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POLICY FORUM
Mothers Matter: Ethics and Research during Pregnancy
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This spring—and for the first time in 30 years—the U.S. Food and Drug Administration approved a medication for the treatment of nausea and vomiting associated with pregnancy (NVP). Though the condition occurs in an estimated 80 percent of pregnancies, up to this point women with NVP had to weigh two less-than-ideal options: either manage the condition with diet and alternative therapies or take a drug "off label" and with limited official guidance regarding safety and efficacy for use during pregnancy.

Such in fact remains the story for most medications used during pregnancy. Due to ethical concerns about exposing pregnant women and fetuses to the risks of research, many researchers and institutional review boards regard pregnancy as a near-automatic cause for exclusion from research studies, even when the risks are negligible and the study addresses a question of critical relevance to maternal or fetal health. Though deployed in the spirit of "protection," decisions to exclude pregnant women and their interests in the research agenda come at a profound cost for women and children alike.

First, it is widely known that pregnancy is no "magic bullet" against illness. It is estimated that at least 10 percent of women face serious medical conditions that require treatment during pregnancy—hypertension and heart disease, diabetes, even cancer. Nearly 90 percent of women take medication at some point in their pregnancy; approximately 50 percent take at least one prescription medication, and use has generally increased over the last 3 decades [1]. Given dramatic increases in the proportion of births to women aged 35 and older and increasing rates of obesity and its associated morbidities, it is likely that the use of medications in pregnancy will only grow. Yet Diclegis (the newly approved NVP drug) is an exception to the rule: few drugs have been approved by the FDA for use in pregnancy (2 from 1962 to 1995) [2]—and all for gestation or birth related issues. Any medicine taken to treat a nonobstetric illness during pregnancy is used without adequate data about its safety or effective dosing.

This can be a serious problem because pregnancy often changes the ways that drugs act in the body—the drug's pharmacokinetics and pharmacodynamics. Several recent studies have shown that using standard adult doses of drugs or vaccines in pregnant women can lead to undertreatment or overtreatment. For instance, in the wake of rates of morbidity and mortality among pregnant women that exceeded that of the general population in the recent H1N1 pandemic [3], researchers investigated the pharmacokinetics of the drug oseltmavir phosphate (Tamiflu) in pregnant women

and found that the standard adult dose (which was recommended for pregnant women during the pandemic) may be inadequate for treatment or prevention of flu during pregnancy [4].

Further, there are few data to address worries about fetal safety. For 98 percent of the drugs approved between 2000 and 2010, the teratogenic risk is unknown [5]; for drugs approved in the previous 20 years, we still don't know enough about nearly 9 out of 10 [5]. The average time it takes for a drug to be categorized in terms of risk is 27 years after market approval [5].

In the absence of clear data about the appropriate dosing or safety of medications, women (and their doctors) are often reticent to use (or prescribe) drugs during pregnancy. But excess precaution has serious downsides. Specifically, untreated illness can present far greater risks than those posed by medications. Untreated asthma is associated with preeclampsia, premature delivery, low birth weight, and hemorrhage, but women whose asthma is controlled have outcomes comparable to women without asthma [6].Treatment delays possibly attributable to reticence had serious consequences for pregnant women during the H1N1 pandemic: women who received treatment more than 4 days after the onset of symptoms were more likely to be admitted to the intensive care unit and receive mechanical ventilation—and more than 50 times as likely to die—than women who received timely treatment with antivirals [7].

How should we redress this state of affairs? Perhaps the most important lesson is that we can no longer hide behind claims that ethics precludes the inclusion of pregnant women and their interests in research. Rather, ethics—and to be more precise, justice—*demands* that we move forward with their responsible inclusion. Pregnant women have not benefitted fairly from the research enterprise. It is well past time that they do.

The first step is recognizing that there are many ways to gather data without having to sort out the ethical complexities of risk trade-offs between pregnant women and their fetuses. There is plenty of what might be called ethical *low-hanging fruit*—ethically unproblematic research that can help fill the evidence gap about health care for pregnant women. For instance, a wealth of critical information about the pharmacokinetics of drugs in pregnancy could be garnered by doing a simple series of blood tests on pregnant women who are *already* taking medications. The National Institutes of Health's Obstetric-Fetal Pharmacology Research Units have funded several such "opportunistic" studies in the last several years [8], yet major gaps remain. For instance, HIV-related tuberculosis accounts for 10 percent of maternal deaths in some developing countries [9], yet there are no pharmacokinetic data on any TB medications and, of the 40 TB trials currently underway, all exclude pregnant women [10].

In addition to opportunistic pharmacokinetic studies, large cohort trials can be a rich source of information, but these golden opportunities are—all too often—

overlooked. For instance, in 2009 the NIH launched the National Children's Study; more than 100,000 women were to be followed during pregnancy and their children would be followed for 20 years to understand the impact of the environment on children's health. The problem is that pregnant women—consenting research participants—were understood not as subjects but as part of the environment to be studied, as the data collected pertained almost exclusively to children's health [11].

Studies that involve more than minimal risks to fetuses tend to raise red flags among researchers, IRBs, and even patients themselves. It is important to remember, however, that participation in a research study—in which there are rigorous standards for informed consent and close monitoring—may well be a safer context for the use of medications in pregnancy than the clinical setting, where the evidence base is so profoundly lacking. In considering the ethics of trial participation, we cannot forget context: if women are excluded from research, their only option may be to take a medication in an uncontrolled clinical environment absent the data to inform dosing or safety considerations specific to pregnancy. Absent systematic research involving pregnant women, their only option will remain having their illnesses treated in this uncontrolled clinical environment in which the data needed to secure FDA approval remains elusive. Indeed, the American College of Obstetricians and Gynecologists endorsed—for nearly a decade before FDA approval—the use of the medications in Diclegis in pregnant women suffering from NVP [12].

Though approval by the FDA, and a pregnancy category A to boot [13], are both reassuring—and in the case of Diclegis, long-awaited by the many women who did take the drug years ago—what we need most are data, so that women can make informed decisions about whether or not to use a medication during pregnancy and so that doctors can prescribe such medicines at appropriate and effective doses. Still, with the FDA's recent decision, it feels like a page has turned in the history of maternal health. Let's hope the momentum continues.

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