VIEWPOINT

WOMEN'S HEALTH

Why It Is Unethical *Not* to Conduct Randomized Trials in Pregnancy

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The Trump administration recently declared prenatal acetaminophen (paracetamol) exposure a cause of autism, misrepresenting scientific consensus and receiving swift criticism from experts and medical organizations. The administration's choice to single out acetaminophen was surprising given the available data: several carefully designed studies, using large sibling cohorts from Norway, Sweden, and Japan, have investigated and disputed a potential acetaminophen-autism link.[1-3]

But underneath headline-grabbing debate, there is indeed a critical, less-discussed problem: the lack of rigorous data on most medications during pregnancy. The Centers for Disease Control and Prevention (CDC) reported that less than 10% of medications approved since 1980 have sufficient evidence to determine pregnancy safety.

Why? Some suggest that doing more definitive, randomized research in pregnant women would be unethical.[4] I believe this is misguided. Excluding pregnant women from randomized research does not prevent them from needing or taking untested medications; it just prevents researchers from learning efficiently when they do. There is an urgent need to develop systematic review processes for medications during pregnancy, including routine randomized clinical trials (RCTs).

The Current State of Drug Regulations

In 1962, the US Food and Drug Administration (FDA) requirements for drug licensing were revised in the aftermath of the tragedy of thalidomide, when a sedative prescribed to pregnant women to treat nausea caused severe birth defects. New regulations required companies to submit "substantial evidence" of safety and efficacy from "adequate and well-controlled investigations," laying the groundwork for modern drug safety standards.

Today, these regulations have come to mean that when a clinician prescribes a medication to a nonpregnant individual, it has been evaluated with RCTs designed to make sure the drug works as expected and to characterize any adverse effects. During RCTs, researchers randomly select patients to receive treatment and compare them with untreated control patients. Randomization ensures that on average, treatment and control patients are similar, even regarding factors that researchers cannot see. Overall, RCTs work extremely well for ensuring that medications are safe and effective.

However, due to concerns about birth defects—partly rooted in the thalidomide crisis that catalyzed modern regulation—there are no similar routine requirements for RCTs during pregnancy. In contrast, pregnant women have typically been restricted from RCT participation. Less than 1% of drug-development RCTs include pregnant women, and nearly all pregnancy evidence comes from observational studies.[5]

The Impact of Exclusion

Although exclusion from RCTs seeks to protect pregnant women and their fetuses from adverse effects, research ethics should consider patient alternatives and population harm, not merely trial risks. By these measures, the approach falls short. Consider what currently happens after a drug has been approved for general use. In most cases, FDA-approved medications can be prescribed to pregnant patients, even without rigorous pregnancy-specific evidence. Patients may report adverse effects through standard mechanisms, and researchers may study a subset of the patients taking a medication to understand pregnancy dosing and safety (eg, identified through a pregnancy registry or electronic health record). However, the process of building a real-world evidence base, especially with more rigorous designs like sibling studies, is slow and typically ad hoc. The studies cited above on acetaminophen, a drug first released in the 1950s and taken by about half of pregnant women, were published after 2020.[1-3] Furthermore, observational studies, even carefully designed, are more prone to bias than RCTs. Without a base of randomized evidence, clinicians and patients must navigate low-quality, misleading, and contradictory analyses.

When medications are indeed safe and beneficial, sparse evidence means pregnant patients may avoid them out of caution—even when the risks of untreated disease can exceed those of medications. For example, COVID-19 vaccine trials excluded pregnant participants, and consequently, the vaccine was not recommended by the CDC during pregnancy until August 2021. As a result, vaccine uptake during pregnancy lagged, with devastating effects during the 2021 Delta wave. Even under conservative assumptions, my work projected that a vaccine RCT in pregnant individuals could have averted 8% of all maternal deaths (20% of maternal COVID-19 deaths) and 1% of all stillbirths during March-November 2021.[6] Similar logic may extend to many medications, including, after recent headlines, acetaminophen to treat fever during pregnancy.

Nevertheless, pregnant individuals and their children are still not protected from adverse effects. Only a very small fraction of those taking medication are observed by researchers, and obtaining enough observational data from real-world use to understand safety requires exposing far more pregnant individuals and fetuses to potential adverse effects than would occur in an RCT. For example, my work projected that more than 99.5% of the birth defects from the drug thalidomide could have been prevented with an RCT, and even

with better surveillance today, detecting adverse effects still requires exposing far more patients than would an RCT.[6]

A Blueprint for Reform

A solution would require a government commitment to ensuring drug safety and efficacy during pregnancy comparable with that for the general population. This should include pregnancy-specific regulatory requirements for new and on-patent medications—routine RCTs, supplemented with systematic observational data to help assess very rare effects—as well as public funding to address longstanding gaps.

Recent draft guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E21) released by the FDA for public comment is an important step in the right direction. It encourages sponsors to plan early in the development process for data collection in pregnant and lactating individuals and to consider trials unless there is a specific rationale to avoid doing so. Adoption would represent a significant advancement over 2018 FDA draft guidance, which outlined a narrower scope of when trial inclusion in pregnancy may be ethically permissible, rather than an inclusion default.[7]

However, these nonbinding recommendations may not be enough given the logistical and financial costs of trials with a sufficient pregnant sample size to draw safety conclusions.[8,9] The ICH E21 uses advisory language throughout—"should" rather than "must"—and imposes no consequences for exclusion of pregnant people. Here, lessons may be drawn from failures and successes in pediatric drug testing, as children represent another population often excluded from trials. In 1994, the FDA issued a Pediatric Labeling Rule encouraging manufacturers to improve and update pediatric dosing information. It produced little change. More significant progress in pediatric drug testing came with financial incentives through the Best Pharmaceuticals for Children Act, offering 6 months of additional market exclusivity for completing pediatric studies, and mandates in the Pediatric Research Equity Act, which required pediatric assessments for new drugs. Although challenges persist with study delays and off-patent medications,[10] a similar combination of requirements and incentives for pregnancy-relevant data in new and on-patent drugs combined with public funding to address research gaps in off-patent drugs could help address pregnancy evidence limitations.[7]

As is, the status quo leaves pregnant women with difficult decisions in trying to discern the right choice amid limited evidence. When I present my research on drug safety during pregnancy, I frequently hear stories from women who wish they could have joined an RCT to allow others to learn from their frustrating experiences. This sentiment is especially fitting given that the current system of drug evaluation was catalyzed by the tragedy of thalidomide, during which pregnant women and their children bore the consequences of inadequate regulation. It is high time for them to be meaningfully protected by modern drug safety standards.

ARTICLE INFORMATION

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