

Summary of Responses to the Request for Information on Research Specific to Pregnant Women and Lactating Women (PRGLAC) (NOT-18-003)

May 14, 2018

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 healthcare 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% 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 eleven 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% of women in the United States give birth by cesarean delivery; 85% 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 U.S. 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, specifically 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 anti-virals 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.