REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

CEJA Report 03-I-25

Subject: Ethical Impetus for Research in Pregnant and Lactating Individuals

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Referred to: Reference Committee on Ethics and Bylaws

Policy D-140.949, "Ethical Impetus for Research in Pregnant and Lactating Individuals," was adopted at the 2024 Annual Meeting and asks "that our Council on Ethical and Judicial Affairs (CEJA) consider updating its ethical guidance on research in pregnant and lactating individuals."

BACKGROUND

More than four million individuals give birth in the United States every year[1] and 70 percent of these individuals will require at least one prescription medication while pregnant.[2] Despite the widespread use of medications during pregnancy, most information about the efficacy and safety of medication used during pregnancy comes from the post-marketing setting and is not derived from clinical research trials.[3]

Only a dozen medications have been approved by the United States Food and Drug Administration (FDA) for use during pregnancy, and those medications are for gestation- or birth-related medical issues.[4] Therefore, any medications utilized to treat chronic health conditions in pregnancy are used without FDA approval ("off label"). Only 2.4 percent of those commonly used medications for chronic health conditions have included pregnant individuals in controlled human clinical trials. The lack of clinical trial data is a result of the historical exclusion of pregnant and lactating individuals from clinical trials. Exclusion of pregnant and lactating individuals from clinical trials has often occurred due to the fear of harming the fetus or newborn, as well as concern that physiologic changes in pregnancy or during lactation will impact the results of pharmacologic trials.[3,5] The effect of this exclusion is that physicians and patients are forced to make decisions about whether to utilize medications during pregnancy without adequate fetal and maternal safety data.[6]

ETHICAL ISSUE

Pregnant and lactating individuals have been systematically excluded from clinical trials for decades out of concern for negative effects on fetuses and nursing infants. This exclusion has resulted in a paucity of evidence regarding safe and effective medication use in these groups of individuals. Due to the existing knowledge gaps surrounding the use of medications during pregnancy and breastfeeding, physicians and patients are faced with making treatment decisions without appropriately understanding the potential benefits and risks to both the pregnant individual and their fetuses or nursing infant. Additionally, these knowledge gaps prevent physicians from

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being able to appropriately counsel pregnant patients regarding the risks, benefits, and alternatives of treatments. At issue is how to balance respect for pregnant and lactating individuals with the potential benefits and harms of research.

REVIEW OF RELEVANT LITERATURE

Pregnant and lactating individuals have historically been considered "vulnerable" and subjected to additional research protections and exclusion from research.[7] This problem is known as the "protection-inclusion dilemma", whereby groups deemed "vulnerable" are "over-protected" and excluded from research, leading to justice issues including a "lack of relevant health data for under-represented populations."[8] The consequence of the protection-inclusion dilemma is that most of the medications pregnant individuals are prescribed are not FDA approved for pregnancy. This is problematic because while "there are significant physiologic changes in pregnancy, including near doubling of maternal blood volume and alterations in binding proteins, the pharmacokinetics [PK] and efficacy of drugs in pregnancy are, by and large, unknown."[7] This uncertainty for prescribers results in dosages labelled for use in nonpregnant individuals being used for pregnant individuals, "with little consideration for the PK changes that occur during pregnancy."[9]

Although the negative effects of excluding pregnant and lactating individuals in clinical trials have been noted for years, little has been done in that time to address the significant knowledge gaps in research that remain. For example, many Institutional Review Boards (IRB) "continue to regard pregnancy as a near-automatic cause for exclusion, regardless of the costs of exclusion or the magnitude or likelihood of the risks of participation," and the lack of research data leads to persistent disparities for chronic disease management among pregnant individuals.[5]

Relevant Laws

The FDA has several relevant regulations. 45 CFR 46, Subpart B "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research", provides regulations regarding research involving pregnant individuals. 45 CFR §46.204 – "Research involving pregnant women or fetuses" states that:

> Pregnant women or fetuses may be involved in research if all of the following conditions are met:
>
> (b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.[10]

Additionally, as of January 21, 2019, the Common Rule no longer labels pregnant individuals as "vulnerable" with regards to IRBs. This is because while pregnant individuals have historically been deemed vulnerable, it has since been recognized that while some individuals who are pregnant may be vulnerable, being pregnant in and of itself does not automatically denote vulnerability. [11,12] The 2024 updated version of the World Medical Association's Declaration of Helsinki reinforces this point, stating that "[w]hen such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their disparities. Therefore, the harms of exclusion must be considered and weighed against the harms of inclusion."[11]

Relevant Code Provision(s)

The *Code of Medical Ethics* encourages the inclusion of pregnant individuals in clinical trials, when appropriate, so long as the research "balance[s] the health and safety of the woman who participates and the well-being of the fetus with the desire to develop new and innovative therapies" (Opinion 7.3.4). However, the *Code* also places constraints on physicians involved in maternal-fetal research, advising that they should "[e]nroll a pregnant woman in maternal-fetal research only when there is no simpler, safer intervention available to promote the well-being of the woman or fetus" (Opinion 7.3.4).

ETHICAL ANALYSIS

A multitude of historical, legal, scientific, and societal factors have resulted in the exclusion of pregnant and lactating individuals from clinical trials for decades. However, the ethical principle of justice necessitates that the benefits and burdens of research participation be fairly distributed across all groups, including pregnant and lactating individuals, because failure to do so produces disparities that impact both safety and quality of care for pregnant and lactating individuals, fetuses, and nursing infants.

Concerns for fetal safety have served as the primary justification for the exclusion of pregnant individuals from clinical trials for decades, but this exclusion has paradoxically resulted in substantial maternal and fetal harm. Because information about toxicity and dosing for pregnant and lactating individuals has not been determined through smaller scale and well-controlled clinical trials for most medications, far more pregnant and lactating individuals who require medications for chronic medical conditions are being exposed to potentially harmful medications via "off label" uses.

Examples of this harm can be seen in the historical use of thalidomide and diethylstilbestrol in pregnant individuals. While the tragic consequences of their use have been cited as reasons to exclude pregnant individuals from clinical trials, it was actually the lack of controlled data from clinical trials that caused such widespread detrimental effects due to the teratogenic effects of these drugs not being examined until post-marketing surveillance data was available. Had smaller scale and better controlled clinical trials been conducted, mass marketing and exposure to these medications for pregnant individuals may have been avoided because the teratogenic effects would have been discovered during trials.[13]. Another example is that of ACE inhibitors, which were used in pregnant individuals for three decades prior to the 1996 discovery that its use in the first trimester can cause congenital anomalies.[5]. Had it been studied more rigorously through smaller scale clinical trials with individuals consenting to the risks of participating in research, this discovery may have been made much sooner and far fewer individuals would have been exposed to this drug in the first trimester without knowing the risks of doing so.

Historically, concern for pregnant individuals and fetuses has centered on defining this population as "vulnerable", thus needing broad shielding from risks, such as medical research. Such an approach to research practices has been deemed "overly paternalistic, disempowering, or coercive."[14] Pregnant and lactating individuals are not automatically vulnerable, and this approach does not respect their autonomy to assess the benefits and risks of participation for themselves and their fetuses or newborns.[15] Pregnant and lactating individuals should always be provided the opportunity to decide whether research participation is in their best interest through informed consent. If pregnant or lactating individuals are unable to be included in research, alternative ways to rectify any gap in knowledge should be developed. For example, pregnant and lactating

individuals should be instructed on how to participate in research registries and adverse event reporting programs.

CONCLUSION

The historical exclusion of pregnant and lactating individuals from clinical trials has resulted in a lack of data about the appropriate safety, dosage, and efficacy of most medications in this group. This knowledge gap has created an ethical imperative to include more pregnant and lactating individuals in clinical trials. While consideration of maternal, fetal, and nursing infant well-being should be important criteria included in guidelines for research, wholesale exclusion of pregnant and lactating individuals from clinical trials comes with its own risk to fetal and maternal safety. Theoretical risks for fetal harm should not automatically be assumed to outweigh potential risks of ongoing nonparticipation. Currently, the *Code* does not reference this disparity. Nor does it refer to lactating individuals. It also does not contain gender neutral language, i.e., it references women and not individuals.

RECOMMENDATION

The Council on Ethical and Judicial Affairs recommends that following being adopted and the remainder of the report be filed:

1. Research involving pregnant and lactating individuals, including but not limited to, research regarding interventions intended to benefit pregnant or lactating individuals and/or their fetuses or nursing infants, must balance the health and safety of individuals who participate and the well-being of their fetuses or nursing infant against the desire to develop new and innovative therapies. Although it is important to carefully consider potential fetal risks involved when pregnant and lactating individuals participate in research, it is critical to realize that large scale exclusion from participation by these individuals has also precluded potential benefits and in some cases resulted in harm for this group. The paucity of data on safe and effective medical treatment during pregnancy and breastfeeding has resulted in physicians and patients choosing between pursuing medical interventions with uncertain risks to themselves and their fetuses or nursing infants, or foregoing the interventions altogether, which might itself cause harm due to undertreatment of medical conditions.

   Understanding both the potential risks of participation and of non-participation, physicians conducting research must obtain the informed, voluntary consent of pregnant or lactating individuals, and adhere to general principles for ethical conduct of research as in all human participant's research. In addition, physicians conducting research should:

   (a) Include pregnant and lactating individuals in research for which they would otherwise be eligible in order to establish a greater knowledge base, produce relevant data, and promote respect for individuals.

   (b) Consider excluding pregnant and lactating individuals only when a study poses a substantial risk of significant harm to them or their fetuses or nursing infants, and:

      i. specify why the research excludes pregnant and lactating individuals;

      ii. seek alternative research methodologies to rectify gaps in knowledge.

(c) Where scientifically appropriate and available, base studies that include pregnant and lactating individuals on well-designed, ethically sound, existing research with nonhuman animals or nongravid human participants to better assess potential risks.

(d) Minimize risks to the fetus or nursing infant to the greatest extent possible, especially when the research is not conducted primarily to investigate potential benefit for fetuses or nursing infants, but rather for the development of important biomedical knowledge that cannot be obtained by any other means. (New HOD/CEJA Policy)

2. AMA Policy D-140.949 be rescinded as having been accomplished by this report. (Rescind AMA Policy)

Fiscal Note: Minimal

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