

# Advancing Clinical Research with Pregnant and Lactating Populations

## Overcoming Real and Perceived Liability Risks

In the United States, more than 3.5 million women give birth and more than 3 million women initiate breastfeeding each year. These women experience pregnancy-specific health conditions, such as pre-eclampsia and gestational diabetes, as well as other universal conditions such as depression and asthma. In consultation with their providers, many pregnant and lactating women use prescription medications to treat their conditions; however, they most often have to do so without the high-quality evidence about a drug's dosage, safety, and efficacy that is available to non-pregnant or non-lactating individuals. This lack of evidence is a result of the exclusion of pregnant and lactating women from clinical studies over the years. Although pregnancy and lactation are physiologically unique, pregnant and lactating women and their health care providers must rely on evidence from non-pregnant and non-lactating individuals, as well as from preclinical studies in pregnant and lactating animals. On a population level, this poses a significant barrier to delivering safe, effective, and timely care for pregnant and lactating women and exacerbates existing health inequalities.

In recent years, a growing number of researchers and advocacy groups have called for the inclusion of pregnant and lactating women in clinical studies and have provided evidence that inclusion is the more ethical and responsible course of action. Despite these calls for inclusion, pregnant and lactating women continue to be systematically excluded from clinical research and evidence on the dosage, safety, and efficacy of medical products in these populations remains scarce. In 2018, a congressionally mandated task force on Research Specific to Pregnant and Lactating Women published a report on the gaps in knowledge about safe and effective therapies



for pregnant and lactating women. Among the findings was a statement indicating that concerns about liability<sup>1</sup> were a major impediment to research on the use of medications in pregnant and lactating women. However, no studies to date have examined the legal liability for conducting clinical studies with pregnant and lactating women. To address this gap, Congress called on the National Academies to examine the real and perceived risks of liability. The study committee comprised experts in obstetrics, maternal fetal medicine, pediatrics, lactation, public health, clinical research, pharmacy, law, policy, pharmacovigilance, and bioethics, and considered ways to safely and ethically include pregnant and lactating women in clinical research while reducing or eliminating the risk of liability. The resulting report, *Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks*, presents conclusions and recommendations that could lead to a more robust evidence base about the safety and efficacy of medications for pregnant and lactating women and facilitate more informed decision making regarding care, while mitigating liability.

#### **EVIDENCE OF LEGAL LIABILITY**

The committee found limited evidence of legal liability related to including pregnant and lactating women in clinical trials. An analysis of case laws related to medical products studied in or used by pregnant or lactating women found no reported claims of liability for research-related injuries after the Food and Drug Administration (FDA) adopted regulations governing research in 1962. However, there were a number of liability claims related to the use of on-market medical products in pregnant populations. There were no cases identified involving injury to a child caused by a medical product used by a lactating woman. Most of the cases associated with pregnant women's use of approved medications—more than 1,000 in total—were brought against the developer, manufacturer, or distributor of the medication and alleged that the medication caused an injury to the fetus that was apparent at birth or within several years. Based on this analysis, the committee made two conclusions. First, although pregnant and lactating women are often

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<sup>1</sup> Legal liability refers to a party's breach of duty that results in harm to another.

referred to as one population, there are significant differences in both the physiology and potential harms for conducting research with these populations. When discussing liability, conflating pregnant and lactating women is inappropriate and associates lactating women with a liability risk for which there is no evidence. Second, excluding pregnant women from clinical trials shifts the risks—and the potential for liability—from the small, regulated context of well-monitored research participants into the much larger and less-regulated context of clinical practice.

#### **BALANCING RISKS**

The inclusion of pregnant and lactating women in clinical research has a risk of harm—such as injury to the woman or fetus—but exclusion causes harm by forcing women and their providers to make care decisions without sufficient information. For example, the use of thalidomide by pregnant women without rigorous testing in the middle of the twentieth century was linked to severe birth defects in their children. Drug development regulatory processes have significantly advanced since the introduction of thalidomide and are designed to protect research participants and the public from harm (see Conclusion 3-1 in the report). Had clinical trials for thalidomide applied modern study design, negative effects would have been revealed earlier, thus minimizing harm. Although current regulatory systems protect research participants from harm, improvements to regulatory systems and ethics oversight for research involving pregnant and lactating women are critical to reduce the risk of harm for these populations, which encompasses the probability and magnitude of harm. Moreover, pregnant and lactating women must be included in clinical research to benefit from the protection that the drug regulatory system offers to populations who are included in the research conducted before medical products reach the market.

#### **PERCEPTION OF LIABILITY AND OTHER DETERRENENTS**

While evidence does not indicate a significant risk of liability related to the inclusion of pregnant and lactating women in clinical research, the perception of potential liability remains a barrier to inclusion. This perception is based on cultural narratives, which often conflate clinical

research with historical stories of drugs that were not subject to modern regulation, such as thalidomide (see Conclusion 2–3 in the report).

For research sponsors and investigators, liability is one of many deterrents to including pregnant and lactating women in clinical studies. Other deterrents include lack of expertise in conducting research with the pregnant and lactating population, cost and complexity of trials, reputational risks, and lack of financial incentives. The committee noted that changing one or more of these factors could influence the decision to include pregnant and lactating women. If the advantages of conducting this research outweigh the disadvantages, research sponsors, research institutions, and investigators may choose to include pregnant and lactating women in their research moving forward.

#### **ADDRESSING THE DETERRENDS**

The committee viewed approaches for addressing the interrelated factors that deter stakeholders as falling into three categories. First, there are ways to directly mitigate liability; that is, reduce the likelihood that a research sponsor will be sued or held liable for injuries associated with a clinical trial. These include more robust informed consent procedures, clearer guidance from FDA about expectations for research, better training for investigators and clinical staff, and compensation for individuals harmed in clinical research. To advance federally funded clinical studies with pregnant and lactating women, the National Institutes of Health (NIH) and other federal funders should cover the cost of clinical trial insurance (see Recommendation 7 in the report).

Second, steps can be taken to minimize potential harms and reduce the potential for legal liability. The committee

highlighted the need for clearer guidance from FDA about when and how to conduct research in pregnant and lactating populations (see Recommendation 1 in the report) and guidance from the Office for Human Research Protections within the U.S. Department of Health and Human Services to inform institutional review boards about how to oversee this research (see Recommendation 3 in the report). To protect pregnant research participants who may themselves face liability following the Supreme Court decision in *Dobbs v. Jackson Women’s Health Organization*, the committee recommends that researchers apply for a certificate of confidentiality, if not already issued one by NIH or another federal agency (see Recommendation 9 in the report).

Finally, concerns about lack of expertise, the cost and complexity of trials, and lack of incentives can be addressed through congressional action to provide funding for research in pregnant and lactating populations and legislation that creates incentives (e.g., patent and data exclusivity) and requirements for conducting this research (see Recommendations 4 and 5 in the report).

#### **LOOKING FORWARD**

The committee made nine recommendations, calling on actors including FDA, Congress, and NIH, aimed at improving clarity and predictability for all stakeholders to facilitate and encourage the appropriate inclusion of pregnant and lactating women in clinical research. It is possible to conduct research with pregnant and lactating women in a way that maximizes evidence generation while minimizing the potential for harm and liability. This is imperative for safeguarding the health and well-being of all pregnant and lactating women and their children.

**COMMITTEE ON DEVELOPING A FRAMEWORK TO ADDRESS LEGAL, ETHICAL, REGULATORY, AND POLICY ISSUES FOR RESEARCH SPECIFIC TO PREGNANT AND LACTATING PERSONS** **Margaret Foster Riley** (*Chair*), University of Virginia; **Ifeyinwa Asiodu**, University of California, San Francisco; **Paul Beninger**, Tufts University; **Alexander M. Capron**, University of Southern California; **Patricia Danzon** (resigned from committee September 2023), University of Pennsylvania; **Ahizechukwu Eke**, Johns Hopkins University; **Mary F. Hebert**, University of Washington; **Leslie Meltzer Henry**, University of Maryland Carey School of Law; Johns Hopkins Berman Institute of Bioethics; **Patricia A. King**, Georgetown University; **Bruce Kuhlik**, Merck & Co., Inc. (Retired); **Anne CC Lee**, Harvard School of Medicine; Brigham and Women’s Hospital; Harvard Medical School; **Anna C. Mastroianni**, Johns Hopkins University; **Jonell Efantis Potter**, University of Miami; **Enrique Schisterman**, University of Pennsylvania; **Brownsyne Tucker Edmonds**, Indiana University School of Medicine

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#### **FOR MORE INFORMATION**

This Consensus Study Report Highlights was prepared by the Board on Health Sciences Policy based on the Consensus Study Report *Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks* (2024).

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Copies of the Consensus Study Report are available from the National Academies Press, (800) 624-6242 or <https://nap.nationalacademies.org/catalog/27595>.

To read the full report, visit [nationalacademies.org/liability-study](https://nationalacademies.org/liability-study).

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