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## Bridging the Gap: Inclusion of Pregnant Women in Clinical Drug Trials

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### Keywords

Pregnancy; pharmacology

Over 3.5 million births occur annually in the United States (1) (1). Many of these pregnancies are affected by acute or chronic medical conditions such as infection, hypertension, diabetes, and obesity, which require therapeutic intervention. Over 90% of pregnant women take at least one medication during pregnancy, and 30% taking five or more medications during pregnancy. (2) Despite this, women have long been underrepresented in clinical trials and pregnant or lactating women largely excluded, leaving a knowledge gap in appropriate and safe use of medications in pregnancy. This gap is due, in part, to the historical classification of pregnant women as a vulnerable population, requiring additional protections from clinical trials. While pregnancy or lactation may require additional considerations for research, it does not limit decision making capacity or the ability to obtain informed consent. Pregnant and lactating patients are complex and understudied, resulting in limited data to guide clinical care.

The exclusion of pregnant and lactating individuals from clinical drug trials is a side effect of attempts to protect potential harm to offspring. In 1977, the FDA excluded women of childbearing potential from early drug research. The NIH Revitalization Act of 1993 mandated inclusion of women in clinical research and the FDA updated their guidelines allowing women of reproductive age. However, it wasn't until 2019 that pregnant women were no longer labeled as a vulnerable population (3). However, as demonstrated by Bilinski *et al.* in an April 2025 study, pregnant women continue to be excluded from clinical drug trials (4). The study evaluated randomized controlled drug trials registered in [ClinicalTrials.gov](https://clinicaltrials.gov) between 2008 and 2023 to determine if pregnant patients were included, excluded or not mentioned explicitly. Out of 44,160 trials that were included, only 362 (0.8%) included pregnant patients. Pregnant patients were excluded in 75% and

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not explicitly mentioned in 24% of trials. Notably, 94% of trials that included pregnant patients excluded any non-pregnant participants, indicating that their focus was specific to pregnancy. Trials including pregnant patients were more often open label, focused on prevention and less likely to be industry sponsored. These trials were predominantly related to labor & delivery, pregnancy related conditions and preterm labor (4).

The exclusion of pregnant patients from clinical studies was historically meant to protect unborn fetuses from potentially harmful exposures. However, this exclusion from clinical research results in a shift of risk. Instead of potential risk being limited to well-controlled studies, the risk is instead imposed during post-marketing, widespread use, as medications can and are commonly used in pregnant patients after approval. This was seen during the height of the COVID-19 pandemic when pregnant women were excluded from vaccine and treatment trials despite being at higher risk of complications related to the virus. Following approval, pregnant patients and their providers were left to make decisions in the absence of evidence from well-designed trials.

As the priority of reducing fetal exposure has prevailed historically, it has left challenges in caring for the millions of pregnant individuals that could benefit from therapeutic treatments for chronic, acute and pregnancy-specific conditions. Prior to pregnancy, women may be taking a medication that is standard of care for a specific condition but lacks sufficient data on safety and dosing in pregnancy, for instance TNF inhibitors for rheumatoid arthritis or montelukast for asthma (Table 1). This may lead to the discontinuation of a drug or switching to a second-line medication with more robust pregnancy data. In other circumstances, patients may develop an acute condition, such as an infection, during pregnancy and require a drug that has not been appropriately studied for use in pregnancy. Additionally, there are many conditions specific to pregnancy, such as preterm labor and preeclampsia that may require treatment. However, options are limited for these conditions due, in part, to difficulties in conducting clinical studies in pregnant populations.

The lack of inclusion of pregnant individuals in drug trials historically has not protected this population but rather exposed them to potential harms of employing substandard treatments of medical comorbidities. Importantly, it is not just the safety and teratogenic potential that is necessary to consider, but also the efficacy of medications, as pharmacokinetics (absorption, distribution, metabolism, and elimination) and pharmacodynamic response are altered during a pregnant state. This may lead to a need to increase or decrease drug dosing in pregnancy to maintain therapeutic efficacy. Therefore, it is important to consider and interrogate the appropriate dosage and timing for treatment in pregnancy using the same rigorous fashion that it is studied for the general population, as subtherapeutic treatment with the appropriate medication does not provide necessary benefit to the mother yet may expose the fetus to potential risk.

Further perpetuating these challenges are the fact that women's health is often underfunded and few researchers have expertise in this area. This is a result of limited funding opportunities, which disincentivize clinical researchers from focusing on the field, additional hurdles in implementing studies due to conservative interpretations of guidelines for "minimal risk" by Institutional Review Boards as well as lack of training or mentorship

for researchers given these historical barriers and exclusions (3). With the de-labeling of pregnant women as “vulnerable”, the U.S. Department of Health and Human Services outlined additional protections required for studies involving pregnant individuals and fetuses. This includes that the risk to the fetus be only related to the intervention that could hold direct benefit (5). To comply with this, some institutions may require additional monitoring of pregnant participants and their fetuses which could add additional costs to studies and further dissuade their inclusion.

Recent efforts have focused on improving this underrepresentation. The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was formed in 2017 to advise the Health and Human Service Secretary regarding gaps in knowledge and research for therapies for pregnant and lactating women. Among the 19 recommendations provided by the PRGLAC Task Force were removing barriers to research studies involving pregnant women, increase pregnant and lactating women in clinical research, expansion of the workforce with expertise in obstetric and lactation pharmacology and therapeutics, and the reduction of liability to facilitate the development of new therapeutics (6). Recently, the American College of Obstetrics and Gynecology as well as the World Health Organization have released statements supporting the inclusion of pregnant and breastfeeding individuals in research, including clinical trials. In a survey of 654 pregnant or recently pregnant individuals, 35% of participants indicated willingness to participate in a medication trial and 25% in a vaccine trial during pregnancy (7). Individuals with a college education or who lived in an urban setting were more likely to be willing to participate in clinical trials for medications. Women were more likely to participate in research if there was likely to be a personal medical benefit. Concern for the safety and wellbeing of the unborn child was the most cited deterrent from participation.

While pregnant women are still largely excluded from studies in early drug development, many organizations are working to fill the gap in evidence left by the exclusion of this population. The Maternal Fetal Medicine Units Network (<https://mfmunetwork.bsc.gwu.edu/>), founded in 1986, includes 14 university-based centers across the country conducting perinatal research on pregnancy and lactation, with more than 50 studies completed or ongoing. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network (<https://www.impaactnetwork.org/>) is a global collaboration evaluating prevention and treatment interventions for HIV and HIV-associated complications and co-morbidities in maternal and pediatric populations. They have conducted numerous pharmacokinetics studies aimed to optimize therapeutic dosing in pregnant and pediatric populations. More recently, the NICHD funded the Maternal Pediatric Precision in Therapeutics (MPRINT) Hub (<https://www.mprint.org/>) to focus specifically on enhancing maternal and pediatric pharmacology through pharmacometric modeling, centralized biobanks, real-world evidence and research support cores. The MPRINT Hub also provides resources and one-on-one consultation to equip researchers and clinician-scientists with expertise in the field to fill the knowledge gaps that have been left by the historical underrepresentation of pregnant women in clinical trials.

While national and international attention has been directed to this important issue, there is still much work to be done. As highlighted in Bilinski’s article, the vast majority of clinical

drug trials including pregnant patients are trials specific to pregnancy related conditions (4). This is an important first step, however pregnant individuals are not just impacted by conditions confined to pregnancy and the evidence must reflect that. In order to best improve the health of pregnant women and their offspring, we must have evidence to make informed decisions regarding therapeutic options available during this important time. A lack of data to support safety or efficacy is not the same as data suggestive of harm. It is important to recognize how the lack of data in pregnancy due to participant exclusion can be harmful and work to fill the gaps accordingly. Increasing the inclusion and recruitment of pregnant and lactating women into clinical studies is an important step to increasing our knowledge of the complex population to optimize treatment outcomes for both mother and infant.

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## References

1. Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2024. 2025 Jul In: NCHS Data Briefs [Internet]. Hyattsville (MD): National Center for Health Statistics (US); No. 535.; Available from <https://www.ncbi.nlm.nih.gov/books/NBK617972/> doi: 10.15620/cdc/174613.
2. Haas DM, Marsh DJ, Dang DT, Parker CB, Wing DA, Simhan HN, et al. Prescription and Other Medication Use in Pregnancy. *Obstet Gynecol* 2018;131:5:789–98. Epub 2018/04/10 doi: 10.1097/AOG.0000000000002579. [PubMed: 29630018]
3. National Academies of Sciences Engineering and Medicine. *Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks*. Washington (DC): National Academies Press 2024. Available from: <https://nap.nationalacademies.org/catalog/27595/advancing-clinical-research-with-pregnant-and-lactating-populations-overcoming-real>.
4. Bilinski A, Emanuel N. Fewer than 1% of United States clinical drug trials enroll pregnant participants. *Am J Obstet Gynecol* 2025;232:4:e136–e9. Epub 20250104 doi: 10.1016/j.ajog.2024.12.028. [PubMed: 39761826]
5. U.S. Department of Health and Human Services; Office for Human Research Protections. 45 CFR 46 Subpart B — Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (§46.204). Washington, DC: 2018. Available from: <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-b/index.html#46.204>.
6. Task Force on Research Specific to Pregnant and Lactating Women. 2018. Report to the Secretary, Health and Human Services, and to Congress. Bethesda, MD: Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services. [https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC\\_Report.pdf](https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf).
7. Jacobson MH, Yost E, Sylvester SV, Renz C, Wyszynski DF, Davis KJ. Understanding willingness and barriers to participate in clinical trials during pregnancy and lactation: findings from a US study. *BMC pregnancy and childbirth* 2024;24:1 doi: 10.1186/s12884-024-06710-w. [PubMed: 38166707]

**Table 1.**  
Common conditions in pregnant women and treatment options

	<b>Preferred Drugs</b>	<b>Drugs to Avoid</b>	<b>Limited Data</b>
<b><i>Hypertension/ Preeclampsia</i></b>	Nifedipine Labetalol Methyldopa Hydralazine	Atenolol Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs)	Thiazides
<b><i>Diabetes / gestational diabetes</i></b>	Insulin Metformin Glyburide (2 <sup>nd</sup> line)	Sulfonylureas (risk of neonatal hypoglycemia)	Other sulfonylureas Meglitinides Thiazolidinediones GLP-1 agonists
<b><i>Rheumatoid arthritis</i></b>	Hydroxychloroquine Sulfasalzine Low-doses of corticosteroids	Methotrexate Leflunomide	TNF inhibitors
<b><i>Migraine</i></b>	Acetaminophen Sumatriptan	NSAIDs Topiramate, Valproate	Other triptans CGRP antibodies
<b><i>Asthma</i></b>	Albuterol Budesonide Long-acting beta agonists	High-dose corticosteroids Epinephrine	Montelukast Biologic agents
<b><i>Tuberculosis</i></b>	Ethambutol Isoniazid Rifampin	Amikacin Capreomycin Ethionamide Kanamycin Streptomycin	Bedaquiline Clofazimine Delamanid Linezolid Pretomanid
<b><i>Mood stabilizers/ antiseizure drugs</i></b>	Lamotrigine	Carbamazepine Valproate	Brivaracetam Eslicarbazepine Lacosamide Levetiracetam Oxcarbazepine Perampanel Topiramate Zonisamide
<b><i>Depression/Anxiety</i></b>	SSRIs (fluoxetine, sertraline, citalopram, paroxetine) SNRIs (venlafaxine, duloxetine) Tricyclic antidepressants	Paroxetine MAO inhibitors	Bupropion Levomilnacipran Mirtazapine Trazadone Vilazodone Vortioxetine
<b><i>Preterm Labor</i></b>	Indomethacin Magnesium sulfate Nifedipine		Aspirin Hydroxyprogesterone Acetate Oxytocin receptor antagonists (atosiban)