vitamins and supplements, including vitamins D and E, omega 3, capsaicin, magnesium, selenium, probiotics, zinc, and iron (among others).⁹⁹

Appendix VI, Figure 23, shows the pregnancy and lactation publications by research type, separately. As with many other conditions, most publications focused on pregnancy, not lactation. Of the lactation publications, a subset focused on the composition of breast milk and how its various components differed between women with and without GDM.

⁹⁷ PMID 25874236 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25874236>)

⁹⁸ PMID 24196401 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24196401>)

⁹⁹ PMID 25771490 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25771490>); PMID 25747955 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25747955>); PMID 25790761 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25790761>); PMID 26016859 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26016859>); PMID 26250486 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26250486>); PMID 28367765 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=28367765>); PMID 26465829 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26465829>); and others

Appendix VI, Figure 23: Pregnancy and Lactation Publications on Medicinal Therapies for Diabetes, Shown Separately, by Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Diabetes | 148 | 19 | 41 | 105 | 404 | 92 | 403 | 43 | 63 |
| Lactation | | | | | | | | | |
| Diabetes | 16 | 2 | 3 | 9 | 19 | 9 | 34 | 6 | 11 |

Current Research Activities

Gestational diabetes mellitus is an important area of research focus for several institutes at NIH, especially NICHD and NIDDK. Currently funded NIH projects include several on screening approaches for GDM,¹⁰⁰ an NIEHS-funded study of BPA (bisphenol A, a chemical compound) exposure and risk of GDM,¹⁰¹ and a study of follow-up care for women with GDM.¹⁰²

Appendix VI, Figure 24, shows external funding sources acknowledged by original research articles published from 2006-2017 on medicinal therapies for diabetes in pregnant women and lactating women. Of the 840 original research publications, 489 (58 percent) did not acknowledge any external funding source. Nearly twice as many publications were associated with research supported by foreign governments, compared to NIH; nonprofit and industry funding were less common. NICHD, NIDDK, and NCATS were most frequently represented among the NIH funders.

¹⁰⁰ [R01HD079647](#)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9275506&icde=36378191&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9275506&icde=36378191&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [R01HD074794](#)
([https://projectreporter.nih.gov/project_info_description.cfm?aid=9180064&icde=36378202&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9180064&icde=36378202&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;))

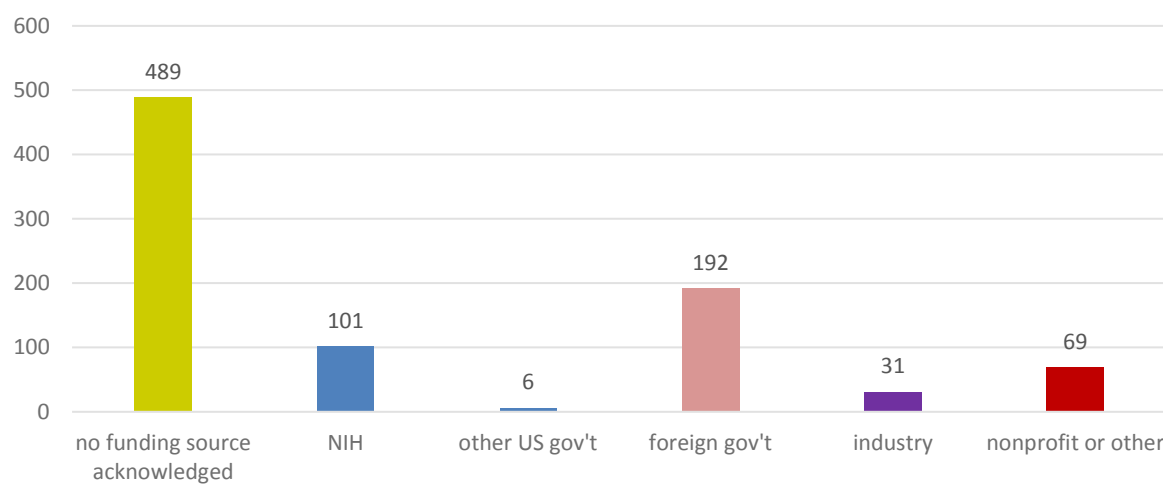
¹⁰¹ [R01ES019196](#)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9181415&icde=36378224&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9181415&icde=36378224&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;))

¹⁰² [R01DK107528](#)

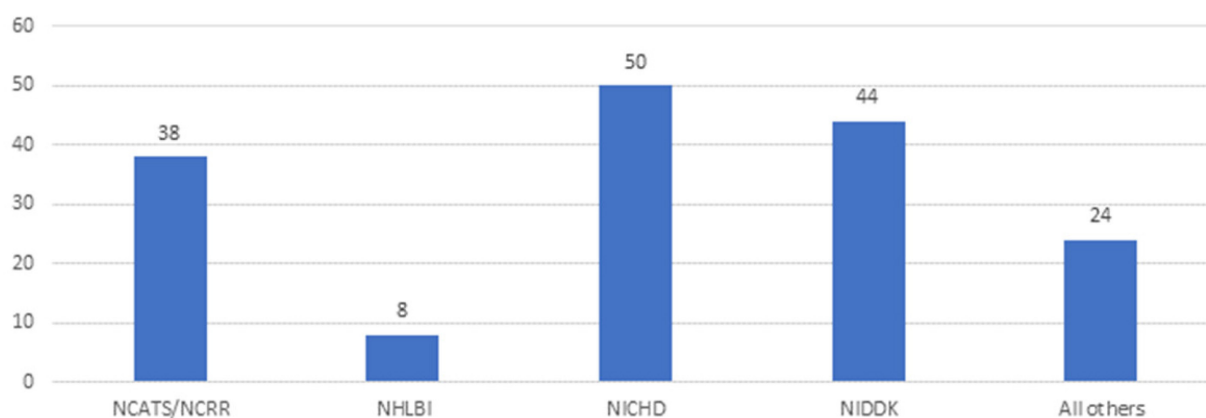
([https://projectreporter.nih.gov/project_info_description.cfm?aid=9244016&icde=36378238&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9244016&icde=36378238&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;))

Appendix VI, Figure 24: Original Research Publications (n=840) on Medicinal Therapies for Diabetes in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.

Original Research Publications on Medicinal Therapies for Diabetes in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Notes: Many articles with NIH funding credited multiple ICs¹⁰³. A single publication may be reported in multiple categories if multiple funding sources were cited.

¹⁰³ Figures for NCATS include relevant publications supported in whole or in part by the CTSA. Some CTSA were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSA are also included in the NCATS totals.

Research Gaps

Importantly, many research gaps in the field of GDM remain. Some, but not all, of the outstanding questions include: when should providers screen for GDM; which screening test(s) should be used; what diagnostic criteria are most appropriate; which pharmacological agents should be used to treat GDM; what are the optimal glycemic goals during the treatment of GDM; and, whether treatment of GDM improves perinatal outcomes. Given the magnitude of GDM and its public health import, appropriately powered clinical trials addressing the above questions (and others) with long-term follow-up of the mothers and offspring are needed.

Although most of the literature on diabetes in pregnancy addressed GDM, not pre-existing type 1 or type 2 diabetes, there is a need for more research on all forms of diabetes in pregnancy. Pre-existing type 1 diabetes, especially, is not well represented. Information about the impact of diabetes and diabetes treatment on lactation is needed.

Endocrine Disorders

Introduction

Endocrine disorders involve dysfunction in one or more of the body's endocrine glands, which may produce either too much or too little of the hormones needed for basic bodily functions. Among the endocrine disorders affecting pregnant women, thyroid problems are the most common, occurring in 1 to 2 percent of pregnant women (Diabetes and hypertensive disorders that may be associated with endocrine system dysfunction are addressed separately in this analysis). It can be challenging to diagnose an emerging endocrine disorder during pregnancy because symptoms of pregnancy and symptoms of some common endocrine disorders are similar, and endocrine function is naturally altered during pregnancy.¹⁰⁴

Scientific Literature

The analysis identified 670 articles, published between January 2006 and July 2017, that are related to medicinal therapies for endocrine disorders in pregnant women and lactating women. Appendix VI, Figure 25, shows the distribution of publications by type of research.

¹⁰⁴ PMID 23681868 (<https://www.ncbi.nlm.nih.gov/pubmed/23681868>)

Appendix VI, Figure 25: Publications on Medicinal Therapies for Endocrine Disorders in Pregnant Women and Lactating Women, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Endocrine | 36 | 2 | 21 | 9 | 89 | 179 | 220 | 39 | 75 |

As shown in Appendix VI, Figure 25, the majority of articles were case reports and reviews; 232 publications (35 percent) were original research. Among all types of research, thyroid disorders were the most common endocrine conditions addressed. Basic science research used animal models to explore the impact of thyroid treatments on fetal development, especially brain development.¹⁰⁵ Case series and cohort studies followed women who were treated for endocrine disorders during pregnancy and recorded a variety of outcomes, including congenital malformations, low birth weight, and preterm birth.¹⁰⁶ Although there have been several studies evaluating the effects of levothyroxine treatment of women with thyroid disorders during pregnancy¹⁰⁷, the reported outcomes and results have been inconsistent, possibly due to the timing of the intervention. However, a recent clinical trial funded by NICHD found that treatment of subclinical thyroid disease, beginning between 8 and 20 weeks of gestation, did not result in significantly better cognitive outcomes in children through 5 years of age, compared to no treatment.

Sixty of the publications (9 percent) addressed vitamins or other supplements for pregnant women with endocrine disorders. The very large majority of this research focused on iodine and/or selenium supplements to prevent or treat thyroid disorders in pregnancy. Of articles on supplements, 35 were original research articles, of which four were RCTs. Two trials found that selenium supplementation

¹⁰⁵ PMID 22192600 (<https://www.ncbi.nlm.nih.gov/pubmed/22192600>); PMID 24712473 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24712473>); PMID 22024639 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=22024639>)

¹⁰⁶ PMID 22547422 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=22547422>); PMID 27112035 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=27112035>); PMID 23811188 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=23811188>)

¹⁰⁷ PMID 28249134 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=28249134>); PMID: 20130074 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=20130074>); PMID: 29126290 (<https://www.ncbi.nlm.nih.gov/pubmed/29126290>); PMID: 22316443 (<https://www.ncbi.nlm.nih.gov/pubmed/22316443>); PMID: 28249134 (<https://www.ncbi.nlm.nih.gov/pubmed/28249134>)

could improve maternal thyroid function.¹⁰⁸ Another study found that in Morocco, where iodine deficiency is common, lactating women who received iodine supplements soon after delivery could provide adequate iodine to their infants through breast milk for at least six months. Direct supplementation to the infants was less effective in improving infant iodine status.¹⁰⁹

Appendix VI, Figure 26, shows the pregnancy-related publications and lactation-related publications, by research type, shown separately. Almost all the pregnancy- and lactation-related research focused on pregnancy, not lactation.

Appendix VI, Figure 26: Pregnancy and Lactation Publications on Medicinal Therapies for Endocrine Disorders, Shown Separately, by Publication Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Endocrine | 34 | 2 | 21 | 8 | 86 | 174 | 212 | 39 | 71 |
| Lactation | | | | | | | | | |
| Endocrine | 2 | 0 | 0 | 1 | 3 | 5 | 8 | 0 | 4 |

Current Research Activities

NIH is funding several projects on endocrine disorders in pregnant women. For example, an NICHD-supported research contract is designed to assess whether the level of iodine deficiency in pregnant women in the United States is severe enough to cause congenital hypothyroidism. The researchers will compare iodine concentrations in blood samples of newborns with the congenital disorder to samples from unaffected newborns.¹¹⁰ An NIEHS-funded study is investigating the association between early-life environmental exposures to phthalate, triclosan, and BPA and maternal/child thyroid hormone

¹⁰⁸ PMID 25524327 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25524327>); PMID 17284630 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=17284630>)

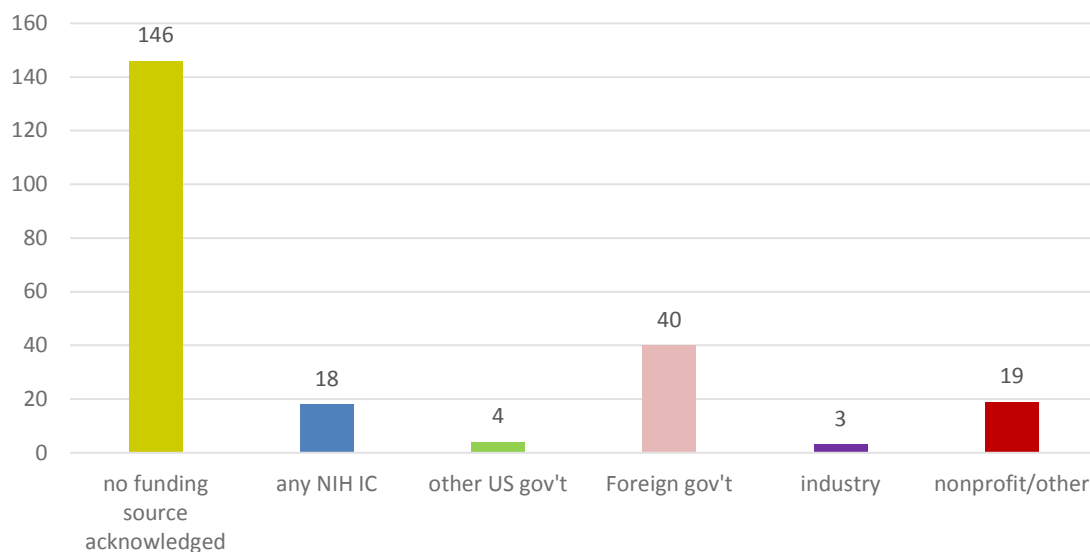
¹⁰⁹ PMID 24622750 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24622750>)

¹¹⁰ NICHD contract (https://projectreporter.nih.gov/project_info_description.cfm?aid=9305299&icde=36305075&ddparam=&ddvalue=&ddsub=&cr=5&csb=default&cs=ASC&pball=)

concentrations to determine if thyroid hormones (prenatal and postnatal) mediate the associations between chemical exposures and neurobehavioral outcomes.¹¹¹

Appendix VI, Figure 27, shows external funding sources acknowledged by original research articles on medicinal therapies for endocrine disorders in pregnant women and lactating women. Nearly two-thirds (63 percent) did not acknowledge any external funding source. Foreign governments (Japan, China, Europe) supported 17 percent of the publications. About 8 percent of articles were supported by nonprofit organizations; very few reflected industry funding.

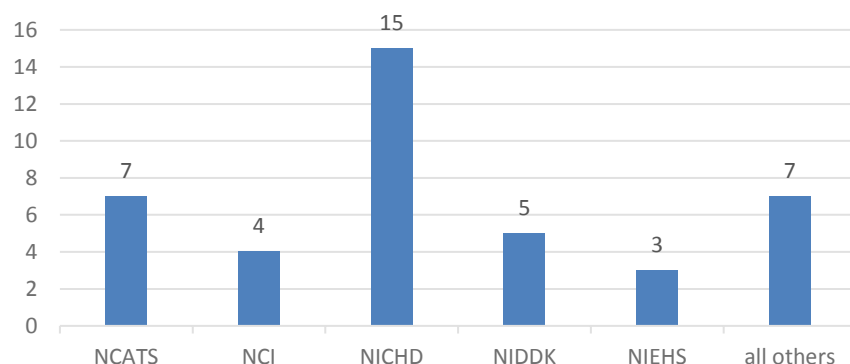
Appendix VI, Figure 27: Original Research Publications (n=232) for Medicinal Therapies for Endocrine Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.

¹¹¹ [R01ES024381](https://projectreporter.nih.gov/project_info_description.cfm?aid=9248209&icde=36305138&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9248209&icde=36305138&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

Original Research Publications for Medicinal Therapies for Endocrine Disorders in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs¹¹² included NIA, NIDCR, NIGMS, and NINDS. A single publication may be reported in multiple categories if more than one IC was acknowledged.

Research Gaps

A limited evidence base is available to physicians to diagnose and treat pregnant women with pre-existing or emerging endocrine disorders. Few recent research studies have assessed the underlying disease mechanism, PK/PD of iodine supplementation, replacement hormone treatment, or other therapies. Few RCTs of endocrine disorder treatment options for pregnant women were published in the past decade. Even less information is available on endocrine disorder therapies for lactating women and their breastfeeding infants.

Hyperemesis Gravidarum and Other Nausea and Vomiting of Pregnancy

Introduction

Nausea and vomiting in pregnancy is typically called “morning sickness,” but can occur at any time. The symptoms usually start before nine weeks of pregnancy and, for most women, resolve by the second trimester (14 weeks of pregnancy). They can last longer, however, even throughout the pregnancy. The most severe form of pregnancy-associated nausea and vomiting is hyperemesis gravidarum, which

¹¹² Figures for NCATS include relevant publications supported in whole or in part by the CTSAAs. Some CTSAAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAAs are also included in the NCATS totals.

occurs in up to 3 percent of pregnancies. Nausea and vomiting are considered hyperemesis if a woman has lost at least 5 percent of her pre-pregnancy weight and/or has other problems related to dehydration. Women with hyperemesis need therapy to stop the vomiting and restore body fluids to prevent harm to mother and fetus.¹¹³

Scientific Literature

The analysis identified 264 articles, published between January 2006 and July 2017, that related to medicinal therapies for nausea and vomiting in pregnant women. Appendix VI, Figure 28, shows the distribution of publications by type of research.

Appendix VI, Figure 28: Publications on Medicinal Therapies for Nausea and Vomiting in Pregnant Women, by Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|---------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Nausea and vomiting | 5 | 6 | 4 | 22 | 30 | 62 | 106 | 17 | 12 |

Although the largest number of publications were reviews and case reports, there were multiple RCTs of therapies for nausea and vomiting in pregnancy. Several of these related to doxylamine-pyridoxine, a combination drug approved by the FDA for treatment of refractory nausea and vomiting in pregnancy.^{114,115} There were five RCTs of herbal or other "natural" therapies for nausea and vomiting in pregnancy; four such studies focused on ginger and one focused on lemon essential oil.¹¹⁶ Almost all of

¹¹³ <https://www.acog.org/Patients/FAQs/Morning-Sickness-Nausea-and-Vomiting-of-Pregnancy>

¹¹⁴ PMID 25884778 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25884778%5Buid%5D>); PMID 20843504 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=20843504>); PMID 27881103 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=27881103>)

¹¹⁵ A product with this same formulation of ingredients was available in the United States where it had been approved in the 1950s. During the 1970s, the drug was widely used, but it was voluntarily withdrawn from the market in 1983 amid litigation. Subsequent clinical and epidemiological research supported its safety profile and when the same formulation was submitted to the FDA, it was again approved for use. See PMID 24645939 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24645939>)

¹¹⁶ PMID 22545357 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=22545357>); PMID 17957907 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=17957907>); PMID 19250006 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=19250006>); PMID 18272271

the 17 editorials and commentaries published on the topic called for more research on nausea and vomiting in pregnancy, and nearly half of these called for additional research on herbal, supplemental, or "natural" remedies.

Of publications on nausea and vomiting in pregnancy, 78 (30 percent) addressed non-drug medicinal therapies. Of these, 33 (42 percent) were original research articles. The majority of these articles reported pregnant women's use of these therapies. A survey of Texas midwives, for example, found that 90 percent had recommended at least one herbal or other complementary medicine product to their patients and nausea and vomiting of pregnancy was one of the most common indications associated with such products.¹¹⁷ One publication addressed the composition of alternative remedies, which are generally unregulated. Researchers examined the composition and product labeling of 10 ginger preparations from different manufacturers and found wide variation in concentrations of the active ingredient (gingerol) and suggested serving sizes of ginger root powder.¹¹⁸

Appendix VI, Figure 29, shows the pregnancy-related publications and lactation-related publications, by type, separately. Because nausea and vomiting of pregnancy is a pregnancy-specific condition, it was unsurprising that nearly all the pregnancy and lactation research in this area addressed pregnancy, not lactation. All the lactation publications were review articles.

Appendix VI, Figure 29: Pregnancy and Lactation Publications on Medicinal Therapies for Nausea and Vomiting of Pregnancy, Shown Separately, by Condition and Publication Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Nausea and vomiting | 5 | 6 | 4 | 22 | 30 | 62 | 101 | 17 | 12 |
| Lactation | | | | | | | | | |
| Nausea and vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 |

(<https://www.ncbi.nlm.nih.gov/pubmed/?term=18272271>); PMID 24829772
(<https://www.ncbi.nlm.nih.gov/pubmed/?term=24829772>)

¹¹⁷ PMID 17826710 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=17826710>)

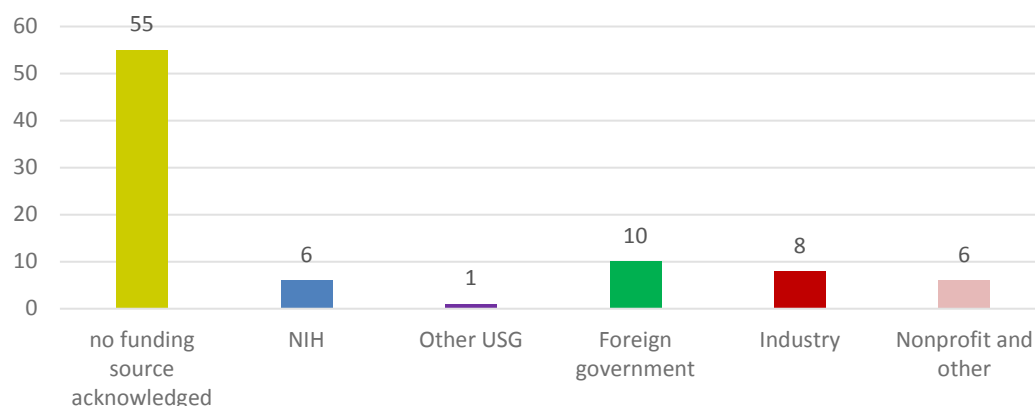
¹¹⁸ PMID 16738161 (<https://www.ncbi.nlm.nih.gov/pubmed/16738161>)

Current Research Activities

NIH is supporting an RCT to compare the efficacy and tolerability of two anti-nausea drugs—gabapentin and ondansetron—for treatment of hyperemesis gravidarum¹¹⁹.

Appendix VI, Figure 30, shows funding sources acknowledged by original research articles on medicinal therapies for nausea and vomiting in pregnancy. Of 84 such publications, 55 (65 percent) did not acknowledge an external funding source. Two NIH ICs—NICHD and NCATS—jointly funded research in this area, as acknowledged by two publications. Three additional articles were funded by NICHD and one additional article was funded by NCATS. Government agencies of foreign countries supported the largest share of funded research, followed by industry and foundations and other nonprofit organizations.

Appendix VI, Figure 30: Original Research Publications (n=84) on Medicinal Therapies for Nausea and Vomiting in Pregnant Women, by External Funding Source, 2006-2017



Notes: Eight countries were represented in the foreign government category, with only one country (Canada) supporting more than one published research project. NICHD and NCATS¹²⁰ were the only NIH ICs that were acknowledged.

¹¹⁹ [R01HD076313](https://projectreporter.nih.gov/project_info_description.cfm?aid=9267838&icde=36177337&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

(https://projectreporter.nih.gov/project_info_description.cfm?aid=9267838&icde=36177337&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

¹²⁰ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Research Gaps

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

Hypertensive Disorders

Introduction

High blood pressure (hypertension), whether chronic or associated with pregnancy, pose health risks for both the pregnant woman and fetus, with adverse effects that may persist well after delivery.

Hypertension is associated with an increased risk for pregnancy complications including preeclampsia (abrupt spike in blood pressure with signs of damage to another organ system, typically renal or liver), placental abruption (separation of the placenta from the wall of the uterus), GDM, and preterm birth. Unchecked preeclampsia can progress to eclampsia, seizures, coma, and death.¹²¹ Between 3 and 4 percent of pregnant women in the United States develop preeclampsia.¹²² CDC has reported that the overall rate of hypertensive disorders in pregnancy has increased substantially over the past 20 years.¹²³

Scientific Literature

The analysis identified 1,027 articles, published between January 2006 and July 2017, that related to medicinal therapies for hypertensive disorders in pregnant women and lactating women. Of these publications, 595 (58 percent) reported on original research.

Over the past decade, scientists have investigated the biological mechanisms of pregnancy-associated hypertensive disorders, identified possible targets and pathways for treatment, and identified and assessed potentially therapeutic compounds in animal models of hypertension in pregnancy. One group of researchers used a mouse model of pregnancy-associated hypertension to determine that hydralazine (an anti-hypertensive drug) increased the levels of tele-methylhistamine (a metabolite of histamine) in the blood during pregnancy. The finding suggested a potential mechanism of action for the

¹²¹ <https://www.nichd.nih.gov/health/topics/preeclampsia/Pages/default.aspx>

¹²² PMID 24201165 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=24201165>)

¹²³ <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-complications-data.htm>

drug.¹²⁴ Another group found that preeclamptic mice treated with injections of vascular endothelial growth factor did not have growth-restricted offspring, compared to mice with untreated preeclampsia.¹²⁵

A large proportion of research on disease and treatment outcomes of hypertensive disorders during pregnancy was case series and cohort studies. A case-control study in the United States and Canada found that both treated and untreated hypertensive disorders in pregnancy were associated with specific birth defects.¹²⁶ A cohort study using VA maternity benefit data found that women veterans had a higher risk of developing hypertensive disorders during pregnancy, compared to other women who delivered in the United States.¹²⁷

Almost a quarter (236 articles) of the literature on hypertensive disorders in pregnancy addressed vitamin or other supplement products. Of 71 RCTs of medicinal therapies for these disorders, more than 40 percent focused on vitamin or mineral supplements, including vitamin D, folic acid, selenium, and fish oil. An analysis of data from one clinical trial in a racially/ethnically diverse sample found that supplementation with vitamins C and E did not reduce pregnant women's risk of preeclampsia, regardless of genetic phenotype.¹²⁸ The results were generally consistent with other findings, although a few studies reported reductions in preeclampsia risk associated with use of various supplements.

Appendix VI, Figure 31, shows the pregnancy and lactation publications on medicinal therapies for hypertension, separately. Because preeclampsia is a common, pregnancy-specific condition, it was unsurprising that nearly all the pregnancy and lactation research for hypertensive disorders addressed pregnancy, not lactation.

¹²⁴ [PMID 28069864 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=28069864\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=28069864)

¹²⁵ [PMID 27996960 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=27996960\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=27996960)

¹²⁶ [PMID 25395267 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=25395267\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=25395267)

¹²⁷ [PMID 25090022 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=25090022\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=25090022)

¹²⁸ [PMID 23573260 \(https://www.ncbi.nlm.nih.gov/pubmed/23573260\)](https://www.ncbi.nlm.nih.gov/pubmed/23573260)

Appendix VI, Figure 31: Pregnancy-and Lactation Publications on Medicinal Therapies for Hypertensive Disorders, Shown Separately, by Publication Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Hypertension | 136 | 10 | 20 | 66 | 288 | 137 | 421 | 44 | 52 |
| Lactation | | | | | | | | | |
| Hypertension | 5 | 1 | 0 | 5 | 7 | 10 | 11 | 2 | 5 |

Current Research Activities

NIH supports an extensive portfolio of research on hypertensive disorders in pregnancy, with grants funded by NICHD, NHLBI, NINDS, NIGMS, NIDDK, and other ICs. Several research groups are assessing the role of genetic factors in preeclampsia.¹²⁹ Others are assessing long-term effects of hypertensive disorders in pregnancy and evaluating therapies.¹³⁰

Appendix VI, Figure 32, shows external funding sources acknowledged by original research articles on medicinal therapies for hypertensive disorders in pregnant women and lactating women. Of the 595 original research publications, 348 (58 percent) did not acknowledge any external funding source. National government agencies and nonprofit organizations in the United States and elsewhere were the primary funders, with little reported research funded by industry. Among NIH ICs, NICHD and NHLBI

¹²⁹ [R37HD0762853](https://projectreporter.nih.gov/project_info_description.cfm?aid=9305120&icde=36424680&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9305120&icde=36424680&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9305120&icde=36424680&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [P20GM109035](https://projectreporter.nih.gov/project_info_description.cfm?aid=9281774&icde=36424700&ddparam=&ddvalue=&ddsub=&cr=8&csb=default&cs=ASC&pball=;)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9281774&icde=36424700&ddparam=&ddvalue=&ddsub=&cr=8&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9281774&icde=36424700&ddparam=&ddvalue=&ddsub=&cr=8&csb=default&cs=ASC&pball=;)); [R01HD084628](https://projectreporter.nih.gov/project_info_description.cfm?aid=9269245&icde=36424718&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9269245&icde=36424718&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9269245&icde=36424718&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;))

¹³⁰ [K08DK101560](https://projectreporter.nih.gov/project_info_description.cfm?aid=9308945&icde=36424742&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9308945&icde=36424742&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9308945&icde=36424742&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [R01HL121527](https://projectreporter.nih.gov/project_info_description.cfm?aid=9198953&icde=36424812&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)

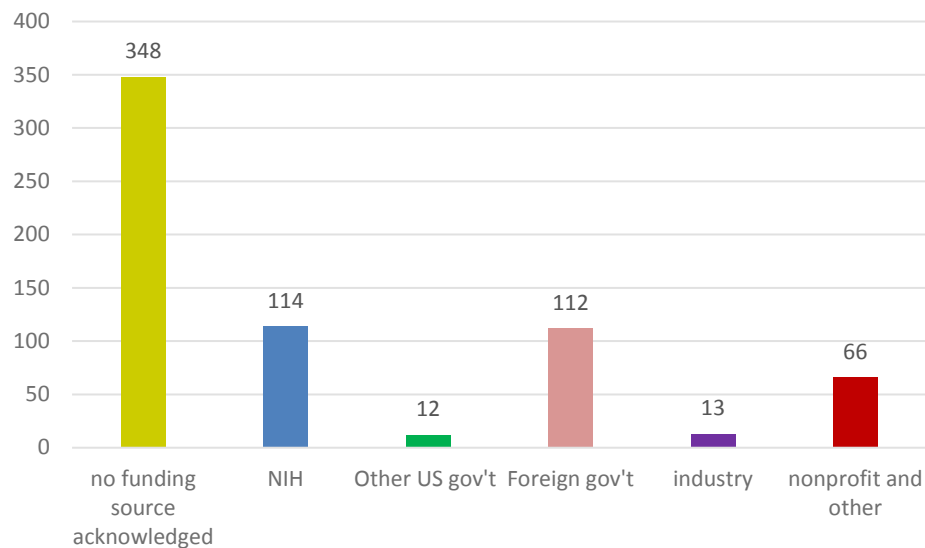
([https://projectreporter.nih.gov/project_info_description.cfm?aid=9198953&icde=36424812&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9198953&icde=36424812&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [F32HL129677](https://projectreporter.nih.gov/project_info_description.cfm?aid=9330244&icde=36424831&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9330244&icde=36424831&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9330244&icde=36424831&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [U54HD047891](https://projectreporter.nih.gov/project_info_description.cfm?aid=9310074&icde=36424848&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9310074&icde=36424848&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9310074&icde=36424848&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;))

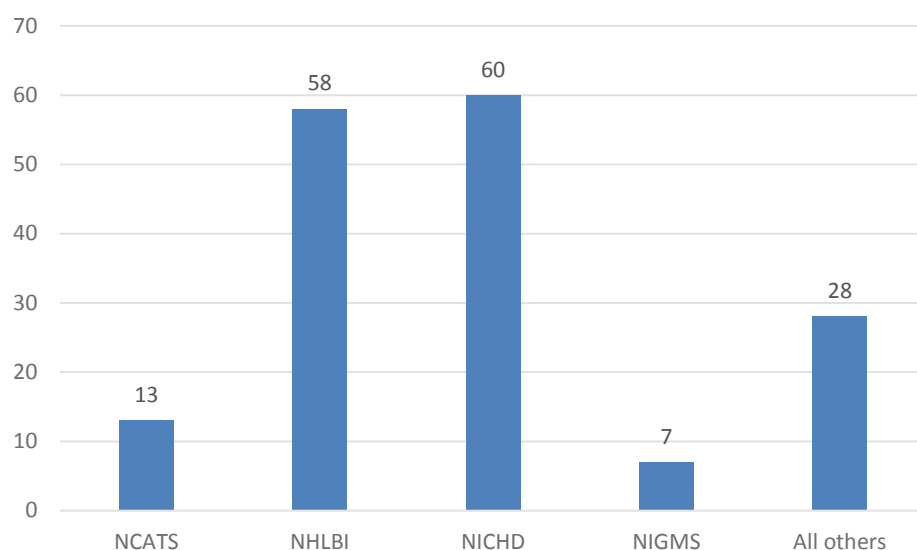
supported research reported in the largest number of publications, but multiple IC sponsorship was common.

Appendix VI, Figure 32: Original Research Publications (n=595) on Medicinal Therapies for Hypertensive Disorders in Pregnancy and Lactation, by External Funding Source, 2006-2017



Notes: A single publication will be reported in multiple categories if more than one type of funding source was acknowledged.

Original Research Publications on Medicinal Therapies for Hypertensive Disorders in Pregnancy and Lactation, by NIH IC, 2006-2017



Notes: Many articles with NIH funding credited multiple ICs¹³¹. A single publication will be counted in multiple categories when more than one IC is credited.

Research Gaps

Although the research community has continued to address hypertensive disorders in pregnancy, the search for more effective prevention therapies continues. Researchers have conducted studies of the effect of vitamins and other supplements on preeclampsia, with mixed results, and few studies have been available to describe the PK/PD of these substances when taken during pregnancy. The effect of hypertension medications on lactation and breast milk remains a substantial gap.

¹³¹ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Infectious Diseases

Introduction

Infections during pregnancy are common; one report of infection rates in a large registry “control” group indicated that nearly two-thirds (63 percent) of 4,967 women experienced at least one infection (respiratory, sexually transmitted, “fever,” urinary tract, others) during pregnancy.¹³² Infectious diseases in pregnant women commonly cause substantial maternal and neonatal morbidity and mortality, especially in low- and middle-income countries. Several maternal mechanical and pathophysiological changes and immune system adaptations that occur during pregnancy may elevate the severity of infection during pregnancy.¹³³ Infections including Zika, hepatitis B virus (HBV) tuberculosis (TB), toxoplasmosis, cytomegalovirus, malaria, group B streptococcus (GBS), and influenza are known risks for both the pregnant woman and fetus. Apart from the well-documented risk of HIV transmission via breast milk, few data appear to be available on the prevalence or effects of infection among lactating women.

Scientific Literature

The analysis identified 1,227 articles, published between January 2006 and July 2017, that are related to medicinal therapies for infectious diseases in pregnant women and lactating women. Appendix VI, Figure 33, shows the literature by type of research (Vaccines are addressed separately in this analysis).

Appendix VI, Figure 33: Publications on Medicinal Therapies for Infectious Diseases in Pregnant Women and Lactating Women, by Research Type, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|--------------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Infection (all) | 78 | 44 | 40 | 62 | 363 | 97 | 420 | 23 | 100 |

A majority of the publications (687, or 56 percent) reported original research. Although case series and cohort studies were the most common type of research, there were 62 RCTs. Many articles focused on maternal-child transmission of infection, both for HIV and other conditions. For example, a case-control

¹³² PMID 19086018 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=19086018>)

¹³³ PMID 25207782 (<https://www.ncbi.nlm.nih.gov/pubmed/25207782>)

study of maternal to child transmission of HBV in China found that family history of HBV infection, intrahepatic cholestasis (a liver disorder in pregnant women), and premature rupture of membranes were risk factors for perinatal transmission of HBV. HBV immunoglobulin injections for HBV-positive pregnant women and systemic treatment prevented the infection in newborns.¹³⁴ Scientists also used cohort studies to investigate risks both of infection and its treatment, for the pregnant woman and fetus. For example, researchers found elevated biomarkers for oxidative stress in Nigerian women with malaria, whether or not they were treated for the infection.¹³⁵ Another RCT compared two treatment regimens for malaria in pregnant women.¹³⁶

Forty-one (about 3 percent) of the publications focused on vitamin or other supplements. About half of the publications were original research, and 7 were RCTs, focused on vitamins or other supplements, including “natural” products. For example, researchers in Finland assessed the impact of black currant seed oil on immune function and the composition of breast milk.¹³⁷ Publications related to various supplements were more likely to focus on urinary tract infections or mastitis, compared to publications related to drugs.

Many studies in the literature focused on medications used for a variety of infections or focused on infection symptoms (such as fever). Because so many different specific infections occur in pregnant women, there were relatively fewer studies for individual infections. However, TB, UTI, and parasitic infections were addressed even less frequently. Appendix VI, Figure 34, shows the distribution of publications by specific infection and type of article.

¹³⁴ [PMID 21987612 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=21987612\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=21987612)

¹³⁵ [PMID 21495615 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=21495615\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=21495615)

¹³⁶ [PMID 27326859 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=27326859\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=27326859)

¹³⁷ [PMID 23980846 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=23980846\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=23980846)

Appendix VI, Figure 34: Publications on Medicinal Therapies for Infections in Pregnant Women and Lactating Women, by Infection and Type of Research, 2006-2017

| Infections | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|------------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| CMV | 3 | 0 | 4 | 2 | 7 | 9 | 21 | 0 | 6 |
| Group B strep | 4 | 0 | 3 | 2 | 19 | 5 | 18 | 2 | 8 |
| Hepatitis B | 6 | 1 | 2 | 2 | 42 | 6 | 21 | 1 | 5 |
| HIV/AIDS | 16 | 7 | 3 | 14 | 44 | 6 | 54 | 2 | 14 |
| Influenza | 13 | 2 | 15 | 2 | 80 | 26 | 86 | 15 | 33 |
| Malaria | 4 | 12 | 1 | 5 | 21 | 6 | 30 | 2 | 3 |
| Parasites | 6 | 1 | 2 | 0 | 8 | 10 | 22 | 0 | 3 |
| Pertussis | 6 | 1 | 2 | 0 | 8 | 4 | 8 | 0 | 2 |
| Rubella | 2 | 0 | 3 | 0 | 22 | 0 | 4 | 0 | 1 |
| Tetanus | 0 | 0 | 0 | 0 | 6 | 4 | 4 | 0 | 2 |
| TB | 0 | 0 | 0 | 0 | 3 | 2 | 2 | 0 | 0 |
| UTI | 1 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 1 |
| Zika | 6 | 0 | 0 | 0 | 0 | 2 | 13 | 9 | 2 |

As with other conditions, most published research on medicinal therapies for infectious diseases in pregnant women and lactating women focused on pregnancy, not lactation. Appendix VI, Figure 35, shows pregnancy-related and lactation-related publications, by type and infection, separately.

Appendix VI, Figure 35: Pregnancy and Lactation Publications on Medicinal Therapies for Infectious Diseases, Shown Separately, by Infection and Type of Research, 2006-2017

| Condition | Basic | PK/PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Pregnancy only | | | | | | | | | |
| CMV | 3 | 0 | 4 | 2 | 7 | 9 | 21 | 0 | 5 |
| Group B strep | 4 | 0 | 2 | 1 | 17 | 1 | 10 | 1 | 6 |
| Hepatitis B | 4 | 1 | 2 | 2 | 40 | 6 | 13 | 0 | 3 |
| HIV/AIDS | 16 | 7 | 3 | 11 | 38 | 6 | 48 | 2 | 11 |
| Influenza | 12 | 2 | 15 | 2 | 78 | 26 | 84 | 14 | 32 |
| Malaria | 4 | 12 | 1 | 5 | 21 | 6 | 29 | 2 | 3 |
| Parasites | 6 | 1 | 2 | 0 | 8 | 10 | 21 | 0 | 3 |
| Pertussis | 6 | 1 | 2 | 0 | 8 | 4 | 7 | 0 | 1 |
| Rubella | 2 | 0 | 2 | 0 | 22 | 0 | 4 | 0 | 1 |
| Tetanus | 0 | 0 | 0 | 0 | 6 | 4 | 2 | 0 | 2 |
| TB | 0 | 0 | 0 | 0 | 3 | 2 | 2 | 0 | 0 |
| UTI | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| Zika | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Lactation | | | | | | | | | |
| CMV | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Group B strep | 0 | 0 | 1 | 1 | 2 | 4 | 8 | 1 | 2 |
| Hepatitis B | 2 | 0 | 0 | 0 | 2 | 0 | 8 | 0 | 0 |
| HIV/AIDS | 0 | 0 | 0 | 3 | 6 | 0 | 6 | 0 | 3 |
| Influenza | 1 | 0 | 0 | 0 | 2 | 0 | 2 | 1 | 1 |
| Malaria | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Parasites | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Pertussis | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Rubella | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tetanus | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| TB | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| UTI | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| Zika | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Current Research Activities

NIH-supported projects are addressing a variety of infections in pregnancy, including HIV/AIDS, malaria, hepatitis C virus, and listeria.¹³⁸ Some of the research focuses on how the placenta can defend the fetus against infection.

Appendix VI, Figure 36, shows funding sources acknowledged by original research articles on medicinal therapies for infectious diseases in pregnant women and lactating women. A total of 411 publications, or 60 percent of the total, did not acknowledge any external funding source. Foreign governments and NIH accounted for nearly 200 publications. Of the NIH ICs, NIAID and NICHD accounted for the most publications.

¹³⁸ [R01HD080485](#)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9065981&icde=36382259&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9065981&icde=36382259&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [R01HD086124](#)

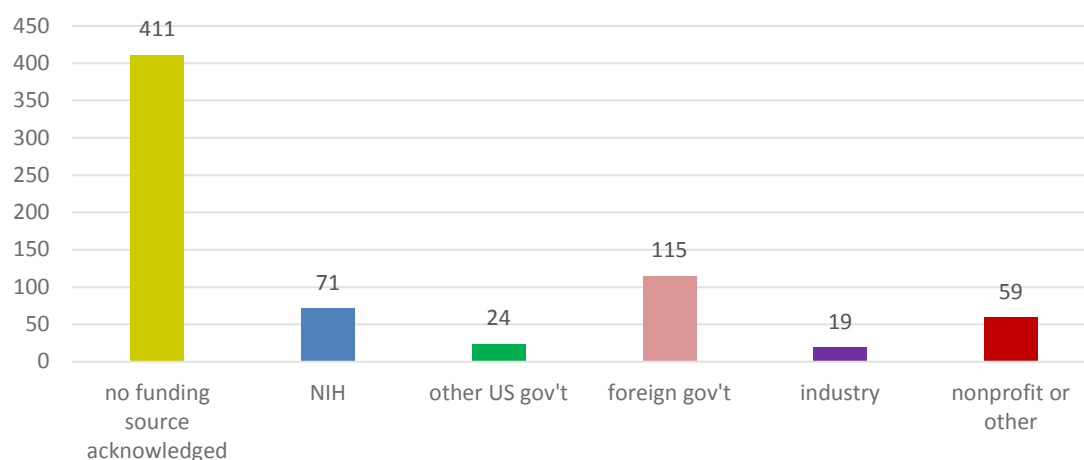
([https://projectreporter.nih.gov/project_info_description.cfm?aid=9199591&icde=36382263&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9199591&icde=36382263&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [R01HD075549](#)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9212174&icde=36382264&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9212174&icde=36382264&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [R21HD090635](#)

([https://projectreporter.nih.gov/project_info_description.cfm?aid=9234679&icde=36382265&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9234679&icde=36382265&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;)); [R01MH113478](#)

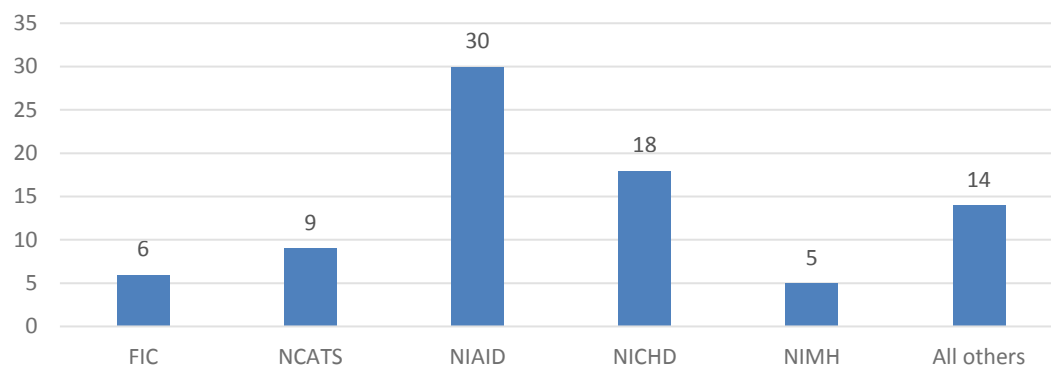
([https://projectreporter.nih.gov/project_info_description.cfm?aid=9483779&icde=40658921&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9483779&icde=40658921&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=;))

Appendix VI, Figure 36: Original Research Publications (n=689) on Medicinal Therapies for Infections in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.

Original Research Publications on Medicinal Therapies for Infections in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Many articles with NIH funding credited multiple ICs¹³⁹. A single publication may be reported in multiple categories if multiple funding sources were cited.

¹³⁹ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Research Gaps

There is very limited scientific information for pregnant women and lactating women and their providers on how and whether to treat infectious diseases during pregnancy and lactation. Some common infections worldwide, such as tuberculosis, are clearly understudied in pregnant women and lactating women. Few original research publications assessed the impact of untreated infection. The effect of infection and its treatment on breast milk and lactation is still largely unknown.

Kidney Disorders

Introduction

Kidney disease can occur in pregnancy either as a result of pregnancy complications (including preeclampsia), or independently. Women with chronic kidney disorders who become pregnant often experience a worsening of their condition during pregnancy and need to be monitored closely.

Scientific Literature

The analysis identified 449 articles published between January 2006 and July 2017 that related to medicinal therapies for kidney disorders in pregnant women and lactating women. Of these, 64 publications (about 14 percent) related to research on vitamins, minerals, or other supplements. Appendix VI, Figure 37, shows the literature by publication type. Publications that were primarily about preeclampsia or disorders covered elsewhere (such as autoimmune diseases) are not included in this total.

Appendix VI, Figure 37: Publications on Medicinal Therapies for Kidney Disorders in Pregnant Women and Lactating Women, by Type of Research, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|-----------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Kidney | 42 | 3 | 21 | 12 | 112 | 25 | 161 | 18 | 55 |

Of the articles, 245 (55 percent) reported on original research. The majority of articles were either case reports or reviews, although observational case series were also common. There were few reports of RCTs in pregnant women and lactating women with kidney disorders. Appendix VI, Figure 38, shows the pregnancy and lactation publications, by type of research, separately. Lactation was very infrequently the subject of kidney-related research.

Appendix VI, Figure 38: Pregnancy and Lactation Publications on Medicinal Therapies for Autoimmune Disorders, Shown Separately, by Disorder and Research Type, 2006-2017

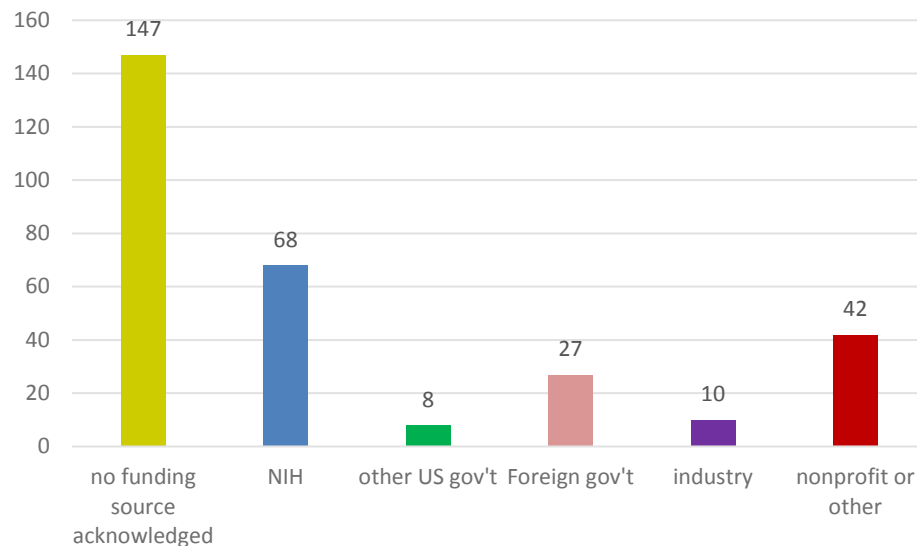
| Condition | Basic | PK/PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Pregnancy only | | | | | | | | | |
| Kidney | 40 | 3 | 21 | 12 | 112 | 23 | 155 | 18 | 55 |
| Lactation | | | | | | | | | |
| Kidney | 2 | 0 | 0 | 0 | 0 | 2 | 6 | 0 | 1 |

Current Research Activities

NIH supports few projects related to kidney disorders in pregnancy, and most are only indirectly related to medication. For example, a NIH-funded study of kidney disorders in general included several women during pregnancy, but the study was not focused on pregnancy or on medication, but on the effect of diet on kidney disorders.

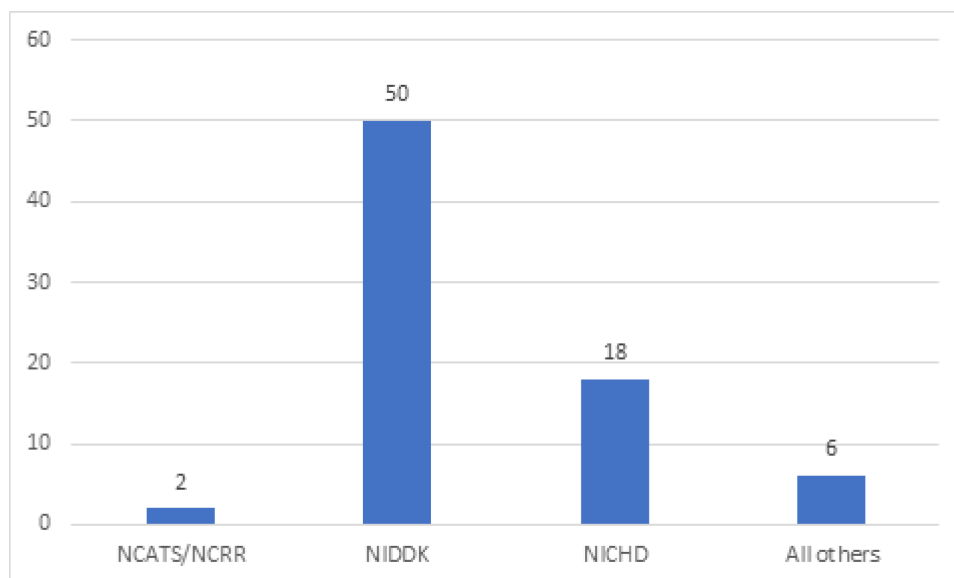
Appendix VI, Figure 39 shows external funding sources acknowledged by original research articles, published from 2006-2017, on autoimmune disorders in pregnant women and lactating women. Of the 245 original research publications, fewer than one third (31 percent) acknowledged at least one external funding source.

Appendix VI, Figure 39: Original Research Publications (n=245) on Medicinal Therapies for Kidney Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other U.S. government agencies included CDC, DoD, and AHRQ.

Original Research Publications on Medicinal Therapies for Kidney Disorders in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Many articles with NIH funding credited multiple ICs¹⁴⁰. A single publication may be reported in multiple categories if multiple funding sources were cited.

Low Milk Supply

Introduction

Breastfeeding is strongly recommended to promote infant health. However, many women perceive that their milk supply is too low, and there may be a clinical reason that milk production or release is inadequate. Insufficient milk supply is one of the most commonly cited reasons for early cessation or decreased exclusivity in women who have initiated breastfeeding.¹⁴¹ However, it is often unclear whether milk production is insufficient, or there is a problem with the breastfeeding process, such as insufficient stimulation.

¹⁴⁰ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

¹⁴¹ [PMID 19094151](https://pubmed.ncbi.nlm.nih.gov/19094151/) (<https://www.ncbi.nlm.nih.gov/pubmed/19094151>)

Scientific Literature

The analysis identified 48 articles, published between January 2006 and July 2017, that are related to medicinal therapies for low breast milk supply. Appendix VI, Figure 40, shows the distribution of publications by type of research.

Appendix VI, Figure 40: Publications on Medicinal Therapies for Low Milk Supply in Lactating Women, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Low milk supply | 1 | 0 | 0 | 8 | 8 | 3 | 18 | 6 | 4 |

Of the different types of research reported, eight were RCTs of various medications. Three trials, all conducted overseas, focused on the drug domperidone. Opinion is mixed on domperidone's use in lactation because of reported risk of cardiac arrhythmias in trials of the drug for gastrointestinal disorders. It is not approved for use in the United States for any purpose, including lactation. The FDA issued a domperidone import alert in 2004 and updated it in 2012, and also issued a public safety warning against the drug's use for lactation. The most recent clinical studies of domperidone found that mothers in the intervention group experienced an increase in milk supply, albeit a modest gain.¹⁴² A previous study found larger reported gains in milk supply as well as no changes to the composition of breast milk.¹⁴³ In a small crossover trial, researchers found that milk supply increased for two-thirds of the women in the domperidone group.¹⁴⁴ None of the studies assessed longer-term effects or addressed possible cardiac concerns.

¹⁴² [PMID 28107101](https://www.ncbi.nlm.nih.gov/pubmed/28107101) (<https://www.ncbi.nlm.nih.gov/pubmed/28107101>)

¹⁴³ [PMID 20008425](https://www.ncbi.nlm.nih.gov/pubmed/20008425) (<https://www.ncbi.nlm.nih.gov/pubmed/20008425>)

¹⁴⁴ [PMID 18507654](https://www.ncbi.nlm.nih.gov/pubmed/18507654) (<https://www.ncbi.nlm.nih.gov/pubmed/18507654>)

Two other RCTs provided data showing that recombinant human prolactin increased milk volume and induced changes in milk composition similar to those that occur during normal lactogenesis (breast milk production).¹⁴⁵ The remaining four trials included herbal therapies or alternative Chinese medicine.¹⁴⁶

Current Research Activities

The majority of NIH's portfolio in lactation research is related to the composition and protective effects of human breast milk, maternal and infant microbiome, immunity, and related areas. However, NIH also funds several grants related to promoting breastfeeding, and this research may directly or indirectly address perceived low milk supply. For example, researchers supported by NINR are testing a mobile, semi-automated text message-based intervention, designed for mothers without prior breastfeeding experience, to prevent or mitigate inaccurate perceptions of low or insufficient milk supply.¹⁴⁷

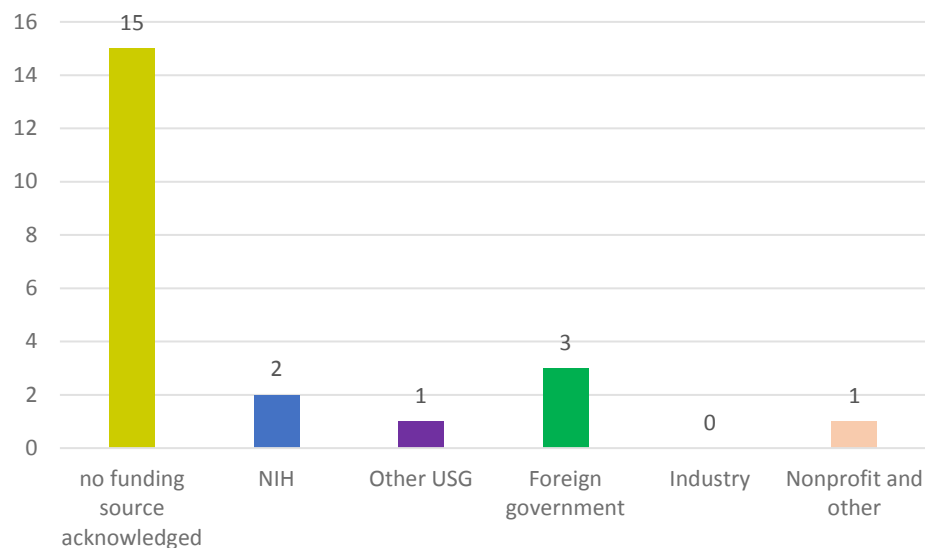
Appendix VI, Figure 41, shows external funding sources acknowledged by original research articles, published 2006-2017, on insufficient milk supply. Of the 20 original research publications, 75 percent (15 articles) did not acknowledge an external funding source. Canadian and Chinese government agencies funded two and three studies, respectively. Two NIH ICs, NIDDK and NCATS, funded research on low milk supply, resulting in one publication each.

¹⁴⁵ PMID 20718766 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=20718766>); PMID 21262884 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=21262884>)

¹⁴⁶ PMID 18652318 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18652318>); PMID 26430522 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26430522>); PMID 28569619 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=28569619>)

¹⁴⁷ R00NR015106 (https://projectreporter.nih.gov/project_info_description.cfm?aid=9343055&icde=36186969&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

Appendix VI, Figure 41: Original Research Publications (n=20) on Medicinal Therapies for Low Milk Supply, by External Funding Source, 2006-2017



Notes: if multiple sources are acknowledged, a single publication may be classified in more than one category.

Research Gaps

Limited research is available on insufficient breast milk supply. Although various supplement products may be widely used to promote lactation, very few studies have been conducted on the effectiveness of these remedies and their safety remains largely unaddressed.

Mental Health

Introduction

Many women experience mental health disorders during pregnancy and the postpartum period, with onset either preceding pregnancy or emerging during pregnancy or subsequently. For example, as many as 1 in 9 women experience depression during pregnancy. Pre-pregnancy mental illness, including

bipolar disorder, schizophrenia, or other conditions, may flare up during pregnancy.¹⁴⁸ Women who rely on medication to treat these conditions face a dilemma when they become pregnant. There is little data to establish whether the medications for the disorders are safe during pregnancy, yet untreated mental illness may also pose risks for both the woman and the developing fetus.¹⁴⁹

Scientific Literature

The analysis identified 1,479 articles, published between January 2006 and July 2017, that related to medicinal therapies for mental health disorders in pregnant women and lactating women. Appendix VI, Figure 42, shows the literature by type of research.

Appendix VI, Figure 42: Publications on Medicinal Therapies for Mental Health in Pregnant Women and Lactating Women, by Research Type, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|------------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Mental health | 87 | 10 | 34 | 15 | 257 | 216 | 709 | 122 | 29 |

There were many reviews, editorials, comments, and case reports discussing the safety of antidepressant and antipsychotic medications during pregnancy. A significant number of basic science studies were conducted, using animal models to assess how prenatal exposure to antidepressants (particularly selective serotonin reuptake inhibitors, SSRIs) may affect the offspring.¹⁵⁰ Researchers have investigated potential effects on neurodevelopment and cardiovascular development, among other systems. However, there is much more limited evidence of effects in human subjects.

A number of studies have leveraged large-scale population databases to identify relationships between prenatal exposure to medications and outcomes in the offspring. These cohort and population studies

¹⁴⁸ <https://www.cdc.gov/features/maternal-depression/index.html> ; <http://www.nhs.uk/Conditions/pregnancy-and-baby/pages/mental-health-problems-pregnant.aspx>

¹⁴⁹ PMID 28237726 (<https://www.ncbi.nlm.nih.gov/pubmed/28237726>)

¹⁵⁰ PMID 18700684 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18700684>); PMID 18716672 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18716672>); PMID 18996131 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18996131>); PMID 19384594 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=19384594>)

have shown mixed results. Several studies of Swedish and Norwegian data found no increased risk to the offspring from exposure to SSRIs.¹⁵¹ However, other studies have found adverse outcomes. A study of data from other countries found an increased risk of pulmonary hypertension in the offspring for children who were prenatally exposed to SSRIs,¹⁵² and a Canadian study suggested a possible increased risk of low birth weight associated with these antidepressants.¹⁵³

Of the 1,479 publications, 53 (about 4 percent) related to vitamin or other supplements. Although a small proportion of the overall total, these publications were disproportionately represented in RCTs. For example, one small trial suggested that supplements with omega 3 fatty acids may have some benefits in treating antenatal depression.¹⁵⁴

Many of the human studies in this literature focus on specific medications rather than specific disorders.¹⁵⁵ Of the research that focused on disorders, the most common was major depression. For the most common mental health disorders in the literature, Appendix VI, Figure 43, shows the distribution of publications by type of research.

Appendix VI, Figure 43: Publications on Medicinal Therapies for Mental Health in Pregnant Women and Lactating Women, by Disorder and Type of Research, 2006-2017

| Condition | Diagnosis | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|------------------|---------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Mental Health | Anxiety | 17 | 0 | 3 | 2 | 31 | 33 | 82 | 7 | 3 |
| | Bipolar | 1 | 1 | 1 | 0 | 15 | 21 | 67 | 10 | 0 |
| | Depression | 23 | 5 | 22 | 8 | 164 | 44 | 423 | 64 | 20 |
| | Schizophrenia | 11 | 0 | 1 | 0 | 6 | 38 | 43 | 1 | 0 |

¹⁵¹ PMID 17216624 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=17216624>); PMID 22367660 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=22367660>)

¹⁵² PMID 22240235 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=22240235>)

¹⁵³ PMID 16894066 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=16894066>)

¹⁵⁴ PMID 18370571 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18370571>)

¹⁵⁵ For example, SSRIs, in addition to treating major depression are used by themselves or in conjunction with other medications for substance use disorders, psychosis, schizophrenia, certain neurological disorders, smoking cessation, and other indications.

Appendix VI, Figure 44, shows pregnancy and lactation publications, by research type, separately. Lactation was only infrequently the subject of this research.

Appendix VI, Figure 44: Pregnancy and Lactation Publications on Medicinal Therapies for Mental Health Disorders, Shown Separately, by Disorder and Type of Research, 2006-2017

| Condition | Basic | PK/PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Pregnancy only | | | | | | | | | |
| Anxiety | 16 | 0 | 3 | 2 | 30 | 32 | 75 | 7 | 3 |
| Bipolar | 1 | 1 | 1 | 0 | 15 | 16 | 52 | 9 | 0 |
| Depression | 21 | 4 | 21 | 8 | 154 | 34 | 358 | 57 | 18 |
| Schizophrenia | 9 | 0 | 1 | 0 | 6 | 30 | 39 | 1 | 0 |
| Lactation | | | | | | | | | |
| Anxiety | 1 | 0 | 0 | 0 | 1 | 1 | 7 | 0 | 0 |
| Bipolar | 0 | 1 | 0 | 0 | 0 | 5 | 15 | 1 | 0 |
| Depression | 2 | 1 | 1 | 0 | 10 | 10 | 65 | 7 | 2 |
| Schizophrenia | 0 | 0 | 0 | 0 | 0 | 8 | 4 | 0 | 0 |

Current Research Activities

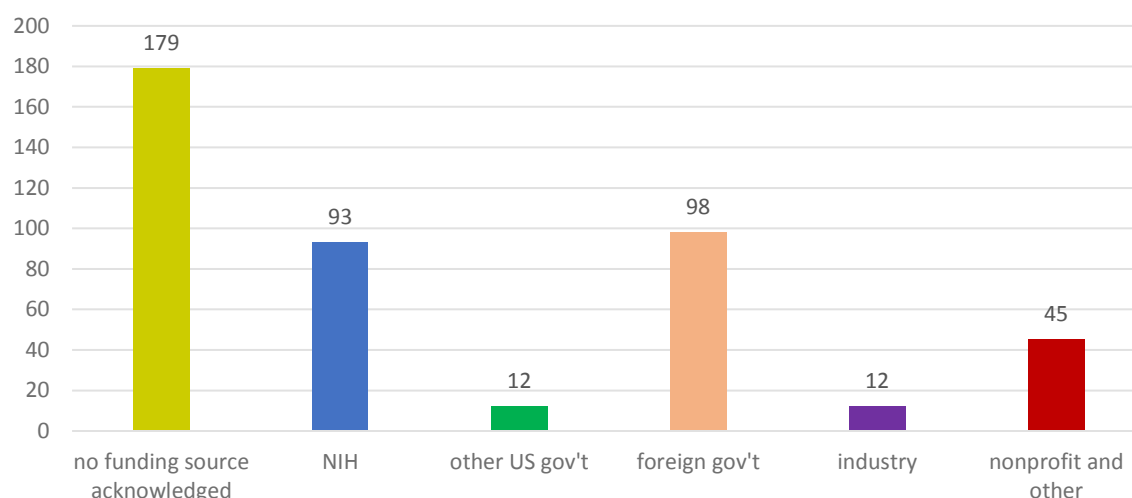
NIH supports research on mental health disorders in pregnant women and lactating women that focuses largely on perinatal and postpartum depression. Moreover, several projects relate to sleep disorders and therapies designed to address circadian rhythms and sleep patterns to improve symptoms in pregnant and postpartum women with depression.¹⁵⁶

Appendix VI, Figure 45, shows external funding sources acknowledged by original research articles published from 2006-2017 on research on medicinal therapies for mental health disorders in pregnant women and lactating women. Of the 432 original research publications, 253 (59 percent) acknowledged at least one external funding source.

¹⁵⁶ [R01HL120354](#)

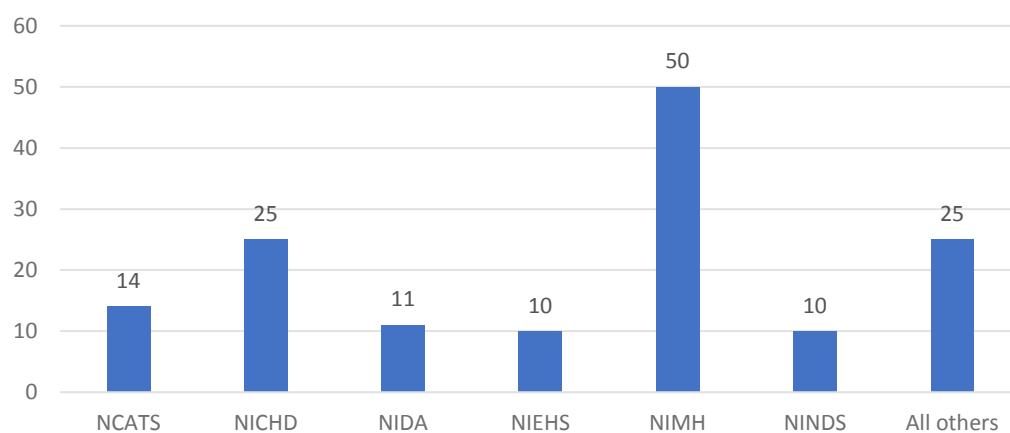
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9487294&icde=39887521&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC&pball)

Appendix VI, Figure 45: Original Research Publications (n=432) on Medicinal Therapies for Mental Health Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.

Original Research Publications on Medicinal Therapies for Mental Health Disorders in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs¹⁵⁷ included NCI, NHLBI, NIA, NIAAA, NIAID, NIDDK, NIGMS, NIH OD, NLM, and NINR. A single publication may be reported in multiple categories if multiple funding sources were cited.

¹⁵⁷ Figures for NCATS include relevant publications supported in whole or in part by the CTSA. Some CTSA were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSA are also included in the NCATS totals.

Research Gaps

Research on medicinal therapies for mental health disorders in pregnant women and lactating women remains limited. Few studies on PK/PD of commonly used medications have been published in the past decade, and few RCTs have been reported. Mental health disorders other than depression, and drugs other than antidepressants, remain especially understudied.

Pain

Introduction

Pregnant women often experience both acute and chronic pain, including that associated with childbirth, pregnancy-associated back pain, pre-existing chronic conditions, or short-term injuries (See CNS disorders for migraine and other headache disorders). Pain left untreated during pregnancy can have negative effects on both mother and offspring, but pain-relieving medications may also have negative consequences, including blood thinning that can initiate or worsen pregnancy complications, maternal dependence and/or neonatal opioid withdrawal syndrome (NOWs).¹⁵⁸

Scientific Literature

Analysis identified 1,188 articles, published between January 2006 and July 2017, that are related to medicinal therapies for pain relief in pregnant women and lactating women. Appendix VI, Figure 46, shows the distribution of publications by type of research.

Appendix VI, Figure 46: Publications on Medicinal Therapies for Pain in Pregnant Women and Lactating Women, by Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pain | 32 | 14 | 20 | 123 | 252 | 257 | 419 | 28 | 43 |

A total of 484 articles represented original research (41 percent of the total). Case series or cohort studies and RCTs were relatively common. The large majority of publications focused on pain during labor and delivery and the impact of anesthesia on women and their offspring. A U.K. trial compared the epidural anesthesia with a single local anesthetic (ropivacaine) to a combination of the local anesthetic

¹⁵⁸ [PMID 26527601](https://pubmed.ncbi.nlm.nih.gov/26527601/) (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26527601>)

ropivacaine and an opioidergic analgesic, sufentanil. The results showed that the single local anesthetic produced comparable pain relief at different stages of labor, with fewer side effects and lower cost.¹⁵⁹ In an Australian clinical trial to compare two analgesic drugs, fentanyl and pethidine, for labor pain. Fentanyl resulted in greater patient satisfaction, less sedation, shorter labor, fewer nursery admissions, and fewer difficulties in establishing breastfeeding.¹⁶⁰ Twenty-six publications addressed vitamins and other supplements for pregnant women with pain. Of these, 40 were original research articles.

Appendix VI, Figure 47, shows the pregnancy lactation-related publications, by type of research, separately. Almost all the pregnancy and lactation research addressed pregnancy, not lactation.

Appendix VI, Figure 47: Pregnancy and Lactation Publications on Medicinal Therapies for Pain, Shown Separately, by Condition and Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Pain | 31 | 12 | 20 | 120 | 242 | 251 | 404 | 26 | 41 |
| Lactation | | | | | | | | | |
| Pain | 1 | 2 | 0 | 3 | 10 | 6 | 15 | 2 | 2 |

Current Research Activities

Current NIH-funded studies include an effort to develop cognitive behavioral therapy approaches to help reduce chronic pain and opioid use in pregnant women, and an RCT to optimize management of the second stage of labor.¹⁶¹

Appendix VI, Figure 48, shows external funding sources acknowledged by original research articles published from 2006-2017 on pain in pregnant women and lactating women. A total of 337 articles (69 percent) did not acknowledge any external funding source. Foundations and other nonprofit organizations supported the highest number of publications, followed by foreign governments and the

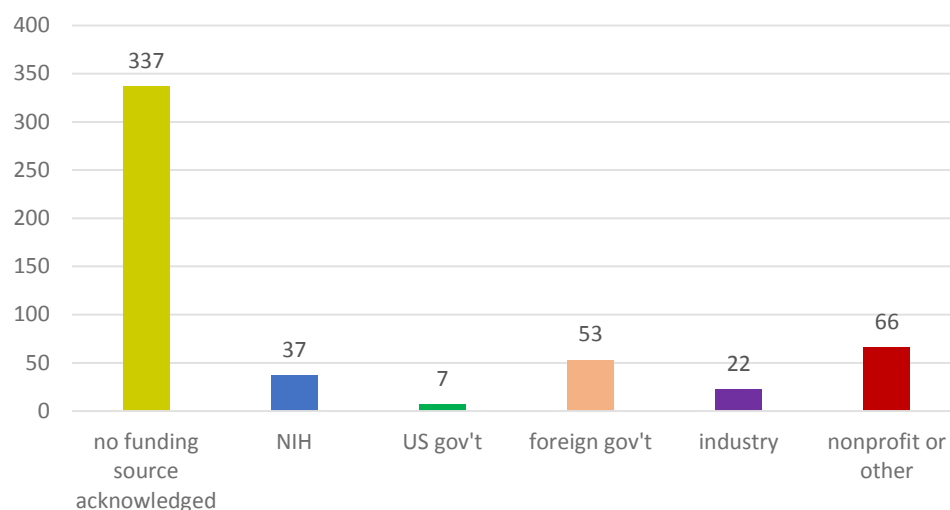
¹⁵⁹ PMID 26512604 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26512604>)

¹⁶⁰ PMID 25558983 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=25558983>)

¹⁶¹ K23DA039318
[https://projectreporter.nih.gov/project_info_description.cfm?aid=9233984&icde=36337141&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=\); U01HD077384](https://projectreporter.nih.gov/project_info_description.cfm?aid=9233984&icde=36337141&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=); U01HD077384)
[https://projectreporter.nih.gov/project_info_description.cfm?aid=9093815&icde=36337160&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=\)](https://projectreporter.nih.gov/project_info_description.cfm?aid=9093815&icde=36337160&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=))

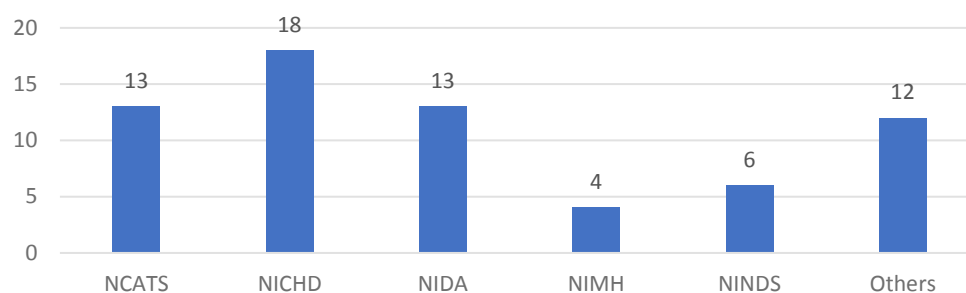
NIH. Among NIH ICs funding this research, NCATS, NICHD, and NIDA supported the greatest number of publications.

Appendix VI, Figure 48: Original Research Publications (n=484) on Medicinal Therapies for Pain in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.

Original Research Publications on Medicinal Therapies for Pain in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs¹⁶² included NIDDK, NIEHS, NIA, NIGMS, and the NIH OD. A single publication may be reported in multiple categories if multiple funding sources were cited.

¹⁶² Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

Research Gaps

Although there have been a substantial number of publications over the last decade about pain and pregnancy, most of these have focused on childbirth pain specifically. However, many pregnant women have chronic pain from pre-existing conditions, as well as pregnancy-associated back, pelvic, and other pain. Few studies have been conducted to describe the effect of pain medications on lactation. Moreover, although many pregnant women try various supplement products to alleviate pain-related conditions, few studies have assessed the efficacy or safety of these therapies.

Preterm Birth

Introduction

Preterm birth, before fetal maturation is complete, poses risks of acute or long-lasting health and/or developmental problems for a child, even if birth is just a few weeks short of full-term pregnancy. The brain, lungs, and liver, for example, need the final weeks of pregnancy to develop fully. In 2013, about one third (36 percent) of infant deaths in the United States were due to preterm-related causes, and preterm newborns are at risk for breathing problems, feeding difficulties, cerebral palsy, developmental delay, and/or impaired vision or hearing.¹⁶³ The adverse effects of preterm births may take an emotional toll on families and impose financial burdens. Although rates of preterm birth in the United States have declined over the last decade, nearly 10 percent of infants still arrive too early.¹⁶⁴ Preterm birth is a global public health problem and is especially prevalent in low-income countries, where preterm infants face even greater risks because of very limited access to advanced medical care.

Scientific Literature

The analysis identified 1,792 articles, published between January 2006 and July 2017, related to medicinal therapies for preterm birth. Appendix VI, Figure 49, shows the distribution of publications by type of research.

¹⁶³ <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm>

¹⁶⁴ <https://www.cdc.gov/mmwr/volumes/65/wr/mm6543a1.htm>

Appendix VI, Figure 49: Publications on Medicinal Therapies for Preterm Birth, by Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|---------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Preterm birth | 159 | 22 | 40 | 193 | 419 | 121 | 633 | 109 | 96 |

The largest number of preterm birth publications were reviews, but more than half (929, or 52 percent) were original research, including RCTs, basic science or mechanistic studies, and case series or cohort studies, conducted in the United States and elsewhere. Nearly 10 percent (173) of the articles reported studies on various supplements to prevent preterm birth. Of these, 55 percent (95) were research articles. Compared to articles on drug therapies, a slightly higher percent of articles on non-drug therapies reported on RCTs (14 percent, compared to 10 percent overall). Very few articles on non-drug therapies concerned basic research or PK/PD.

Appendix VI, Figure 50, shows the pregnancy and lactation-related publications, by type, separately. Because preterm birth is a pregnancy-specific condition, it was unsurprising that nearly all the pregnancy- and lactation-related research for preterm birth involves pregnancy only, and not lactation.

Appendix VI, Figure 50: Pregnancy and Lactation on Medicinal Therapies for Preterm Birth, Shown Separately, by Type of Research, 2006-2017

| Condition | Basic | PK/PD | Pop/DB | RCT | Case series | Case Reports | Reviews | Edit/Comment | Other |
|-----------------------|-------|-------|--------|-----|-------------|--------------|---------|--------------|-------|
| Pregnancy only | | | | | | | | | |
| Preterm birth | 158 | 22 | 40 | 193 | 416 | 121 | 623 | 109 | 96 |
| Lactation | | | | | | | | | |
| Preterm birth | 1 | 0 | 0 | 0 | 3 | 0 | 10 | 0 | 0 |

Current Research Activities

NIH supports research on preterm birth, focused on therapies to prevent early delivery. For example, NICHD and the NIH OD currently support an assessment of whether DHA supplementation (an essential

omega 3 fatty acid) in early pregnancy can reduce the risk of preterm birth.¹⁶⁵ Another NICHD-funded study is examining the PK and optimal dosing of betamethasone, a corticosteroid often used in pregnant women at high risk of preterm birth, to improve fetal lung development.¹⁶⁶ Studies funded by NIMHD and NINR are exploring possible mechanisms (e.g. microbiome, epigenetic) underlying racial and ethnic disparities in preterm birth.¹⁶⁷ Basic understanding of mechanisms underlying disorders is an essential preliminary step in developing effective therapies.

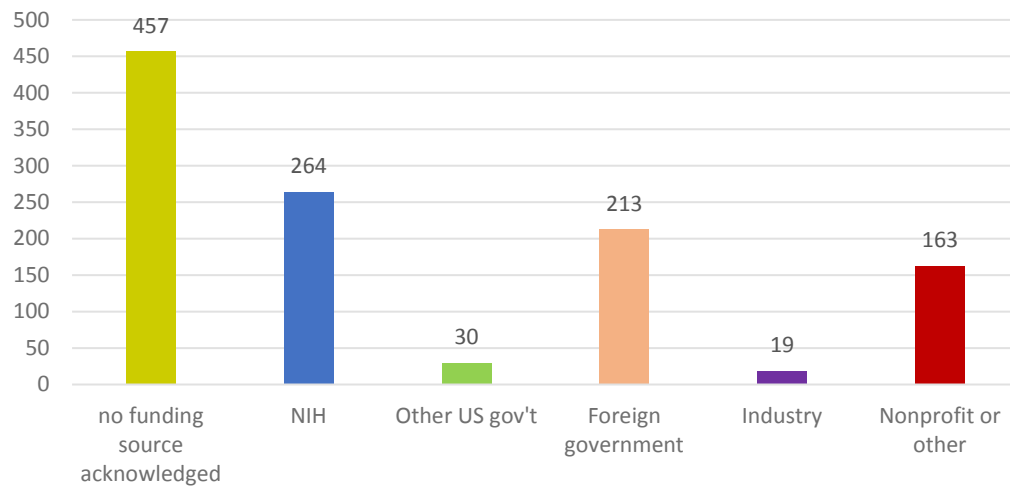
Appendix VI, Figure 51, shows external funding sources acknowledged by original research articles, published from 2006-2017, on medicinal therapies for preterm birth. Of the 929 original research publications, 49 percent (457 articles) did not acknowledge an external funding source. Government agencies and nonprofit organizations in the United States and elsewhere supported the research. Little industry support was reported, but several reported studies were funded by European and multinational companies that manufacture prenatal vitamins and dietary supplements. Among NIH ICs, NICHD supported by far the largest number of research projects reported in the articles. Still, 22 NIH ICs plus the NIH Office of the Director were acknowledged in this literature, with several acknowledging more than one NIH IC.

¹⁶⁵ [R01HD083292](https://projectreporter.nih.gov/project_info_description.cfm?aid=9207090&icde=36269125&ddparam=&ddvalue=&ddsub=&csr=2&csb=default&cs=ASC&pball=)
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9207090&icde=36269125&ddparam=&ddvalue=&ddsub=&csr=2&csb=default&cs=ASC&pball=)

¹⁶⁶ [R01HD088014](https://projectreporter.nih.gov/project_info_description.cfm?aid=9234578&icde=36269146&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=)
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9234578&icde=36269146&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=)

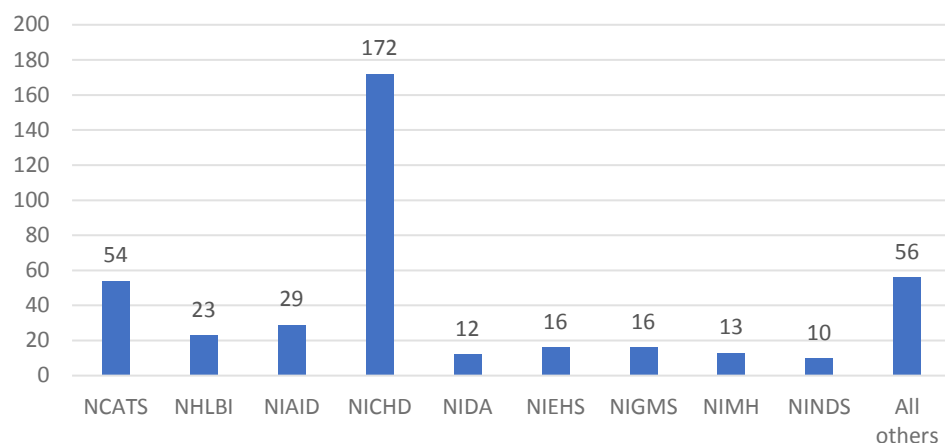
¹⁶⁷ [R01MD009064](https://projectreporter.nih.gov/project_info_description.cfm?aid=9261390&icde=36269184&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=)
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9261390&icde=36269184&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=); [R01MD011504](https://projectreporter.nih.gov/project_info_description.cfm?aid=9241046&icde=36269198&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=)
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9241046&icde=36269198&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=); [R01NR014800](https://projectreporter.nih.gov/project_info_description.cfm?aid=9302532&icde=36269203&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=)
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9302532&icde=36269203&ddparam=&ddvalue=&ddsub=&csr=1&csb=default&cs=ASC&pball=)

Appendix VI, Figure 51: Original Research Publications (n=929) on Medicinal Therapies for Preterm Birth, by External Funding Source, 2006-2017



Notes: A single publication will be reported in multiple categories if more than one type of funding source was acknowledged.

Original Research Publications on Medicinal Therapies for Preterm Birth, by NIH IC, 2006-2017



Notes: Many articles with NIH funding credited multiple ICs¹⁶⁸. A single publication will be counted in multiple categories when more than one IC is credited. Other ICs include FIC, NCCIH, NCI, NIA, NIAAA, NIAMS, NIBIB, NIDCD, NIDCR, NIDDK, NIH OD, NIMHD, NINR, and NLM.

Research Gaps

Although the research literature on preterm birth is relatively large compared with other conditions in this analysis, there is still limited scientific understanding of the mechanisms underlying preterm birth, and the search for more effective preventive therapies continues. Researchers have conducted studies of the effect of vitamins and other supplements on preterm birth, with mixed results, and few studies have been available to describe the safety and efficacy or PK/PD of the substances when taken during pregnancy.

Substance Abuse

Introduction

The use of alcohol, tobacco, or illicit drugs during pregnancy or lactation is a significant public health concern in the United States. In the 2013 National Survey on Drug Use and Health, 5.4 percent of

¹⁶⁸ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

women reported using illicit drugs during pregnancy (including cocaine, methamphetamine, marijuana, and other substances). About 3 percent reported binge or heavy alcohol consumption and 9.4 percent reported using alcohol. More than 15 percent of pregnant women reported using tobacco.¹⁶⁹ The opioid epidemic has spread among pregnant women, and a large and increasing number of infants have been adversely affected. From 2009 to 2012, the incidence of neonatal opioid withdrawal syndrome (NOWs) increased nationally from 3.4 to 5.8 per 1,000 hospital births, or 21,732 newborns.

Scientific Literature

The analysis identified 949 articles, published between January 2006 and July 2017, that are related to medicinal therapies for substance abuse in pregnant women and lactating women. Of these, about 3 percent (27 articles) related to vitamins or other supplements. The latter group of articles primarily reported case series studies examining how prenatal use of vitamin or other supplements may affect outcomes for children with prenatal exposure to alcohol and/or tobacco. For the literature as a whole, Appendix VI, Figure 52, shows the number of publications by type of research.

Appendix VI, Figure 52: Publications on Substance Abuse in Pregnant women and lactating women, by Type, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|--------------------------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Substance abuse (all) | 125 | 13 | 48 | 82 | 257 | 44 | 274 | 48 | 80 |

Many studies focused on the mechanisms of how fetal development is affected by prenatal exposure to alcohol, tobacco, or illicit drugs, and how medication-assisted maternal treatment for addiction may affect these outcomes. For example, a recent study found that certain placental changes were more likely in pregnancies of women on medication-assisted treatment for opioid use.¹⁷⁰ Studies in animal

¹⁶⁹ <https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf>

¹⁷⁰ [PMID 28024988 \(https://pubmed.ncbi.nlm.nih.gov/28024988/\)](https://pubmed.ncbi.nlm.nih.gov/28024988/)

models have assessed how alcohol, tobacco, and opioids affect neurological, respiratory, and other fetal systems.¹⁷¹

Many clinical trials have evaluated nicotine-replacement therapies for tobacco addiction or medication-based treatment for opioid dependence in pregnant women. For nicotine replacement therapy, the trials suggested only limited benefit. For example, one study in the U.K. found that adding a nicotine replacement patch to behavioral support for women who smoked during pregnancy was ineffective, largely because of poor adherence.¹⁷² A longer-term study, also conducted in the UK also found that nicotine patches had no enduring, significant effect on smoking in pregnancy; however, at 2 years old, children born to women who used the patches were more likely not to have impaired development.¹⁷³ A study of nicotine gum found that although the gum did not increase maternal smoking cessation rates, children of women in the intervention arm had increased birth weight and gestational age.¹⁷⁴ Clinical trials of medication-assisted therapies for opioid dependence in pregnant women have demonstrated that these treatments can be effective. For example, a recent study showed that antenatal buprenorphine exposure results in superior neurobehavioral scores and less severe withdrawal for the children than does antenatal methadone exposure.¹⁷⁵

Alcohol, tobacco, and opioids were the substances of abuse most commonly addressed in this literature. Methamphetamines drew relatively little attention from researchers. A substantial number of the clinical trials addressed use of multiple substances, with tobacco frequently addressed with other substances. Appendix VI, Figure 53, shows the distribution of publications by substance and type of research.

¹⁷¹ [PMID 23174390 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=23174390\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=23174390); [PMID 20043989 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=20043989\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=20043989); [PMID 18852877 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=18852877\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=18852877).

¹⁷² [PMID 22375972 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=22375972\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=22375972)

¹⁷³ [PMID 25158081 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=25158081\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=25158081)

¹⁷⁴ [PMID 18827129 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=18827129\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=18827129)

¹⁷⁵ [PMID 23106928 \(https://www.ncbi.nlm.nih.gov/pubmed/?term=23106928\)](https://www.ncbi.nlm.nih.gov/pubmed/?term=23106928)

Appendix VI, Figure 53: Publications on Medicinal Therapies for Substance Abuse in Pregnant women and lactating women, by Type of Research and Substance, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Alcohol | 3 | 1 | 1 | 31 | 10 | 4 | 18 | 2 | 5 |
| Cocaine | 0 | 1 | 0 | 6 | 7 | 2 | 7 | 1 | 1 |
| Meth/amph | 3 | 1 | 0 | 10 | 4 | 1 | 3 | 0 | 1 |
| Opioids | 6 | 10 | 26 | 24 | 102 | 17 | 90 | 23 | 22 |
| Tobacco | 3 | 17 | 28 | 24 | 34 | 7 | 65 | 15 | 26 |

Appendix VI, Figure 54, shows the pregnancy and lactation publications, by type, separately. Lactation was studied less frequently. Several articles on various supplements focused on lactation, but clinical trials of medication-assisted substance abuse therapies focused only on pregnancy.

Appendix VI, Figure 54: Pregnancy and Lactation Publications on Medicinal Therapies for Substance Abuse, Shown Separately, by Substance and Type of Research, 2006-2017

| Condition | Basic | PK/PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Pregnancy only | | | | | | | | | |
| Alcohol | 6 | 1 | 1 | 31 | 9 | 4 | 17 | 2 | 5 |
| Cocaine | 0 | 1 | 0 | 6 | 7 | 2 | 7 | 1 | 1 |
| Meth/amph | 3 | 1 | 0 | 10 | 4 | 1 | 3 | 0 | 1 |
| Opioids | 4 | 9 | 25 | 24 | 94 | 13 | 78 | 22 | 18 |
| Tobacco | 2 | 17 | 27 | 24 | 33 | 7 | 64 | 15 | 23 |
| Lactation | | | | | | | | | |
| Alcohol | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Cocaine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Meth/amph | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Opioids | 3 | 1 | 1 | 0 | 8 | 4 | 12 | 1 | 4 |
| Tobacco | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 3 |

Current Research Activities

NIH supports a portfolio of research related to substance use among pregnant women and lactating women. For example, researchers supported by NICHD are working to develop a drug therapy that could

prevent fetal opioid dependence, to reduce or mitigate NOWs.¹⁷⁶ Scientists funded by NIDA are conducting a unique long-term study of adults exposed *in utero* to cocaine. They hope to understand how individuals with prenatal cocaine exposure may differ from the unexposed, with respect to substance use, psychiatric disorders, and risky sexual behaviors in early adulthood.¹⁷⁷ NIDCR-funded researchers are working to characterize the effect of *in utero* and lactation nicotine exposure on craniofacial development.¹⁷⁸

Appendix VI, Figure 55, shows external funding sources acknowledged by original research articles published from 2006-2017 on medicinal therapies for substance abuse in pregnant women and lactating women. Of the 605 original research publications, 275 (45 percent) acknowledged at least one external funding source. NIH funded more than twice as many publications as foreign government agencies. Among the NIH ICs, NIDA supported the most publications, followed by NCATS, NICHD, and NIAAA.¹⁷⁹ A small number of publications reported research supported by other federal agencies, including CDC, AHRQ, HRSA, and USDA. Government agencies in a variety of countries supported this research, with Australia, the UK, and Canada supporting the largest portfolios. Industry funding was acknowledged in few publications.

¹⁷⁶ [R21HD092011](https://projectreporter.nih.gov/project_info_description.cfm?aid=9333782&icde=36262488&ddparam=&ddvalue=&ddsub=&cid=1&csb=default&cs=ASC&pball=)

(https://projectreporter.nih.gov/project_info_description.cfm?aid=9333782&icde=36262488&ddparam=&ddvalue=&ddsub=&cid=1&csb=default&cs=ASC&pball=)

¹⁷⁷ [R01DA008916](https://projectreporter.nih.gov/project_info_description.cfm?aid=9300899&icde=36262555&ddparam=&ddvalue=&ddsub=&cid=1&csb=default&cs=ASC&pball=)

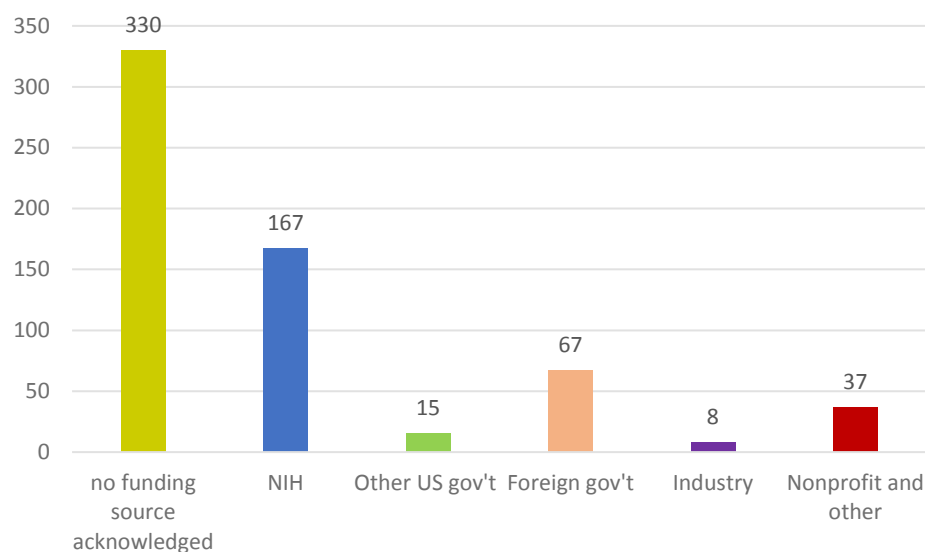
(https://projectreporter.nih.gov/project_info_description.cfm?aid=9300899&icde=36262555&ddparam=&ddvalue=&ddsub=&cid=1&csb=default&cs=ASC&pball=)

¹⁷⁸ [R03DE026192](https://projectreporter.nih.gov/project_info_description.cfm?aid=9316806&icde=36262570&ddparam=&ddvalue=&ddsub=&cid=1&csb=default&cs=ASC&pball=)

(https://projectreporter.nih.gov/project_info_description.cfm?aid=9316806&icde=36262570&ddparam=&ddvalue=&ddsub=&cid=1&csb=default&cs=ASC&pball=)

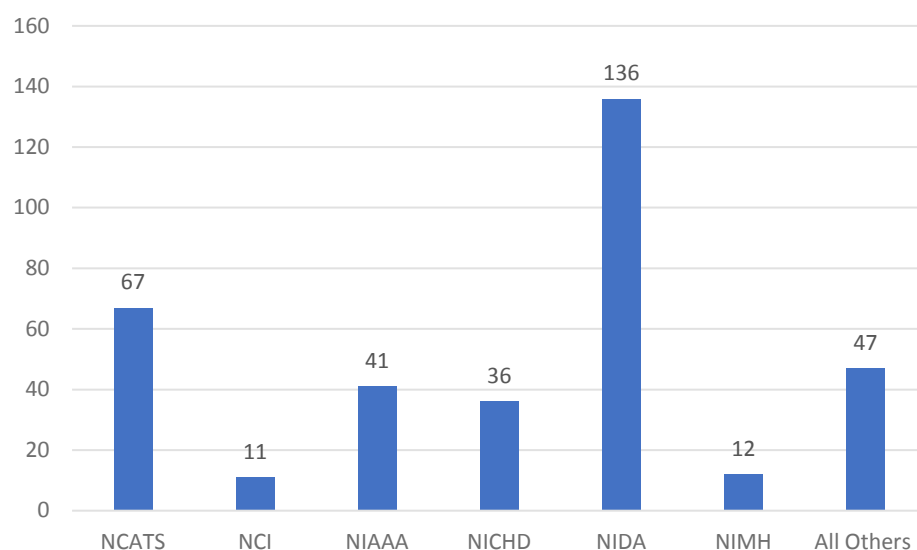
¹⁷⁹ Publications that acknowledged funding from NCRR were included in the NCATS total.

Appendix VI, Figure 55: Original Research Publications (n=275) on Medicinal Therapies for Substance Abuse in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other US government agencies included AHRQ, CDC, FDA, HRSA, USDA, and VA.

Original Research Publications on Medicinal Therapies for Substance Abuse in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Publications may be counted in more than one column if multiple NIH ICs¹⁸⁰ were acknowledged.

Research Gaps

Few studies have addressed how substance abuse, and medicinal therapies for it, affect lactation and breast milk. Similarly, basic mechanistic studies of substance use in pregnancy, which could contribute to better understanding of possible therapies, are limited. Relatively few studies of any type were available to inform understanding of possible therapeutic approaches in pregnant women using several commonly-abused illicit drugs, including amphetamines, methamphetamine, and cocaine.

Vaccines

Introduction

Vaccination for pregnant women and lactating women is a public health priority because infectious disease is not uncommon during pregnancy and poses potentially serious risks for both a woman and

¹⁸⁰ Figures for NCATS include relevant publications supported in whole or in part by the CTSA. Some CTSA were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSA are also included in the NCATS totals.

the developing fetus or breastfed infant. In some instances, maternal vaccination can extend protection to her child. Certain vaccines (tetanus, diphtheria and pertussis (Tdap), seasonal influenza) are now recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) for pregnant women generally. Other vaccines (such as hepatitis A or hepatitis B) may also be recommended for women at high risk of these infections during pregnancy.¹⁸¹

Scientific Literature

The analysis identified 1,451 articles, published between January 2006 and July 2017, that are related to vaccination in pregnant women and lactating women. Of these articles, 50 percent (719) were original research publications. Appendix VI, Figure 56, shows the literature by publication type.

Appendix VI, Figure 56: Publications on Vaccines in Pregnant women and Lactating women, by Research Type, 2006-2017

| Condition | Basic | PK/ PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ comment | Other |
|-----------|-------|-----------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Vaccines | 128 | 2 | 58 | 131 | 262 | 39 | 552 | 134 | 138 |

More than 100 RCTs were reported that addressed maternal immunization. The trials occurred in multiple foreign countries, including (for example) Australia, Nepal, Nigeria, Pakistan, South Africa, and Vietnam. The most common outcome variables in the trials were infant immune response to antenatal exposure to maternal vaccination, though maternal immune response and pregnancy outcomes were also assessed in a number of trials. For example, a clinical trial of influenza vaccine for pregnant women and infants in Bangladesh showed benefits to both mothers and infants.¹⁸² A trial of an investigational GBS vaccine in Canada and Belgium showed that maternal immunization during pregnancy resulted in transplacental transfer of antibodies to infants.¹⁸³ Clinical trials of behavioral interventions that addressed vaccine decision-making were also published during this period. Researchers tested video, text messaging, tailored education, and other interventions in several populations to see if they improved vaccine uptake. Although some of the interventions increased uptake, vaccination rates

¹⁸¹ <https://www.cdc.gov/vaccines/pregnancy/pregnant-women/index.html>

¹⁸² PMID 18799552 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=18799552>); PMID 22353593 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=22353593>)

¹⁸³ PMID 26942345 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26942345>)

tended to remain suboptimal. In several studies, the suboptimal rates were attributed to the lack of a recommendation for vaccination from pregnant women's primary care providers.¹⁸⁴

Multiple vaccines were addressed in this literature, with the following addressed most frequently: cholera, CMV, diphtheria, GBS, hepatitis B, HPV, influenza, malaria, pertussis, rubella, and tetanus. Because so many different vaccines were studied, the number of publications on vaccines in general is far greater than the available evidence on any one specific vaccine might suggest.

Appendix VI, Figure 57, shows the pregnancy lactation publications on vaccine research by type of research, separately. Lactation was infrequently the subject of vaccine research.

Appendix VI, Figure 57: Pregnancy and Lactation Publications for Vaccines, Shown Separately, by Research Type, 2006-2017

| Condition | Basic | PK/PD | Pop/ DB | RCT | Case series | Case Reports | Reviews | Edit/ Comment | Other |
|-----------------------|-------|-------|------------|-----|----------------|-----------------|---------|------------------|-------|
| Pregnancy only | | | | | | | | | |
| Vaccines | 126 | 2 | 58 | 129 | 259 | 39 | 547 | 129 | 133 |
| Lactation | | | | | | | | | |
| Vaccines | 2 | 0 | 0 | 2 | 3 | 1 | 12 | 5 | 5 |

Current Research Activities

NIH supports several projects on vaccination in pregnancy. NIAID-supported researchers have been studying the mechanisms by which maternal immunity is transmitted through the placenta and/or breast milk to prevent shigellosis in young infants.¹⁸⁵ Researchers funded by NINR are examining the roles of obesity and stress in determining the immune response of pregnant women to seasonal influenza vaccine and the transfer of protective maternal antibodies to the fetus.¹⁸⁶

¹⁸⁴ PMID 28216190 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=28216190>); PMID 28062124 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=28062124>); PMID 27667330 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=27667330>); PMID 26775454 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=26775454>)

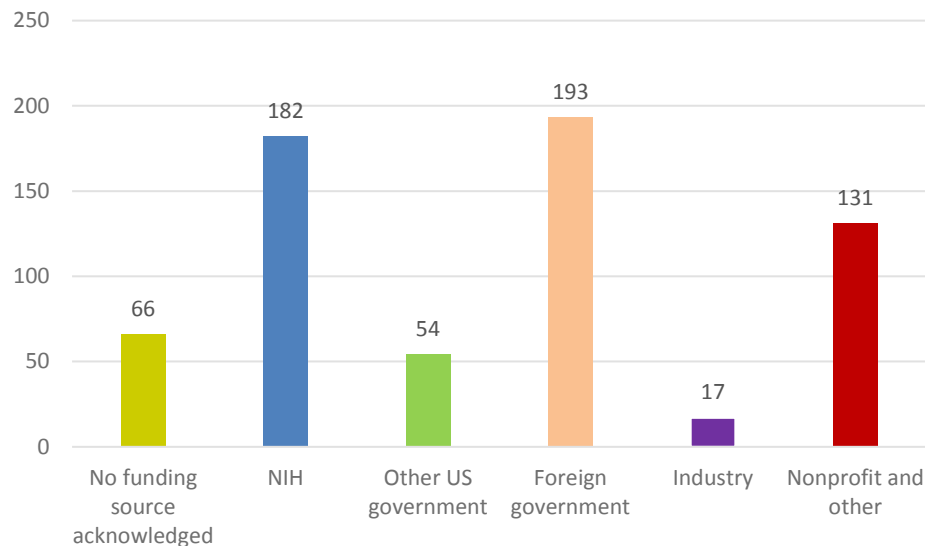
¹⁸⁵ R01AI117734 (https://projectreporter.nih.gov/project_info_description.cfm?aid=9206438&icde=36235185&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

¹⁸⁶ R01NR013661 (https://projectreporter.nih.gov/project_info_description.cfm?aid=9305779&icde=36235458)

Appendix VI, Figure 58, shows external funding sources acknowledged by original research articles published from 2006-2017 on vaccines in pregnant women and lactating women. Of the 719 original research publications, 653 (90 percent) acknowledged at least one external funding source—a much higher percentage than was the case for other categories of research on medicinal therapies for pregnant women and lactating women. As was the case for cancer research, many foreign countries dedicated funding for this area of science. Nonprofit and other organizations also supported such research.

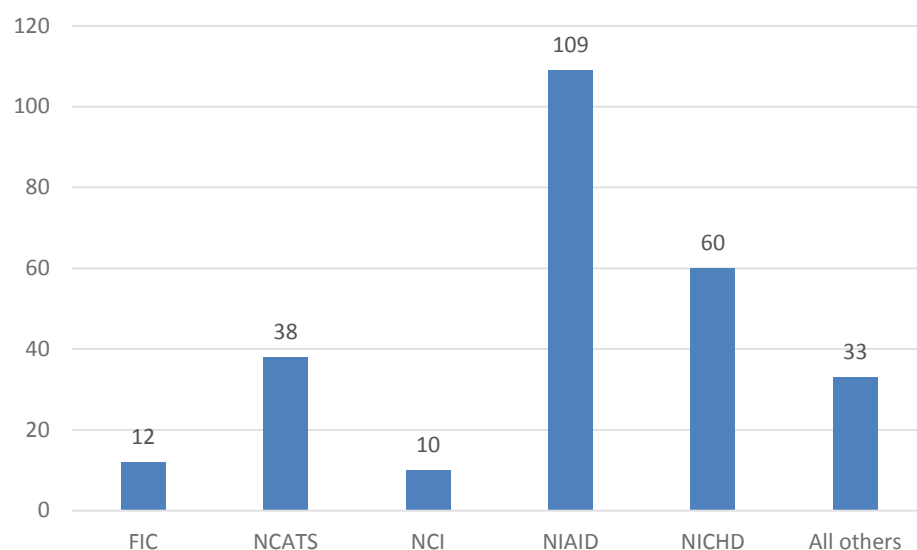
The largest proportion of NIH support for this research was from NIAID, but NICHD and NCATS also supported a substantial number of projects. Of non-NIH federally supported research in this area, 76 percent of the articles acknowledged CDC funding.

Appendix VI, Figure 58: Original Research Publications (n=719) for Vaccines in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.

Original Research Publications for Vaccines in Pregnant and/or Lactating Women, by NIH IC, 2006-2017



Note: Other NIH ICs¹⁸⁷ included NIMH, NIAAA, and NHLBI. A single publication may be reported in multiple categories if multiple funding sources were cited.

Research Gaps

Although many original research studies have been conducted on vaccines, primarily in pregnant rather than lactating women, there are few clinical studies of many individual vaccines. Very few studies address vaccination in lactating women.

¹⁸⁷ Figures for NCATS include relevant publications supported in whole or in part by the CTSAs. Some CTSAs were previously funded under NCRR, and the grants were subsequently migrated from NCRR to NCATS. Publications supported by these CTSAs are also included in the NCATS totals.

APPENDIX VII - Federal Activities Related to Pregnancy and Lactation, by Agency

Introduction

An array of federal agencies support research, health care and clinical practice, communications, and collaborative efforts that are directly applicable to the Task Force on Research Specific to Pregnant Women and Lactating Women. Federal activities for 12 key agencies were identified by Task Force agencies, supplemented by systematic searches of agency databases, websites, and publications.

These agencies include:

- Agency for Healthcare Research and Quality (AHRQ)
- Centers for Disease Control and Prevention (CDC)
- Department of Agriculture (USDA)
- Department of Defense (DoD)
- Department of Veterans' Affairs (VA)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)
- National Institutes of Health (NIH)
- National Vaccine Program Office (NVPO)
- Office of the Assistant Secretary for Health (OASH)
- Substance Abuse and Mental Health Services Administration (SAMHSA)

Agency for Healthcare Research and Quality (AHRQ)

Research

A key part of AHRQ's mission is to invest in research to improve safety and quality of health care

(<https://www.ahrq.gov/research/ahrq-research.html>). AHRQ supports extramural and intramural research related to pregnant women and lactating women, often using large population-based and claims data. AHRQ also provides research resources, including health services databases, that can be used to develop evidence about utilization and effectiveness of treatments and quality of care.

AHRQ supports some studies specifically related to the safety and effectiveness of medications and therapies in pregnant women and lactating women. These studies address a variety of conditions that are common in pregnant women. Some examples include:

- Researchers supported by AHRQ are combining previously collected data on the management of lupus during pregnancy to yield new information about optimal medication therapies to control lupus and improve pregnancy outcomes. In addition, researchers will be obtaining information from community rheumatologists to identify better ways to integrate expert recommendations for lupus management into medical practice.
- AHRQ supports multiple projects on the safety and effectiveness of antidepressants in pregnancy. One of these projects is using a large population-based Medicaid claims database to conduct a comparative effectiveness study, incorporating both maternal and fetal outcomes. A two-stage cohort study, using a large claims database, is designed to assess whether treatment of depression during pregnancy reduces the risk of postpartum depression.
- Researchers are assessing risks of various asthma medications for the woman and the fetus when used during pregnancy. Asthma is one of the most common conditions requiring medication during pregnancy, yet there is insufficient information on the safety of current asthma medications for pregnant women. A second demonstration project supported by AHRQ is combining data from multiple cohorts to identify the risks and relative safety of newly introduced and older asthma medications with respect to relatively rare outcomes, including specific major birth defects.
- Using several large claims databases, researchers assessed the risk of adverse fetal outcomes following exposure to immunosuppressive drugs in pregnant women with chronic immune-mediated diseases.
- AHRQ-supported scientists are examining trends in the prevalence of pre-existing diabetes among pregnant women, assessing utilization and anti-diabetic drugs during pregnancy, and exploring the relative safety of three commonly utilized oral antidiabetic drug classes in pregnant women.

AHRQ also has supported behavioral and educational intervention research in pregnant women and lactating women. One AHRQ-funded project aims to help physicians encourage physical activity for pregnant women. Another team of AHRQ-supported researchers is developing a bilingual touch screen educational support program to promote breast feeding among Hispanic women living in rural Nebraska.

AHRQ's largest portfolio of research relevant to pregnant women and lactating women is concerned with the quality, cost, and value of maternity and obstetric care. This portfolio includes research on variation across hospitals and providers in obstetric practice, acceptance and implementation of recommended therapies, matching the risks to mother and baby to higher levels of care, and risks and benefits of specific interventions such as cesarean section or labor induction. Specific examples of these research projects include:

- Although neonatal and trauma care is typically defined in terms of increasing levels of care, obstetric care has not yet fully adopted this approach. A team of researchers is describing how levels of care vary across hospitals in California and assessing how circumstances and hospital characteristics are associated with both obstetric levels of care and maternal and neonatal

outcomes. Another similar study is assessing obstetric levels of care in Georgia, focusing on high risk pregnant women.

- Using a large-scale administrative database from a chain of hospitals with varying staffing ratios and organizations, researchers are evaluating the relationship between nursing staffing levels and maternal and fetal pregnancy outcomes.
- Because pregnant women typically have sufficient time and strong motivation to consider their choice of hospital, they may become highly interested consumers of hospital quality information and reporting. AHRQ-supported scientists are designing and testing an interactive website concerning material hospital delivery, tailored to individuals from diverse racial and ethnic groups and women with limited English proficiency.
- Although a Healthy People 2020 goal is to immunize 80 percent of pregnant women for pertussis, immunization rates remain significantly lower, especially among Medicaid recipients. AHRQ-supported researchers are using a large Louisiana Medicaid database to evaluate how factors such as language preference, race and ethnicity, and characteristics of birthing facilities are associated with immunization.

Other AHRQ-supported studies describe utilization of health care services among pregnant women and prevalence of specific health conditions among pregnant women. For example, researchers analyzed data from Colorado to document trends in accidental overdoses and suicides among pregnant and postpartum women.

In addition to supporting research directly, AHRQ supports large databases that can be used by independent researchers, and some of this research is applicable to pregnant women and lactating women. The [Medical Expenditure Panel Survey \(MEPS\)](#), which began in 1996, is a set of large-scale surveys of families and individuals, their medical providers (doctors, hospitals, pharmacies, etc.), and employers across the United States. MEPS collects data on the specific health services that Americans use, how frequently they use them, the cost of these services, and how they are paid for, as well as data on the cost, scope, and breadth of health insurance held by and available to workers in the United States. The [Healthcare Cost and Utilization Project \(HCUP\)](#) is the nation's most comprehensive source of hospital care data, including information on in-patient stays, ambulatory surgery and services visits, and emergency department encounters. HCUP enables researchers, insurers, policymakers, and others to study health care delivery and patient outcomes over time, and at the national, regional, state, and community levels.

Clinical Practice Information and Recommendations

AHRQ does not directly support clinical care, but the agency creates materials to teach and train health care systems and professionals to help them improve care for their patients. Although these services and materials cover a variety of areas, several are focused on or include information related to pregnancy and lactation.

AHRQ is the lead federal agency for the U.S. Preventive Services Task Force (USPSTF), an independent, volunteer panel of national experts in prevention and evidence-based medicine

(<https://www.uspreventiveservicestaskforce.org/Page/Name/home>). USPSTF works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications. All recommendations are published on USPSTF's website and/or in a peer-reviewed journal. Task Force members come from the fields of preventive medicine and primary care, including internal medicine, family medicine, pediatrics, behavioral health, obstetrics and gynecology, and nursing. A total of 18 USPSTF recommendations are directly related to pregnancy and/or lactation, and 26 recommendations include a component related to pregnancy and/or lactation. USPSTF topics (found at <https://www.uspreventiveservicestaskforce.org/BrowseRec/Index>) that relate most strongly to pregnancy and lactation include:

- Hepatitis B Virus Infection in Pregnant Women: Screening
- Bacterial Vaginosis in Pregnancy to Prevent Preterm Delivery: Screening
- Breastfeeding: Primary Care Interventions
- Drug Use in Adolescents and Adults, Including Pregnant Women: Screening
- Elevated Blood Lead Levels in Childhood and Pregnancy: Screening
- Folic Acid for the Prevention of Neural Tube Defects: Preventive Medication
- Gestational Diabetes Mellitus, Screening
- Hepatitis B in Pregnant Women: Screening
- Human Immunodeficiency Virus (HIV) Infection in Pregnant Women: Screening
- Iron Deficiency Anemia in Pregnant Women: Screening and Supplementation
- Lead Levels in Childhood and Pregnancy: Screening
- Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: Preventive Medication
- Perinatal Depression: Interventions
- Preeclampsia: Screening
- Rh(D) Incompatibility: Screening
- Syphilis Infection in Pregnancy: Screening
- Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions
- Unhealthy Alcohol Use in Adolescents and Adults, Including Pregnant Women: Screening and Behavioral Counseling Interventions

AHRQ worked with OASH, HRSA, SAMHSA, and Ohio State University on an initiative called Healthier Pregnancy (<https://www.ahrq.gov/professionals/prevention-chronic-care/healthier-pregnancy/index.html>). The purpose of this initiative is to increase screening and referral for six preventive services in pre- and perinatal care settings. The six areas of focus include tobacco use, alcohol use, depression, intimate partner violence, obesity, and breastfeeding. Continuing education modules are available for health professionals (<https://www.ahrq.gov/professionals/prevention-chronic-care/healthier-pregnancy/initiative/index.html>).

AHRQ sponsors the development of various reports to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reports provide comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The Evidence-Based Practice Reports review all relevant scientific literature on a wide spectrum of clinical and health services topics. For example, AHRQ supported and has made available the report “Antidepressant Treatment of Depression During Pregnancy and the Postpartum Period,” which evaluates the benefits and harms of pharmacological therapy for depression in women during pregnancy or the postpartum period (<https://www.ahrq.gov/research/findings/evidence-based-reports/er216-abstract.html>).

Communications

As described above, AHRQ focuses its communications efforts on providers and health service organizations, rather than the general public. However, AHRQ’s website does include facts sheets and infographics suitable for a broad public audience. For example, AHRQ uses infographics to describe information and statistics related to public health concerns, including the impact of substance abuse on pregnant women and infants (<https://www.ahrq.gov/sites/default/files/wysiwyg/research/data/data-infographics/images/neonatal-maternity.html>).

Other Collaborative Efforts

In addition to efforts noted above, AHRQ participates in the Federal Interagency Forum on Child and Family Statistics, an interagency group designed to improve both the quality and use of data on children and families by investigating questions of data quality, data measurement, and data integration and by coordinating the development and use of statistical data bases among federal agencies (<http://childstats.gov>).

Centers for Disease Control and Prevention

Research

CDC’s mission involves fighting disease and promoting public health across populations, including pregnant women and lactating women. CDC supports a large portfolio of extramural and intramural research related to pregnant women and lactating women, often at the population level. CDC also provides research resources, including health services databases that can be used to develop evidence about public health needs for pregnant women and lactating women.

CDC Research Assessing Risk Factors during Pregnancy and Lactation

CDC’s National Center on Birth Defects and Developmental Disabilities funds several Centers for Birth Defects Research and Preventions across the United States to identify risk factors for birth defects and to answer questions about medications taken during pregnancy (<https://www.cdc.gov/ncbddd/birthdefects/cbdrp.html>). These centers collaborate on two large case-

control studies: NBDPS, which includes births from 1997–2011, and the BD-STEPS, which began with births in 2014. Over the course of 14 years of NBDPS interviews, 43,000 women from 10 states took part. These maternal interview data are essential to establishing whether a woman took the prescribed or over the counter medication. Examples of recent findings include:

- A recent study of antibiotic use among pregnant women showed that certain antibiotics may be associated with specific birth defects.
- Another recent CDC study found that women who took NSAIDs and opioid pain medicines during early pregnancy were more likely to have babies affected with certain birth defects, compared to women who took acetaminophen. In this study, slightly more than half of women reported taking pain medicine during early pregnancy. Taking both NSAIDs and opioids during early pregnancy may be related to gastroschisis, cleft palate, spina bifida, and congenital heart defects.

CDC's epidemiological research addresses the impact of occupational and environmental exposures, exposures to medication, and other factors on the health of pregnant women and their offspring. CDC's National Institute for Occupational Safety and Health (NIOSH) works with other CDC centers and supports several studies to make use of existing cohort data to analyze the long- and short-term effects of occupational exposures on maternal and child health.

Other epidemiological research from CDC documents the use of medication during pregnancy and describes the impact of both medication exposure and disease on developing infants. For example, CDC researchers analyzed a large state database and found that women with gestational diabetes (GD) had a higher risk than women without GD of serious complications, including preterm birth and macrosomia. In another study, CDC researchers developed a method to identify pregnant women in health insurance databases and find important information about their pregnancies and their use of antidepressants during pregnancy. Researchers identified nearly 490,000 pregnancies in 2013 health insurance claims data and found that 1 in 16 pregnant women filled a prescription for an antidepressant during pregnancy.

The Study to Explore Early Development (SEED) is a multi-year research study funded by CDC. It is currently the largest study in the United States to help identify factors that may put children at risk for autism spectrum disorder (ASD) and other developmental disabilities. Through SEED, CDC is evaluating many possible risk factors that seem to be associated with or related to ASD, including the mother's exposure to certain medications during pregnancy.

CDC Research Regarding Specific Illnesses and Treatments

CDC supports research on health care delivery, as related to public health interventions. Much of this research is focused on immunizations.

- The Pregnancy Vaccine Effectiveness Network (PREVENT) was established in April 2016 to: i) estimate incidence of influenza and vaccination rates; ii) describe epidemiologic characteristics

associated with illness; and iii) estimate influenza vaccine effectiveness in preventing acute respiratory or febrile hospitalizations during pregnancy associated with influenza confirmed by real-time reverse transcription polymerase chain reaction assay. It includes sites in Australia, Canada, Israel, and the United States.

- CDC is currently funding a study on immunization delivery in obstetrics and gynecology settings to promote administration of vaccines to women in preconception period and in pregnancy.
- The Internet Panel Survey of Pregnant Women, another CDC effort, is conducted in November and April of each year to monitor vaccination trends in pregnant women and includes topical questions on areas of special interest, such as Zika Virus (<https://www.cdc.gov/flu/fluview/pregnant-women-nov2013.htm>).
- CDC's New Vaccine Surveillance Network conducts surveillance and evaluation activities for acute respiratory illness to assess the burden of currently vaccine-preventable and potentially vaccine-preventable childhood diseases and to evaluate the impact of new and upcoming vaccines and other strategies. With respect to pregnant women, sites are collecting self-reported data related to influenza vaccination during pregnancy and verifying vaccination status using state registries and medical records. Information on breastfeeding practices is also collected (<https://www.cdc.gov/surveillance/nvsn>).
- Influenza Hospitalization Surveillance Network (FluSurvNet) conducts surveillance for influenza related hospitalizations. FluSurv-NET plans to pilot the use of data for estimation of influenza vaccine effectiveness among pregnant women during the upcoming 2017-2018 influenza season in the United States. CDC is also using data from FluSurv-Net to model the burden of hospitalizations and cases averted by vaccination among pregnant women.
- The Pregnancy and Influenza Multinational Epidemiologic (PRIME) study is following pregnant women in low- and middle-income country to evaluate effect of influenza during pregnancy, estimate incidence, and describe clinical spectrum of illness. Zika virus and hMPV/RSV sub-studies will be included at some sites.
- CDC researchers are developing pandemic protocols for rapid deployment of research studies during future pandemics.
- CDC researchers are addressing gaps in knowledge about racial disparities and preterm birth by examining maternal vitamin D status and vitamin D receptor genetic variation.

CDC also has supported behavioral and educational intervention research in pregnant women and lactating women. Examples include:

- CDC is working with scientists from an NIH clinical research network to support a clinical trial of a brief screening and educational intervention to prevent CMV infection
- As many as 1 in 5 pregnant women experience depression, which poses significant, ongoing risks for both the woman and her child. Researchers are now evaluating the efficacy of their low-cost, comprehensive intervention for these women in the “real-world” setting of obstetrics/gynecology clinics, where referrals and consultations and access to appropriate levels of psychiatric care are offered in conjunction with pregnancy-related clinical services.

CDC supports a range of efforts relating to opioid use during pregnancy:

- In a systematic review of previous studies on opioid use during pregnancy and risk for birth defects, CDC researchers found that use of opioids during pregnancy may be linked to various birth defects such as oral clefts, congenital heart defects, and clubfoot. However, many of the studies reviewed had issues with study methods and quality.
- Opioid use during pregnancy can also lead to neonatal abstinence syndrome (NAS). CDC is supporting two pilot projects to better understand the incidence, severity, and long-term developmental and educational outcomes associated with NAS.
- CDC is tracking trends in prescription opioid use among pregnant and reproductive aged women to monitor the opioid epidemic and progress towards the goal of reducing opioid use in these women.

CDC's National Center on Birth Defects and Developmental Disabilities conducts research and implements programs to reduce the risk and impact of Zika virus infection in pregnant women, infants, and children. Data are used to update recommendations for clinical care; plan for services for pregnant women, their infants, and families affected by Zika; and improve prevention of Zika infection during pregnancy. Activities include:

- The Zika Pregnancy and Infant Registries, which are enhanced national surveillance efforts coordinated by CDC in collaboration with state, tribal, territorial, and local health departments. CDC also established rapid birth defects surveillance to identify all infants with Zika-associated birth defects, regardless of whether there was Zika virus exposure or laboratory evidence of Zika.
- Enhanced surveillance of pregnant women with Zika in Colombia has been established in collaboration with Colombia's Instituto Nacional de Salud (INS). Additionally, CDC collaborates with INS on a cohort study to identify risk factors for Zika virus transmission; the full spectrum of adverse maternal, fetal, and infant health outcomes associated with Zika virus infection; and risk factors for occurrence of these outcomes.
- A prospective cohort study "Persistence of Zika Virus in Pregnant Women and Infants in Puerto Rico," aims to estimate the prevalence and duration of persistent Zika virus RNA in pregnant women and congenitally infected infants.
- The Local Health Department Initiative was launched to reduce the effect of Zika on mothers, their babies, and their communities, by placing highly skilled local field assignees in local health departments. Field assignees work to increase pregnancy and birth defects surveillance, participate in community events, partner with local and national professional organizations, and provide outreach to health care systems and providers in their local communities.

CDC Research to Improve Outcomes around the World

CDC is conducting research to improve pregnancy outcomes around the world. Examples include:

- In Kenya, CDC supports an influenza vaccine demonstration project, using an inactivated influenza vaccine already licensed in Kenya to vaccinate pregnant women in a high HIV prevalence and malaria-endemic setting.

- Through the Partnership for Influenza Vaccine Introduction (PIVI), CDC has several efforts to expand the use of seasonal influenza vaccines in countries outside the United States, and many of these efforts target pregnant women.
- In Morocco, CDC is supporting efforts to enhance surveillance for severe acute respiratory disease among pregnant women.
- In Thailand, CDC and NIH are supporting a large, randomized placebo-controlled trial, where 6 percent to 7 percent of adults are chronically infected with hepatitis B virus (HBV). Researchers will test the safety and efficacy of a short course of antiviral therapy to prevent pregnant women with HBV from passing the infection along to their children.
- In China, CDC is supporting a randomized controlled clinical trial among HIV-HBV co-infected women. This study will test the safety of tenofovir during pregnancy with regards to the infant bone mineral density, as well as other potential toxicities.
- In Swaziland, CDC-supported scientists are implementing a quality improvement intervention utilizing patient feedback from a clinical visit satisfaction survey to improve retention of HIV-infected pregnant women and lactating women receiving antenatal or postpartum care services.
- In multiple countries, CDC-supported scientists are conducting operational research supported through the PEPFAR Implementation Science initiative. Specifically, CDC-supported scientists are conducting research designed to improve the quality of care and patient outcomes, including research on:
 - Establishing a surveillance system for major external birth defects among all live and still births delivered or registered as being born to assess the maternal risk factors associated with major external birth defects among newborns in Uganda
 - The readiness of pregnant women to begin lifelong HIV treatment (ART) and an enhanced ART adherence package of care for pregnant women and lactating women in Zambia
 - The effectiveness of an intervention to enhance outreach worker capacity to increase the uptake and adherence to prevention of mother-to-child transmission of HIV services among pregnant women in India
 - The feasibility, acceptability, and impact of point-of-care systems to facilitate earlier identification and treatment of HIV-exposed and HIV-infected infants in Zambia
 - Improved HIV case identification and care for lactating women and their infants, as well as the optimal points for assessing HIV viral load during lactation in South Africa
 - The impact of an enhanced service package for adolescents living with HIV in Zimbabwe.
- As partners in the Child Health and Mortality Prevention Surveillance Network (CHAMPS), CDC-supported scientists are providing technical assistance to design and implement pregnancy surveillance. Routine health and demographic information will be obtained from all consenting pregnant women in the surveillance catchment area. The goal is to facilitate timely and accurate detection of stillbirths and neonatal deaths, and to classify pregnancy outcomes within 24 hours of delivery. Expansion to four additional pregnancy surveillance sites within the CHAMPS network is planned from 2018-2025. This platform may serve as a foundation for additional implementation science studies to reduce maternal or neonatal mortality or to prepare for future maternal immunization clinical trials.

CDC Surveillance and Data Collection Efforts

In addition to supporting research directly, CDC supports surveys and large-scale data collection efforts, and these resources can be used by independent researchers to conduct studies applicable to pregnant women and lactating women. Key efforts in this area include:

- CDC's Pregnancy Risk Assessment Monitoring System (PRAMS)
<https://www.cdc.gov/prams/index.htm>. PRAMS collects state-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy. PRAMS surveillance currently covers about 83 percent of all births in the United States. PRAMS provides data not available from other sources. These data can be used to identify groups of women and infants at high risk for health problems, to monitor changes in health status, and to measure progress toward goals in improving the health of mothers and infants. PRAMS data are used by researchers to investigate emerging issues and by state and local governments to plan and review programs and policies aimed at reducing health problems among mothers and babies. PRAMS includes core questions asked in every state and optional questions available to states and localities. Core PRAMS questions cover areas including flu shots, gestational diabetes, preeclampsia, depression, tobacco use, alcohol use, violence, breastfeeding, and infant sleep positions. Optional questions expand available information about breastfeeding; vitamin use; other vaccines; medication for thyroid, epilepsy, and mental health conditions; substance use and abuse, and environmental health, among other topics.
- Maternity Practices in Infant Nutrition and Care (mPINC) Survey: CDC has developed and supported the mPINC survey since 2007. Every other year, all facilities in the United States that provide maternity care are invited to participate. Nationwide, 82 percent of facilities contribute data on practices and policies in seven dimensions of medical and nursing care that support breastfeeding <https://www.cdc.gov/breastfeeding/data/mpinc/index.htm>.
- CDC's National Biomonitoring Program (NBP) uses measurements in blood and urine (biomonitoring) to help identify harmful environmental exposures or nutrition deficiencies among the United States population. CDC measures more than 300 chemicals and nutrition indicators in participants of the National Health and Nutrition Examination Survey (NHANES) and publishes findings in a summary report, the National Report on Human Exposure to Environmental Chemicals (National Exposure Report). In addition, CDC collaborates on more than 75 studies each year that examine exposures among vulnerable populations, including pregnant and/or lactating women, or investigates the relationship between exposure levels and adverse health effects. For these investigations, CDC provides unique, high-quality measurements for environmental chemicals or nutrition indicators.

Through the National Center for Health Statistics, CDC spearheads the development of new questions and methods to obtain key information about public health issues related to maternal health, pregnancy, and breastfeeding. CDC is developing new questions for NCHS surveys and the National Vital Statistics to better capture contemporary practices in breastfeeding, and to rigorously test new questions to ensure their validity and reliability. Other examples include:

- National Vital Statistics System, information on whether the mother breastfed her newborn prior to discharge from the hospital is available from birth certificates for varying numbers of states from 2009 on (https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm). These data can be analyzed by numerous maternal (e.g., age, education, race) and infant (gestational age, NICU admission, birthweight) characteristics. A recent study assessing the quality of this and other new items from the birth certificate found high agreement between breastfeeding data reported on the birth certificate and information recorded in hospital medical records https://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_02.pdf.
- The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews, physical examinations, and biomonitoring. Data from NHANES has been used for studies of pregnant women and nutrition and exposures (<https://www.cdc.gov/nchs/nhanes/index.htm>).
- The National Survey of Family Growth (NSFG) is a household-based, nationally representative survey of reproductive aged women and men (<https://www.cdc.gov/nchs/nsfg/index.htm>). Since 1973, the survey has included questions on breastfeeding initiation and duration, as part of the full pregnancy and birth history collected from all female respondents. NSFG is co-funded by NIH.
- The National Health Interview Survey (NHIS) is a population-based national household survey. CDC has included questions to determine influenza vaccination among women pregnant during the influenza season and is working to develop new questions to determine tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination during pregnancy among women having live births in the past 12 months.
- Since July 2001, breastfeeding questions were included on the NIS to assess the population's breastfeeding practices. The parent or guardian is asked about breastfeeding, formula feeding, and first time feeding of something other than breast milk or formula (https://www.cdc.gov/breastfeeding/data/nis_data/index.htm). These data help to inform CDC's Breastfeeding Report Card (<https://www.cdc.gov/breastfeeding/data/reportcard.htm>), which is released every other year. CDC estimates alcohol use among pregnant women using the Behavioral Risk Factor Surveillance System (BRFSS). This telephone survey tracks national and state-specific health risk behaviors of adults, aged 18 years and older, in the United States. The BRFSS is administered and supported by the Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, CDC.

In addition to these efforts, CDC's Data Hub acquires and manages external data sources that complement the information obtained from its data. Below are a few examples of these acquired external data that provide information not available otherwise to public health surveillance:

- American Hospital Association (AHA) Annual Survey database, a comprehensive census of United States hospitals that is a reliable resource for health services research and trends analyses. That includes obstetric care services provided to pregnant women.
- Centers for Medicare and Medicaid (CMS) claims, specifically Medicaid claims, and IBM/Truven Health Analytics' MarketScan commercial claims databases including encounters, admission and

discharge data, and beneficiary enrollment data that can be used to estimate cost and rates of health care utilization during pregnancy and postpartum.

- Healthcare Cost and Utilization Project (HCUP) databases and related software tools and products are developed through a federal-state-industry partnership and are sponsored by the Agency for Healthcare Research and Quality (AHRQ).

Clinical Practice Information and Recommendations

CDC does not directly support clinical care, but the agency creates materials that can help inform health care systems, patients, and providers. Although these services and materials cover a variety of areas, several are focused on or include information related to pregnancy and lactation.

CDC's Treating for Two initiative, which involves collaboration with a range of partners and other federal agencies, is designed to address the need for clinical information. Treating for Two is working to expand and accelerate research to fill knowledge gaps; evaluate available evidence to facilitate reliable guidance; and deliver up-to-date information to support decision making among prescribers, pharmacists, and consumers (<https://www.cdc.gov/treatingfortwo>).

- Through a small business grant, CDC is testing whether delivering information through mobile devices can improve knowledge and communication of data on drug safety to pregnant women.
- CDC, in collaboration with the March of Dimes, conducted a research project to triangulate findings from formative research with women (recently pregnant or planning pregnancy), prescribers, and pharmacists to develop an understanding of shared challenges and opportunities in improving medication safety during pregnancy.

The *U.S. Medical Eligibility Criteria for Contraceptive Use, 2016*, are evidence-based, clinical guidelines provide information for health care providers on the safety of contraceptive methods for women with certain characteristics or medical conditions, including pregnant, postpartum, and lactating women (<https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html>).

Environmental exposure information for providers is another important area for CDC:

- The Prenatal Assessment of Environmental Risk (PEAR) is an online environmental exposure assessment toolkit to help providers assist patients to lower environmental exposure risk.
- Pediatrics Environmental Health Specialty Units are a source of medical information providing advice on the prevention, diagnosis, management, and treatment of environmentally related health effects in adults and children
- CDC provides guidelines for identifying and managing lead exposure in pregnant women and lactating women (<https://www.cdc.gov/nceh/lead/publications/leadandpregnancy2010.pdf>).
- Handouts and fact sheets about environmental exposures are also available for providers.

The Advisory Committee on Immunization Practices (ACIP) develops recommendations on the use of vaccines, including for pregnant women (<https://www.cdc.gov/vaccines/acip/index.html>).

CDC supports evidence-based strategies in hospitals to help women who choose to breastfeed start and continue breastfeeding, by promoting the [Ten Steps to Successful Breastfeeding](#) (Ten Steps), a set of practices outlined by the WHO/UNICEF Baby-Friendly Hospital Initiative (BFHI) that have been shown to support breastfeeding mothers and infants. *CDC Health Information for International Travelers* (the Yellow Book) provides recommendations to clinicians advising travelers who are pregnant or breastfeeding (<https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/pregnant-travelers> and <https://wwwnc.cdc.gov/travel/yellowbook/2018/international-travel-with-infants-children/travel-and-breastfeeding>).

Communications

CDC focuses its communications efforts on public health professionals and the general public, although health care providers are also an important audience. CDC's website provides a broad array of consumer information on issues relevant for pregnant women and lactating women, including:

- Gestational diabetes (<https://www.cdc.gov/pregnancy/diabetes-gestational.html>)
- Zika (<https://www.cdc.gov/zika/reporting/pregnancy-outcomes.html>)
- Infections (<https://www.cdc.gov/ncbddd/birthdefects/infographics/prevent2protect/index.html>)
- Folic acid (<https://www.cdc.gov/ncbddd/folicacid/index.html>)
- Preventing birth defects (<https://www.cdc.gov/ncbddd/birthdefects/prevention.html>)
- Safe medication use in pregnancy (<https://www.cdc.gov/treatingfortwo>)
- Pregnancy and opioid pain medication (https://www.cdc.gov/drugoverdose/pdf/pregnancy_opioid_pain_factsheet-a.pdf)
- International travel (<https://wwwnc.cdc.gov/travel/page/pregnant-travelers>) and special information for pregnant women on all international travel destination pages (www.cdc.gov/travel)
- Listeriosis (<https://www.cdc.gov/listeria/risk-groups/pregnant-women.html>)
- Blood pressure (<https://www.cdc.gov/bloodpressure/about.htm>)
- Breastfeeding (<https://www.cdc.gov/breastfeeding/>)
- Alcohol Use in Pregnancy (<https://www.cdc.gov/ncbddd/fasd/alcohol-use.html>)
- Workplace health information for pregnant and nursing women (<https://www.cdc.gov/niosh/topics/repro/pregnancy.html>)

Other Collaborative Efforts

In addition to efforts noted above, CDC participates in the Federal Interagency Forum on Child and Family Statistics, an interagency group designed to improve both the quality and use of data on children and families (<http://childstats.gov>). CDC co-chairs the Federal Interagency Breastfeeding Work Group, an interagency group designed to increase sharing of information and expertise, prevent duplication, and increase collaboration on projects and initiatives with mutual goals. This work group has also

collaborated with the Federal SIDS/SUIDS Work Group to mutually promote safe sleep and the safe implementation of maternity practices supportive of breastfeeding.

Department of Defense (DoD)

Research

DoD supports research related to pregnant women and lactating women through over 300 extramural grants funded over the past 30 years and the efforts of scientists in several branches of the military. This research portfolio addresses a range of topics of special interest to the military. A few key examples include:

- To reduce adverse pregnancy outcomes due to obstructive sleep apnea, researchers supported by the DoD are conducting a randomized controlled trial that examines the use of continuous positive airway pressure (CPAP) therapy compared with standard prenatal care only, in high risk pregnant women.
- DoD supports a range of studies designed to explore how both fetal exposures and pregnancy may affect the long-term risks for breast cancer. For example, DoD is supporting a team of scientists who are looking to determine whether epigenetic changes from *in utero* estrogenic exposures are the cause for Tamoxifen resistance.
- DoD supports studies on the effects of high-altitude hypoxic exposure and placental insufficiency on congenital heart defects and fetal oxygen metabolism.
- DoD conducts studies on environmental exposures on women as seen in The Gulf War Women's Health Cohort study.
- Disruptions in maternal-fetal interactions during the perinatal period due to inflammation or other immune responses can result in fetal neuropsychiatric disorders. The objective of one DoD-funded study is to gain more knowledge about the effect of inflammation during pregnancy on placental tryptophan metabolic pathways and the impact on serotonin-relevant circuits and fetal brain development.
- DoD has supported several studies on perinatal exposures, including illness, environmental exposures and placental abnormalities and their impact on the brain and the risk of autism. For example, the objective of one DoD-funded study is to evaluate the relationship between prostaglandin release due to fever during pregnancy and changes in brain development. Another DoD-funded study evaluates the relationship between exposure to environmental contaminants during pregnancy, alterations in the placental serotonin biosynthetic pathway, and autism risk.
- In the 2000s, DoD researchers assessed the impact of anthrax vaccination of pregnant women and their offspring. The military health system has established registries to follow families where anthrax or smallpox vaccines were given during pregnancy (<https://health.mil/vaccines>).
- Serotonin Selective Reuptake Inhibitor (SSRI) antidepressants used by pregnant women have been linked to an increased risk of autism spectrum disorder in offspring. One DoD-funded research study aims to assess the changes to the behavioral and serotonin systems of rat

offspring exposed to two SSRI drugs (Celexa and Prozac) versus a non-SSRI drug (Wellbutrin) to demonstrate the disruptive effect that SSRI antidepressants have on brain development.

- DoD supports research that investigates the potential relationship between gut bacteria, GI inflammation, behavioral, and neurodevelopmental problems associated with autism by examining the effects of a novel probiotic therapy on maternal immune activation (MIA) in a mouse model.
- DoD has developed a large database linking medical records of women who gave birth in the military health system and their offspring. Among the matched singleton live birth pregnancies, 7 percent of mothers were dispensed an antidepressant at any point during pregnancy, and about 1.3 percent of mothers were given an antiepileptic drug.
- Several military branches have studied questions related to military physical fitness assessments in the pregnancy and postpartum periods.
- DoD has supported several studies describing prenatal and obstetric practice in military settings or by military physicians.
- DoD physicians have described support for breastfeeding in the military (on at least one occasion, in cooperation with VA researchers).

Clinical Care

DoD provides health care services to pregnant women and lactating women through TRICARE, the health care system for active duty military, dependents, and retirees (<https://www.tricare.mil>). In FY 2015, about 120,000 babies were born in the military health system (<https://www.tricare.mil/About/Facts>). The military health system provides comprehensive coverage that includes substance abuse and mental health services, breast pumps and lactation support as well as maternity care (<https://tricare.mil/tricareu/PublicCourses.aspx>). Special military health programs related to pregnancy or lactation include:

- The Family Advocacy Program is designed to promote healthy family relationships and prevent family violence (http://www.militaryonesource.mil/phases-military-leadership?content_id=266712).
- The New Parent Support Program (NPSP) offers home visitation, parenting education, and other services to help young families provide a safe and nurturing environment for their children (http://www.militaryonesource.mil/phases-military-leadership?content_id=266712).

Related to its health care services programs, DoD provides policies, regulations, and guidance related to the health impacts of therapies on pregnant women and lactating women and their offspring. DoD has also developed case definitions to support surveillance of pregnancy-related conditions in military populations. These policies and guidance help women and their clinicians make informed decisions about medication in pregnancy. VA and DoD have together implemented a clinical practice guideline on management of pregnancy (https://www.healthquality.va.gov/guidelines/WH/up/mpg_v2_1_full.pdf).

Communications

DoD's military health websites provide resources to pregnant women and lactating women and their health care providers. DoD seeks to inform a wide range of audiences about medication use and safety among pregnant women and lactating women. DoD is a federal partner in Text4Baby, a text messaging application free to pregnant women and women with infants to inform them of a variety of pregnancy- and lactation-related health issues (<https://partners.text4baby.org/index.php/about/partners>).

Other Collaborative Efforts

Collaborations noted above include DoD's work with VA on practice guidelines and with other federal agencies on Text4Baby. Other collaborations include:

- DoD participates in the Federal Interagency Forum on Child and Family Statistics, an interagency group designed to improve both the quality and use of data on children and families by investigating questions of data quality, data measurement, and data integration and by coordinating the development and use of statistical data bases among Federal agencies (<http://childstats.gov>).
- In 2016, DoD partnered with NIH, FDA, CDC, and SAMHSA to sponsor a workshop addressing critical gaps in research on opioid misuse and pregnancy. Topics included (1) Screening for opioid use in pregnancy (2) Complications of pregnancy associated with opioid use (3) Most appropriate treatment of pregnant women with opioid use disorders given risks and benefits (4) Treatment and management of infants with neonatal abstinence syndrome and (5) long-term effects of prenatal opioid exposure on children and the role of preventive interventions to improve childhood outcomes for this high-risk population.

Department of Veterans Affairs (VA)

Research

VA supports research related to pregnant women and lactating women through its intramural research program in the Office of Research and Development, and primarily through its Health Services Research and Development Service, which funds research addressing all aspects of VA health care. Women's health research is a priority for the VA, and the VA has established a comprehensive Women's Health Research Agenda (https://www.hsrd.research.va.gov/for_researchers/womens_health/default.cfm). This program of research is aimed at understanding the health and health care needs of women veterans and informing systematic improvements in their care through partnerships with the VA health care system.

VA supports research on medication safety for pregnant women and their offspring, and research on the effect of military service, trauma, and co-occurring conditions on reproductive health and pregnancy, health care delivery, and care coordination. VA scientists have also contributed to the basic science literature related to pregnancy-associated conditions. Some specific examples of research include:

- Through the Pregnancy Outcomes of Veterans (PROVE) project, scientists are linking VA and California data to describe the effect of maternal post-traumatic stress disorder (PTSD) on birth outcomes, confirming an increased risk of preterm birth and quantifying the distribution and character of preterm births.
- Researchers are assessing the coordination of pregnancy care experienced by women veterans by examining health care utilization data and interviewing women veterans and their health care providers.
- Researchers are investigating the effects of opioid use on pregnant veterans.
- Researchers have assessed counseling of female veterans about the teratogenic risks of prescription medications and are testing new programs to enhance provider-patient communication about these risks.

Clinical Care

VA provides health care services to pregnant women and lactating women veterans, usually in the community but also through the Veterans Health Administration (VHA). All VHA medical centers have a maternity care coordinator who assists pregnant women veterans with coordinating VA and community resources for prenatal care and delivery and ensures that women veterans receive appropriate lactation support and screening for post-partum depression. VA researchers have documented a significant recent increase in the utilization of VA maternity benefits among eligible women veterans. Moreover, a VA-supported research study found that women who use VA benefits tend to be at higher risk, especially for depression, compared to women who do not use these benefits. VA provides counseling or mental health services, substance abuse counseling, and/or treatment, as well as training for providers specifically related to the needs of pregnant or lactating women.

Related to its health care services programs, VA provides policies, regulations, and guidance related to the health impacts of therapies on pregnant women and lactating women and their offspring. These policies and guidance help women and their clinicians make informed decisions about medication in pregnancy. Examples include:

- VA's Pharmacy Benefit Management Program includes decision tools to help women and their physicians make informed decisions when they prescribe medication for pregnant or lactating women. VA formularies and decision aids are based on information from FDA and from NLM's LactMed®
- VA's Teratogenic Drugs Project is an information technology initiative that enhances VHA's electronic medical records system to display pregnancy and lactation information in the vital signs display, implements automatic order checks for medication and imaging studies, includes notification to providers about potential teratogenic medications, and provides reminders to providers addressing pregnancy and lactation status.
- VA and DoD have together implemented a clinical practice guideline on management of pregnancy (https://www.healthquality.va.gov/guidelines/WH/up/mpg_v2_1_full.pdf). The guideline is designed to reduce clinical practice variation, provide evidence-based

recommendations to patients and providers, and identify outcome measures to improve clinical practice.

- VHA's Handbook established procedures for the coordination of maternity care for veterans.
- VHA is establishing a Maternity Tracker to enhance the coordination of care of pregnant women veterans using shared information between providers to improve screening, care, patient safety, and health outcomes. The Maternity Tracker web application, to be available to each VA site in 2018, allows VA maternity care coordinators to track and monitor the antenatal and postnatal maternity care for women veterans. The web-based tool is designed to interact with VA's electronic health record and computerized patient record system (VistA, CPRS and the Women's Health Data Package) to track and share educational items, phone calls, notes, and other information for pregnant veterans.

Communications

VA's website provides an array of resources to pregnant women and lactating women and their health care providers. VA seeks to inform a wide range of audiences about medication use and safety among pregnant women and lactating women (<https://www.pregnancyatoz.org>; https://www.tucson.va.gov/docs/WomenHealth/Maternity_Care_Benefits_08052015.pdf). VA's communication activities related to pregnancy and lactation include:

- The Purple Book is a resource for pregnant patients to help explain VA's and DoD's evidence-based practices for pregnancy care (https://www.va.gov/COMMUNITYCARE/docs/providers/VHA_CC-Provider_Toolkit.pdf and <https://www.tucson.va.gov/services/women/Maternity.asp>)
- MomMoodBooster, a free online program for women veterans designed to help women veterans recover from postpartum depression. In addition to online information, women complete six sessions and receive phone calls from a phone coach to assist in their recovery (<https://mummoodbooster.com/public/us>).
- As part of its women's health continuing education webinar series, VA has sponsored webinars on the use of medications during pregnancy.
- As part of VA's training web site, pregnancy-related information is available to VA providers (https://www.va.gov/COMMUNITYCARE/docs/providers/VHA_CC-Provider_Toolkit.pdf and <https://www.tucson.va.gov/services/women/Maternity.asp>).

Other Collaborative Efforts

Collaborations noted above include VA's work with DoD on practice guidelines. VA also collaborates with federal, state, and local governments; community-based care organizations; professional societies; and others on issues related to research and clinical care for pregnant women and lactating women. For example, VA served as a member of CDC's Preconception Health and Health Care Committee, which issued recommendations to improve preconception health to prevent adverse pregnancy outcomes (<https://www.cdc.gov/preconception/documents/actionplannationalinitiativepchhc2012-2014.pdf>).

Food and Drug Administration (FDA)

Research

FDA designs and performs research to advance knowledge related to drugs, devices, biologics, cosmetics, foods, and tobacco used by pregnant women and lactating women. FDA-supported science includes basic research into the mechanisms of therapies in pregnancy and lactation; preclinical studies, especially in toxicity; utilization of medication by pregnant women and lactating women; safety and effectiveness of therapies and medications during pregnancy and lactation; pharmacokinetics and pharmacodynamics; effects of exposure to medical devices; and the impact of tobacco product use during pregnancy and lactation. Multiple FDA organizational units support intramural and extramural research portfolios applicable to the work of the Task Force.

- The FDA's Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) is a multi-site collaborative research program developed to enable the conduct of studies of medication use and outcomes in pregnancy. Collaborators include the U.S. Food and Drug Administration and researchers at the HMO Research Network, Kaiser Permanente Northern and Southern California, and Vanderbilt University. Datasets have been created at each site linking health care data for women delivering an infant from 2001-2008 and infants born to these women.
- The FDA Office of Women's Health (OWH) funds, promotes, and conducts research related to sex differences and conditions unique to women, including pregnancy.
- The Tobacco Regulatory Science Program (TRSP) works with other FDA organizations and with the NIH to fund research supporting regulatory activities on tobacco products. For example, TRSP funds studies that investigate the impact of health warnings on tobacco use, ultrasound markers of maternal smoking, how design and flavors affect waterpipe use, and response to reduced nicotine content in pregnant smokers compared to non-pregnant smokers. FDA has described the likelihood of electronic nicotine delivery systems among pregnant smokers.
- The CDRH funds studies of prenatal exposures to medical devices. For example, researchers used a computational modeling approach to evaluate electromagnetic exposure to hand-held metal detectors and MRIs.
- The FDA's NCTR worked with NIH's National Institute for Environmental Health Sciences (NIEHS) on a preclinical toxicology study of exposure to oxybenzone, a UV filter that is often incorporated into consumer products. NCTR has worked with a number of other FDA groups and NIEHS on a group of studies to address exposure to BPA, including in pregnant women and lactating women. NCTR has also modeled the physiology of pregnancy to test drug metabolism.
- CBER conducts animal and human studies related to the safety and efficacy of vaccines in a variety of populations, including pregnant women. Examples include studies of maternal immunization and Zika infection in pregnant populations. CBER's Office of Biostatistics and Epidemiology (OBE) is involved in pilot studies to evaluate linkage of neonatal outcomes with pregnancies in Sentinel data.

- The FDA Center for Food Safety and Applied Nutrition conducts research on infant feeding practices, contaminants in dietary supplements, and the potential of birth defects from cosmetic products containing retinol.
- The CBER intramural grant program funds a variety of programs including a study on the assessment of Zika virus glycoprotein immunogen placental transmission and an evaluation of pharmacokinetics of thrombogenic impurity following different routes of immune globulin administration during pregnancy.

FDA has supported research on the utilization of medication among pregnant and/or lactating women for a wide variety of health conditions. These studies primarily describe how many women with a condition use medication and what types of medications they use. FDA researchers have assessed medication use among pregnant women with asthma, convulsive disorders, mental health disorders, and bacterial and viral infections.

Clinical Practice Information and Recommendations

FDA generally does not provide direct clinical care. However, the information produced and analyzed by the FDA forms the foundation for the regulation of prescription drugs, biologics, and medical devices. FDA's role as a regulatory agency also includes development of guidance, policies, and information to ensure the safety and effectiveness of therapies for pregnant women and lactating women.

FDA's Pregnancy and Lactation Labeling Rule requires industry to provide standardized information in prescription drug labeling to help health care providers in assessing benefit and risk and in discussing these factors with pregnant women and lactating women who need medication.

Other examples of relevant regulation and/or guidance include:

- FDA regulates human donor milk under the FDA's regulatory authorities for foods as per the Food Safety and Modernization Act (FSMA).
- Facilities producing foods (i.e., donor human milk) covered by FDA's rule implementing mandatory preventive controls for human food are subject to FSMA's risk-based mandated inspection frequencies. FSMA mandates that these non-high-risk domestic facilities be inspected every 5 years and high-risk domestic facilities every 3 years.
- FDA's CDRH is working to provide more information about MRI exposure in pregnancy.
- On December 3, 2014, the FDA published the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule) (<https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm>, <https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/actsrulesregulations/ucm445102.htm>, and <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093311.htm>).

- FDA is providing guidance on toxicity potential in infectious disease therapies for women of childbearing age and pregnant women in *Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications* (<https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074827.htm>).

FDA also participates in provider training activities to help inform clinical practitioners about the safety and effectiveness of drugs in pregnancy. FDA webinars or briefing materials are available on a wide range of medications and related topics, including:

- Vaccines in pregnancy (<https://www.fda.gov/aboutfda/transparency/basics/ucm508553.htm>)
- Pain medication in pregnancy (<https://www.fda.gov/drugs/drugsafety/ucm429117.htm>)
- Use of amoxicillin in pregnancy (<https://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm072124.htm>)
- Flu treatment in pregnancy (<https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm184917.htm>)
- Use of valproate in pregnancy (<https://www.fda.gov/Drugs/DrugSafety/ucm350684.htm>)
- Use of doxycycline in pregnancy (<https://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm131011.htm>)
- Use of ciprofloxacin in pregnancy (<https://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130712.htm>)
- Use of magnesium sulfate in pregnancy (<https://www.fda.gov/drugs/drugsafety/ucm353333.htm>)

FDA connects health professionals and consumers to registries and provides links to drug information and educational resources for pregnant women via the [FDA Pregnancy Registry List](#).

In 2016, FDA issued the Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood to address blood safety in response to the Zika virus. Although these recommendations were not specific to pregnant women, they were important as a preventive measure to reduce pregnant women's potential exposure to the virus.

Communications

FDA uses a wide range of forms of print, digital, and web-based communications related to pregnancy and lactation. FDA's websites provide detailed information to pregnant women and lactating women and their health care providers about medications in pregnancy and lactation. FDA seeks to inform a wide range of audiences about use and safety for medications, biologics, and medical devices among pregnant women and lactating women. Some examples include:

- FDA's Pregnancy web page includes consumer-oriented information on medication in pregnancy, breast pumps, food safety, and X ray and ultrasound exposure (<https://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm117976.htm>).
- FDA's CDRH provides information on the availability, safety, and use of breast pumps (<https://www.fda.gov/forconsumers/consumerupdates/ucm335261.htm>).
- FDA's Drug Safety Communications provide up to date information about drug safety issues, including those of special interest to pregnant women and lactating women (<https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm413118.htm>; <https://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>). For example, a recent communication recommended against the use of prescription codeine pain and cough medicines and tramadol pain medicines in breastfeeding women (<https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm>).
- FDA's OWH created a web portal to help connect pregnant women and health professionals with medical product and disease-based registries that collect information on drug exposures during pregnancy (<https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm>).

Other Collaborative Efforts

In addition to those noted above, FDA is involved in a wide range of collaborative efforts with other federal agencies to promote scientific and communications efforts to benefit pregnant women and lactating women. For example, FDA is a collaborating agency in the Treating for Two initiative, which reviews medication safety data in pregnancy to develop treatment guidelines (<https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html>).

FDA often collaborates with professional groups and other federal agencies on scientific workshops:

- In 2016, FDA also collaborated with NIH, other HHS divisions, EPA, and USAID to hold a scientific workshop to identify optimal approaches for treating and caring for the generation of children exposed to Zika virus in the womb.
- FDA and CDC collaborated on a conference on Zika Virus in the Americas in March 2016; FDA presented material on regulatory considerations in the development of drugs for use in pregnant women (<https://www.cdc.gov/zap/index.html>).
- In November 2014, FDA and CDC held a workshop, in collaboration with the ACOG, to discuss new and emerging tobacco product use in pregnant and reproductive age women (<https://www.fda.gov/downloads/tobaccoproducts/newsevents/ucm542886>).
- In 2016, FDA representatives participated in the Academy of Breastfeeding Medicine's 8th annual summit on breastfeeding (<http://www.bfmed.org/>).
- FDA collaborated with NIH on an expert panel to advance inclusion of pregnant and postpartum women in tuberculosis drug trials (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772846/pdf/civ991.pdf>).

- FDA and NIH collaborated on a scientific review conference on phenylketonuria (PKU), including PKU and pregnancy (<http://www.sciencedirect.com/science/article/pii/S1096719214000857>).

FDA's CDRH and CDER participate as liaisons to the ACOG OB Practice Committee. FDA collaborates with CDC on the National Health and Nutrition Examination Survey (NHANES), which includes medical, diet, dental, and physiologic measurements that may contribute to the understanding of medical and nutritional issues in pregnant women and lactating women

(<https://www.cdc.gov/nchs/nhanes/index.htm>). FDA also collaborates with CDC on the Pregnancy Risk Assessment Monitoring System (PRAMS) (<https://www.cdc.gov/prams/index.htm>).

FDA and NIH collaborate in the Consortium Linking Academic and Regulatory Insights on the Toxicity of BPA (CLARITY – BPA) study. This collaboration joins federal regulators and academic researchers to help inform regulatory decision-making regarding BPA

(https://www.niehs.nih.gov/research/programs/endocrine/bpa_initiatives/index.cfm). FDA also collaborates with NIH in the Biomarkers, EndpointS, and other Tools (BEST) Resource effort. This resource provides clarity about terminology related to biomarkers, including pregnancy biomarkers, and surrogate endpoints, which is vital for collaborations across agencies.

Health Resources and Services Administration (HRSA)

Research

HRSA is not primarily a research agency; HRSA's mission involves improving health care to people who are geographically isolated and economically or medically vulnerable. HRSA also supports the training of health professionals, the distribution of providers to areas where they are needed most, and improvements in health care delivery (<https://www.hrsa.gov/about/index.html>). However, HRSA does support some research on topics related to the health of pregnant women and lactating women.

Most of HRSA's research efforts are supported by its Maternal and Child Health Bureau. These grants typically do not address safety and effectiveness of medication for pregnant women directly. Instead, these projects are primarily focused on health care utilization, impact of HRSA's programs, and dissemination of evidence-based practices in the community. Between 30 and 50 such HRSA-supported research projects related to pregnancy and/or lactation have been active in each of the previous 5 years. Examples of HRSA-funded research projects include:

- Researchers supported by HRSA are examining the impact of the mandate to provide lactation support services under the Affordable Care Act and assessing this mandate's effects on breastfeeding behaviors.
- Another HRSA-supported study was designed to examine the efficacy of an exercise intervention to prevent perinatal depression among women attending federally qualified health centers serving high-risk women. Possible effects on gestational weight gain and retention will also be explored.

- HRSA-supported scientists are conducting a pilot randomized controlled trial to generate data on the impact of tele-lactation services via video calls on personal electronic devices. Data on breastfeeding duration and exclusivity, as well as perceptions and satisfaction with breastfeeding, will be captured via surveys and in-depth interviews and compared across groups.
- A recently-completed HRSA project was designed to adapt and test an evidence-based intervention for pregnant women with PTSD (and sub-threshold PTSD symptoms) served by the HRSA-funded Healthy Start program.

HRSA supports the MCH Research Network on Pregnancy Related Care (also known as the CARN network), a group of practicing obstetrician-gynecologists affiliated with ACOG. The CARN network conducts multi-site research on critical issues affecting pregnancy-related care and maternal health across the lifespan and administers survey studies to inform clinical practice. Recent findings from the CARN network include:

- Researchers found variation in practice patterns of obstetricians related to screening for group B streptococcal colonization and providing preventive antibiotics before or during labor.
- CARN researchers studied patient and provider reports about recommendations for and receipt of the flu vaccine among pregnant women. They found substantial discrepancies between self-reports of medical providers and patients and medical records; for example, nearly 80 percent of patients self-reported accepting the influenza vaccine, but medical record data indicated only 36 percent of patients accepting the vaccine. Similarly, all medical providers reported giving recommendations for the vaccine, but only 85 percent of patients reported receiving a recommendation.
- Researchers investigated physician practice patterns for pregnant patients around the influenza vaccine during the 2009-2010 H1N1 flu seasons. The data showed that a higher proportion of women eligible for Medicaid in a practice was associated with a lower estimate of vaccination rate. Ob-gyns with more than 20 years of practice were more likely to be concerned about the risks of antivirals and less likely to routinely prescribe them. An earlier CARN survey had also demonstrated that some barriers existed to vaccination within ob-gyn practices.
- A survey conducted by CARN indicated that many ob-gyns are not utilizing the recommended validated resources such as the DSM-IV or PHQ-2 for diagnosis of depression or prior to prescribing antidepressants.

HRSA has also recently funded a Home Visiting Research network to facilitate research and research-based practice in home visiting programs (<http://www.hvrn.org/index.html>).

Clinical Care

HRSA's **Health Center Program** is a national network of health centers that provide comprehensive primary health care services to more than 24 million people nationwide, regardless of a patients' ability to pay. About 1 in 13 people relies on a HRSA-funded center for primary care (<https://www.hrsa.gov/about/organization/bureaus/bphc/index.html>). In addition, more than half of

pregnant women and more than a third of infants and children benefit from HRSA's **Title V Maternal and Child Health Block Grant** program. The MCH Block Grant contains three major funding categories: (1) MCH Formula Grants to States are awarded to state health agencies based on the number of children in poverty in a state and represent the largest funding component of Title V (roughly 85 percent); (2) Special Projects of Regional and National Significance (SPRANS) grants; and (3) Community Integrated Service Systems (CISS) grants. Both SPRANS and CISS grants are awarded on a competitive basis and support such activities as research, training, and systems-building to improve access and equity in health care (<https://www.hrsa.gov/about/pdf/mchb.pdf>).

HRSA's **Healthy Start** program provides grants in geographic areas with high infant mortality. In these areas, pregnant women who enroll in Healthy Start receive health care services, but also may receive (as needed) case management, outreach, home visiting, adolescent pregnancy prevention, childbirth education, parenting skill-building, self-esteem building, transportation, translation, child care, breastfeeding and nutrition education, father support, housing assistance, job training, and prison/jail-based services (<https://mchb.hrsa.gov/maternal-child-health-initiatives/healthy-start>). The **Maternal, Infant, and Early Childhood Home Visiting Program** gives pregnant women and families, particularly those considered at-risk, necessary resources and skills to raise children who are physically, socially, and emotionally healthy and ready to learn (<https://mchb.hrsa.gov/maternal-child-health-initiatives/home-visiting-overview>). The **Ryan White HIV/AIDS program** provides primary medical care and essential support services for people living with HIV who are uninsured or underinsured. Part D of the Ryan White program is designated specially for women, infants, children, and youth living with HIV (<https://hab.hrsa.gov/about-ryan-white-hiv-aids-program/about-ryan-white-hiv-aids-program>).

The **Healthy Tomorrows Partnership for Children** program, through several projects across the country, supports services for pregnant women and lactating women and their children (https://www.grants.gov/view-opportunity.html?oppld=284005&utm_campaign=enews06022016&utm_medium=email&utm_source=govdelivery). Examples of program activities include:

- The Medical Care Management for Complex Prenatal Patients project provides coordinated medical care management to complex and high-risk prenatal patients to improve care coordination and address poor perinatal health outcomes in South Los Angeles.
- The Healthy Tomorrows Hawaii program works to make prenatal and pediatric care more culturally appropriate and accessible.
- The Maternal and Child Health Coordination Project in Chicago provides services to new mothers and babies in low-income, medically underserved neighborhoods. The program encourages breastfeeding, postpartum follow-up, and preventive screenings.
- The ReadNPlay for a Bright Future program in Tennessee provides lactation education and support for mothers of infants.

Through its **training programs**, HRSA provides some guidance and/or information related to the care of pregnant and/or lactating women. For example:

- The Leadership Education in Adolescent Health (LEAH) training program may provide training related to the care of pregnant or lactating teens.
- The Maternal and Child Health Nutrition Training program (<https://mchb.hrsa.gov/training/projects.asp?program=12>) may also include information related to nutrition in pregnancy.
- MCH training programs also prepare health care professionals, including visiting nurses and home workers.
- Centers of Excellence in Maternal and Child Health Education, Science, and Practice prepares students for careers in maternal and child health fields. Several centers within this program offer education related directly to pregnancy and/or lactation. For example:
 - The University of Minnesota's program offers continuing education materials on breastfeeding
 - The University of North Carolina's program established accredited training for lactation consultants
 - The University of Washington's program serves as a regional resource on a variety of maternal and child health issues, including breastfeeding

Communications

In addition to the activities noted above, HRSA is a federal partner in Text4Baby, a text messaging application free to pregnant women and women with infants to inform them of a variety of pregnancy- and lactation-related health issues.

HRSA also supports MotherToBaby, which is a national call system that provides information about the safety of medications, herbal products, substances of abuse, chemicals, and other exposures during pregnancy and nursing.

HRSA's websites provide resources to pregnant women and lactating women and their health care providers. HRSA seeks to inform a wide range of audiences about medication use and safety among pregnant women and lactating women (<https://mchb.hrsa.gov/maternal-child-health-topics/maternal-and-womens-health>).

Other Collaborative Efforts

In addition to efforts noted above, HRSA participates in the Federal Interagency Forum on Child and Family Statistics, an interagency group designed to improve both the quality and use of data on children and families by investigating questions of data quality, data measurement, and data integration and by coordinating the development and use of statistical databases among federal agencies (<http://childstats.gov>).

In 2016, HRSA also collaborated with NIH, other HHS divisions, EPA, and USAID to hold a scientific workshop to identify optimal approaches for treating and caring for the generation of children exposed to Zika virus in the womb.

National Institutes of Health (NIH)

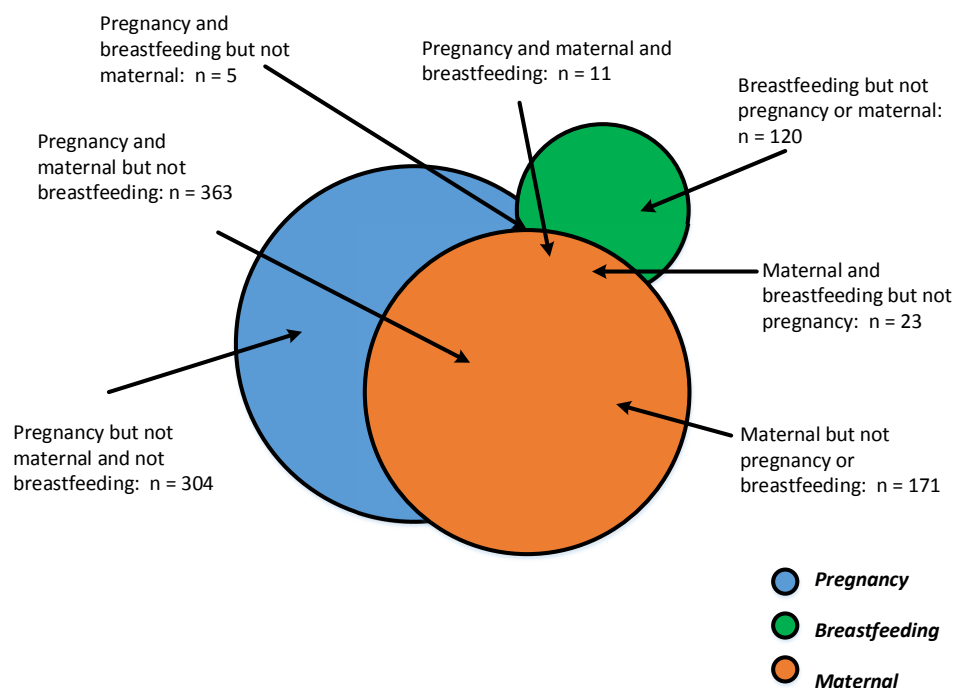
Research

NIH is the largest biomedical research agency in the world. Through its institutes and centers (ICs), as well as the NIH Office of the Director, the NIH supports extramural, intramural, and interagency research related to pregnant women and lactating women. These studies range from investigations into the fundamental processes that drive biological changes during pregnancy to the development and testing of new interventions in pregnant women and lactating women. NIH's studies specifically related to pregnant women and lactating women cover a range of conditions, both those associated with pregnancy itself and chronic conditions that many pregnant women experience before and during pregnancy and lactation.

NIH reports on its research to the public by scientific category, using a standardized process that combines scientific expertise with sophisticated automated systems. In 2017, NIH developed and implemented two new scientific categories, (1) Pregnancy and (2) Breastfeeding, Lactation, and Breast Milk, to enable the agency to analyze and track research in these areas.

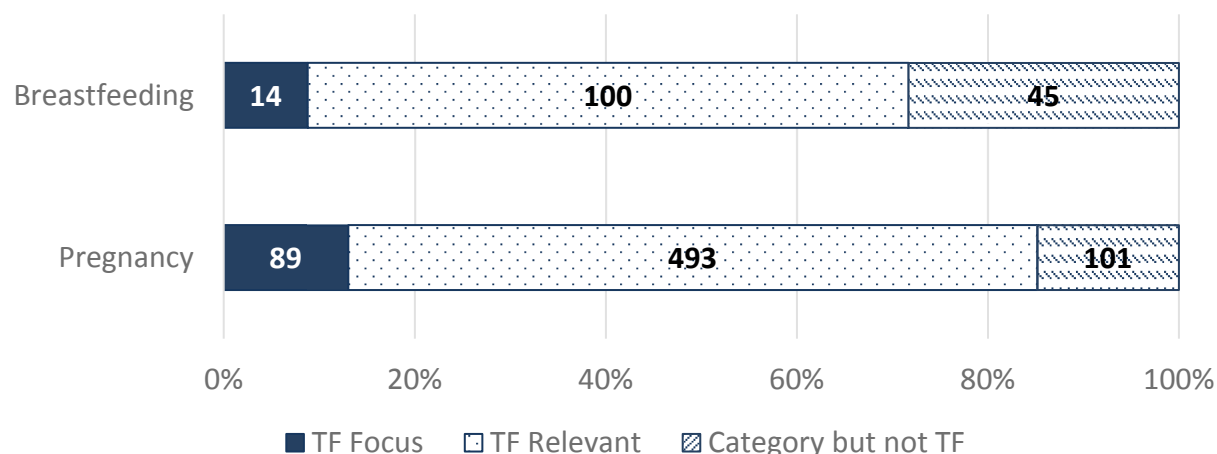
According to FY 2017 data, NIH funds over 900 research projects in three scientific categories related to the Task Force: pregnancy; breastfeeding, lactation, and breast milk; and maternal health. Many of these research projects overlap more than one of these categories (see Appendix VII, Figure 1).

Appendix VII, Figure 1. NIH-Funded Projects in Task Force Related Categories, FY 2017



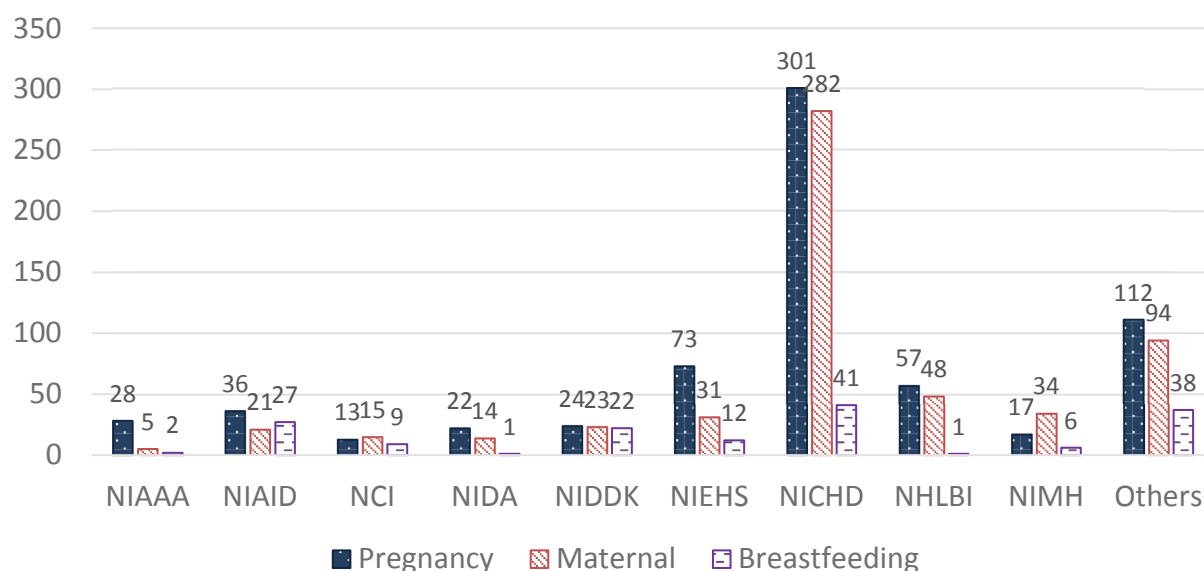
Most of the projects within the pregnancy and breastfeeding categories are relevant to the Task Force (See Appendix VII, Figure 2), although many are primarily focused on research questions that do not directly address the Task Force mission. For example, much of the research in the pregnancy category describes physiological aspects of pregnancy and/or lactation. This knowledge is important to understanding safe medication use, even though it is not primarily focused on medication. A much smaller number of grants—9 percent of the breastfeeding projects and 13 percent of the pregnancy projects—directly focus on the use of medications and supplements in pregnant and lactating populations.

Appendix VII, Figure 2. NIH Pregnancy and Breastfeeding Research Projects by Relationship to the Task Force, FY 2017



Research related to pregnancy and breastfeeding, lactation, and breast milk is supported across the NIH, including most NIH ICs and the NIH Office of the Director (OD). The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funded the most projects in each of the Task Force-related categories in FY17 (see Appendix VII, Figure 3).

Appendix VII, Figure 3. NIH-Funded Projects in Task-Force Related Categories, FY 2017



Pregnancy

For pregnancy, a review of NIH grants in FY 2017 indicates that:

- A total of 21 of NIH's 27 ICs support at least one grant or project related to pregnancy (A list of NIH ICs is included in Appendix I).
- Six hundred and eighty-three research projects are related to pregnancy. These grants accounted for \$319M in NIH spending in FY 2017.
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports the largest share of NIH grants on pregnancy. Other ICs with significant research investments include the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Drug Abuse (NIDA), the National Institute of Environmental Health Sciences (NIEHS), and the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK).
- The largest share of these grants is funded using the R01 type of research grant mechanism (see Appendix VII, Figure 4).
- Thirteen percent of NIH's pregnancy research grants are directly related to medication and/or supplement use by pregnant women. For example, the drug indomethacin has been widely used in patients with spontaneous preterm labor to delay delivery and prolong pregnancy. However, the dose of indomethacin is based largely on clinical experience and not on rigorous pharmacokinetic (PK)/pharmacodynamic (PD) studies. NICHD-supported researchers are conducting a PK/PD study to assess the appropriate dose and to determine if dosing should

reflect such factors as genotype, race/ethnicity, and BMI ([R01HD083003](#)¹⁸⁸). Nearly three-quarters of NIH's pregnancy research grants—72 percent—are applicable to the Task Force mission but not directly focused on the development, testing, or use of drugs and therapies. For example, NIAID-supported researchers are conducting a study of how malaria during pregnancy affects the placenta ([R21AI105506](#)¹⁸⁹). The remaining grants are related to pregnancy but are not applicable to therapies for pregnant women and lactating women. For example, NIH supports some research on the impact of short pregnancy intervals on maternal and child health ([F31HD086970](#)¹⁹⁰).

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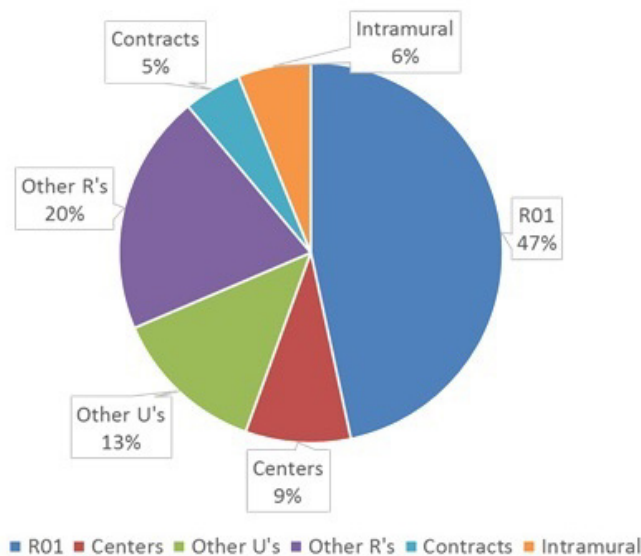
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Appendix VII, Figure 4. NIH Pregnancy Research Projects by Mechanism, FY 2017



Examples of NIH research centers, networks, and major studies related to pregnancy include:

- The [Obstetric-Fetal Pharmacology Research Unit Network](#) is designed specifically to improve the safety and effective use of therapeutic drugs in women during pregnancy and lactation. The network provides the expert infrastructure needed to test therapeutic drugs during pregnancy and conducts multidisciplinary research to enhance the understanding of obstetric pharmacokinetics and pharmacodynamics. This program allows researchers to conduct safe, technically sophisticated, and complex studies that will help clinicians protect women's health, improve birth outcomes, and reduce infant mortality. Some research by the network focuses on pharmacology, efficacy, placental transfer, and placental biotransformation of therapies and drugs to treat a variety of medical conditions. Studies conducted by the network have focused on a variety of conditions, including gestational diabetes, type 2 diabetes, pregnancy side effects like nausea, uterine complications that lead to preterm labor, and other critical conditions in pregnant women.
- The [Maternal Fetal Medicine Unit Network](#) conducts rigorous clinical trials in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. The network's research studies are designed to address maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications, and to provide the rationale for evidence-based, cost-effective obstetric practice. For example, current studies are examining: (1) the use of antenatal steroids at 34-36 weeks gestation to reduce the need for neonatal respiratory support, (2) treatment for pregnant women with mild gestational diabetes to decrease the risk of childhood obesity for their offspring, and (3) administration of congenital cytomegalovirus infection (CMV) hyperimmune globulin before 23 weeks gestation in women with primary CMV infection.

- A cohort of 10,000 nulliparous women were enrolled in the [nuMoM2b study](#) to ascertain pregnancy outcomes, particularly adverse outcomes such as preterm birth, preeclampsia, gestational diabetes, stillbirth and small for gestational age. Half of the cohort is currently being followed 2-7 years postpartum in the nuMoM2b Heart Health Study to elucidate the relationship between adverse pregnancy outcomes and future CVD and to use knowledge gained for modification of risk factors for cardiovascular disease.
- The [Chronic Hypertension and Pregnancy \(CHAP\) project](#) is a large multi-center randomized clinical trial designed to evaluate the comparative effectiveness and safety of pharmacologic treatment of mild chronic hypertension in pregnancy.
- Researchers are assessing how pregnancy-related hormones and/or growth factors affect specific enzymes and placental drug transporters during pregnancy ([P01DA032507, sub-project 8581¹⁹¹](#)).
- Researchers are exploring how maternal arsenic exposure and micronutrient deficiencies alter maternal and newborn influenza antibody function, respiratory morbidity, and systemic immune function following maternal influenza vaccination ([R01ES026973¹⁹²](#)).
- The [International Maternal, Pediatric, Adolescent AIDS Clinical Trials \(IMPAACT\) Network](#) is a collaboration of investigators and institutions that study and evaluate HIV/AIDS therapies in pregnant women, infants, children, and adolescents, in the United States and around the world. Topic areas for the network's current clinical trials include: antenatal and postnatal strategies to prevent mother-to-child transmission of HIV, antiretroviral drug use in pregnant and postpartum HIV-infected women, and the pharmacokinetics of antiretroviral therapies for HIV-infected pregnant women and children.
- The [National Toxicology Program \(NTP\)](#) is an interagency program, involving NIH, EPA, and others. The NTP provides scientific information about hazardous substances in the environment and serves as a scientific source for programs, activities, and policies that advocate for health and disease prevention. One NTP effort is a study that examines the developmental effects and pregnancy outcomes associated with cancer chemotherapy use in pregnant women.

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- Researchers are enabling the molecular epigenetic validation of postpartum depression biomarkers on pregnant women. This study will generate an important postpartum depression resource as well as confirm and expand the utility of early screening and identify new targets and time points for therapeutic intervention ([R01MH112704¹⁹³](#)).
- A team of NIH-funded researchers are studying the effects of BMI-based prenatal vitamins as opposed to standard prenatal vitamin supplementation on markers of oxidative stress and inflammation in obese pregnant women ([K23HD074648¹⁹⁴](#)).
- Researchers are evaluating a Longitudinal Remote Consultation implementation strategy to improve patient outcomes from team based collaborative care for depressed pregnant women receiving primary care in federally qualified health centers ([R01MH108548¹⁹⁵](#)).

Breastfeeding, Lactation, and Breast Milk

For breastfeeding, a review of NIH grants in FY 2017 indicates that:

- A total of 20 of NIH's 27 ICs support at least one grant related to breastfeeding.
- One hundred and fifty-nine research projects are related to breastfeeding, lactation, and/or breast milk. These research projects accounted for \$91.7M in NIH spending in FY 2017.
- NICHD, NIAID, and NIDDK support the greatest shares of NIH grants on breastfeeding and lactation.
- The largest share of these grants is funded using the R01 type of research grant mechanism (See Appendix VII, Figure 5).
- Nine percent of the grants reported in NIH's breastfeeding category are directly related to medication and/or supplement use by lactating women. For example, the drug buprenorphine has been used in pregnant patients with opioid addiction to help reduce or prevent opioid withdrawal symptoms in the newborn. NICHD-supported researchers are conducting a PK/PD

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study to assess the appropriate dose in pregnant women ([U54HD047905, subproject 8647](#)¹⁹⁶). Nearly two-thirds of NIH's breastfeeding research grants—63 percent—are applicable to the Task Force mission but not directly focused on the development, testing, or use of drugs and therapies. For example, scientists are conducting a study of naturally occurring peptides in human milk ([R00HD079561](#)¹⁹⁷). The remaining grants are related to breastfeeding but are not applicable to therapies for pregnant women and lactating women. For example, NIH supports some research on the most effective ways to promote breastfeeding in general, particularly in disadvantaged communities ([R01HD055191](#)¹⁹⁸).

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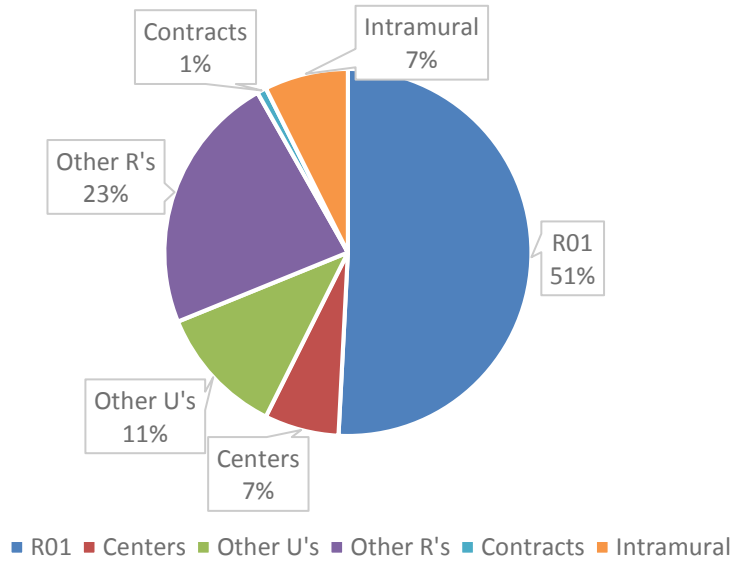
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Appendix VII, Figure 5. NIH Breastfeeding Research Projects by Mechanism, FY 2017



Examples of NIH research grants related to breastfeeding include:

- Because infants less than 6 months of age rely on maternal antibodies for protection against influenza, it is important to know the types of maternal influenza vaccines that best protect infants. Scientists aim to compare maternal response to the intranasal live-attenuated influenza vaccine and the systemic inactivated influenza vaccine and to evaluate levels of influenza-specific antibodies and cellular immunity in breast milk and blood ([K23HD072774](https://projectreporter.nih.gov/project_info_description.cfm?aid=9301621&icde=38681244)¹⁹⁹).
- Since little information is known about the specific molecular mechanisms responsible for the development of necrotizing enterocolitis (NEC), a neonatologist is examining the relationship between breast milk and NEC pathogenesis, including characterizing the effects of breast milk on intestinal epithelial cell proliferation and mucosal healing ([K08DK101608](https://projectreporter.nih.gov/project_info_description.cfm?aid=9418041&icde=38681326&ddparam=&ddvalue=&ddsub=&cr=1&cbs=default&cs=ASC&pbll=)²⁰⁰).

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- Researchers are investigating if a non-pharmacologic treatment (chronotherapy) for depression is effective and accepted in pregnant women and lactating women ([R34MH104377²⁰¹](#)).

Clinical Practice Information and Recommendations

NIH does not directly support clinical care, but the agency works with professional societies, federal agencies, and other stakeholders to help ensure that the scientific evidence produced by NIH research is effectively translated into clinical practice. For example, many of the clinical practice guidelines of the American Congress of Obstetricians and Gynecologists are rooted in NIH-funded studies (<https://www.acog.org/About-ACOG/ACOG-Departments/Deliveries-Before-39-Weeks/ACOG-Clinical-Guidelines>).

NIH works with the Agency for Healthcare Research and Quality to inform the U.S. Preventive Services Task Force (USPSTF), an independent, volunteer panel of national experts in prevention and evidence-based medicine (<https://www.uspreventiveservicestaskforce.org/Page/Name/home>). The Task Force works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications. A total of 18 USPSTF recommendations are directly related to pregnancy and/or lactation, and 26 recommendations include a component related to pregnancy and/or lactation.

Communications

NIH supports several public health campaigns related to pregnant women and lactating women. The Mom's Mental Health Matters campaign, spearheaded by the National Child and Maternal Health Education Program (NCMHEP), focuses on depression and anxiety around pregnancy. Other NCMHEP efforts have focused on preventing preterm birth, especially elective deliveries before 39 weeks of gestation. The long-standing Safe to Sleep campaign was designed to educate parents and caregivers about ways to reduce the risk of Sudden Infant Death Syndrome and other sleep-related causes of infant death, such as suffocation. The Safe to Sleep campaign recognizes the importance of breastfeeding and has worked with breastfeeding advocacy groups.

Many NIH ICs provide resources to the public on pregnancy and treatment of pre-existing conditions. For example, NIDDK includes information on its website about pregnancy for women who have diabetes, thyroid disease, or kidney disease. The National Cancer Institute provides detailed information for women undergoing breast cancer treatment during pregnancy. The National Heart, Lung, and Blood

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Institute provides information on high blood pressure in pregnancy. The NIH's National Library of Medicine (NLM), through its Medline Plus resource, provides both general information on pregnancy and more detailed information on specific conditions in pregnancy.

NLM also supports the LactMed® database, an important resource for lactating women and their health care providers. The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced (<https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>).

Other Collaborative Efforts

In addition to efforts noted above, NIH participates in the Federal Interagency Forum on Child and Family Statistics, an interagency group designed to improve both the quality and use of data on children and families by investigating questions of data quality, data measurement, and data integration and by coordinating the development and use of statistical databases among federal agencies (<http://childstats.gov>). NIH participates in the CDC's Treating For Two initiative, which is working to expand and accelerate research to fill knowledge gaps; evaluate available evidence; and deliver up to date information to support decision making among prescribers, pharmacists, and consumers (<https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html>). NIH also partners on Text4baby, a text messaging application free to pregnant women and women with infants to inform them of a variety of pregnancy- and lactation-related health issues (www.text4baby.org).

NIH has supported a variety of inter-agency scientific collaborations and has received support from other agencies interested in using NIH-funded infrastructure for pregnancy-related research. Several NIH ICs recently worked with the FDA and other agencies to bring experts together and develop a research agenda on Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes. Other examples include the Antiretroviral Pregnancy Registry, a collaborative effort of NIH, CDC, FDA, and HRSA, and the Zika Experimental Science Team (ZEST) data portal, an electronic collaboration tool for Zika researchers supported by NIH, FDA, and HRSA.

Appendix VII, Figure 6. NIH Institutes and Centers Supporting Pregnancy- and Lactation-Related Research Grants and Projects

| Acronym | Organization | Pregnancy | Lactation |
|---------|--|-----------|-----------|
| FIC | Fogarty International Center | X | X |
| NCCIH | National Center for Complementary and Integrative Health | X | X |
| NCI | National Cancer Institute | X | X |
| NHLBI | National Heart, Lung, and Blood Institute | X | X |
| NHGRI | National Human Genome Research Institute | X | X |
| NIA | National Institute on Aging | X | X |
| NIAAA | National Institute on Alcohol Abuse and Alcoholism | X | X |
| NIAID | National Institute of Allergy and Infectious Diseases | X | X |
| NIAMS | National Institute of Arthritis and Musculoskeletal and Skin Diseases | X | X |
| NIBIB | National Institute of Biomedical Imaging and Bioengineering | X | |
| NICHD | <i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development | X | X |
| NIDA | National Institute on Drug Abuse | X | X |
| NIDCD | National Institute on Deafness and Other Communication Disorders | X | |
| NIDCR | National Institute of Dental and Craniofacial Research | X | X |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases | X | X |
| NIEHS | National Institute of Environmental Health Sciences | X | X |
| NIGMS | National Institute of General Medical Sciences | X | X |
| NIMH | National Institute of Mental Health | X | X |
| NIMHD | National Institute on Minority Health and Health Disparities | X | X |
| NINDS | National Institute of Neurological Disorders and Stroke | X | X |
| NINR | National Institute of Nursing Research | X | X |
| NLM | National Library of Medicine | | X |
| OD | Office of the Director, National Institutes of Health | X | X |

National Vaccine Program Office, Office of the Assistant Secretary for Health, HHS

Research

The National Vaccine Program Office (NVPO) provides strategic leadership to further the five goals of the [National Vaccine Plan](#) and ensure that collaborative, coordinated immunization activities are carried out in an efficient, consistent, and timely manner. To meet the statutory goals outlined for the National Vaccine Program, administered by the Assistant Secretary for Health, NVPO works with both federal and non-federal stakeholders to develop and implement strategies to prevent human infectious diseases through immunization, prevent adverse events following vaccination, and overcome barriers in the planning of immunization activities. NVPO also supports the National Vaccine Advisory Committee and the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (<https://www.hhs.gov/nvpo/about/index.html>).

The first two objectives of the National Vaccine Plan—(1) to develop new and improved vaccines and (2) to enhance the vaccine safety system—depend crucially on research. NVPO supports research projects specifically related to immunization of women during pregnancy. Key examples include:

- Clinical study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular pertussis vaccine (Tdap) Safety in Pregnant Women: This is an observational study of both pregnant and non-pregnant women. Detailed data will be collected from study participants on prior Tdap/Td/TT receipt. With Day 0 serving as the day of vaccination, participants will be followed through Day 7 for reaction symptoms, and data will be analyzed to see if there is a difference in reaction symptoms between pregnant and non-pregnant women. Pregnant women will be followed through delivery for collection of pregnancy outcome data. In addition, follow-up will be conducted for infants born to mothers who received Tdap during pregnancy to assess health outcomes and growth through 6 months of life.
- Clinical Study of the Safety of Simultaneous Administration of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap), and Inactivated Influenza Vaccine in Pregnant Women: This is a pilot, prospective, randomized, open-label clinical trial. During the study, pregnant women will be randomized (1:1) to receive co-administration of a single dose of influenza vaccine and a single dose of Tdap, or sequential administration of the vaccines—first influenza, followed by Tdap approximately 21 days later. Researchers will analyze whether reaction symptoms, antibody levels, and adverse maternal and infant outcomes vary across the study groups.
- NVPO is also currently supporting a research study in collaboration with BARDA and FDA to analyze possible associations between infections, vaccinations, and medications during pregnancy with possible birth defects outcomes. Tdap, HPV, and influenza vaccines are the vaccines being researched. VPO is also trying to identify possible causal associations with crucial birth outcomes, such as microcephaly (other than Zika virus).

NVPO also supports efforts to improve research methods and infrastructure to benefit the field of maternal immunization research. For example:

- NVPO funded the creation of a maternal-neonatal vaccine safety database and analysis of outcomes using the database. The first analysis compares the likelihood of fever in babies born to vaccinated versus unvaccinated mothers after receiving their first pertussis vaccination. The second analysis compares alternative benefits to influenza vaccination during pregnancy (<https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html>).
- NVPO has supported the development of a study to improve the algorithms used to identify miscarriages and stillbirths in post-licensure immunization safety surveillance databases (www.cdc.gov/vaccinesafety).
- NVPO is currently supporting research to validate vaccine safety definitions in studies that include pregnant women and newborns (www.hhs.gov/nvpo/featured-priorities-vaccine-safety/index.htm; <https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html>).

Clinical Practice Information and Recommendations

NVPO is responsible for staffing the National Vaccine Advisory Committee. The Committee serves an advisory role, providing peer review, consultation, advice, and recommendations to the Assistant Secretary for Health, in his or her capacity as the Director of the National Vaccine Program, on matters related to the program's responsibilities. Specifically, the committee studies and recommends ways to encourage the availability of an adequate supply of safe and effective vaccination products in the United States; recommends research priorities and other measures to enhance the safety and efficacy of vaccines; advises the Assistant Secretary for Health in the implementation of Sections 2102 and 2103 of the PHS Act; and identifies annually the most important areas of government and non-government cooperation that should be considered in implementing Sections 2102 and 2103 of the PHS Act.

In 2014 and 2016, the committee issued two reports with recommendations regarding maternal immunizations. These reports addressed the charge issued by the Assistant Secretary for Health to i) review the current state of maternal immunization and existing best practices and identify programmatic barriers to the implementation of current recommendations related to maternal immunization and make recommendations to overcome these barriers and ii) identify barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers (https://www.hhs.gov/sites/default/files/nvpo/nvac/reports/nvac_reducing_patient_barriers_maternal_immunizations.pdf; <http://journals.sagepub.com/doi/full/10.1177/0033354917698118>).

Communications

NVPO administers the www.vaccines.gov website, which provides extensive information about vaccines generally. The website includes specific materials about vaccinations administered during pregnancy (www.vaccines.gov/who_and-when/pregnant/index.htm). NVPO also held a webinar in 2016 about vaccine safety in pregnancy and supports social media efforts to connect NVPO with stakeholders and the public.

Other Collaborative Efforts

NVPO works in close collaboration with CDC and FDA on vaccine safety related issues in general. NVPO also supports the Immunization Safety Task Force, an interagency effort involving CDC, NIH, DoD, IHS, VA, FDA, and DoD (<https://www.hhs.gov/nvpo/featured-priorities/vaccine-safety/index.html>). The NVPO has contracted with the National Committee for Quality Assurance to incorporate maternal immunization composite measures (including Tdap and influenza) into the Healthcare Effectiveness Data and Information Set (HEDIS).

NVPO is also partnering with Kaiser Permanente to create a new health outcomes database. NVPO wants to improve ways to survey vaccinations during pregnancy through insurance claims and medical health records.

Office of the Assistant Secretary for Health (OASH)

Research

OASH sponsors research related to therapies for pregnant women and lactating women mostly through the National Vaccine Office Program.

Clinical Practice Information and Recommendations

OASH's Office of Disease Prevention and Health Promotion supports guidelines on diet and physical activity for all Americans. This includes specific information related to physical activity for women during pregnancy (<https://health.gov/paguidelines/guidelines/chapter7.aspx>). The dietary guidelines also will incorporate comprehensive guidance for women during pregnancy, starting with the next edition (<http://www.dietaryguidelines.gov>). Information about children from birth to 24 months will also be included in future editions of the Dietary Guidelines for Americans.

OASH's Regional Offices have incorporated USPSTF recommendations into provider training and resources in collaboration with AHRQ. For example, the Healthier Pregnancy provider training initiative informs providers about successful efforts to implement USPSTF recommendations.

OASH's Region 5 held an education and training event in August 2016 to engage health and social services professionals who serve pregnant women and young mothers to help promote breastfeeding. In the same region, the Trauma-Informed Care: Understanding and Responding to the Health Effects of Adverse Experiences Through the Lifespan program trains providers about the impact of traumatic exposure on pregnancy health and breastfeeding. OASH's Region 7 supports a regional breastfeeding outreach effort. The Successes in Adolescent Health program provides tools and techniques to support pregnant and parenting young people with breastfeeding.

Research Policies and Regulation

The Office for Human Research Protections within OASH oversees regulations for the protection of human research subjects, including rules that specifically address research involving pregnant women (<https://www.hhs.gov/ohrp/>).

Communications

The Office on Women's Health (OWH) within OASH includes a wide array of pregnancy-related information on its website, <https://www.womenshealth.gov/pregnancy>. Examples of specific items include:

- Information on medications in pregnancy: <https://www.womenshealth.gov/a-z-topics/pregnancy-and-medicines>
- Resources on Zika and pregnancy, updated for the summer of 2017: <https://www.hhs.gov/blog/2017/05/15/zika-and-pregnancy-protecting-babies-protecting-yourself.html>
- Information on tobacco and pregnancy <https://betobaccofree.hhs.gov/gallery/pregnant.html>
- Supporting nursing moms at work <https://www.womenshealth.gov/breastfeeding/employer-solutions/?from=breastfeeding>
- Other information about breastfeeding and lactation: <https://www.womenshealth.gov/printables-and-shareables/resource/guides?from=breastfeeding>; <https://www.womenshealth.gov/itsonlynatural/?from=breastfeeding>

OWH also supports a National Breastfeeding Helpline at 1-800-994-9662, which provides telephone access to trained breastfeeding peer counselors in English and Spanish.

Other Collaborative Efforts

OWH supported a conference and subsequent publication on opioid use that incorporates information on use by pregnant women: <https://www.womenshealth.gov/files/documents/final-report-opioid-508.pdf>. OWH also supports the United States Breastfeeding Committee, an independent nonprofit collaboration of over 50 organizations that support breastfeeding initiatives across the United States.

Appendix VIII - Pregnancy Registries, Cohorts, and Databases

Although there is a clear need for new, prospective basic and clinical research studies of pregnant women and lactating women, existing data sources may also yield useful information to help scientists, clinicians, and women address research gaps. For example, a number of pregnancy registry databases have been established to incorporate information from pregnant women and/or their offspring based on a woman's medical condition or exposure to a drug or therapy. Some of these registries are initiated by private companies, nonprofits, federal agencies, or academic health centers. Because pregnant women have often been excluded from pre-market drug development trials, the FDA may require medical product manufacturers to conduct a pregnancy registry after the product is approved. Data from pregnancy registries may be used to obtain safety data on medication use in pregnancy, and to include this information in product labeling if the data are sufficiently robust. Generally, the FDA may require post-marketing pregnancy registries when (1) there is a high likelihood that the product will be used (deliberately or inadvertently) by women who are or may become pregnant; or (2) there is potential safety concern based on the pharmacologic class, data from animal studies or data from clinical trials.²⁰² Industry and other sponsors may develop registries without FDA involvement for similar reasons, or to facilitate pregnancy-related research with other scientific goals. Examples of pregnancy registries that are currently open are listed in Appendix VIII, Table 1.

Aside from registries, researchers may collect data on cohorts of pregnant women and their offspring as part of an epidemiological study; a clinical research study with specific research aims; or a broad data collection effort to learn about pregnancy in general. Some cohort studies are initiated by clinical research networks, combining information from their ongoing clinical studies. Other cohort databases receive data from pregnant women who are sharing their experiences. Another group of cohort databases arise from epidemiological and/or longitudinal studies of pregnant women and their offspring that have specific scientific goals. Large databases--from very large cohort studies, national health systems, vital records systems, and large insurers--also hold promise of useful information. Many of these databases are sponsored by European countries with national health systems, where information on an entire population can be more easily assembled. These databases vary in scope – some include individuals based on a health condition of the mother or offspring, and others include data on all pregnant women in a geographic area. Examples of these types of datasets that are currently open or regularly updated are listed in Appendix VIII, Table 2.

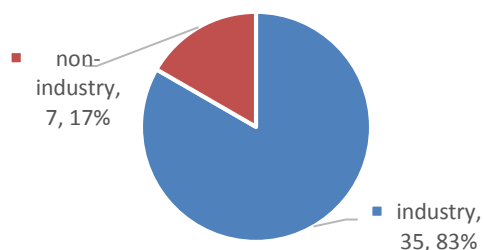
²⁰² Guidance for Industry: Establishing Pregnancy Exposure Registries. August 2002. Accessed at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071639.pdf>

Pregnancy registries, cohort studies, and databases included in this review were identified based on several separate but overlapping data sources: a listing posted by the FDA’s Office of Women’s Health²⁰³, information from www.clinicaltrials.gov, and publications obtained through literature analysis. For each registry, cohort study, or database, information on the size of the database, sponsor, eligibility criteria, and other details were obtained from the primary website of the database. If the information was not available from a primary website, secondary sources (such as the FDA website or www.clinicaltrials.gov) were used. A list of the pregnancy registries and large databases is provided below. This list is not comprehensive but includes information readily available from the sources above as of May 2018. Only registries, cohorts, or databases that are currently open, or are regularly updated with new records, are included in the listing below. Many other closed databases related to pregnancy are available for analysis, but including all these was beyond the scope of this report.

Pregnancy Registries

A total of 42 active, distinct registries were identified. Some of these registries were originally separate entities, but were later merged or linked; these are shown on the listing below as a single entity. For example, the National Pregnancy Registry for Atypical Antipsychotics includes data from a variety of drugs that are also sometimes listed as single-drug registries. When it was unclear whether two entities were distinct, but they shared a website, they are listed together. As shown in Appendix VIII, Figure 1, over three-quarters of the registries were sponsored by industry and the remainder by nonprofits or other non-industry organizations.

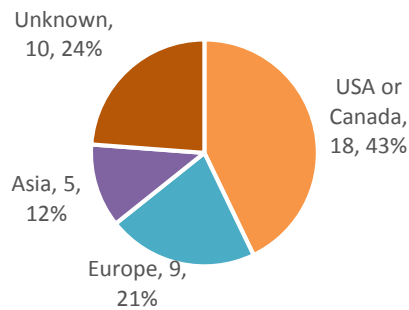
Appendix VIII, Figure 1: Pregnancy Registries, by Type of Sponsoring Organization



²⁰³ <https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm>. The list of pregnancy exposure registries on this webpage may not be comprehensive and are posted based on sponsor or investigator request.

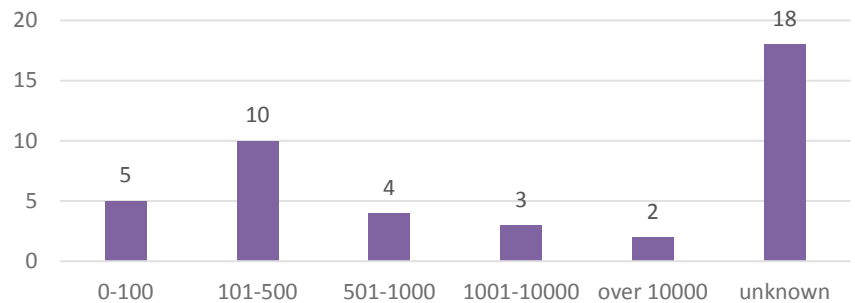
Organizations all over the world sponsor pregnancy registries. Area of origin for the sponsoring organization is shown in Appendix VIII, Figure 2. Many registries, particularly those based in Europe, accept participants from multiple countries.

Appendix VIII, Figure 2: Pregnancy Registries by Area of Origin



For many registries, enrollment figures were not provided. For some of the other registries identified, enrollment was limited. Estimated or target enrollment numbers are shown in Appendix VIII, Figure 3.

Appendix VIII, Figure 3: Number of Pregnancy Registries by Estimated or Target Enrollment



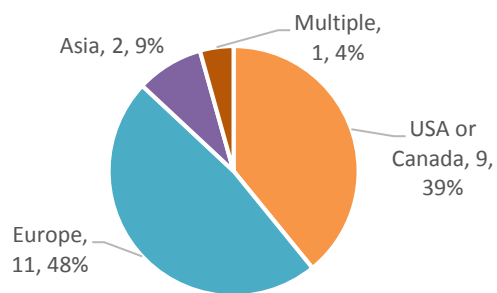
Pregnancy Databases

In addition to the registries, 23 distinct databases were identified. These databases typically have information about pregnant women and the use of therapies generally, without focus on specific disease or drug. Many are sponsored by the national health systems of governments with single-payer or other national or regional health systems. Population based databases and electronic data sources (insurance claims and electronic health care data) have also been used to further pregnancy research. For example, datasets from countries with universal health care systems, and surveillance data from the United States, have been used to conduct case control studies to assess outcomes following exposure to a medical product. Claims data from large health insurance companies or health maintenance organizations have been used to identify therapies commonly used in pregnant women. Data from large health systems have been used to identify therapies commonly used in pregnant women and to provide

data on pregnancy outcomes. In addition, large databases have been used for natural history studies to better understand the experiences of women with chronic health conditions who become pregnant.

As shown in Appendix VIII, Figure 4, most of the large databases identified were from foreign countries, although the United States had more databases than any other single country.

Appendix VIII, Figure 4: Large Pregnancy Databases by Area of Origin



Appendix VIII, Table 1: List of Currently Open Pregnancy Registries

(scope defined by medical condition or medication exposure)

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|--|---|----------------------|---|-------------------------|------------------|---|
| The North American Antiepileptic Drug (AED) Pregnancy Registry | Aptiom® (eslicarbazepine acetate), Banzel® (rufinamide), Carbatrol® (carbamazepine), Celontin® (methsuximide), Depakene® (valproic acid), Depakote® & Depakote ER (divalproex sodium), Diamox® (acetazolamide), Dilantin® (phenytoin), Eptol® (carbamazepine), Felbatol® (felbamate), Frisium® (clobazam), Gabitril® (tiagabine), Keppra®/Keppra XR® (levetiracetam), Klonopin® (clonazepam), | Epilepsy | Massachusetts General Hospital | 10,200 (as of May 2016) | 1997 | http://www.aedpregnancyregistry.org/about-history/ |

²⁰⁴ This refers to the organization that hosts the registry and does not indicate the funder of the registry.

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---------------|---|----------------------|---|----------------------|------------------|---------|
| | Lamictal [®] /Lamictal XR [®] (lamotrigine), Lyrica [®] (pregabalin), Mebaral [®] (mephobarbital), Mesantoin [®] (mephenytoin), Mysoline [®] (primidone), Neurontin [®] (gabapentin), Onfi [®] (clobazam), Peganone [®] (ethotoin), Phenobarbital (generic), Phenytek [®] (phenytoin), Potiga [®] (ezogabine), Sabril [®] (vigabatrin), Seconal Sodium [®] (secobarbital), Serax [®] (oxazepam), Tegretol [®] (carbamazepine), Topamax [®] (topiramate), Tranxene [®] (clorazepate dipotassium), Trileptal [®] (oxcarbazepine), Valium [®] (diazepam), Vimpat [®] (lacosamide), Xanax [®] (alprazolam), Zarontin [®] (ethosuximide), Zonegran [®] (zonisamide) | | | | | |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|--|--|---|---|----------------------|------------------|--|
| Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project | Multiple drugs including Actemra® (tocilizumab), Arava® (leflunomide), Aubagio® (teriflunomide), Cimzia® (certolizumab pegol), Entyvio® (vedolizumab), Kevzara® (sarilumab), Nucala® (mepolizumab), Orencia® (abatacept), Otezla® (apremilast), Pertussis/Tdap vaccine (“Whooping Cough” vaccine), Praluent® (alirocumab), Repatha® (evolocumab), Stelara® (ustekinumab), Xeljanz® (tofacitinib citrate) | Multiple conditions including ankylosing spondylitis, asthma, connective tissue disease, Crohn’s disease, fibromyalgia, giant cell arteritis, high cholesterol, juvenile rheumatoid arthritis, lupus, multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, systemic sclerosis, | OTIS (nonprofit) at the University of California, San Diego | Unknown | Unknown | https://mothertobaby.org/ongoing-studies/ ; https://clinicaltrials.gov/ct2/show/NCT01797224 |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---|---|---|--|----------------------|------------------|---|
| | | ulcerative colitis | | | | |
| Vaccines and Medications in Pregnancy Surveillance Study (VAMPSS) | H1N1 and seasonal influenza vaccines, antivirals, asthma medications, Menveo (meningococcal vaccine), Afluria (influenza vaccine) | Asthma, influenza, and meningococcal meningitis | Collaboration between American Academy of Allergy, Asthma & Immunology (AAAAI); Organization of Teratology Information Specialists Research Center at the University of California-San Diego (OTIS); Slone Epidemiology Center at Boston University (SEC); Harvard | Unknown | 2009 | https://www.aaaai.org/about-aaaai/strategic-relationships/vampss ; http://www.bu.edu/slone/research/studies/vampss/ |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|-----------------------------------|--|----------------------|--|---------------------------------|---|--|
| | | | Pregnancy Research Group. Funders include BARDA, FDA, CDC, NVPO, AHRQ, Novartis, and CSL Limited depending on the research topic | | | |
| Pregnancy and Cancer Registry | Multiple chemotherapies | Cancer | Cooper Medical School at Rowan University | Unknown | Unknown | http://www.cancerandpregnancy.com/treating-cancer-in-pregnant-women/ |
| Antiretroviral Pregnancy Registry | Abacavir (ZIAGEN [®] , ABC), abacavir + lamivudine (EPZICOM [®] , EPZ), abacavir + lamivudine + zidovudine (TRIZIVIR [®] , TZV), lamivudine + dolutegravir + lamivudine (TRIUMEQ [®] , TRI), adefovir dipivoxil (HEPSERA [®] , ADV), atazanavir (REYATAZ [®] , ATV), atazanavir + cobicistat (EVOTAZ [®] , EVO), cobicistat (TYBOST [®] , COBI), darunavir | HIV/AIDS | AbbVie, Alvogen Inc, Amneal Pharmaceuticals LLC, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Dr. Reddy's Laboratories (UK) Ltd, F.Hoffmann-La Roche, Gilead | roughly 21,681 (as of Dec 2017) | 1989 (inception); 2/1/1993 (all antiretroviral drugs) | https://clinicaltrials.gov/ct2/show/NCT00404989?cond=NCT00404989&rank=1 http://www.apregistry.com/forms/interim_report.pdf |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---------------|--|----------------------|---|----------------------|------------------|---------|
| | (PREZISTA [®] , DRV), darunavir + cobicistat (PREZCOBIX [™] , REZOLSTA [™] , PCX), delavirdine mesylate (RESCRIPTOR [®] , DLV), didanosine (VIDEX [®] , VIDEX [®] EC, DDI), dolutegravir (TIVICAY [®] , DTG), efavirenz (SUSTIVA [®] , STOCRIN [®] , EFV), efavirenz + emtricitabine + tenofovir disoproxil fumarate (ATRIPLA [®] , ATR), elvitegravir (VITEKTA [®] , EVG), elvitegravir + cobicistat + tenofovir alafenamide (GENVOYA [®] , GEN), elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate (STRIBILD [®] , STB), emtricitabine (EMTRIVA [®] , FTC), emtricitabine + tenofovir | | Sciences Inc, Hetero Labs Ltd, Janssen Scientific Affairs, LLC, Lupin Pharmaceuticals Inc, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Princeton, Ranbaxy Inc (a Sun Pharma Company), Sandoz Inc, ScieGen Pharmaceuticals Inc, SigmaPharm Laboratories, Silarx Pharmaceuticals Inc. (a wholly- owned subsidiary of Lannett Company Inc.), Strides Shasun Ltd, Teva | | | |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---------------|---|----------------------|--|----------------------|------------------|---------|
| | alafenamide (DESCOVY [®] , DVY), enfuvirtide (FUZEON [®] , T-20), entecavir (BARACLUDE [®] , ETV), etravirine (INTELENCE [®] , ETR), fosamprenavir calcium (LEXIVA [®] , FOS), indinavir (CRIXIVAN [®] , IDV), lamivudine (EPIVIR [®] , 3TC), lamivudine + zidovudine (COMBIVIR [®] , CBV), lopinavir + ritonavir (KALETRA [®] , ALUVIA [®] , LPV/r), maraviroc (SELZENTRY [®] , CELSENTRI [®] , MVC), nelfinavir (VIRACEPT [®] , NFV), nevirapine (VIRAMUNE [®] , VIRAMUNE XR [®] , NVP), raltegravir (ISENTRESS [®] , RAL), rilpivirine (EDURANT [®] , RPV), rilpivirine + emtricitabine + tenofovir | | Pharmaceuticals USA, Inc., ViiV Healthcare, West-Ward Pharmaceuticals, and Zentiva Group | | | |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---------------|---|----------------------|---|----------------------|------------------|---------|
| | alafenamide (ODEFSEY [®] , ODE), rilpivirine + emtricitabine + tenofovir disoproxil fumarate (COMPLERA [®] , CPA; EVIPLERA [®] , EPA), ritonavir (NORVIR [®] , RTV), saquinavir mesylate (INVIRASE [®] , SQV-HGC), stavudine (ZERIT [®] , d4T), telbivudine (SEBIVO [®] , TYZEKA [®] , LdT), tenofovir alafenamide (VEMLIDY [®] , TAF), tenofovir disoproxil fumarate (VIREAD [®] , TDF), tenofovir disoproxil fumarate + emtricitabine (TRUVADA [®] , TVD), tipranavir (APTIVUS [®] , TPV), zidovudine (RETROVIR [®] , ZDV) | | | | | |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---|---|----------------------|--|----------------------|------------------|---|
| Transplantat Pregnancy Registry International | Anti-rejection medicines and immunosuppressants including Nulojix (belatacept) and mycophenolate products | Transplants | Gift of Life Institute, housed at the Gift of Life Donor Program | Over 2300 | 1991 | https://www.transplantpregnancyregistry.org/about-us/ |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---|--|---|---|-------------------------|------------------|--|
| National Pregnancy Registry for Atypical Antipsychotics | Abilify (aripiprazole), Aristada (aripiprazole lauroxil), Clozaril (clozapine), Fanapt (iloperidone), Geodon (ziprasidone), Invega (paliperidone), Latuda (lurasidone), Ruxulti (brexpiprazole), Risperdal (risperidone), Saphris (asenapine), Seroquel (quetiapine), Zyprexa (olanzapine) | Mental health disorders including schizophrenia, bipolar disorder, depression, and schizoaffective disorder | Center for Women's Mental Health at Massachusetts General Hospital; supported by Sunovion; Alkermes, Inc.; Forest Laboratories, Inc./Actavis PLC; Otsuka Pharmaceutical; and Teva Pharmaceuticals, Ltd. | 800 (target enrollment) | November 2008 | https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/atypicalantipsychotic/ ; https://clinicaltrials.gov/ct2/show/NCT01246765 |
| T.A.P.P. (Take Action to Prevent Pregnancy) | Acitretin | Psoriasis | Teva Pharmaceuticals | Unknown | Unknown | https://www.tevagenerics.com/acitretin |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---|---|--|--|--|------------------|---|
| National Pregnancy Registry for Psychiatric Medications | Adderall (Amphetamine), Concerta, Daytrana, (Methylphenidate), Desoxyn (Methamphetamine HCl), Dexedrine (Dextroamphetamine), Focalin (Dextroamphetamine), Metadate CD, Methylin (methylphenidate HCL), Provigil (modafinil), Ritalin (methylphenidate HCL), Vyvanse (lisdexamfetamine Dimesylate) | ADD/ADHD | Center for Women's Mental Health at Massachusetts General Hospital | Unknown | Unknown | https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/ |
| Mucopolysaccharidosis I (MPS-I) Registry | Aldurazyme (laronidase) | Mucopolysaccharidosis type I; Hurler Syndrome; Scheie Syndrome; Hurler-Scheie Syndrome | Sanofi Genzyme Corporation | Unknown (includes pregnant and non-pregnant registrants) | November 2003 | https://clinicaltrials.gov/ct2/show/NCT00144794 |
| National Pregnancy Registry for Antidepressants | Anafranil (clomipramine), Asendin (amoxapine), Brintellix (vortioxetine), Celexa (citalopram), Cymbalta (duloxetine), Desyrel (trazodone), | Mood, anxiety, or psychiatric disorders | Center for Women's Mental Health at Massachusetts General Hospital | Unknown | Unknown | https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/ |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | |
|---------------|--|----------------------|---|----------------------|------------------|--|
| | Effexor (venlafaxine), Effexor XR (Venlafaxine Hydrochloride), Elavil (amitriptyline), Emsam (selegiline), Fetzima (levomilnacipran), Fluoxetine (Fluoxetine Hydrochloride), Forfivo (Bupropion Hydrochloride), Lexapro (escitalopram), Ludiomil (maprotiline), Luvox (fluvoxamine), Marplan (Isocarboxazid), Nardil (phenelzine), Norpramin (desipramine), Pamelor (nortriptyline), Parnate (tranylcypromine), Paxil (paroxetine), Pristiq (desvenlafaxine), Prozac (fluoxetine), Remeron (mirtazapine), Serzone (nefazodone), Sinequan (doxepin), Surmontil (trimipramine), Tofranil (imipramine), Viibryd (Vilazodone Hydrochloride), Vivactil (protriptyline), Wellbutrin (bupropion), | | | | | |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|----------------------------------|--|--|---|-------------------------|------------------|---|
| | Wellbutrin SR (bupropion Hydrochloride), Zoloft (sertraline) | | | | | |
| Benlysta Pregnancy Registry | Benlysta (belimumab) | Systemic Lupus Erythematosus (SLE) | GlaxoSmithKline | 500 | November 2011 | http://pregnancyregistry.gsk.com/belimumab.html |
| Bexsero Pregnancy Registry | Bexsero (Meningococcal Group B Vaccine) | Meningococcal diseases including meningitis | GlaxoSmithKline | 50 | January 2016 | http://pregnancyregistry.gsk.com/bexsero.html |
| Mycophenolate Pregnancy Registry | Cellcept (mycophenolate), Myfortic (mycophenolate) and any generic mycophenolate formulation | Heart, kidney, or liver transplantation or autoimmune diseases | Genentech. Collaborators include Accord Healthcare, Inc.; Sandoz; Apotex Corporation; Novartis Pharmaceuticals; Pfizer; Mylan Pharmaceuticals; Teva Pharmaceuticals USA; Alkem Laboratories, Ltd.; Roxane Laboratories; | 500 (target enrollment) | November 2012 | https://clinicaltrials.gov/ct2/show/NCT01733082 |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|-----------------------------|-----------------------------|--|---|--|------------------|--|
| | | | Vintage Pharmaceuticals, LLC | | | |
| Cymbalta Pregnancy Registry | Cymbalta (duloxetine HCl) | Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Peripheral Neuropathic Pain (DPNP), Fibromyalgia, chronic musculoskeletal pain | Lilly USA, LLC | 484 (target enrollment) | July 2009 | https://clinicaltrials.gov/ct2/show/NCT01074151 ; https://lillypregnancyregistry.com/ |
| Fabry Disease Registry | Fabrazyme (agalsidase beta) | Fabry Disease | Sanofi Genzyme | Unknown (includes pregnant and non-pregnant registrants) | July 2001 | https://clinicaltrials.gov/ct2/show/NCT00196742 |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|--|---|-------------------------|---|-------------------------|------------------|--|
| Seqirus Influenza Vaccine Pregnancy Registry | Flucelvax Quadrivalent | Influenza | Seqirus | 600 (target enrollment) | Unknown | https://flu.seqirus.com/flucelvax/pregnancy-registry.html |
| The Gilenya Pregnancy Exposure Registry | Gilenya (fingolimod) | Multiple Sclerosis (MS) | Novartis Pharmaceuticals | 500 (target enrollment) | October 2011 | http://n.neurology.org/content/78/1_Supplement/P06.189 ; https://clinicaltrials.gov/ct2/show/NCT01285479 |
| MotHER Pregnancy Registry | Herceptin (Trastuzumab), Kadcyla (ado-trastuzumab emtansine), Perjeta (pertuzumab) | Breast Cancer | Genentech | 100 (target enrollment) | January 2009 | http://www.motherpregnancyregistry.com/ ; https://clinicaltrials.gov/ct2/show/NCT00833963 |
| Merck Pregnancy Registry Program | Janumet (sitagliptin phosphate plus metformin hydrochloride), Januvia (sitagliptin phosphate) | Type 2 Diabetes | Merck & Co., Inc. | Unknown | Unknown | http://www.merckpregnancyregistries.com/januvia.html |
| Merck Pregnancy Registry Program | Maxalt (rizatriptan) | Migraine Headaches | Merck & Co., Inc. | Unknown | Unknown | http://www.merckpregnancyregistries.com/maxalt.html |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|--|---|---|---|-------------------------|------------------|--|
| Global Lomitapide Pregnancy Exposure Registry | Juxtapid (lomitapide) | Homozygous familial hypercholesterolemia | Aegerion Pharmaceuticals, Inc. | 30 (target enrollment) | October 2014 | https://clinicaltrials.gov/ct2/show/NCT02399839 |
| Lemtrada Pregnancy Exposure Registry | Lemtrada (alemtuzumab) | Multiple sclerosis | Sanofi Genzyme | 185 (target enrollment) | 2015 | https://cmsc.confex.com/cmsc/2017/webprogram/Paper4861.html |
| Sanofi Pasteur Pregnancy Registry (includes the Menactra vaccine Pregnancy Registry) | Menactra® (meningococcal polysaccharide diphtheria toxoid conjugate vaccine), Adacel® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed), Fluzone® Intradermal (Influenza Virus Vaccine), Fluzone® Quadrivalent (Influenza Virus Vaccine) | Meningitis, (Menactra®); tetanus, diphtheria, and pertussis (Adacel®); influenza (Fluzone®) | Sanofi Pasteur | Unknown | Unknown | http://www.sanofipasteurpregnancyregistry.com/ ; http://www.sanofipasteurpregnancyregistry.com/?fa=menactra |
| Menveo Pregnancy Registry | Menveo (Meningococcal oligosaccharide diphtheria CRM-197 conjugate vaccine) | Meningococcal diseases | GlaxoSmithKline | 100 | September 2014 | http://pregnancyregistry.gsk.com/menveo.html ; https://clinicaltrials.gov/ct2/show/NCT02223637 |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---|--|---|---|--|------------------|---|
| Pompe Disease Registry | Myozyme (alglucosidase alfa) | Pompe disease (GAA deficiency), glycogen storage disease type II | Sanofi Genzyme | Unknown (includes pregnant and non-pregnant registrants) | August - 2004 | https://clinicaltrials.gov/ct2/show/NCT00231400 |
| Mucopolysaccharidosis VI (MPS VI) Clinical Surveillance Program | Naglazyme (galsulfase) | Mucopolysaccharidosis VI, Maroteaux-Lamy Syndrome | BioMarin Pharmaceutical | Unknown (includes pregnant and non-pregnant registrants) | July 2005 | https://clinicaltrials.gov/ct/show/NCT00214773?order=2 |
| Nuvigil and Provigil Pregnancy Registries | Nuvigil (armodafinil) and Provigil (modafinil) | Obstructive sleep apnea, Hypopnea Syndrome, narcolepsy, shift work sleep disorder | Teva Pharmaceuticals; United BioSource Corporation | 300 (target enrollment) | June 2009 | http://www.nuvigilpregnancyregistry.com/ ; http://provigilpregnancyregistry.com/ ; https://clinicaltrials.gov/ct2/show/NCT01792583 |
| Praluent® (Alirocumab) Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study | Praluent (alirocumab) | High cholesterol (high cholesterol familial hypercholesterolemia, atherosclerotic cardiovascular disease) | Sanofi. Regeneron Pharmaceuticals is a collaborator | 375 (target enrollment) | December 2017 | https://clinicaltrials.gov/ct2/show/NCT03379558?term=praluent&rank=1 |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|--|-----------------------------|------------------------|---|-------------------------|------------------|---|
| Amgen's Pregnancy Surveillance Program | Prolia (denosumab) | Osteoporosis | Amgen | Unknown | Unknown | https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125320s0051mg.pdf |
| A Rollover Study to Provide Continued Treatment With Eltrombopag | Promacta (eltrombopag) | Thrombocytopenia (ITP) | Novartis Pharmaceuticals | 22 | October 2013 | https://clinicaltrials.gov/ct2/show/NCT01957176 |
| Evolocumab Pregnancy Exposure Registry | Rapatha (evolocumab) | Hypercholesterolemia | Amgen. OTIS is a collaborator | 375 (target enrollment) | December 2016 | https://clinicaltrials.gov/ct2/show/NCT02957604?term=repatha&type=PReg&gndr=Female&rank=1 |
| Ribavirin Pregnancy Registry (one of the Merck Pregnancy Registries) | Ribavirin | Hepatitis C | INC Research, LLC. This is a Merck pregnancy registry. Collaborators are Aurobindo Pharma; Genentech, Inc.; Sandoz; Merck | Unknown | January 2004 | http://www.ribavirinpregnancyregistry.com/announce.htm ; https://clinicaltrials.gov/ct2/show/NCT00114712 |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|-----------------------------|--|--------------------------------------|--|-------------------------|------------------|--|
| | | | Sharp & Dohme Corp.; Teva Pharmaceuticals USA; Zydus Pharmaceuticals USA, Inc.; and Kadmon Pharmaceuticals | | | |
| Savella Pregnancy Registry | Savella (milnacipran HCl) | Fibromyalgia | INC Research, LLC/Allergan | 350 (target enrollment) | November 2009 | https://savellapregnancyregistry.com/ ; https://clinicaltrials.gov/ct2/show/NCT01026077 |
| Vibativ Pregnancy Registry | Vibativ (telavancin HCl) | Antibacterial for skin infection | Theravance Biopharma R & D, Inc. | 300 (target enrollment) | November 2009 | https://clinicaltrials.gov/ct2/show/NCT01130324 |
| Boostrix pregnancy registry | Boostrix (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) | Diphtheria/tetanus/pertussis vaccine | GlaxoSmithKline | 800 (target enrollment) | March 2014 | http://pregnancyregistry.gsk.com/boostrix.html ; https://clinicaltrials.gov/ct2/show/NCT02096276 |
| Varilrix pregnancy registry | Varilrix (varicella vaccine, live attenuated) | Varicella | GlaxoSmithKline | Unknown | Unknown | http://pregnancyregistry.gsk.com/Varilrix.html |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|---|---|---|---|--------------------------|------------------|---|
| Priorix pregnancy registry | Priorix (live measles, mumps, and rubella vaccine) | Measles, mumps, and rubella | GlaxoSmithKline | Unknown | Unknown | http://pregnancyregistry.gsk.com/Priorix.html |
| Seasonal influenza vaccine pregnancy registry | Multiple (Fluarix, Fluarix Quadrivalent, Flulaval, Flulaval Quadrivalent) | Seasonal influenza vaccine | GlaxoSmithKline | Unknown | Unknown | http://pregnancyregistry.gsk.com/seasonalInfluenzaVaccines.html |
| Biogen Multiple Sclerosis Pregnancy Exposure Registry | Tecfidera (dimethyl fumarate); Pegylated human interferon beta-1a, and Dalclizumab High Yield Process | Multiple Sclerosis | Biogen | 1125 (target enrollment) | October 2013 | https://www.pei.de/SharedDocs/Downloads/awb/nis-0301-0400/0372-beoplan.pdf?__blob=publicationFile&v=1 ; https://www.tecfiderapregnancyregistry.com/TECFIDERA-Pregnancy-Exposure-Registry ; https://clinicaltrials.gov/ct2/show/NCT01911767 |
| Vaxchora Pregnancy Registry | Vaxchora (cholera vaccine, live, oral) | Cholera | PaxVax | Unknown | Unknown | https://www.paxvaxconnect.com/vaxchora-pregnancy-registry |
| EllaOne pregnancy registry | ellaOne (female emergency contraceptive) | Emergency contraceptive | HRA Pharma | Unknown | Unknown | http://www.hra-pregnancy-registry.com/en/ |
| Gardasil 9 Pregnancy Registry (one of the Merck) | Gardasil 9 (human papillomavirus 9-valent vaccine, recombinant) | Cervical, vulvar, vaginal, and anal cancers caused by HPV | Merck & Co, Inc. | Unknown | Unknown | http://www.merckpregnancyregistries.com/gardasil9.html |

| Registry Name | Medicine(s) | Medical Condition(s) | Organization/ Sponsor ²⁰⁴ | Estimated Enrollment | Date established | Website |
|-----------------------|-------------|----------------------|---|----------------------|------------------|---------|
| Pregnancy Registries) | | | | | | |

Appendix VIII, Table 2: Additional Pregnancy Cohorts and Databases, Currently Open or Regularly Updated

| Database Name | Country | Sponsor | Date Established | Website |
|---|----------------|--|------------------|---|
| Evaluation chez la femme enceinte des médicaments et de leurs risques | France | URCAM, INSERM, and ANSM, France | 2004 | http://www.efemeris.fr/ |
| Danish Medical Birth Registry; Danish National Prescription Registry; Danish National Patient Registry (linked) | Denmark | Data Agency Health, Denmark | 1977 | http://www.medstat.dk/ |
| Health Insurance Review and Assessment Services | South Korea | Korean National Health Insurance Service | Unknown | https://www.hira.or.kr/eng/ |
| Regie de l'Assurance Maladie du Quebec | Quebec, Canada | Province of Quebec | 1992 | http://www.ramq.gouv.qc.ca/en/Pages/home.aspx |
| Medical birth registry of Norway; Norwegian Prescription database (linked) | Norway | Norwegian Institute of Public Health | 1/1/2004 | http://www.norpd.no/ |
| National Health and Nutrition Examination Survey | USA | CDC | 1959 | https://www.cdc.gov/nchs/nhanes/index.htm |

| Database Name | Country | Sponsor | Date Established | Website |
|---|-----------------|--|------------------|---|
| Clinical Practice Research Database/General Practice Research Database | UK | UK Department of Health | 1986 | https://www.cprd.com/home/ |
| Medical birth register of Sweden Prescription Drug Register; National Patient Register (linked) | Sweden | Swedish National Board of Health and Welfare | | https://lakemedelsverket.se/english/ |
| MarketScan Medicaid Research Databases | USA | Truven Health | | https://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases |
| MarketScan Commercial Claims Research Databases | USA | Truven Health | | https://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases |
| Kaiser Permanente Research Bank pregnancy cohort | USA | Kaiser Permanente | | https://researchbank.kaiserpermanente.org/our-research/for-researchers/ |
| The Health Improvement Network | UK | In Practice systems and IMS Health | | https://epi.grants.cancer.gov/pharm/pharmacoepi_db/thin.html |
| Alberta Vital Statistics - Birth; Discharge Abstract Database; CLAIM Fee for service database; Alberta health care insurance registry; Alberta provider registry (all linked) | Alberta, Canada | Province of Alberta | | http://www.servicealberta.gov.ab.ca/1233.cfm |
| International Clearinghouse for Birth Defects Surveillance & Research | multiple | WHO | 1974 | http://www.icbdsr.org/ |
| Icelandic Medical Birth Register; Icelandic Medications Registry (linked) | Iceland | | | https://www.ima.is/publications/statistics/ |
| Western Australian Data Linkage System; Western Australia Pharmaceutical Benefits Scheme (linked) | Australia | Australian Bureau of Statistics | | http://www.pbs.gov.au/pbs/home;jsessionid=15pyqmv9b9kv1xa3rqfgpaefr |

| Database Name | Country | Sponsor | Date Established | Website |
|--|----------------|--|------------------|---|
| Hungarian Case-Control Surveillance System of Congenital Abnormalities | Hungary | | 1980 | http://www.eurocat-network.eu/AboutUs/Publications/Publications/Prevention%20And%20Risk%20Factors |
| International Registry of Antiepileptic Drugs and Pregnancy | European Union | | 1999 | http://www.eurapinternational.org/ |
| German Multiple Sclerosis and Pregnancy Registry | Germany | | | https://fastlegeportalen.no/veiledararkiv/?gc=cat_1&gid=1054 |
| US Zika Pregnancy and Infant Registry | United States | CDC | 2017 | https://www.cdc.gov/pregnancy/zika/research/registry.html |
| BD-STEPS | United States | CDC | 2012 | https://www.cdc.gov/ncbddd/birthdefects/bd-steps.html |
| PregSource® | United States | NIH | 2017 | https://pregsource.nih.gov/ |
| Finnish Medical Birth Register (linked to pregnancy records) | Finland | National Institute of Health and Welfare | 1998 | https://thl.fi/fi/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns |

Appendix IX - Request for Information (RFI) and RFI Summary

Request for Information (RFI): Research Specific to Pregnant Women and Lactating Women (PRGLAC)

Notice Number: NOT-HD-18-003

Key Dates

Release Date: February 15, 2018

Response Date: April 2, 2018

Related Announcements

None

Issued by

Unice Kennedy Shriver National Institute of Child Health and Human Development ([NICHD](#))

Purpose

The 21st Century Cures Act established a [Task Force on Research Specific to Pregnant Women and Lactating Women \(PRGLAC\)](#), to advise the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC is tasked with identifying these gaps and will report its findings back to the Secretary. A series of workshops, open to the public, are being held to develop this report. In addition, the NIH is publishing this Notice to solicit input from the wider scientific community and welcomes comments from the public.

Background

The 21st Century Cures Act states in part that the report will include:

- A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies;
- Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research;
- Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women;
- Identification of Federal activities, including:
 - The state of research on pregnancy and lactation;
 - Recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;

- Dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public; and
- Existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities; and
- Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

Details of the workshops, archived videocasts, materials and information on upcoming workshops can be found on the [PRGLAC](#) website.

Under the Common Rule (<https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html>), pregnant women are listed as an example of a vulnerable population. The revised common rule would no longer include pregnant women as an example of a vulnerable population, although the provisions of Subpart B (<https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartb>) still need to be met; however, implementation of the revised rule has been delayed (<https://www.hhs.gov/ohrp/interim-final-rule-common-rule.html>). As part of the requirements of Subpart B, “If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained” (Subpart B, §46.204). Once born, only one parent’s consent is required for research studies.

Information Requested

The NIH is interested in soliciting comments and suggestions from the scientific community regarding this topic.

The NIH is interested in responses to the following topics:

- Insight on possible changes if regulations on the protection of human subjects in research were changed to remove pregnant women as a “vulnerable population” and its effects on research.
- Differences in ethics considerations for conducting research with pregnant women and lactating women.
- Appropriateness of having different consent requirements for research involving the fetus or for research involving a child. (Currently, consent for research with a child can be by either parent, but consent for a pregnant woman to participate in research requires both maternal and paternal consent.)
- Ideas on how research design and research would be affected by the inclusion of pregnant and/or lactating women. (Please include specific examples to support your comments.)
- Specific needs of the scientific community in order to conduct more research on therapies used by pregnant and/or lactating women.
- Research opportunities and/or potential new research designs when pregnant or lactating women are included in research studies. (Please cite relevant examples.)
- Methods that may alleviate or alter reluctance to include pregnant or lactating women in research. (Please provide specific examples that showcase suggested methods.)

- Best practices or promising practices to reach pregnant women and lactating women, their partners, and their health care providers when new clinical or practice guidelines are released.

How to Submit a Response

To ensure consideration, responses should be submitted by email to kaeserl@mail.nih.gov no later than Monday, April 2, 2018.

Responses to this RFI are voluntary. Do not include any proprietary, classified, confidential, trade secret, or sensitive information in your response. The responses will be reviewed by NIH staff, and individual feedback will not be provided to any responder. The Government will use the information submitted in response to this RFI at its discretion. The Government reserves the right to use any submitted information on public NIH websites, in reports, in summaries of the state of the science, in any possible resultant solicitation(s), grant(s), or cooperative agreement(s), or in the development of future funding opportunity announcements.

This RFI is for information and planning purposes only and shall not be construed as a solicitation, grant, or cooperative agreement, or as an obligation on the part of the Federal Government, the NIH, or individual NIH Institutes and Centers to provide support for any ideas identified in response to it. The Government will not pay for the preparation of any information submitted or for the Government's use of such information. No basis for claims against the United States Government shall arise as a result of a response to this request for information or from the Government's use of such information.

Inquiries

Please direct all inquiries to:

Lisa Kaeser, JD

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

Telephone: 301-496-0536

Email: kaeserl@mail.nih.gov

Summary of Responses to the Request for Information on Research Specific to Pregnant Women and Lactating Women (PRGLAC) (NOT-18-003)

The purpose of the Request for Information (RFI) is to receive input on and augment the discussions of the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC or Task Force) and to inform its recommendations to the Secretary of Health and Human Services. The RFI was published on February 15, 2018, and open for comment through April 2, 2018. It was issued by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) on behalf of PRGLAC.

In the RFI, the Task Force expressed interest in receiving input on the following topics:

- Would the removal of pregnant women as a “vulnerable population” from the federal regulations on the protection of human subjects in research change research in this population? If yes, how so? If not, please explain.
- Are the ethics of conducting research with pregnant women different from the ethics of conducting research for lactating women, and if so, how?
- Currently, consent for research with a child can be by either parent, but consent for a pregnant woman to participate in research requires both maternal and paternal consent. Is it appropriate to have different consent requirements for a fetus and child? Please cite specific examples or literature to support your comments.
- If inclusion of pregnant and/or lactating women were presumed, how would that affect research design or research? Please include specific examples to support your comments.
- Is the scientific community adequately prepared to conduct more research on therapies used by pregnant and/or lactating women? If yes, describe; if no, what is needed?
- Does inclusion of pregnant or lactating women provide new opportunities for research designs? If so, please describe the potential designs or cite relevant examples.
- What methods may alleviate or alter reluctance to include pregnant or lactating women in research? Please provide specific examples that showcase suggested methods.
- What are best or promising practices to reach pregnant and lactating women, their partners, and their health care providers when new clinical or practice guidelines are released? Please cite specific examples to support your suggestions.

Responses

As of April 2, 2018, NICHD received a total of 34 responses. Common themes and the striking range of points made are summarized below. About half of the comment letters represented multiple individuals or organizations. Eight letters were virtually identical.

The points most commonly made by respondents to the RFI were:

- Support for removing pregnant women from the “vulnerable population” category in the Federal Policy for the Protection of Human Subjects (Common Rule) and shifting to a presumption of inclusion of pregnant and lactating women in clinical research.
- Only the consent of the pregnant woman should be required for participation in research.
- Opportunistic studies of drugs commonly used by pregnant or lactating women provide a pathway to including these populations in research.
- There is little to no research on maternal milk supply, or medications used to treat inadequate production of breast milk.
- The safety and efficacy of herbal supplements for use in pregnancy or during lactation have not been well studied.
- An effort is needed to communicate with pregnant or lactating women about the value of research and its risks and benefits.

A more detailed summary of the comments follows.

I. Study Design for Research on Therapies Used by Pregnant and/or Lactating Women

Multiple comments addressed potential clinical study designs and considerations that could fill gaps in knowledge regarding therapies used by pregnant and lactating women.

Overall, several comments supported using opportunistic studies, where pregnant or lactating women are already taking prescription medications for common conditions, as an approach that would help begin research with these populations. One comment stated that there is a need for more and stronger data for health care providers to make accurate dosing decisions, and to inform product labels for pregnancy and lactation. A pregnancy registry should be established for all studies of drugs used to treat serious conditions in women who become or are pregnant. Another respondent recommended disease-specific patient registries that would include pregnant and lactating women.

One respondent cautioned that it would still be unethical to expose pregnant women in sufficient numbers to identify teratogenesis and urged the development of in vitro or animal models to make those predictions, along with post-market studies. However, as two comments pointed out, Institutional Review Boards are equipped to determine whether pregnant and lactating women should be excluded from individual trials. To address confusion within the scientific community, one comment requested that the FDA review and clarify when reprotoxicity studies provide sufficient evidence to make initial assessments of a product's safety for responsible study during pregnancy; when these studies are not required, the FDA should provide guidance on what preclinical evidence may be needed before research with pregnant women can proceed. Two respondents stated that our regulatory system should develop systems and structures that support inclusion of pregnant and lactating women in drug development, including clinical trials.

Prior to clinical trials, one respondent pointed out that risk can be assessed based on using such tools as predictive animal models, drug or disease-specific patient registries, breast milk repositories, or *ex vivo* human placental transfer. With further advances in understanding how pregnancy affects drug metabolism, distribution, and elimination, modeling and simulation could be used to estimate drug dosages in pregnancy. Clinical studies should not be known to introduce great risk of birth defects or miscarriage. Drug dosing can be confirmed in pharmacokinetic studies to ensure that pregnant and lactating women are receiving the optimal dose. Mathematical modeling that includes data from non-pregnant participants and accounts for covariates such as gestational age may alleviate concerns that pregnant women are exposed to suboptimal doses. Designing clinical trials that account for maternal adverse events as well as adverse events for the fetus or breastfed infant may alleviate safety concerns. One comment suggested that already-established obstetrical research networks could include pharmacokinetic and pharmacodynamic drug trials in their portfolios to foster higher consent rates for these studies in pregnant women.

Fifteen comments stated that the currently held presumption that pregnant or lactating women be excluded from research studies should shift to a presumption of inclusion of these populations.

Exclusion from studies could make these groups even more vulnerable due to a lack of data to inform health care decisions. Pregnant women should be included in phase III trials that are studying drugs for use in treating serious medical conditions that occur in both pregnant and non-pregnant individuals (treatment for tuberculosis was offered as an example); if a woman becomes pregnant during a trial, she can continue after providing informed consent with careful follow up to collect continued safety data and pregnancy outcomes. The same individuals can provide information on the drug's use during lactation if she breastfeeds. To ensure a study population that is truly representative, pregnant women should be included in healthy control groups. Another comment pointed to participant-engaged research as an emerging, useful method for ensuring inclusion of pregnant and lactating women in research studies.

Other respondents suggested that researchers gather knowledge by conducting studies on pregnant and lactating women who are already taking drugs for common conditions. For most clinical trials, the inclusion of pregnant and lactating women should not affect research design; however, in some studies, special considerations include assessing the effects of the proposed interventions on pregnancy, the effects of pregnancy on any adverse events associated with the intervention, and optimal dosing in pregnancy. In addition, drug-specific pharmacokinetic changes in pregnancy and any underlying pregnancy-associated conditions (hyperemesis gravidarum, preeclampsia) may alter the response to the proposed intervention. To account for physiological changes in pregnant women, trimester-specific enrollment should be considered, and for lactating women, the amount of drug or metabolite in breast milk should be measured to determine exposure to the infant. In ideal settings, clinical trials should be designed to include pre- or post-pregnancy evaluations.

Regarding enrollment into trials, one respondent pointed out that engaging the target population directly would help to define effective recruitment methods, develop relevant questions, and assist in disseminating results. Nurses can be involved in recruitment and obtaining consent for studies, and partnerships between the research and maternal health communities would be beneficial. If possible, bringing the clinical trial to the participants through home health nurses, or provision of childcare and transportation, would reduce the burden of participation. Other incentives could include nutritional education, provision of prenatal vitamins, or genetic testing and counseling.

Two comments stated that study designs should include greater data sharing, post-market surveillance, and public private partnerships using pregnancy exposure registries to add to the data collected on drugs used by pregnant and lactating women. New sampling and bioanalytical techniques should also be developed. In addition, a comment mentioned the need for capturing the health outcomes of the infant and child. However, other comments urged that the collection of data not be left only to post-market studies. One comment suggested that innovative research models, such as those that the *All of Us* research initiative is using (specific case use studies and various technologies to gather data) should be considered to build an evidence base.

Two potential study models were provided by different respondents. One suggested using the HIV-related IMPAACT P1026 study as a model of an opportunistic study to obtain information on pharmacokinetics and safety used for clinical care of pregnant women; a standard protocol is used to

allow the study of multiple separate arms of different drugs, with closure of study arms that have enrolled sufficient patients and opening of new arms for evaluating new drugs. Postpartum data are also collected. Note that these drugs have been approved for non-pregnant women.

Another model proposed for consideration is the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), which coordinates prospective registry surveillance, case-control surveillance, and database surveillance arms to study the safety of exposures in pregnancy, including recognition of important confounders.

II. Ethical Issues, Including Consent for Participation in Research

More than ten comments submitted stated support for removing pregnant women from the “vulnerable population” category in the Federal Policy for the Protection of Human Subjects (Common Rule). Instead, some organizations suggested that pregnant and lactating women should be considered “scientifically complex” or “medically complex.” They pointed out that while concern for the well-being of these populations is understandable, pregnant women are capable of making decisions about research participation, and that the practical effect of current restrictions is to limit the quality of the data used to guide clinical decision-making.

As noted above, fifteen comments supported shifting the presumption that pregnant women be excluded from clinical trials to a presumption that pregnant and lactating women be included. Several other comments recommended that the standard for inclusion of pregnant women in clinical research be revised to mirror that of pediatric research: acceptance of “no greater than minimal risk.” In addition, one comment recommended a review and clarification of standards of evidence that are necessary to responsibly include pregnant women in clinical trials. To gauge how pregnant women would perceive this change and how best to convey the messages, one respondent suggested soliciting their feedback through focus groups or another means.

Several commenters stated that having different consent requirements for research involving a fetus or for research involving a child is onerous and inequitable, particularly since about 40 percent of women in the United States are unmarried. One comment stated that there is no justification in the research context for providing more protection to the fetus than is accorded to a child. All 11 of the comments submitted on this topic agreed that only the consent of the pregnant woman should be required for participation in research.

III. Issues Concerning Research on Lactation

Although most comments referred to the research needed to fill information gaps on therapies used by pregnant and lactating women, several comments addressed some particular concerns about research related to lactation.

Ten comments stated that there is little to no research on maternal milk supply or on medications used to treat inadequate production of breast milk. One respondent objected to a study that looked at small amounts of supplementation during breastfeeding. Since under-resourced women may have reduced access to formula, the financial impact of participation in a study that includes supplementation should be considered.

Another comment suggested that researchers consider opportunities to study and reduce pregnancy-associated health disparities that may manifest in pregnant or lactating women, including population-specific studies on human milk composition in racial or ethnic minorities.

One comment pointed out that although the number of breast pump manufacturers in the United States has increased, there are issues with many of the pumps currently available and recommended that an independent review is needed so that women can choose the best pump for their own needs.

IV. Communications Among Researchers, Health Care Providers, and Pregnant and/or Lactating Women

Nine respondents observed that currently, there is little effort to communicate with pregnant or lactating women about the value of research and its risks and benefits. The comments all stated their agreement that a clear and harmonized strategy is required among all stakeholders, including patients, health care providers, research advocacy groups, industry, payers, and government. Among other approaches, they suggested strategies regarding best practices for reaching pregnant and lactating women, their partners, and health care providers when new clinical guidelines are released. These included having lactation consultants in hospitals, updating discharge instructions on warning signs to look for after birth, using pregnancy classes or breastfeeding support groups to communicate information, using a wide range of channels including social media, and incorporating new guidelines into existing provider training programs. Several comments said that a reliable web source is critical.

To address these issues, two comments stated that medical professional societies and organizations can best educate and inform their members via online education modules and continuing medical education credits. State and local health departments, mommy blogs, and nonprofits also can reach consumers, in this case, pregnant and lactating women.

A particular issue mentioned by two respondents is that prescribers, consumers, and pharmacists need to be better educated on the data on the new pregnancy and lactation label. One commenter pointed out that there is still a misperception that provision of an approved drug to a pregnant woman constitutes “off-label” use, and that clarification for health care providers would be helpful. One comment stated that although there is plenty of information on medications used during breastfeeding, too many lactating women stop taking their medications for fear of hurting their babies. This respondent expressed the opinion that breastfeeding women consult their lactation consultants, not pediatricians, for information on medication use.

V. Additional Issues Specific to Research on Therapies Used by Pregnant and/or Lactating Women

In addition to the major topics covered above, other issues related to research involving therapies used by pregnant and lactating women were raised by some respondents. Ten comments mentioned that the safety and efficacy of herbal supplements have not been well studied, although pregnant women take them (especially herbal galactogogues). Several of these respondents urged that the Task Force include herbal supplements in their review to provide opportunities for standardization of information about use during pregnancy and lactation.

Adding to the current public health crisis around opioid use, one comment pointed out that about 30 percent of women in the United States give birth by cesarean delivery; 85 percent of these are discharged with a prescription for an opioid analgesic. Two comments stated that best practices for postpartum pain and treatment are lacking, in addition to insufficient knowledge about risk factors for opioid use postpartum.

Another respondent suggested that mental health issues affect many pregnant women and women postpartum, which can also have effect on fetus/newborn, and that further research on treatments is needed.

One comment recommended that the Task Force take safe and effective therapies other than medications into account, including evidence-based psychotherapies, and alternative methods such as acupuncture, yoga, exercise, movement and light therapies, massage, nutritional dietary supplements, and diet. These should be evaluated in a controlled scientific manner, and the Task Force should be extended to address these issues.

Two respondents suggested that the dual approach of incentives (BPCA) and a regulatory mandate (PREA) should be considered as a potential model for research involving pregnant and lactating women. Other legislative models, such as the Orphan Drug Act, could help in treatment of diseases that are less prevalent in the United States. Incentives such as tax breaks, priority review vouchers, discounts on new drug application fees, and other approaches also should be explored.

VI. Additional Input

Respondents to the RFI also took the opportunity to weigh in on issues related to research on pregnancy and lactation.

Eight comments included thoughts on research on diseases and conditions that affect women of reproductive age and effect of treatment on lactation, particularly diseases and conditions that affect younger women who may become pregnant, including thyroid disorders, pituitary tumors, congenital adrenal hyperplasia, polycystic ovarian syndrome, depression, and diabetes.

One respondent pointed to the need for research on management of preconception, pregnancy, and lactation in women with multiple sclerosis. Reflecting the current public health crisis of opioid use disorder, another comment called for treatments specific to pregnant and lactating women. One respondent requested that instead of “woman,” the Task Force use the word “person” to demonstrate inclusion of transgender individuals.

Another topic deserving more research concerns optimal weight gain during pregnancy, and exercise that can help with weight control, along with community interventions to promote breastfeeding. One respondent specifically urged the Task Force to include recommendations for universal viral hepatitis screening of pregnant women and inclusion of pregnant and lactating women in HCV vaccine trials, research on direct-acting antivirals that can be used by pregnant and lactating women, and developing pediatric formulations. Another comment recommended increasing support for existing and new research networks that can conduct research in these populations. Another respondent requested funding for long-term observational studies linking diet, microbiomic, metabolomic, and epigenetic data to delivery outcomes, with the goal of reducing preterm birth rates. One comment noted that there are very few data on marijuana use during pregnancy and the long-term outcomes for the infant, although an increasing number of pregnant women are using it.

Conclusion

The PRGLAC Task Force would like to thank the respondents for their thoughtful comments. This feedback will help to inform deliberations about potential policy changes and future study designs that could be aimed at addressing the knowledge gaps regarding therapies used by pregnant and lactating women.

Appendix X – Historical Recommendations Regarding Testing of Therapies Used by Pregnant Women and Lactating Women

Timeline: Meetings & Publications with Recommendations for Pregnant and/or Lactating Women

1985: U.S. Department of Health and Human Services, Report of the Public Health Service Task Force on Women's Health Issues, *DHHS Publication No. (PHS) 88-50206*. Public Health Reports Jan-Feb 1985 Vol 100(1) 73-106.

1985: Report of the Public Health Service Task Force on Women's Health Issues Public Health Reports Jan-Feb 1985 Vol 100(1) 73-106.

1991: Institute of Medicine convened a meeting at which a panel was asked to (a) assess the adequacy of the existing knowledge base for formulating gender-specific hypotheses and (b) consider the advisability of conducting a study to explore further women's participation in clinical studies. The panel concluded that important unresolved problems and questions remained. Given changes in societal attitudes and advances in medical technology, the panel felt a reexamination of existing policies and practices would be productive

1992: IOM convened the Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies.

1993: The National Institutes of Health (NIH) Revitalization Act introduced new requirements for the inclusion of women and minorities in federally funded clinical studies except where specific criteria for the exclusion of these groups can be satisfied.

1994: Publication of the IOM committee report: Institute of Medicine, Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies; Mastroianni AC, Faden R, Federman D eds. Women and health research: Ethical and legal issues of including women in clinical studies: Volume 1. 1994; National Academies Press. [PMID 25144026](https://pubmed.ncbi.nlm.nih.gov/25144026/)²⁰⁵

1995: LaRosa JH et al. Including Women and Minorities in Clinical Research, *Applied Clinical Trials*, 1995(4)31-38.

²⁰⁵ <https://www.ncbi.nlm.nih.gov/pubmed/25144026>

2002: US FDA Guidance for Industry: Guidance for Industry: Establishing Pregnancy Exposure Registries

2004: US FDA draft Guidance for Industry: Guidance for Industry: Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling

2005: US FDA draft Guidance for Industry: Clinical Lactation Study – Study Design, Data Analysis, and Recommendations for Labeling

2007: ACOG Committee Opinion #377 Research Involving Women
American College of Obstetricians and Gynecologists, Committee on Ethics. Committee Opinion 377: Research involving women. *Obstet Gynecol* 2007;110:731-736. [PMID 17766625²⁰⁶](#))

2009: The second wave: Toward responsible inclusion of pregnant women in research (Lyerly AD, Little MO, Faden R. *Int J Fem Approaches Bioeth* 2008;1(2)5-22

2010: National Institutes of Health Office of Research on Women's Health convened a workshop to address ethical, regulatory, and scientific issues raised by the enrollment of pregnant women in clinical research

- Blehar MC, Spong C, Grady C et al. Enrolling pregnant women: Issues in clinical research. *Women's Health Issues* 2013;23:e39-e45. [PMID 23312713²⁰⁷](#)
- Foulkes MA, Grady C, Spong CY et al. Clinical research enrolling pregnant women: A workshop summary. *Journal of Women's Health* 2011;20:1429-1432. [PMID 21819233²⁰⁸](#)

2011 and 2012: Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, held a series of meetings to provide guidance to investigators regarding study design of clinical trials of vaccines and antimicrobial medications that enroll pregnant women

²⁰⁶ <https://www.ncbi.nlm.nih.gov/pubmed/?term=17766625>

²⁰⁷ <https://www.ncbi.nlm.nih.gov/pubmed/?term=23312713>

²⁰⁸ <https://www.ncbi.nlm.nih.gov/pubmed/?term=21819233>

- Rasmussen SA, Hernandez-Diaz S, Abdul-Rahman OA et al. Assessment of congenital anomalies in infants born to pregnant women enrolled in clinical trials *Clin Infect Dis* 2014;59(Suppl7):S428-S436. [PMID 25425721²⁰⁹](#) (See Beigi, above)
- Munoz FM, Weisman LE, Read JS et al. Assessment of safety in newborns of mothers participating in clinical trials of vaccines administered during pregnancy. *Clinical Infectious Disease* 2014;59(Suppl 7): S415-S427. [PMID 25425720²¹⁰](#) (See Beigi, above)

2012: National Vaccine Advisory Committee established the Maternal Immunization Working Group (Aug 2012) – report published in 2017

- Overcoming barriers and identifying opportunities for developing maternal immunizations: Recommendations from the National Vaccine Advisory Committee. *Public Health Reports* 2017;132:271-284. [PMID 28379782²¹¹](#)

2013: Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) meeting

- Beigi RH, Fortner KB, Munoz FM et al. Maternal immunization: Opportunities for Scientific Advancement. *Clinical Infectious Disease* 2014;59 (Suppl 7):S408-S414. [PMID 25425719²¹²](#)
- Frew PM, Saint-Victor DS, Isaacs MB et al. Recruitment and retention of pregnant women into clinical research trials: An overview of challenges, facilitators and best practices. *Clinical Infectious Disease*;59 (Suppl 7):S400-S407. [PMID 25425718²¹³](#)
- Munoz FM, Sheffield JS, Beigi RH et al. Research on vaccines during pregnancy: protocol design and assessment of safety. *Vaccine* 2013 31:4274-9
- Sheffield JS, Munoz RM, Beigi RH et al. Research on vaccines during pregnancy: reference values for vital signs and laboratory assessments. *Vaccine* 2013 31:4264-73.

²⁰⁹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425721>

²¹⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425720>

²¹¹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28379782>

²¹² <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425719>

²¹³ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425718>

2015: ACOG Committee Opinion #646 published

- American College of Obstetricians and Gynecologists, Committee on Ethics. Committee Opinion 646: Ethical considerations for including women as research subjects. *Obstet Gynecol* 2015;126:e100-107. [PMID 26488521](https://pubmed.ncbi.nlm.nih.gov/26488521/)²¹⁴

2015: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) convened a group of experts to review the "current" state of the clinical care and science regarding medication use during the perinatal period

- Riley LE, Cahill AG, Beigi R et al. Improving safe and effective use of drugs in pregnancy and lactation: Workshop summary. *Am J Perinatal* 2017;34:826-832. [PMID 28142152](https://pubmed.ncbi.nlm.nih.gov/28142152/)²¹⁵

2016: Division of Pediatric and Maternal Health, Office of Drug Evaluation IV at the FDA meeting *Evaluation of the Safety of Drugs and Biological Products Used During Lactation* held on April 27–28, 2016.

- Wang J, Johnson T, Sahin L et al. Evaluation of the safety of drugs and biological products used during lactation: Workshop summary. *Clin Pharmacol Ther* 2017;101:736-744. [PMID 28510297](https://pubmed.ncbi.nlm.nih.gov/28510297/)²¹⁶

2016: Panel at annual meeting of the American Society for Clinical Pharmacology and Therapeutics, March 11, 2016

- Illamola SM, Bucci-Rechtweg C, Costantine MM et al. Inclusion of pregnant and breastfeeding women in research – efforts and initiatives. *Br J Clin Pharmacol* 2018;84:214-222. [PMID 28925019](https://pubmed.ncbi.nlm.nih.gov/28925019/)²¹⁷

²¹⁴ <https://www.ncbi.nlm.nih.gov/pubmed/?term=26488521>

²¹⁵ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28142152>

²¹⁶ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28510297>

²¹⁷ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28925019>

2017: Cures Act establishing Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

2018: FDA Risk Communication Advisory Committee Meeting Requirements for Pregnancy and Lactation Labeling

2018: US FDA Draft Guidance for Industry: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials

| COMPARISON OF PRGLAC TASK FORCE RECOMMENDATIONS AND HISTORICAL RECOMMENDATIONS | |
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| PRGLAC TASK FORCE RECOMMENDATIONS | HISTORICAL RECOMMENDATIONS |
| Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics | <ul style="list-style-type: none"> • “[E]ssential to establish well-trained researchers and clinicians specialized in obstetric clinical pharmacology” (Illamola 2018) |
| Remove regulatory barriers to research in pregnant women Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research Include and integrate pregnant women and lactating women in the clinical research agenda Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women | <p>Consent</p> <ul style="list-style-type: none"> • Except for a few scenarios, requiring consent from...a[n] intimate partner is neither warranted nor ethically justified...” (ACOG 2015) • Women’s consent and “parental consent” for infant participation in lactation study “must be obtained.” (Wang 2017) <p>Regulation and legislation</p> <ul style="list-style-type: none"> • Subpart B: OPRR should revise and reissue (IOM 1994) • “[C]onsiderable efforts [are] required to develop guidance for IRBs...members may lack training or guidance regarding how to recognize or respond to the potential harm of exclusion...” (Lyerly 2008) • Clarify existing regulations and focus on IRB behavior; ambiguities in regulations and conservative and variable IRB interpretations are problems, especially with interpretation of “minimal risk” (Blehar 2013); • Need “clear and standardized definitions” of minimal risk. (NVAC 2017) • Labeling: consistent approach to labeling for lactating women needed (Wang 2017) • “[E]quivalents of PREA and BPCA could be valuable.” (Riley 2017) • “...[L]egislative actions that provide the regulatory framework” for study of medication use in pregnancy and lactation are needed...” (Illamola 2018) <p>Inclusion of pregnant women and lactating women in clinical research</p> <ul style="list-style-type: none"> ○ “Pregnant women should be presumed eligible for participation in clinical trials... Investigators should not exclude lactating women from clinical studies.” (IOM 1994) ○ “[E]thically we are obliged to confront the challenges of including pregnant women in clinical research studies...we need an adequate ethical framework for determining what are and are not suitable justifications for exclusion of pregnant women from research...progress will not happen until we shift the burden of justification” from exclusion to inclusion. (Lyerly 2008) ○ Define pregnant women as “scientifically complex” and change the presumption of exclusion. NIH should “consider adopting a policy of inclusion and a need to justify exclusion of pregnant women” (Blehar 2013) ○ All women should be presumed eligible for participation in research studies. The potential for pregnancy should not automatically exclude women...from...clinical study, although...contraception may be required...”(ACOG 2015). ○ Define pregnant women as “scientifically complex [not] vulnerable...” (ACOG 2015) ○ Modify “regulations, statutes and policies...to indicate that pregnant women are not a vulnerable population for purposes of ethical review.” (NVAC 2017) • “...[R]evise current exclusionary climate of research in pregnancy...” A pregnancy-specific ethical framework is needed for |

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| PRGLAC TASK FORCE RECOMMENDATIONS | HISTORICAL RECOMMENDATIONS |
| | <p>guidance on inclusion, for IRBs and investigators... Professional societies should support inclusion of pregnant women in clinical research" (NVAC 2017)</p> <p>Opportunistic studies and distinction between medication decisions for therapeutic purposes and for research purposes</p> <ul style="list-style-type: none"> • [Opportunistic studies may] "[e]nroll pregnant women already using medication...prescribed...for therapeutic purposes (Blehar 2013) • Distinguish between maternal decision to use medically necessary drug for illness, during lactation, and decision to participate in a lactation study. Former does not pose research-related risk for the infant, but taking new drug in research setting poses research risk for infant and must be discontinued unless switch to formula is greater risk. Same considerations for healthy volunteers. (Wang 2017) |
| <p>Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women</p> <p>Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women</p> | <ul style="list-style-type: none"> • "Effective education of providers and patients on current recommendations" for vaccines during pregnancy and postpartum" is needed. (Beigi 2014) • "Contemporary common [information] resource (for lactating women) that is...easily accessed by or integrated into internet and social media; is needed" also needed are "trusted sources" of drug safety information" (Wang 2017) • Electronic medical record platforms should "disseminate best available information" at point of decision-making for lactating patients (Wang 2017) • Develop approaches to improve provider-patient communications about risks and benefits of medication use in perinatal period. (Riley 2017) • Provider training should include lactation information. (Wang 2017) • Professional societies should...increase provider awareness of importance of research (NVAC 2017) • Publish all CT.gov obstetrics study results: "Dissemination of all available obstetric clinical pharmacology knowledge is fundamental" (Illamola 2018) |
| <p>Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are or may become pregnant and by lactating women</p> <p>Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women</p> | <p>Incentives</p> <ul style="list-style-type: none"> • Potential funding sources: incentives for industry (e.g. FDA written request); public/private partnerships; -type legislation (Wang 2017) • Obstetric research calls for a structure that could do what BPCA and PREA [have done] i.e. incentives for drug development in pregnant women and lactating women...[and] motivation for specific percentage of both...in all...studies." (Illamola 2018) <p>Liability</p> <ul style="list-style-type: none"> • NIH should review compensation for research injury, including preconceptional and perinatal injuries resulting from parents' participation in a clinical study; no recommendation for such compensation "at this time" because of problems in establishing |

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| PRGLAC TASK FORCE RECOMMENDATIONS | HISTORICAL RECOMMENDATIONS |
| | <p>compensation and potential for many “questionable recoveries.” (IOM 1994)</p> <ul style="list-style-type: none"> • [A]ddressing the liability concerns that animate so much of the behavior around research and drug development during pregnancy will require substantial efforts at both state and federal levels.” (Lyerly 2008) |
| Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women | <ul style="list-style-type: none"> • “[Expand the NICHD’s Obstetric-Fetal Pharmacology Research Unit Network] OPRU and other groups to perform opportunistic studies involving women already taking medication during pregnancy.” (Lyerly 2008) |
| Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the National Institute of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model | <p>Recruitment</p> <ul style="list-style-type: none"> • “Leverage the influence...of prenatal providers in combination with strong...engagement with existing community-based organizations (Frew 2014) • “...address [such obstacles specific to women] as lack of adequate child care [while participating in research]. (ACOG 2015) • Recruit for lactation studies through pregnancy exposure registries (but expand data collected to include postnatal infant environment, growth, development; also, recruit through NICUs and milk banks (Wang 2017) • Open enrollment, home health care nursing visits and multidisciplinary team with external expert advisors...all helpful in in recruitment for lactation studies; also potential of social media (Wang 2017) <p>Methods</p> <ul style="list-style-type: none"> • Develop “scientific models that address the [birth defects] baseline rate and attribution of causation in clinical interventional research in pregnancy” (Blehar 2013) • Although in vitro models “cannot fully account for all physiological and variables in the mother, placenta, and fetus and how these variables change throughout gestation, they should be the first-line test when new substance is to be investigated for potential use during pregnancy” (Sheffield 2014) • “Standardization of research methods on vaccines administered during pregnancy” is needed (Beigi 2014) • Core adverse event definitions provided [in this article] for use on vaccine safety monitoring (Munoz 2014) • Congenital anomalies data should be routine collected in vaccine clinical trials and more research on “approaches to...assessment of congenital anomalies” is needed (Rasmussen 2014) • Need “standardized approaches to [vaccine] data collection, analysis...safety evaluation...also standardized definitions of...maternal and neonatal outcomes.” (NVAC 2017) • Improve existing animal models...to address...mechanisms of actions of drugs and drug toxicity in pregnancy, while addressing clinical outcomes; [e]ffective animal models and newer research techniques to study...medication during lactation are lacking (Riley 2017) |

| COMPARISON OF PRGLAC TASK FORCE RECOMMENDATIONS AND HISTORICAL RECOMMENDATIONS | |
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| PRGLAC TASK FORCE RECOMMENDATIONS | HISTORICAL RECOMMENDATIONS |
| | <ul style="list-style-type: none"> • Physiologically-based and population pharmacokinetic modeling of drug concentration in milk potentially useful to identify, prioritize “drugs of concern,” but need further development and refinement for use to predict drug levels in milk and human exposures. (Wang 2017) • “Simulation approaches can provide probability measures of exposure levels...to inform...clinical study” (Illamola 2018) • Big data from electronic medical records “reflect routine daily practice;” also there is “good correlation between observational studies and clinical trials” but further development and refining are needed. (Illamola 2018) • Clinical trials of drugs for chronic conditions should include “prepregnancy [for baseline comparison], all...trimesters, and...postpartum data, [with which the participant] “can serve as their own control.” (Illamola 2018) <p>Topics</p> <ul style="list-style-type: none"> • “[D]etermine the public health impact of the current lack of knowledge around medications in pregnancy.” (Lyerly 2008) • Develop a pregnancy research agenda, elements of which would be to include pregnant women in ongoing clinical trials on conditions not related to pregnancy and do more trials specific to pregnancy. Identify questions that can be addressed with existing studies and resources (e.g opportunistic pharmacokinetic studies and pregnancy registries) (Blehar 2013) • Need epidemiologic understanding of burden of vaccine-preventable disease,” vaccine-elicited immunity in pregnant, fetuses and infants, and effect of breast milk-derived antibodies elicited by immunization (Beigi 2014). • Priority drugs for lactation studies: “Products commonly used by women of reproductive age, i.e. antimicrobials, anti-inflammatory[ies]...immunotherapies; cardiovascular drugs; hormonal therapies; drugs for neurological and psychiatric disorders...also drugs [with] potential...risk for exposed infant that...have no...data...in the literature...[d]rugs for which validated or commercially available assays have been developed [and] drugs used commonly in women with no available lactation data and presumed low risk to nursing infant based on nonclinical data...low priority: drug “considered safe for neonates if physiochemical properties suggest transfer into breast milk unlikely.” (Wang 2017) • Better understanding needed of “public health burden” of diseases preventable by maternal immunization (NVAC 2017) • Prioritize preclinical and early clinical vaccine research on immune response during pregnancy and develop vaccines for pregnant women. Need...“evaluation of maternal...neonatal outcomes” of vaccines administered during pregnancy...[including “safety...effectiveness...risks and benefits.” (NVAC 2017) |
| <p>Optimize registries for pregnancy and lactation</p> <p>Utilize and improve existing resources for data to inform the evidence and provide a foundation for</p> | <p>INFRASTRUCTURE AND RESOURCES</p> <ul style="list-style-type: none"> • Review of birth defects monitoring programs needed, to define capabilities, suggest improvements (IOM 1994) • Continue “surveillance and evaluation of safety of...recommended and investigational vaccines given during pregnancy” (Beigi 2014) |

| COMPARISON OF PRGLAC TASK FORCE RECOMMENDATIONS AND HISTORICAL RECOMMENDATIONS | |
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| PRGLAC TASK FORCE RECOMMENDATIONS | HISTORICAL RECOMMENDATIONS |
| research on pregnant women and lactating women Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women | <ul style="list-style-type: none"> • Postmarketing vaccine surveillance will continue to be needed (Rasmussen 2014) • Expand “pharmacovigilance systems that “link maternal and infant electronic health records and safety surveillance systems. (NVAC 2017) • “...vaccine surveillance system is...”excellent model...for drugs.” The birth defect focus of the post-market Vaccine and Medications in Pregnancy Surveillance System (VAMPS) should be broadened to include long-term effects of [its] drugs...and vaccines. (Riley 2017) • Federal agency collaboration in implementing existing safety system “enhancements” and “data sources” is needed...obstetric academic community and professional societies may collaborate as liaisons to federal agencies for topics dealing with research, practice and surveillance...” (Riley 2017) • Prospective pregnancy registers...”require continuous commitment to enrollment, recruitment...retention...prespecification of a similar comparator group.” (Illamola 2018) |

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²¹⁸ <https://www.ncbi.nlm.nih.gov/pubmed/?term=26488521>

²¹⁹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=17766625>

²²⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425719>

- Blehar MC, Spong C, Grady C et al. Enrolling pregnant women: Issues in clinical research. *Women's Health Issues* 2013;23:e39-e45. [PMID 23312713](https://pubmed.ncbi.nlm.nih.gov/23312713/)²²¹ (Report from 2010 meeting, convened by NIH Office of Research on Women's Health; an earlier report summarized the meeting but did not include specific recommendations. Foulkes MA, Grady C, Spong CY et al. Clinical research enrolling pregnant women: A workshop summary. *Journal of Women's Health* 2011;20:1429-1432. [PMID 21819233](https://pubmed.ncbi.nlm.nih.gov/21819233/)²²²)
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²²¹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=23312713>

²²² <https://www.ncbi.nlm.nih.gov/pubmed/?term=21819233>

²²³ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425718>

²²⁴ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28925019>

²²⁵ <https://www.ncbi.nlm.nih.gov/pubmed/25144026>

²²⁶ <https://www.ncbi.nlm.nih.gov/pubmed/19774226>

²²⁷ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425720>

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²²⁸ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28379782>

²²⁹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425721>

²³⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=28142152>

²³¹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=25425722>

²³² <https://www.ncbi.nlm.nih.gov/pubmed/?term=28510297>

Appendix XI - Lessons Learned from Implementing the Best Pharmaceuticals for Children Act: Implications for PRGLAC

Despite the long-standing recognition that “children are not little adults,” pediatric labeling of prescription drugs has consistently lagged behind adult labeling. Rather than protecting children, the lack of pediatric studies to determine appropriate dosing, safety, and efficacy has had serious consequences, some tragic. Over more than two decades, Congress has made numerous attempts to address this issue. In 1994, Congress passed legislation requesting pharmaceutical companies to submit any pediatric data they had to the Food and Drug Administration (FDA) for consideration when developing drug labeling. This approach did not yield sufficient information. In 1997, the FDA Modernization Act was passed, which provided an additional six-month market exclusivity for a drug already on the market if the company submitted pediatric data requested by the FDA in a Written Request. In 2002, this exclusivity provision was renewed for on-patent drugs with enactment of the Best Pharmaceuticals for Children Act (BPCA), along with a new directive to NIH to conduct research on drugs (e.g. off-patent medications) when companies declined Written Requests (This program was reauthorized by Congress in 2007, 2012, and for NIH in 2017). And in 2003, Congress addressed applications for new drugs, requiring companies to submit plans for pediatric testing or justifications for not doing so under the Pediatric Research Equity Act (PREA).

NIH and BPCA

BPCA charges NIH with prioritizing drugs and therapeutic areas in need of study, with sponsoring required pediatric clinical trials, and with submitting these data to FDA for consideration of a labeling change. During implementation of the program, NIH faced many of the same issues long faced by researchers: the lack of incentives to conduct research in children, ethical/consent issues, new technologies to permit testing in small humans, the unforeseeable nature of clinical responses in immature systems, potential need for different formulations, measuring long-term effects of a drug on growth and development, and a suitable infrastructure for the conduct of pediatric pharmacology research.

Refined over the years, NICHD now leads a prioritization process, with widespread input from the scientific community, that balances a complex range of issues, including the frequency of medication use in children and for what indications, whether it is needed to treat a life-threatening condition, probable side effects, and whether a pediatric formulation of the drug is available. Because NICHD does not fund all pediatric research supported by NIH, it leads a trans-NIH Working Group on BPCA; many of the NIH Institutes and Centers contribute to BPCA-related research projects. To carry out its pediatric clinical program, NICHD established the Pediatric Trials Network, a Data Coordinating Center, a pediatric clinical pharmacology centers program at five sites, and a clinical pharmacology training program. More than 60 drugs have been studied to date.

Lessons Learned from Implementing BPCA

In conducting drug trials aimed at acquiring FDA approval and labeling, critical components include understanding the pathophysiology of disease that is being treated, the mechanism of action of the drug under study, and any safety, efficacy, and dosing differences depending on the specific populations intended to use the drug. For some drugs, efficacy extrapolation may be possible. But for diseases that are population-specific or that do not occur in adults/non-pregnant or lactating women, extrapolation of efficacy is not possible. For example, in neonates, intraventricular hemorrhage, hypoxia-induced encephalopathy, and bronchopulmonary dysplasia are population-specific diseases. The mechanism of disease is not clear, and there are no labeled treatments.

Before implementing clinical trials on drugs used in the pediatric population, epidemiologic data are needed, as well as information about the natural history of the disease. Protocol design requires pharmacokinetic and statistical expertise, and careful consideration of recruitment plans, investigator training, and ethical issues around informed consent must be considered.

Analogous situations in obstetrics occur for specific conditions such as pregnancy-induced hypertension, preeclampsia, preterm labor, and postpartum hemorrhage. Basic science investigations of these conditions are relatively sparse, with unclear pathophysiology, no identified drug targets or drugs developed for these conditions, and few investigators involved in this area of research. In addition, pregnant and lactating women are unique populations. In each case, balancing two connected organisms whose development and physiology is constantly changing requires additional basic research on disease mechanisms and the development of specified drug targets. Consequently, consideration should be given to whether this information be collected outside a randomized controlled trial, using big data sources or opportunistic pharmacokinetic studies, or whether pharmacokinetic-pharmacodynamic modeling could be utilized. Like pediatrics, development of pregnancy-specific pharmacodynamic markers may also have potential for information on safety and dosing.

Overall, as with children, inclusion in clinical trials may assist in obtaining the information needed for safety and dosing in pregnant and lactating women.

With an interest to understand how the current state of obstetric and lactation research compares to the state of pediatrics prior to BPCA and PREA, the Task Force created a Table (Appendix XI, Table 1) to facilitate the comparison. Although there are many similarities, including limited numbers of researchers, involvement by industry, and basic science knowledge, there are also differences, especially for lactation.

Appendix XI, Table 1. Comparison of state of pediatrics prior to BPCA/PREA and current state of Ob/Lactation

| Components necessary for successful trials/collection of data | Effects of BPCA/PREA on Pediatrics field | Obstetrics Pharmacology – current state of field | Lactation Pharmacology – current state of field |
|---|---|--|--|
| | BPCA (2002), PREA (2003) | | |
| Adequately trained researchers | <p>Suboptimal numbers of pediatric pharmacologists prior to BPCA</p> <p>Pediatric Pharmacology Research Units (PPRU) established in 1994 to support training prior to passage of BPCA; PPRU provided proof of concept – feasibility of including children in clinical trials</p> <p>54 pediatric pharmacologists trained using BPCA funds (T32 mechanism)</p> <p>Industry has also trained pediatric trialists (unknown number)</p> | <p>Approximately 15 OB pharmacologists in US; 1 T32 training program plus 5 academic institutions (OPRU)</p> <p>Few OB pharmacologists</p> | <p>Limited experts cross-trained in lactation and pharmacology, however often lactation is discussed and investigated by pediatricians, opportunity to tap into the richness of the pediatrician expertise</p> |

| Components necessary for successful trials/collection of data | Effects of BPCA/PREA on Pediatrics field | Obstetrics Pharmacology – current state of field | Lactation Pharmacology – current state of field |
|---|--|---|--|
| Infrastructure to conduct needed studies/clinical trials | <p>PPRU grew from 7 to 13 sites between 1994 and 2008</p> <p>NICHD developed the Pediatric Trials Network to conduct pediatric drug trials to obtain information for pediatric labeling; established mid-2000s.</p> <p>Industry has also invested in building internal infrastructure (clinical pharmacologists, pharmacometricians, technical development experts) to support translational and clinical development trials in pediatrics to support regulatory decision making</p> | <p>NICHD established the Obstetric-Fetal Pharmacology Research Centers (OPRC) in 2004 as a proof of concept that research in these populations could be conducted; currently 5 institutions funded</p> <p>Strong infrastructure for studies/trials in obstetrics and high-risk pregnancy in NICHD's Maternal Fetal Medicine Units Network since 1985</p> <p>Very few individual RO1s- issues with lack of expertise by applicants and reviewers</p> | <p>OPRC could perform studies such as developing measuring techniques for assessing drugs in breast milk</p> |
| Legal requirement to include target population | No requirement for inclusion of children until PREA passed in 2003 ²³³ | No requirement to include pregnant women in drug studies | No requirement to include lactating women in drug studies |

²³³ The first incentive provisions for pediatric studies were included under the Food and Drug Administration Modernization Act (FDAMA) in 1997; and the Pediatric Rule (1998) which was struck down in federal court.

| Components necessary for successful trials/collection of data | Effects of BPCA/PREA on Pediatrics field | Obstetrics Pharmacology – current state of field | Lactation Pharmacology – current state of field |
|---|---|--|---|
| Industry involvement | Very little involvement until BPCA (incentives) and PREA (mandate) enacted; most studies are done under PREA; when a written request under BPCA is declined (off-patent), it can be referred to NIH | Industry largely involved in post-marketing safety studies and data collection in pregnancy. Differential approach to drugs used by pregnant women compared to drugs used to treat diseases of pregnancy | Little industry involvement |
| Basic science | Multiple gaps in developmental pharmacology relating to drug dosing | Poor - fundamental lack of knowledge of disease mechanism of pregnancy-specific conditions; teratogenicity/overlap of pathways of drug action and teratogenicity; how to know if teratogenicity from drug or other mechanism in order to de-risk drug development; and Unknown appropriate dosing of common medications in pregnancy, distribution, metabolism and excretion characteristics in pregnant women | Lack of knowledge about transfer of drug into human breast milk, transfer of drugs from human milk to infants, and determining whether animal data applicable to human studies Field could be advanced by developing PBPK models and in obtaining more robust human data |

| Components necessary for successful trials/collection of data | Effects of BPCA/PREA on Pediatrics field | Obstetrics Pharmacology – current state of field | Lactation Pharmacology – current state of field |
|---|---|--|---|
| Adequate # reviewers (FDA) | FDA has the Office of Pediatric Therapeutics and the CDER Division of Maternal and Child Health | Extremely limited | Extremely limited |
| Adequate # reviewers/program (NIH) | Somewhat limited | Extremely limited | Extremely limited |
| Relevant legislative directives | AAP critical to getting BPCA/PREA passed | SMFM/ACOG coalition of organizations responsible for Task Force legislation | SMFM/ACOG coalition of organizations responsible for Task Force legislation |
| Professional Society Engagement | AAP | SMFM/ACOG/AAP | SMFM/ACOG/AAP |
| FDA | Prior to BPCA and PREA: many drugs used were off-patent After BPCA and PREA were enacted, Written Requests issued under BPCA and Pediatric Study Plans required under PREA | As noted in discussions during PRGLAC public meetings, many drugs utilized in the obstetrics population are off-label Few specific treatments approved for pregnancy-induced conditions | As noted in discussions during PRGLAC public meetings, many drugs used by lactating women are off-label |
| NIH | PPRU preceded BPCA; now PTN implements NIH BPCA research on off-patent drugs for pediatric use; coordination across NIH Institutes and Center | NICHD's OPRC preceded Task Force mandate; limited number of sites supported | No formal structure in place |

Appendix XII – Pregnancy and Lactation Labeling Rule Data

Detailed labeling data for new drugs and biological applications approved between June 30, 2015 and September 30, 2017 as explained in Section 3 of the Report.

Chart 1

| Center | CDER Review Division or CBER Office | Approximate Total Number of Labels approved in PLLR Format between June 30, 2015, and September 30, 2017 |
|---------------|---|---|
| CDER | Anesthesia, Analgesia, and Addiction | 83 |
| CDER | Anti-Infective | 28 |
| CDER | Antiviral | 40 |
| CDER | Bone, Reproductive and Urologic | 13 |
| CDER | Cardiovascular and Renal | 39 |
| CDER | Dermatology and Dental | 12 |
| CDER | Gastroenterology and Inborn Errors | 37 |
| CDER | Hematology and Oncology | 96 |
| CDER | Medical Imaging | 18 |
| CDER | Metabolism and Endocrinology | 31 |
| CDER | Multiple | 14 |
| CDER | Neurology | 28 |
| CDER | Psychiatry | 20 |
| CDER | Pulmonary, Allergy, and Rheumatology | 44 |
| CDER | Transplant and Ophthalmology | 11 |
| CBER | Office of Tissues and Advanced Therapies (OTAT) | 25 |
| CBER | Office of Blood Research and Review (OBRR) | 14 |
| CBER | Office of Vaccine Research and Review (OVRR) | 22 |
| | Total | 575 |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| Drug Name (brand) ⁺ | Date Approved ⁺ | Active Ingredient | Approved Indication ^{*,+} | Number of Participants in Pivotal Clinical Trials ⁺ | % Women participation ^{*,+} | Description of Pregnancy Data in PLLR Formatted Label [^] | Description of Lactation Data in PLLR Formatted Label [^] |
|---|----------------------------|----------------------|--|--|--------------------------------------|---|--|
| <p>Data Source: *Drug snapshot report 2015-2016: https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM541327.pdf</p> <p>+Individual drug trial snapshot: https://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm</p> <p>^ Pregnancy and Lactation Labeling Information: https://www.accessdata.fda.gov/scripts/cder/daf/</p> | | | | | | | |
| 1 ORKAMBI | 7/2/2015 | lumacaftor/ivacaftor | Treatment of cystic fibrosis. | | 49% | Limited and incomplete human data from clinical trials and PMR and animal embryo fetal development study data. | Lactation study completed on animals (rats). There is no information regarding the presence of lumacaftor or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 2 ENTRESTO | 7/7/2015 | sacubitril/valsartan | Treatment of heart failure. | 8442 | 22% | Human epidemiological data on antihypertensives (not specifically Entresto) and animal data ENTRESTO can cause fetal harm when administered to a pregnant woman. | Lactation study completed on animals (rats). Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with ENTRESTO. |
| 3 REXULTI | 7/10/2015 | brexpiprazole | Treatment of depressive disorder. | 1054 | 69% | Pregnancy registry and animal reproduction data. | Label notes drug is present in rat milk, referenced from label section 8.1 data. Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production. |
| 4 REXULTI | 7/10/2015 | brexpiprazole | Treatment of schizophrenia. | 1220 | 37% | Pregnancy registry and animal reproduction data. | Label notes drug is present in rat milk, referenced from label section 8.1 data. Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production. |
| 5 DAKLINZA | 7/24/2015 | daclatasvir | Treatment of chronic hepatitis C virus genotype 3 infection. | 152 | 41% | Animal reproduction data (fetal embryo toxicity). | Daclatasvir is present in the milk of lactating rats [see Use in Specific Populations (8.1)]. No information regarding the presence of daclatasvir in human milk, the effects on the breastfed infant, or the effects on milk production is available. |
| 6 ODOMZO | 7/24/2015 | sonidegib | Treatment of locally advanced basal cell carcinoma. | 230 | 37% | Based on its mechanism of action and data from animal reproduction studies, ODOMZO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | No data are available regarding the presence of sonidegib in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions in breastfed infants from sonidegib, advise a nursing woman not to breastfeed during treatment with ODOMZO and for 20 months after the last dose. |
| 7 PRALUENT | 7/24/2015 | alirocumab | Treatment of certain patients with high cholesterol. | 3752 | 40% | Animal reproduction data. There are no available data on use of PRALUENT in pregnant women to inform a drug associated risk. | There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant, or the effects on milk production. |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| | Drug Name (brand)* | Date Approved* | Active Ingredient | Approved Indication*+ | Number of Participants in Pivotal Clinical Trials* | % Women participation*+ | Description of Pregnancy Data in PLLR Formatted Label^ | Description of Lactation Data in PLLR Formatted Label^ |
|----|--------------------|----------------|------------------------|---|--|------------------------------|--|--|
| 8 | ADDYI | 8/18/2015 | flibanserin | Treatment of acquired generalized HSDD who have not gone through menopause. | 3099 | 100% | Animal reproduction data (fetal toxicity). | Flibanserin is excreted in rat milk. It is unknown whether flibanserin is present in human milk, whether ADDYI has effects on the breastfed infant, or whether ADDYI affects milk production. |
| 9 | REPATHA | 8/27/2015 | evolocumab | Hypercholesterolemia (High LDL treatment) HoFH (homozygous). | 49 | 49% | Animal reproduction data. | There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 10 | REPATHA | 8/27/2015 | evolocumab | Hypercholesterolemia (High LDL treatment) HeFH (Heterozygous). | 4177 | 50% | Animal reproduction data. | There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 11 | VARUBI | 9/1/2015 | rolapitant | Prevent delayed form of nausea and vomiting after Chemotherapy. | 2595 | 60% | Animal reproduction data. | Lactation study completed on animals (rats). There are no data on the presence of rolapitant in human milk, the effects of rolapitant in the breastfed infant, or the effects of rolapitant on milk production. |
| 12 | XURIDEN | 9/4/2015 | uridine triacetate | Treatment for rare and hereditary disease orotic aciduria. | 4 | 25% | Animal reproduction data. | There are no data on the presence of uridine triacetate in human milk, the effect on the breastfed infant or the effect on milk production. |
| 13 | VRAYLAR | 9/17/2015 | cariprazine | Treatment of bipolar disorder with manic mixed episode. | 1065 | 41% | Pregnancy registry and animal reproduction data on toxicity. | No lactation study completed (label noted that drug found in rat milk). Lactation studies have not been conducted to assess the presence of cariprazine in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 14 | VRAYLAR | 9/17/2015 | cariprazine | Treatment of schizophrenia. | 1754 | 28% | Pregnancy registry and animal reproduction data on toxicity. | No lactation study completed (label noted that drug found in rat milk). Lactation studies have not been conducted to assess the presence of cariprazine in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 15 | LONSURF | 9/22/2015 | trifluridine and tipir | Treatment of Metastatic Colorectal cancer. | 800 | 39% | Animal reproduction data. Based on animal data and its mechanism of action, LONSURF can cause fetal harm. | Lactation study completed on animals (rats). Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. |
| 16 | RYZODEG | 9/26/2015 | insulin degludec an | Improved blood sugar control in adults with diabetes mellitus (DM). | Type 1 - 548 Type 2 - 1860 | Type 1 - 50% Type 2 - 46% | Human data on insulin aspart (one of the two active ingredients)- 5 RCTs on 441 pregnant women w/ DM, animal reproduction data on both active ingredients (insulin aspart and insulin degludec). | Lactation study completed on animals (rats) on insulin degludec. |
| 17 | TRESIBA | 9/26/2015 | insulin degludec inj | To improve glucose control in adults with diabetes mellitus (Type 1). | 1577 | 44% | Animal reproduction data. | Lactation study completed on animals (rats). There are no data on the presence of insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 18 | TRESIBA | 9/26/2015 | insulin degludec inj | To improve glucose control in adults with diabetes mellitus (Type 2). | 4048 | 44% | Animal reproduction data. | Lactation study completed on animals (rats). There are no data on the presence of insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 19 | ARISTADA | 10/5/2015 | aripiprazole laurixil | Treatment of schizophrenia. | 623 | 32% | Pregnancy registry and animal reproduction data. | No lactation study completed (label noted that drug found in human breast milk; insufficient data to assess amount or effects on nursing infants). |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| | Drug Name (brand) ⁺ | Date Approved ⁺ | Active Ingredient | Approved Indication ^{*,+} | Number of Participants in Pivotal Clinical Trials ⁺ | % Women participation ^{*,+} | Description of Pregnancy Data in PLLR Formatted Label [^] | Description of Lactation Data in PLLR Formatted Label [^] |
|----|--------------------------------|----------------------------|--------------------------|---|--|--------------------------------------|---|--|
| 20 | PRAXBIND | 10/16/2015 | idarucizumab | Reversal of anticoagulant effects of Pradaxa during emergency situations or when there is a need to reverse its blood-thinning effects. | 123 | 47% | There are no adequate and well-controlled studies of PRAXBIND in pregnant women to inform on associated risks. Animal reproductive and development studies have not been conducted with idarucizumab. It is also not known whether PRAXBIND can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. | There are no data on the effects of PRAXBIND on the breastfed child or on milk production. It is not known whether idarucizumab is excreted in human milk. |
| 21 | VELTASSA | 10/21/2015 | patiomer | Used to treat hyperkalemia. | 715 | 39% | Veltassa is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk. | Veltassa is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk. |
| 22 | YONDELIS | 10/23/2015 | trabectedin | Treat patients with liposarcoma and leiomyosarcoma that is unresectable or metastatic. | 518 | 70% | Based on its mechanism of action, trabectedin can cause fetal harm when administered during pregnancy [see Clinical Pharmacology (12.1)]. | There are no data on the presence of trabectedin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions from YONDELIS in breastfed infants, advise a nursing woman to discontinue nursing during treatment with YONDELIS. |
| 23 | STRENSIQ | 10/23/2015 | asfotase alfa | Treatment of perinatal, infantile hypophosphatasia (HPP). | 79 | 52% | Animal reproduction data. | There are no data on the presence of asfotase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 24 | STRENSIQ | 10/23/2015 | asfotase alfa | Treatment of juvenile-onset hypophosphatasia (HPP). | 20 | 50% | Animal reproduction data. | There are no data on the presence of asfotase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 25 | NUCALA | 11/4/2015 | mepolizumab | Severe asthma. | 1327 | 59% | A pregnancy registry is available for this drug and animal reproduction data. | Label notes drug present in monkey milk referenced in 8.1 data. There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 26 | GENVOYA | 11/5/2015 | elvitegravir, cobicistat | Complete regimen for the treatment of HIV-1 in adults. | 3171 | 13% | Pregnancy registry, human data from prospective reports from pregnancy registry on 2 of the 3 active ingredients, and animal reproduction data. | Lactation data on human data from 5 samples of breast milk from 5 HIV infected mothers in 1 of 3 active ingredients, and animal lactation data. The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. |
| 27 | GENVOYA | 11/5/2015 | elvitegravir, cobicistat | Complete regimen for the treatment of HIV-1 in children age 12 and older. | 23 | 48% | Pregnancy registry, human data from prospective reports from pregnancy registry on 2 of the 3 active ingredients, and animal reproduction data. | Lactation data on human data from 5 samples of breast milk from 5 HIV infected mothers in 1 of 3 active ingredients, and animal lactation data. The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. |
| 28 | COTELLIC | 11/10/2015 | (cobimetinib) | Used in combination with another drug to treat melanoma. | 495 | 42% | Animal reproduction data. (Based on findings from animal reproduction studies and its mechanism of action, COTELLIC can cause fetal harm when administered to a pregnant woman). | There is no information regarding the presence of cobimetinib in human milk, effects on the breastfed infant, or effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise a nursing woman not to breastfeed during treatment with COTELLIC and for 2 weeks after the final dose. |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| | Drug Name (brand) ⁺ | Date Approved ⁺ | Active Ingredient | Approved Indication ^{*,+} | Number of Participants in Pivotal Clinical Trials ⁺ | % Women participation ^{*,+} | Description of Pregnancy Data in PLLR Formatted Label [^] | Description of Lactation Data in PLLR Formatted Label [^] |
|----|--------------------------------|----------------------------|-------------------|---|--|--------------------------------------|--|--|
| 29 | DARZALEX | 11/16/2015 | daratumumab | Multiple myeloma. | 156 | 46% | There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations [see Clinical Considerations]. | There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 30 | NINLARO | 11/20/2015 | ixazomib | Multiple myeloma. | 722 | 43% | Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no human data available regarding the potential effect of NINLARO on pregnancy or development of the embryo or fetus. | No data are available regarding the presence of NINLARO or its metabolites in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because the potential for serious adverse reactions from NINLARO in breastfed infants is unknown, advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose. |
| 31 | PORTRAZZA | 11/24/2015 | necitumumab | Metastatic squamous non-small cell lung cancer. | 1093 | 17% | Based on animal data and its mechanism of action, PORTRAZZA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | There is no information regarding the presence of necitumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from PORTRAZZA, advise a nursing woman not to breastfeed during treatment with PORTRAZZA and for three months following the final dose. |
| 32 | EMPLICITI | 11/30/2015 | elotuzumab | Multiple myeloma. | 646 | 40% | There are no studies with EMPLICITI with pregnant women to inform any drug associated risks. Animal reproduction studies have not been conducted with elotuzumab. Note: Contraindicated for use in pregnancy with lenalidomide which can cause embryo-fetal harm. | There is no information on the presence of EMPLICITI in human milk, the effect on the breastfed infant, or the effect on milk production. Because of the potential for serious adverse reactions in breast-fed infants from elotuzumab administered with lenalidomide and dexamethasone, breastfeeding is not recommended. |
| 33 | TAGRISSO | 12/3/2015 | osimertinib | Advanced non small cell lung cancer (NSCLC). | 411 | 68% | Animal reproduction data. Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. | Unknown 8.2 data (label notes drug present in rat milk referenced in 8.1 data). Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose. |
| 34 | KANUMA | 12/8/2015 | sebelipase alfa | Treatment of Lysosomal Acid Lipase (LAL) deficiency (Adults- CESD). | 66 | 50% | Animal reproduction data. | There are no data on the presence of sebelipase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 35 | KANUMA | 12/8/2015 | sebelipase alfa | Treatment of Lysosomal Acid Lipase (LAL) deficiency (infants). | 9 | 44% | Animal reproduction data. | There are no data on the presence of sebelipase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| | Drug Name (brand) ⁺ | Date Approved ⁺ | Active Ingredient | Approved Indication ^{*,+} | Number of Participants in Pivotal Clinical Trials ⁺ | % Women participation ^{*,+} | Description of Pregnancy Data in PLLR Formatted Label [^] | Description of Lactation Data in PLLR Formatted Label [^] |
|----|--------------------------------|----------------------------|--------------------------|---|--|--------------------------------------|--|--|
| 36 | ALECENSA | 12/11/2015 | alectinib | Metastatic non-small cell lung cancer (NSCLC). | 253 | 55% | Animal reproduction data. Based on animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from alectinib, advise a lactating woman not to breastfeed during treatment with ALECENSA and for 1 week after the final dose. |
| 37 | VISTOGARD | 12/11/2015 | uridine triacetate | Emergency treatment of an overdose with fluorouracil or capecitabine. | 135 | 44% | Animal reproduction data. Limited case reports of uridine triacetate use during pregnancy are insufficient to inform a drug associated risk of birth defects and miscarriage. | There are no data on the presence of uridine triacetate in human milk, the effect on the breastfed infant or the effect on milk production. |
| 38 | BRIDION | 12/15/2015 | sugammadex | Reversal of neuromuscular blocking agents. | 3458 | 52% | Animal reproduction data. | No data are available regarding the presence of sugammadex in human milk, the effects of sugammadex on the breast fed infant, or the effects of sugammadex on milk production. However, sugammadex is present in rat milk. |
| 39 | UPTRAVI | 12/21/2015 | selexipag | Treatment of adults with pulmonary arterial hypertension (PAH). | 1156 | 80% | Animal reproduction data. | It is not known if UPTRAVI is present in human milk. Selexipag or its metabolites were present in the milk of rats. |
| 40 | ZURAMPIC | 12/22/2015 | lesinurad | Lowers uric acid levels in patients with gout. | 1027 | 4% | Animal reproduction data. | Label notes drug present in rat milk referenced in 8.1 data. There is no information regarding the presence of ZURAMPIC in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 41 | ZEPATIER | 1/28/2016 | elbasvir and grazoprevir | Treatment of chronic Hepatitis C genotypes 1 or 4 infection. | 2704 | 39% | Animal reproduction data. | Lactation study completed on animals (rats). It is not known whether ZEPATIER is present in human breast milk, affects human milk production, or has effects on the breastfed infant. |
| 42 | BRIVIACT | 2/18/2016 | brivaracetam | Treatment of partial-onset seizures. | 1558 | 49% | Pregnancy registry, animal reproduction data. | Lactation study completed on animals (rats). No data are available regarding the presence of brivaracetam in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. |
| 43 | ANTHIM | 3/18/2016 | obiltoximab | For the treatment of inhalational anthrax. | 370 | 46% | Animal reproduction data. | ANTHIM has not been evaluated in nursing women. |
| 44 | TALTZ | 3/22/2016 | ixekizumab | Treatment of moderate to severe plaque psoriasis in adults. | 1958 | 32% | Animal reproduction data. | There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. |
| 45 | CINQAIR | 3/23/2016 | reslizumab | For the treatment of a specific type of severe asthma (called eosinophilic phenotype asthma). | 1758 | 62% | Animal reproduction data. | Lactation study completed on animals (mice). It is not known whether reslizumab is present in human milk, and the effects of reslizumab on the breast fed infant and on milk production are not known. |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| | Drug Name (brand) ⁺ | Date Approved ⁺ | Active Ingredient | Approved Indication ^{*,+} | Number of Participants in Pivotal Clinical Trials ⁺ | % Women participation ^{*,+} | Description of Pregnancy Data in PLLR Formatted Label [^] | Description of Lactation Data in PLLR Formatted Label [^] |
|----|--------------------------------|----------------------------|--------------------|---|--|--------------------------------------|---|---|
| 46 | DEFITELIO | 3/30/2016 | defibrotide sodium | Treatment of hepatic veno-occlusive disease (VOD). | 528 | 45% | Animal reproduction data. | There is no information regarding the presence of DEFITELIO in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including bleeding in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with DEFITELIO. |
| 47 | VENCLEXTA | 4/11/2016 | venetoclax | Treatment of chronic lymphocytic leukemia (CLL). | 240 | 31% | Animal reproduction data. Based on toxicity observed in mice, VENCLEXTA may cause fetal harm when administered to pregnant women. | There are no data on the presence of VENCLEXTA in human milk, the effects of VENCLEXTA on the breastfed child, or the effects of VENCLEXTA on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in breastfed infants from VENCLEXTA is unknown, advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA. |
| 48 | NUPLAZID | 4/29/2016 | pimavanserin | Treatment of hallucinations and delusions in patients with Parkinson's disease. | 433 | 36% | Animal reproduction data. There are no data on NUPLAZID use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. | There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 49 | TECENTRIQ | 5/18/2016 | atezolizumab | Treatment of a type of bladder cancer called urothelial carcinoma. | 310 | 22% | Animal reproduction data. Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of TECENTRIQ in pregnant women. | Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise a lactating woman not to breastfeed during treatment and for at least 5 months after the last dose. |
| 50 | AXUMIN | 5/27/2016 | fluciclovine F 18 | Detection of prostate cancer recurrence. | 596 | 0% | No data in label. Note: This is a male specific indication. | No data in label. Note: This is a male specific indication. |
| 51 | OCALIVA | 5/27/2016 | obeticholic acid | Treatment of primary biliary cholangitis in adults. | 216 | 91% | Animal reproduction data. The limited available human data on the use of obeticholic acid during pregnancy are not sufficient to inform a drug-associated risk. | There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed infant or the effects on milk production. |
| 52 | ZINBRYTA | 5/27/2016 | daclizumab | Treatment of relapsing forms of multiple sclerosis (MS). | 2253 | 67% | Animal reproduction data. Administration of ZINBRYTA to monkeys during gestation resulted in embryofetal death and reduced fetal growth at maternal exposures greater than 30 times that expected clinically [see Data]. | There are no data on the presence of daclizumab in human milk, the effects on the breastfed child, or the effects of the drug on milk production. |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

| | Drug Name (brand)* | Date Approved* | Active Ingredient | Approved Indication*,+ | Number of Participants in Pivotal Clinical Trials* | % Women participation*,+ | Description of Pregnancy Data in PLLR Formatted Label^ | Description of Lactation Data in PLLR Formatted Label^ |
|----|--------------------|----------------|---------------------|--|--|--------------------------|---|---|
| 53 | NETSPOT | 6/1/2016 | gallium dotatate Ga | For detection of a specific type of tumors called somatostatin receptor positive neuro-endocrine tumors (NETs). | 265 | 52% | There are no studies with Ga 68 dotatate in pregnant women to inform any drug-associated risks; however, all radiopharmaceuticals, including Ga 68 dotatate have the potential to cause fetal harm. | There is no information on the presence of Ga 68 dotatate in human milk, the effect on the breastfed infant, or the effect on milk production. |
| 54 | EPCLUSA | 6/28/2016 | sofosbuvir and velp | Treatment of chronic Hepatitis C virus genotypes 1, 2, 3, 4, 5 or 6 infection. | 1825 | 38% | Animal reproduction data. If EPCLUSA is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. | Lactation study completed on animals (rats). It is not known whether the components of EPCLUSA and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. |
| 55 | XIIDRA | 7/11/2016 | lifitegrast | Treatment of the signs and symptoms of dry eye disease. | 2133 | 76% | Animal reproduction data. | There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. Note: Systemic exposure to lifitegrast from ocular administration is low. |
| 56 | ADLYXIN | 7/27/2016 | lixisenatide | Treatment of type 2 diabetes mellitus. | 4508 | 52% | Animal reproduction data. | Lactation study completed on animals (rats). There is no information regarding the presence of ADLYXIN in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 57 | ADLYXIN | 7/27/2016 | lixisenatide | Treatment of type 2 diabetes mellitus who recently had a heart attack. | 6068 | 31% | Animal reproduction data. | Lactation study completed on animals (rats). There is no information regarding the presence of ADLYXIN in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 58 | EXONDYS 51 | 9/19/2016 | eteplirsen | Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping (trial 1 + 2). | 12 | 0% | No data in label. Note: DMD almost exclusively affects males, and all trial participants were male. | Note: DMD almost exclusively affects males, and all trial participants were male. |
| 59 | EXONDYS 51 | 9/19/2016 | eteplirsen | Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping (Trial 3). | 13 | 0% | No data in label. Note: DMD almost exclusively affects males, and all trial participants were male. | No data in label. Note: DMD almost exclusively affects males, and all trial participants were male. |
| 60 | LARTRUVO | 10/19/2016 | olaratumab | Treatment of soft tissue sarcoma. | 133 | 56% | Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm [see Clinical Pharmacology (12.1)]. | Because of the potential risk for serious adverse reactions in breastfeeding infants from olaratumab, advise women not to breastfeed during treatment with LARTRUVO and for 3 months following the last dose. |
| 61 | ZINPLAVA | 10/21/2016 | bezlotoxumab | Decreasing the risk of <i>Clostridium difficile</i> infection recurrence. | 1567 | 57% | Adequate and well controlled studies with ZINPLAVA have not been conducted in pregnant women. No animal reproductive and developmental studies have been conducted with bezlotoxumab. | There is no information regarding the presence of bezlotoxumab in human milk, the effects on the breast-fed infant, or the effects on milk production. |

Chart 2 - Participation of Women and Pregnancy and Lactation Data Included in the Labelling for NMEs Approved from 6/30/2015-9/30/2017

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|----|--------------------------------|----------------------------|-------------------|--|--|--------------------------------------|---|---|
| 62 | EUCRISA | 12/14/2016 | crisaborole | To treat mild to moderate eczema (atopic dermatitis) in patients two years of age and older. | 1522 | 56% | Animal reproduction data. | There is no information available on the presence of EUCRISA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production after topical application of EUCRISA to women who are breastfeeding. |
| 63 | RUBRACA | 12/19/2016 | rucaparib | Treatment of women with certain type of advanced ovarian cancer. | 377 | 100% | Animal reproduction data. Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. | Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose. |
| 64 | SPINRAZA | 12/23/2016 | nusinersen | Treatment of spinal muscular atrophy. | 121 | 55% | Animal reproduction data. | There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. |
| 65 | TRULANCE | 1/19/2017 | plecanatide | Treatment of chronic idiopathic constipation in adults. | 1733 | 79% | Animal reproduction data. Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration [see Clinical Pharmacology (12.3)] and maternal use is not expected to result in fetal exposure to the drug. | There is no information regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant. Note: Plecanatide and its active metabolite negligibly absorbed systemically following oral administration. |
| 66 | PARSABIV | 2/7/2017 | etelcalcetide | Treat high levels of parathyroid hormone (PTH). | 1023 | 40% | Animal reproduction data. | Lactation study completed on animals (rats). There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding. |
| 67 | EMFLAZA | 2/9/2017 | deflazacort | Treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older. | 225 | 0% | Human data (multiple cohort in case controlled studies). Note: DMD almost exclusively affects males, and all trial participants were male. | No data in label. Note: DMD almost exclusively affects males, and all trial participants were male. |
| 68 | SILIQ | 2/15/2017 | brodalumab | SILIQ is used for treatment of moderate to severe plaque psoriasis in adults. | 2915 | 31% | Animal reproduction data. | Detected in the milk of lactating cynomolgus monkeys. There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 69 | XERMELO | 2/28/2017 | telotristat ethyl | Treatment of diarrhea in adult patients with carcinoid syndrome. | 90 | 50% | Animal reproduction data. | There are no data on the presence of telotristat ethyl in human or animal milk, the effects on the breastfed infant, or the effects on milk production. |
| 70 | KISQALI | 3/13/2017 | ribociclib | Treatment of a specific form of advanced breast cancer. | 668 | 100% | Animal reproduction data. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | Lactation study completed on animals (rats). Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose. |
| 71 | XADAGO | 3/21/2017 | safinamide | Treatment of "off episodes" in patients with Parkinson's disease. | 1218 | 33% | Animal reproduction data. | Unknown whether drug is present in breast milk (Source : Drug Label Section 8.3). |
| 72 | SYMPROIC | 3/23/2017 | naldemedine | Treatment for adults with constipation caused by prescription pain drugs called opioids. | 2336 | 62% | Animal reproduction data. | Lactation study completed on animals (rats). |

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| Drug Name (brand)* | Date Approved* | Active Ingredient | Approved Indication*+ | Number of Participants in Pivotal Clinical Trials* | % Women participation*+ | Description of Pregnancy Data in PLLR Formatted Label^ | Description of Lactation Data in PLLR Formatted Label^ |
|--------------------|----------------|-------------------|---|--|----------------------------------|---|---|
| 73 BAVENCIO | 3/23/2017 | avelumab | Treatment of Merkel cell carcinoma. | 88 | 26% | Animal reproduction data. Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. | Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants. |
| 74 ZEJULA | 3/27/2017 | niraparib | Treatment of adult patients with recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. | 553 | 100% | Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. (Source Drug Label 8.1) | Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose. |
| 75 OCREVUS | 3/28/2017 | ocrelizumab | Treatment of patients with two types of multiple sclerosis. | Trial 1 & 2: 1656 Trial 3: 732 | Trial 1 & 2: 66% Trial 3: 49% | Animal reproduction data. There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. | Excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. (Source: Drug Label 8.2) |
| 76 DUPIXENT | 3/28/2017 | dupilumab | Treatment of moderate to severe atopic dermatitis in adults. | 1338 | 42% | Animal reproduction data. There are no available data on DUPIXENT use in pregnant women to inform any drug associated risk. | There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 77 AUSTEDO | 4/3/2017 | deutetrabenazine | Treatment of chorea in patients with Huntington's disease. | 90 | 44% | Animal reproduction data. However, administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality [see Data]. | There are no data on the presence of deutetrabenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. |
| 78 INGREZZA | 4/11/2017 | valbenazine | Treatment of tardive dyskinesia. | 445 | 42% | Animal reproduction data. The limited available data on INGREZZA use in pregnant women are insufficient to inform a drug-associated risk. | Label notes drug present in rats milk. There is no information regarding the presence of valbenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. |
| 79 BRINEURA | 4/27/2017 | cerliponase alfa | Slowing loss of walking ability (ambulation) in symptomatic patients with a specific form of Batten disease. | 24 | 63% | No data in label. Note: Batten Disease often fatal by late teens or twenties. | No data in label. Note: Batten Disease often fatal by late teens or twenties. |
| 80 RYDAPT | 4/28/2017 | midostaurin | Treatment of adults with advanced systemic mastocytosis (SM). | 142 | 36% | Animal reproduction data. Based on mechanism of action and findings in animal reproduction studies, RYDAPT may cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | Label notes drug present in rats milk. Because of the potential for serious adverse reactions in breastfed infants from RYDAPT advise women not to breastfeed during treatment with RYDAPT and for at least 4 months after the last dose. |

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|----|--------------------------------|----------------------------|-------------------|--|--|--------------------------------------|--|--|
| 81 | RYDAPT | 4/28/2017 | midostaurin | Treatment of adults with acute myeloid leukemia (AML) that has a mutation in a gene called FLT3, in combination with chemotherapy. | 717 | 56% | Animal reproduction data. Based on mechanism of action and findings in animal reproduction studies, RYDAPT may cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | Label notes drug present in rats milk. Because of the potential for serious adverse reactions in breastfed infants from RYDAPT advise women not to breastfeed during treatment with RYDAPT and for at least 4 months after the last dose. |
| 82 | TYMLOS | 4/28/2017 | abaloparatide | Treatment of postmenopausal women with osteoporosis who are at high risk for bone fracture. | 1645 | 100% | No data in label. Note: Not indicated in use of women of reproductive age. | No data in label. Note: Not indicated in use of women of reproductive age. |
| 83 | ALUNBRIG | 4/28/2017 | brigatinib | Treatment of a type of lung cancer called non-small cell lung cancer (NSCLC) that is advanced (metastatic). | 222 | 57% | Animal reproduction data. Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman [see Data and Clinical Pharmacology (12.1)]. | Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose. |
| 84 | IMFINZI | 5/1/2017 | durvalumab | Treatment of a type of bladder and urinary tract cancer called urothelial carcinoma. | 182 | 28% | Animal reproduction data. Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | Lactation study completed on animals (monkeys). Because of the potential for adverse reactions in breastfed infants from durvalumab, advise a lactating woman not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose. |
| 85 | RADICAVA | 5/5/2017 | edaravone | Treatment of Amyotrophic Lateral Sclerosis (ALS). | 368 | 39% | Animal reproduction data. There are no adequate data on the developmental risk associated with the use of RADICAVA in pregnant women. | Label notes drug present in rats milk. There are no data on the presence of edaravone in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. |
| 86 | KEVZARA | 5/22/2017 | sarilumab | Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). | 1740 | 82% | Pregnancy registry, limited human data, animal reproduction data. | No information is available on the presence of sarilumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. |
| 87 | BAXDELA | 6/19/2017 | delafloxacin | Treatment of adult patients with bacterial skin infections. | 1510 | 37% | Animal reproduction data. | Lactation study completed on animals (rats). There are no data available on the presence of delafloxacin in human milk, the effects on the breast-fed infant, or the effects on milk production. |
| 88 | BEVYXXA | 6/23/2017 | betrixaban | Prevention of venous thromboembolism (VTE). | 7513 | 54% | Animal reproduction data. There are no data with the use of BEVYXXA in pregnant women, but treatment is likely to increase the risk of hemorrhage during pregnancy and delivery (see Clinical Considerations). | No data are available regarding the presence of betrixaban or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. |
| 89 | TREMFYA | 7/13/2017 | guselkumab | Treatment of moderate to severe plaque psoriasis in adults. | 1829 | 29% | Animal reproduction data. There are no available data on TREMFYA use in pregnant women to inform a drug associated risk of adverse developmental outcomes. | Not detected in the milk of lactating cynomolgus monkeys. |

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|----|--------------------------------|----------------------------|------------------------------|---|--|--------------------------------------|--|--|
| 90 | NERLYNX | 7/17/2017 | neratinib | Treatment of an early stage HER2 - positive breast cancer. | 2840 | 100% | Animal reproduction data. Based on findings from animal studies and the mechanism of action, NERLYNX can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. | No data are available regarding the presence of neratinib or its metabolites in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from NERLYNX, advise lactating women not to breastfeed while taking NERLYNX and for at least 1 month after the last dose. |
| 91 | VOSEVI | 7/18/2017 | sofosbuvir,velpatasvir | Treatment of adults who have a specific type of hepatitis C virus (HCV) infection, called chronic hepatitis C virus genotypes 1, 2, 3, 4, 5 or 6 infection. | 748 | 23% | Animal reproduction data. No adequate human data are available to establish whether or not VOSEVI poses a risk to pregnancy outcomes. | Lactation study completed on animals (rats). It is not known whether the components of VOSEVI and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. |
| 92 | IDHIFA | 8/1/2017 | enasidenib | Treatment of adults with acute myeloid leukemia (AML) that have a mutation in a gene called IDH2 and whose disease has come back or has not improved after previous treatment(s). | 214 | 49% | Animal reproduction data. Based on animal embryo-fetal toxicity studies, IDHIFA can cause fetal harm when administered to a pregnant woman. | There are no data on the presence of enasidenib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Advise women not to breastfeed during treatment with IDHIFA and for at least 1 month after the last dose. |
| 93 | MAVYRET | 8/3/2017 | glecaprevir and pibrentasvir | Treatment of adults who have a specific type of hepatitis C virus (HCV) infection, called chronic hepatitis C virus genotypes 1, 2, 3, 4, 5 or 6 infection. | 2369 | 44% | Animal reproduction data. No adequate human data are available to establish whether or not MAVYRET poses a risk to pregnancy outcomes. | Lactation study completed on animals (rats). It is not known whether the components of MAVYRET are excreted in human breast milk, affect human milk production, or have effects on the breastfed infant. |
| 94 | BESPONSA | 8/17/2017 | inotuzumab ozogamicin | Treatment of adults with B-cell acute lymphoblastic leukemia (ALL). | 326 | 41% | Animal reproduction data. Based on its mechanism of action and findings from animal studies [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)], BESPONSA can cause embryo-fetal harm when administered to a pregnant woman. | Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with BESPONSA and for at least 2 months after the last dose. |
| 95 | VABOMERE | 8/29/2017 | meropenem and vaborbactam | Treatment of adults who have a complicated urinary tract infection (abbreviated as cUTI). | 545 | 66% | Animal reproduction data. Fetal malformations were observed in vaborbactam-treated rabbits, therefore advise pregnant women of the potential risks to the fetus. | No information is available on the effects of meropenem and vaborbactam on the breast-fed child or on milk production. |

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|--------------------|----------------|-------------------|--|--|--------------------------|---|--|
| 96 BENZNIDAZOLE | 8/29/2017 | Benznidazole | Treatment of Chagas disease in children 2 to 12 years of age. | 235 | 46% | <p>Animal reproduction data. Note: Pediatric Indication, Nevertheless, based on findings from animal studies, Benznidazole Tablets may cause fetal harm when administered to a pregnant woman. Published postmarketing reports on benznidazole use during pregnancy are insufficient to inform a drug -associated risk of adverse pregnancy -related outcomes. Based on findings from animal studies, Benznidazole Tablets may cause fetal harm when administered to a pregnant woman. Published postmarketing reports on benznidazole use during pregnancy are insufficient to inform a drug -associated risk of adverse pregnancy -related outcomes.</p> <p>Note: Pediatric Indication.</p> | <p>Note: Pediatric Indication. However, limited published literature based on breast milk sampling reports that benznidazole is present in human milk at infant doses of 5.5 to 17% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.3-2.79. There are no reports of adverse effects on the breastfed infant and no information on the effects of benznidazole on milk production.</p> |
| 97 ALIQOPA | 9/14/2017 | copanlisib | Treatment of adults with follicular lymphoma whose disease has come back after at least two previous treatments. | 168 | 54% | <p>Animal reproduction data. Based on findings from animal studies and the mechanism of action, ALIQOPA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)].</p> | <p>No data in label. Because of the potential for serious adverse reactions in a breastfed child from copanlisib, advise a lactating woman not to breastfeed during treatment with ALIQOPA and for at least 1 month after the last dose.</p> |
| 98 SOLOSEC | 9/15/2017 | secnidazole | Used to treat adult women with vaginal infections caused by bacteria known as bacterial vaginosis. | 333 | 100% | <p>Animal reproduction data. Limited available data with SOLOSEC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes.</p> | <p>Because of the potential for serious adverse reactions, including tumorigenicity, advise patients that breastfeeding is not recommended during treatment with SOLOSEC and for 96 hours (based on half-life) after administration of SOLOSEC.</p> |
| 99 VERZENIO | 9/28/2017 | abemaciclib | Treatment of specific forms of breast cancer. | Trial 1: 669 Trial 2: 132 | 100% | <p>Animal reproduction data. Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)].</p> | <p>There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.</p> |

| APPLICANT_NAME | PRODUCT_NAME | PROPRIETARY_NAME | INDICATION | Approval Date | Application Type | Package Insert Info |
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| ALK - Abello A/S | House Dust Mites Allergenics Extract | Odactra | An allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to Dermatophagoides farinae or Dermatophagoides pteronyssinus house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age. | 1-Mar-17 | Original Application (BLA) | Pregnancy: Risk Summary: In a fetal/embryo developmental toxicity study performed in mice, administration of ODACTRA during gestation did not reveal adverse developmental outcomes in fetuses (see 8.1 data). Data: Animal: In a developmental toxicity study, the effect of ODACTRA on embryo/fetal development was evaluated in mice. Animals were administered ODACTRA subcutaneously daily from day 6 to 17 of the gestation period at up to 5 times the human sublingual dose. There were no ODACTA-related post-implantation loss, fetal malformations or variations. Lactation: No data. |
| Baxalta US Inc. | Immune Globulin Subcutaneous (Human), 20% Solution | CUVITRU | An Immune Globulin Subcutaneous (Human), 20% solution indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older. | 13-Sep-16 | OA | No human or animal data. Risk summary states: Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. |
| PaxVax Bermuda Ltd. | Cholera Vaccine Live Oral | Vaxchora | A vaccine indicated for active immunization against disease caused by Vibrio cholerae serogroup O1. VAXCHORA is approved for use in adults 18 through 64 years of age traveling to cholera-affected areas. | 10-Jun-16 | OA | Pregnancy Registry exists. Pregnancy Risk Summary: VAXCHORA is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Clinical Considerations: Disease-associated maternal and/or embryo/fetal risk: Maternal cholera disease is associated with adverse pregnancy outcomes including fetal death. Fetal/neonatal adverse reactions: The vaccine strain may be shed in the stool of the vaccinated mother for at least 7 days, with a potential for transmission of the vaccine strain from mother to infant during vaginal delivery. Lactation: Risk Summary: VAXCHORA is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to VAXCHORA. |

| APPLICANT_NAME | PRODUCT_NAME | PROPRIETARY_NAME | INDICATION | Approval Date | Application Type | Package Insert Info |
|--|---|---|--|---------------|------------------|---|
| Vericel Corporation | autologous cultured chondrocytes on porcine collagen membrane | MACI | An autologous cellularized scaffold product indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults | 13-Dec-16 | OA | Pregnancy Risk Summary: MACI implantation requires invasive surgical procedures; therefore use during pregnancy is not recommended. Limited clinical data on patients exposed to MACI during pregnancy are available. There are insufficient data with MACI use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with MACI. Lactation: Risk Summary: There is no information regarding the presence of MACI in human milk, the effects on the breastfed infant, or the effects on milk production. |
| CSL Behring GmbH | C1 Esterase Inhibitor Subcutaneous (Human) | HAEGARDA | A plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients. (| 22-Jun-17 | OA | Pregnancy: Risk Summary: No prospective clinical data. C1-INH is a normal component of human plasma. Animal developmental or reproduction toxicity studies have not been conducted with HAEGARDA. Data: In a retrospective case collection study, 22 pregnant women with type I HAE and ranging in age from 20 to 38 years received C1-INH doses of 500 or 1000 IU per I.V. administration for the treatment of acute attacks before, during, and/or after pregnancy (total of 35 pregnancies). No adverse events were associated with C1-INH treatment before, during, or after pregnancy. In an observational registry (overall 318 subjects) data were collected on 11 pregnancies in 10 subjects (16 to 40 years old) receiving up to 3000 IU C1-INH (I.V. administration) to treat or prevent HAE attacks. No adverse events were associated with C1-INH treatment. Lactation: Risk Summary: There is no information regarding the excretion of HAEGARDA in human milk, the effect on the breastfed infant, or the effects on milk production. |
| Novo Nordisk Inc. | Coagulation Factor IX (Recombinant), GlycoPEGylated | REBINYN | A recombinant DNA-derived coagulation Factor IX concentrate indicated for use in adults and children with hemophilia B | 31-May-17 | OA | No human or animal data. |
| Octapharma Pharmazeutika Produktionsges.m.b.H. | Fibrinogen (Human) | FIBRYGA [OA approved PI used Fibryna as Prop name, a labeling supplement subsequently changed the proprietary name to FIBRYGA (STN 125615/5)] | A human fibrinogen concentrate indicated for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. | 7-Jun-17 | OA | No human or animal data. |

| APPLICANT_NAME | PRODUCT_NAME | PROPRIETARY_NAME | INDICATION | Approval Date | Application Type | Package Insert Info |
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| Kamada Ltd. | Rabies Immune Globulin (Human) | KEDRAB | Rabies Immune Globulin (Human) is indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. Rabies Immune Globulin (Human) should be administered concurrently with a full course of rabies vaccine. | 23-Aug-17 | OA | No human or animal data. |
| Novartis Pharmaceuticals Corporation | Tisagenlecleucel | KYMRIAH | Indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. | 30-Aug-17 | OA | Pregnancies are to be reported, but PI does not say there is an established pregnancy registry. No human or animal data. Pregnancy Risk section also states: It is not known if KYMRIAH has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH infusion should be discussed with the treating physician. |

Appendix XIII – List of Acronyms

- Absorption, distribution, metabolism, and excretion (ADME)
- Advisory Committee on Immunization Practices (ACIP)
- Agency for Healthcare Research and Quality (AHRQ)
- American Academy of Allergy, Asthma & Immunology (AAAAI)
- American Academy of Pediatrics (AAP)
- American College of Obstetricians and Gynecologists (ACOG)
- American Hospital Association (AHA)
- Antiphospholipid antibody syndrome (AA syndrome)
- Attention-deficit/hyperactivity disorder (ADD/ADHD)
- Autism spectrum disorder (ASD)
- Baby-Friendly Hospital Initiative (BFHI)
- Best Pharmaceuticals for Children Act (BPCA)
- Biologics License Applications (BLA)
- Biomedical Advanced Research and Development Authority (BARDA)
- Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS)
- Bisphenol A (BPA)
- Cardiovascular disease (CVD)
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Centers for Disease Control and Prevention (CDC)
- Central nervous system (CNS)
- Child Health and Mortality Prevention Surveillance Network (CHAMPS)
- Chronic Hypertension and Pregnancy (CHAP) project
- Community Integrated Service Systems (CISS)
- Continuing Education (CE)
- Cytomegalovirus (CMV)
- Department of Agriculture (USDA)
- Department of Defense (DoD)
- Department of Health and Human Services (HHS)
- Department of Veterans Affairs (VA)
- Diethylstilbestrol (DES)
- Environmental Protection Agency (EPA)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- Fogarty International Center (FIC)
- Food and Drug Administration (FDA)
- Food Safety and Modernization Act (FMSA)
- Gestational diabetes mellitus (GDM)
- Health Resources and Services Administration (HRSA)
- Healthcare Cost and Utilization Project (HCUP)

- Hepatitis B virus (HBV)
- Indian Health Service (HIS)
- Influenza Hospitalization Surveillance Network (FluSurvNet)
- Institutional review boards (IRB)
- International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT)
- Maternal and Child Health (MCH)
- Maternal-Fetal Medicine Unit Network (MFMU)
- Maternity Practices in Infant Nutrition and Care (mPINC)
- Medical Expenditure Panel Survey (MEPS)
- Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP)
- National Biomonitoring Program (NBP)
- National Birth Defects Prevention Study (NBDPS)
- National Cancer Institute (NCI)
- National Center for Advancing Translational Sciences (NCATS)
- National Center for Research Resources (NCRR)
- National Center for Complementary and Integrative Health (NCCIH)
- National Child and Maternal Health Education Program (NCMHEP)
- National Eye Institute (NEI)
- National Health and Nutrition Examination Survey (NHANES)
- National Health Interview Survey (NHIS)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Human Genome Research Institute (NHGRI)
- National Institute for Occupational Safety and Health (NIOSH)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute of General Medical Sciences (NIGMS)
- National Institute of Mental Health (NIMH)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Nursing Research (NINR)
- National Institute on Aging (NIA)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute on Drug Abuse (NIDA)
- National Institute on Minority Health and Health Disparities (NIMHD)
- National Institutes of Health (NIH)
- National Library of Medicine (NLM)
- National Science Foundation (NSF)

- National Survey of Family Growth (NSFG)
- National Toxicology Program (NTP)
- National Vaccine Program Office (NVPO)
- Necrotizing enterocolitis (NEC)
- Neonatal opioid withdrawal syndrome (NOWs)
- new molecular entities (NMEs)
- New Parent Support Program (NPSP)
- NIH Clinical Center (CC)
- NIH Institute and Center (IC)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be (nuMoM2b)
- Office of the Assistant Secretary for Health (OASH)
- Office of the Director, National Institutes of Health (OD)
- Office on Women's Health (OWH)
- Partnership for Influenza Vaccine Introduction (PIVI)
- Pediatric Research Equity Act (PREA)
- Pharmacokinetic/pharmacodynamic modeling (PK/PD)
- Pregnancy and Influenza Multinational Epidemiologic (PRIME) Study
- Pregnancy and Lactation Labeling Rule (PLLR)
- Pregnancy Risk Assessment Monitoring System (PRAMS)
- Pregnancy Vaccine Effectiveness Network (PREVENT)
- President's Emergency Plan For AIDS Relief (PEPFAR)
- Prevention of mother-to-child transmission of HIV (PMTCT)
- Post-traumatic stress disorder (PTSD)
- Principal Investigator (PI)
- Randomized controlled trial (RCT)
- Society for Maternal-Fetal Medicine (SMFM)
- Special Projects of Regional and National Significance (SPRANS)
- Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)
- Study to Explore Early Development (SEED)
- Substance Abuse and Mental Health Services Administration (SAMHSA)
- Sudden Infant Death Syndrome (SIDS)
- Systemic lupus erythematosus (SLE)
- Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
- Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap)
- The Obstetric-Fetal Pharmacology Units (OFPU)
- Tuberculosis (TB)
- U.S. Food and Drug Administration (FDA)
- U.S. Preventive Services Task Force (USPSTF)
- Vaccine Injury Compensation Program (VICP)
- Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

- Zika Experimental Science Team (ZEST)