

THE SECOND WAVE

Ending the knowledge gap on treating illness in pregnant women

Each year, over 400,000 women in the U.S. confront significant medical illness while pregnant: hypertension, diabetes, serious psychiatric illnesses, autoimmune diseases, even cancer. But information about how to treat these conditions in pregnancy is profoundly limited. Despite a 1994 Institute of Medicine report urging that pregnant women be included in appropriately regulated research, researchers and institutional review boards continue to regard pregnancy as a near-automatic cause of exclusion, even in studies carrying no additional risk to the fetus.

The result is a troubling lack of knowledge about how to treat pregnant women's illnesses, and limited understanding of how illness during pregnancy affects women's health over time. As a consequence, pregnant women and their doctors face difficult and anxiety-filled decisions about medication use. Without evidence specific to the special state of pregnancy, they must guess about what medications to use, what doses to prescribe or take, and – given concerns about fetal safety – whether to use medications during pregnancy at all.

Women and children are thus in harm's way, and for several reasons. First, the quality of medical care for pregnant women is compromised. Pregnancy acts as a wild card in how drugs and biologics are processed by the body. Standard doses can be processed so quickly that therapeutic levels are not achieved, leaving woman and fetus exposed to the dangers of the underlying illness. Second, inadequate research leaves little data to guide decisions about which medicines are safest for fetuses. Two-thirds of women use prescription medications during pregnancy. Without information about comparative safety, women and their clinicians must guess at the trade-offs involved in managing illness while protecting the fetus – guesses that often miss the mark. Third, in the absence of reassuring data on safety, doctors and patients often discontinue medications, even when the harms of untreated disease outweigh the risks of medication. Poorly treated asthma during pregnancy, for example, is associated with higher rates of pregnancy complications and worse outcomes for babies; in contrast, women whose asthma is controlled with medication do as well with outcomes as those without asthma.

Finally, in addition to issues of harm, there are issues of justice. Because the health needs of pregnant women are largely ignored in medical research, pregnant women are not benefiting fairly from society's substantial investment in biomedical science. Moreover, seriously ill pregnant women who might medically benefit from participating in research can be denied access without any justification or review -- a standard not applied to any other population.

We believe that the current paucity of research on effective and safe treatment of pregnant women's illnesses is unethical. It is unfair and irresponsible to continue a system that compels physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for pregnant women, and for women, and the fetuses they carry, to shoulder those risks when pregnancy is complicated by illness. As we learned in pediatric and

geriatric research, if a population is going to use a medication, it must be studied *in* that population. Pregnant women and the children they bear are best protected through responsible inclusion in research, not broad-based exclusion from it.

To this end we urge the following as priorities in the critical task of advancing the health of women during and after pregnancy, as well as the health of the children they bear:

- ***Pursue innovative study designs.*** A wealth of information on efficacy and safety can be procured from pharmacokinetic studies of women already taking medication during pregnancy, cohort registries, and case-control surveillance studies that involve no additional risk to the fetus. We urge strongly expanded funding for such studies.
- ***Develop more nuanced research regulations.*** Certain questions will require trials that involve imposition of at least some risk to the fetus. Currently, regulations employ either highly restrictive bright-line criteria or vague standards that give little guidance to Institutional Review Boards. We urge development of a more nuanced framework for research involving additional risks to the fetus. Such a framework should be developed in consultation with scientists, women's advocates, and ethicists knowledgeable about the distinctive context of pregnancy, and should consider indexing levels of acceptable fetal risk to the severity of need in pregnant women for the proposed therapeutic.
- ***Alter labeling to more effectively communicate evidence-based guidance to medication use in pregnancy.*** Such labeling should better reflect the need to balance risks of medication with the need for and benefit of medication use during pregnancy, the harms of under-treating illness, and current knowledge gaps.
- ***Establish an Institute of Medicine working group to issue a report on the under-representation of pregnant women in research.*** Such a report should work to identify the ethical, legal, policy, and scientific issues and barriers to research, to quantify the health costs of our ignorance, and to fashion funding and policy recommendations.
- ***Create incentives for inclusion of pregnant women in biomedical research.*** Legislative and regulatory action is needed to balance the many current incentives not to study pregnant women. This legislation should draw on past initiatives that have addressed other under-represented populations, especially children, and that have resulted in significant progress toward evidence-based therapeutics.

In the absence of information about the safety and efficacy of medications, pregnant women and the clinicians who care for them are left with two unsavory options—use a drug with unknown safety and efficacy, or leave the woman and her fetus vulnerable to the consequences of the underlying illness. Women and the children they will bear deserve better. Clinical research with pregnant women is morally challenging, but it is a challenge we must confront. For the alternative to responsible research with pregnant women is relegating pregnant women to second-class medical citizens—something, it turns out, that is good for neither pregnant women nor the fetuses they carry.