

7.3.4.1 Research Involving Pregnant and Lactating Individuals

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.

AMA Principles of Medical Ethics: I,III,V

Background *report(s)*:

CEJA Report 03-I-25 Ethical Impetus for Research in Pregnant and Lactating Individuals

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

1 Policy D-140.949, “Ethical Impetus for Research in Pregnant and Lactating Individuals,” was
2 adopted at the 2024 Annual Meeting and asks “that our Council on Ethical and Judicial Affairs
3 (CEJA) consider updating its ethical guidance on research in pregnant and lactating individuals.”
4

5 BACKGROUND

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7 More than four million individuals give birth in the United States every year¹ and 70 percent of
8 these individuals will require at least one prescription medication while pregnant.² Despite the
9 widespread use of medications during pregnancy, most information about the efficacy and safety of
10 medication used during pregnancy comes from the post-marketing setting and is not derived from
11 clinical research trials.³
12

13 Only a dozen medications have been approved by the United States Food and Drug Administration
14 (FDA) for use during pregnancy, and those medications are for gestation- or birth-related medical
15 issues.⁴ Therefore, any medications utilized to treat chronic health conditions in pregnancy are used
16 without FDA approval (“off label”). Only 2.4 percent of those commonly used medications for
17 chronic health conditions have included pregnant individuals in controlled human clinical trials.
18 The lack of clinical trial data is a result of the historical exclusion of pregnant and lactating
19 individuals from clinical trials. Exclusion of pregnant and lactating individuals from clinical trials
20 has often occurred due to the fear of harming the fetus or newborn, as well as concern that
21 physiologic changes in pregnancy or during lactation will impact the results of pharmacologic
22 trials.^{3,5} The effect of this exclusion is that physicians and patients are forced to make decisions
23 about whether to utilize medications during pregnancy without adequate fetal and maternal safety
24 data.⁶
25

26 ETHICAL ISSUE

27
28 Pregnant and lactating individuals have been systematically excluded from clinical trials for
29 decades out of concern for negative effects on fetuses and nursing infants. This exclusion has
30 resulted in a paucity of evidence regarding safe and effective medication use in these groups of
31 individuals. Due to the existing knowledge gaps surrounding the use of medications during
32 pregnancy and breastfeeding, physicians and patients are faced with making treatment decisions
33 without appropriately understanding the potential benefits and risks to both the pregnant individual
34 and their fetuses or nursing infant. Additionally, these knowledge gaps prevent physicians from

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

4
5 REVIEW OF RELEVANT LITERATURE

6
7 Pregnant and lactating individuals have historically been considered “vulnerable” and subjected to
8 additional research protections and exclusion from research.⁷ This problem is known as the
9 “protection-inclusion dilemma”, whereby groups deemed “vulnerable” are “over-protected” and
10 excluded from research, leading to justice issues including a “lack of relevant health data for under-
11 represented populations.”⁸ The consequence of the protection-inclusion dilemma is that most of the
12 medications pregnant individuals are prescribed are not FDA approved for pregnancy. This is
13 problematic because while “there are significant physiologic changes in pregnancy, including near
14 doubling of maternal blood volume and alterations in binding proteins, the pharmacokinetics [PK]
15 and efficacy of drugs in pregnancy are, by and large, unknown.”⁷ This uncertainty for prescribers
16 results in dosages labelled for use in nonpregnant individuals being used for pregnant individuals,
17 “with little consideration for the PK changes that occur during pregnancy.”⁹

18
19 Although the negative effects of excluding pregnant and lactating individuals in clinical trials have
20 been noted for years, little has been done in that time to address the significant knowledge gaps in
21 research that remain. For example, many Institutional Review Boards (IRB) “continue to regard
22 pregnancy as a near-automatic cause for exclusion, regardless of the costs of exclusion or the
23 magnitude or likelihood of the risks of participation,” and the lack of research data leads to
24 persistent disparities for chronic disease management among pregnant individuals.⁵

25
26 *Relevant Laws*

27
28 The FDA has several relevant regulations. 45 CFR 46, Subpart B “Additional Protections for
29 Pregnant Women, Human Fetuses and Neonates Involved in Research”, provides regulations
30 regarding research involving pregnant individuals. 45 CFR §46.204 – “Research involving
31 pregnant women or fetuses” states that:

32
33 Pregnant women or fetuses may be involved in research if all of the following conditions are
34 met:

35
36 (b) The risk to the fetus is caused solely by interventions or procedures that hold out the
37 prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit,
38 the risk to the fetus is not greater than minimal and the purpose of the research is the
39 development of important biomedical knowledge which cannot be obtained by any other
40 means.¹⁰

41
42 Additionally, as of January 21, 2019, the Common Rule no longer labels pregnant individuals as
43 “vulnerable” with regards to IRBs. This is because while pregnant individuals have historically
44 been deemed vulnerable, it has since been recognized that while some individuals who are pregnant
45 may be vulnerable, being pregnant in and of itself does not automatically denote vulnerability.^{11,12}
46 The 2024 updated version of the World Medical Association’s Declaration of Helsinki reinforces
47 this point, stating that “[w]hen such individuals, groups, and communities have distinctive health
48 needs, their exclusion from medical research can potentially perpetuate or exacerbate their
49 disparities. Therefore, the harms of exclusion must be considered and weighed against the harms of
50 inclusion.”¹¹

1 *Relevant Code Provision(s)*

2
3 The *Code of Medical Ethics* encourages the inclusion of pregnant individuals in clinical trials,
4 when appropriate, so long as the research “balance[s] the health and safety of the woman who
5 participates and the well-being of the fetus with the desire to develop new and innovative
6 therapies” ([Opinion 7.3.4](#)). However, the *Code* also places constraints on physicians involved in
7 maternal-fetal research, advising that they should “[e]nroll a pregnant woman in maternal-fetal
8 research only when there is no simpler, safer intervention available to promote the well-being of
9 the woman or fetus” (Opinion 7.3.4).

10
11 ETHICAL ANALYSIS

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

19
20 Concerns for fetal safety have served as the primary justification for the exclusion of pregnant
21 individuals from clinical trials for decades, but this exclusion has paradoxically resulted in
22 substantial maternal and fetal harm. Because information about toxicity and dosing for pregnant
23 and lactating individuals has not been determined through smaller scale and well-controlled clinical
24 trials for most medications, far more pregnant and lactating individuals who require medications
25 for chronic medical conditions are being exposed to potentially harmful medications via “off label”
26 uses.

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

41
42 Historically, concern for pregnant individuals and fetuses has centered on defining this population
43 as “vulnerable”, thus needing broad shielding from risks, such as medical research. Such an
44 approach to research practices has been deemed “overly paternalistic, disempowering, or
45 coercive.”¹⁴ Pregnant and lactating individuals are not automatically vulnerable, and this approach
46 does not respect their autonomy to assess the benefits and risks of participation for themselves and
47 their fetuses or newborns.¹⁵ Pregnant and lactating individuals should always be provided the
48 opportunity to decide whether research participation is in their best interest through informed
49 consent. If pregnant or lactating individuals are unable to be included in research, alternative ways
50 to rectify any gap in knowledge should be developed. For example, pregnant and lactating

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

3
4 CONCLUSION

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

16
17 RECOMMENDATION

18
19 The Council on Ethical and Judicial Affairs recommends that following being adopted and the
20 remainder of the report be filed:

- 21
22 1. Research involving pregnant and lactating individuals, including but not limited to, research
23 regarding interventions intended to benefit pregnant or lactating individuals and/or their fetuses
24 or nursing infants, must balance the health and safety of individuals who participate and the
25 well-being of their fetuses or nursing infant against the desire to develop new and innovative
26 therapies. Although it is important to carefully consider potential fetal risks involved when
27 pregnant and lactating individuals participate in research, it is critical to realize that large scale
28 exclusion from participation by these individuals has also precluded potential benefits and in
29 some cases resulted in harm for this group. The paucity of data on safe and effective medical
30 treatment during pregnancy and breastfeeding has resulted in physicians and patients choosing
31 between pursuing medical interventions with uncertain risks to themselves and their fetuses or
32 nursing infants, or foregoing the interventions altogether, which might itself cause harm due to
33 undertreatment of medical conditions.

34
35 Understanding both the potential risks of participation and of non-participation, physicians
36 conducting research must obtain the informed, voluntary consent of pregnant or lactating
37 individuals, and adhere to general principles for ethical conduct of research as in all human
38 participant's research. In addition, physicians conducting research should:

- 39
40 (a) Include pregnant and lactating individuals in research for which they would otherwise be
41 eligible in order to establish a greater knowledge base, produce relevant data, and promote
42 respect for individuals.
43
44 (b) Consider excluding pregnant and lactating individuals only when a study poses a
45 substantial risk of significant harm to them or their fetuses or nursing infants, and:
46
47 i. specify why the research excludes pregnant and lactating individuals;
48
49 ii. seek alternative research methodologies to rectify gaps in knowledge.

- 1 (c) Where scientifically appropriate and available, base studies that include pregnant and
2 lactating individuals on well-designed, ethically sound, existing research with nonhuman
3 animals or nongravid human participants to better assess potential risks.
4
- 5 (d) Minimize risks to the fetus or nursing infant to the greatest extent possible, especially when
6 the research is not conducted primarily to investigate potential benefit for fetuses or
7 nursing infants, but rather for the development of important biomedical knowledge that
8 cannot be obtained by any other means. (New HOD/CEJA Policy)
9
- 10 2. AMA Policy D-140.949 be rescinded as having been accomplished by this report. (Rescind
11 AMA Policy)

Fiscal Note: Minimal

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