The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Friday, March 8, 2024 | 11:00 AM – 2:00 PM ET
Hybrid Meeting

Advancing Inclusion: Integrating Pregnant and Lactating People in Research
Meeting Summary

Introduction

There is widespread recognition, including among pregnant and lactating people (PLP), of the need for better evidence on which to base medical treatment decisions during pregnancy and the post-partum period. Despite this, pregnant and lactating people continue to be left out of clinical trials that test drugs, vaccines, devices, and other medical products for safety and efficacy. Study eligibility criteria routinely exclude both pregnant and lactating individuals, even though the biological bases for exclusion of the two populations differ; the effects of exposure of medicinal products to the fetus at the varying stages of development differ from the effects on the neonate or newborn of medicinal products possibly transferred through breast milk. Eligibility often requires negative pregnancy tests prior to enrollment and effective methods of contraception for the duration of the study. Further, people who become pregnant while on an interventional trial protocol are typically withdrawn from further participation. During the March 6, 2024, meeting of the MRCT Center Bioethics Collaborative, we discussed the current climate of defaulting to the exclusion of PLP from clinical research, the types of data needed and potential ways to collect them, challenges with regulation and oversight, and more.

Presentations and Discussion

The meeting opened with a brief presentation that provided historical context and covered central ethical and regulatory issues related to the inclusion of pregnant and lactating people in research. Events in the 1960s and 1970s – namely, the discovery that thalidomide and diethylstilbestrol are teratogenic – laid the foundation for a conservative culture regarding the inclusion of PLP in research and instilled a sense of fear about the administration of drugs to pregnant individuals. While many restrictions on the inclusion of PLP in research have been altered or removed, the culture of perceived protection through exclusion persists, and regulatory ambiguity continues to pose challenges. PLP, like all other populations, have medical concerns requiring treatment. Exclusion from research does not protect these individuals; it merely shifts the risk from the highly controlled research environment to the clinic. Because of

this, there has been a push in recent years to think about protecting PLP *through* research rather than from it. Central questions related to conducting research in PLP include who gets to determine acceptable levels of risk for the fetus and pregnant person, who gets to decide to expose a fetus to a drug or device, and how studies might be designed to include PLP in a safe manner.

A common argument against conducting research in pregnant populations is that we do not want "another thalidomide." The first guest speaker began his talk by rebutting this point: the thalidomide tragedy occurred due to a lack of clinical research, not because of it. If clinical research had been conducted, there still would have been serious adverse consequences, but they would have occurred on a much smaller scale. At present, the default in clinical research is to exclude PLP. Shifting from exclusion is important but will not lead to research involving PLP unless it is accompanied by structural changes to facilitate robust and meaningful research on pregnant people. One major component of this is the institutional review board (IRB) process. The speaker noted that he is aware of many instances in which research studies including PLP have failed to gain IRB approval. Other meeting attendees agreed that IRBs tend to take a conservative approach when considering studies that include PLP even if less restrictive alternatives may exist.

Lack of understanding – both of pregnancy-related risks and of how best to interpret existing laws and regulations – was identified as a main driver of this conservative approach among IRBs. In the United States, research involving pregnant individuals is regulated under Subpart B of the Common Rule. Subpart B does not prohibit research on pregnant individuals, but sets out precise conditions, many of them highly subject to interpretation, that must be met before IRBs may approve research with pregnant people. Further, the conditions imposed by Subpart B are arguably more stringent than the conditions that must be met to include children in research, viz., Subpart D. For example, while Subpart D permits greater than minimal risk research with no prospect of direct benefit for the child under certain circumstances, Subpart B requires greater than minimal risk research to hold a prospect of benefit for either the pregnant person or the fetus. In addition, the requirements for parental consent in Subpart B differ from those in Subpart D, with Subpart B requiring consent from the father of the fetus in many cases. The nature of these regulations and the challenging interpretive issues they involve may result in conservative and cautious approaches from IRBs when reviewing studies involving PLP.

Discussion then turned, with the second speaker's remarks, to the dearth of knowledge for treating pregnant patients. Cardiovascular disease (CVD), a leading cause of death during pregnancy, was used to illustrate the need for better evidence-based treatments for pregnant

individuals. Most current guidelines for treating PLP with cardiovascular disease are based on subpar sources of evidence (e.g., so-called "Level C" evidence that includes published case reports and reviews but no randomized controlled trials), which would not be acceptable in other areas of medicine.[1,2] Thus, clinicians are left to use outdated medications that are known, through years of clinical use, to be safe (or safe enough) during pregnancy, while other newer and potentially more effective therapies are avoided. Unless they are included in research, the care of PLP will continue to lag behind the current standard of care. There are times when the exclusion of PLP from research studies is justified – such as studies specific to male biology or when animal studies demonstrate likely biological harm to the fetus – but in general, the speaker argued, people should not be excluded from research studies simply because they are pregnant or lactating. Even when the pregnant individual and fetus do not receive an active intervention the pregnant person and the fetus benefit from the increased monitoring and high levels of care that come with participation in research.

A main topic of discussion throughout the meeting was how to change the presumption that PLP should be excluded from research. The third speaker proposed six reasons that exclusion remains the default: (1) habit, (2) culture, (3) ethical emphasis on protection, (4) regulatory ambiguity, (5) fear of liability, and (6) the practical, logistical, scientific, statistical, and financial difficulties of inclusion. Habits are difficult to change, particularly when they reflect the culture in which they are situated. Our society has a strong preference for "zero risk" to the fetus during pregnancy, even if risks are merely perceived.[3] It is important to remember that while all treatments carry risk, there is also risk associated with not treating a condition. The speaker recommended the need for thoughtful inclusion of PLP in research. In general, people should only be included in research if they are going to contribute valid and helpful data. Including PLP in studies not designed for them may contaminate the data from the rest of the study population.[*] Additionally, studies that are not targeted at PLP are unlikely to enroll sufficient numbers of PLP to perform PLP-specific analysis. Studies including PLP in a way that would allow for meaningful data analysis are likely to be time and resource-intensive and logistically difficult.

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[*] A sub-study could be envisioned for the inclusion of PLP if the study is of potential benefit. Even if the enrollment numbers are insufficient for the analysis of safety or efficacy, pharmacokinetic and pharmacodynamic studies at different timepoints during pregnancy will be very useful.

The fourth speaker extended the discussion of the need for adequate data by discussing current approaches to drug safety surveillance in pregnancy. She emphasized the need to focus on reliable and actionable data and the importance of recognizing—and discounting—false signals, that can generate unnecessary concern or false reassurance. Prospective pregnancy exposure registries and cohort studies nested in large healthcare utilization databases are two methods for collecting data on pregnancy exposure and outcomes. Large numbers are necessary to capture rare but clinically significant outcomes; a sample size of 500 provides enough statistical power to detect the "thalidomides," but not more moderate effects or rare but clinically significant outcomes. For this reason, cohort studies are increasingly being relied upon by regulators, as registry study target enrollment typically ranges from 150 to 500, and many of these (86%) do not hit their enrollment goals.[4] One issue with cohort studies, however, is that they can be significantly impacted by sparse data. Meeting participants discussed the importance of data on dosing and window of exposure, given the different risks and pharmacokinetic/pharmacodynamic profiles at different points throughout pregnancy. One participant also noted that obstetricians may be able to assist with the collection of safety data, but that few in the OB/GYN community are likely to be aware of this need since PLP have been generally excluded from clinical research. Others agreed that leaning on the clinicians who work with PLP the most is likely to be beneficial but would require raising awareness due to the historic lack of research involving this community.

Conclusion and Next Steps

The presentations and discussion during the March 3, 2024, meeting of the MRCT Center Bioethics Collaborative clarified the need for greater nuance and care in approaches to including PLP in clinical research. As one meeting participant put it, there is a tendency to lump together like groups; in this case, however, there is a need to divide the populations and make finer distinctions among pregnant and lactating people, and distinguish issues of pregnancy in the first trimester from the third, as groups to achieve what is needed. In this case, there appeared to be consensus among meeting participants that the following groups be considered separately in discussions about inclusion: people at different time points in pregnancy and particularly in each of the three trimesters; lactating as opposed to pregnant people; and individuals who become pregnant while participating in a clinical trial. Properly addressing the needs of each group and conducting trials accordingly will be difficult and expensive, particularly for interventions not aimed specifically at those populations. There is also a need for education and regulatory guidance.

Shifting away from a culture where exclusion is the default will be challenging. There has been progress over the past several years, and there is historical precedent with pediatric research achieving a greater culture of inclusion. There is also work occurring at the national level, including from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). Meeting participants highlighted the PRGLAC webinar and report release on April 10, 2024.[†] The MRCT Center plans to continue work in this area and welcomes thoughts, feedback, and questions related to this meeting or work on including PLP in research more generally.

References

1. Van Spall, Harriette Gillian Christine. "Exclusion of Pregnant and Lactating Women from COVID-19 Vaccine Trials: A Missed Opportunity." *European Heart Journal* 42, no. 28 (July 21, 2021): 2724–26. https://doi.org/10.1093/eurheartj/ehab103.

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3. Anne Drapkin Lyerly, Lisa M. Mitchell, Elizabeth Mitchell Armstrong, Lisa H. Harris, Rebecca Kukla, Miriam Kuppermann, and Margaret Olivia Little. "Risk and the Pregnant Body." *Hastings Center Report* 39, no. 6 (2009): 34–42. https://doi.org/10.1353/hcr.0.0211.

4. Gelperin, Kate, Hoda Hammad, Kira Leishear, Steven T. Bird, Lockwood Taylor, Christian Hampp, and Leyla Sahin. "A Systematic Review of Pregnancy Exposure Registries: Examination of Protocol-Specified Pregnancy Outcomes, Target Sample Size, and Comparator Selection: Systematic Review of Pregnancy Registry Methods." *Pharmacoepidemiology and Drug Safety* 26, no. 2 (February 2017): 208–14. https://doi.org/10.1002/pds.4150.

[†] The prepublication report is located at https://nap.nationalacademies.org/catalog/27595/advancing-clinical-research-with-pregnant-and-lactating-populations-overcoming-real.