Studying Medication Safety in Pregnancy: A Call for New Approaches, Resources, and Collaborations

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In this month’s issue of *Pediatrics*, Bandoli et al. report the results of their study, "Prenatal Antidepressant Use and Risk of Adverse Neonatal Outcomes," in which they examine important outcomes, including congenital malformations and preterm delivery, in relation to in utero antidepressant exposure. The topic matters because 14% to 23% of pregnant women experience depression, and many struggle with decisions about whether to take medications because of incomplete and conflicting information about fetal risks. More broadly, given that the vast majority of pregnant women take at least one medication, we know concerningly little about the impact of these exposures on children, both short- and long-term. Although Bandoli et al. have conducted a thorough and thoughtful study, their article also illuminates key challenges in this field.

To answer critical questions about medication exposures in pregnancy, we need to assemble substantially larger databases than most researchers have successfully constructed thus far. Typical “large” studies in this field often start with a cohort of 600,000 to 2 million births. Although large, these sample sizes may not be adequate to assess relatively rare exposures and outcomes of interest. Even for common medications, the prevalence of use in pregnancy may be <10%, and the prevalence of outcomes may be ~1%. For example, Bandoli et al. observed that 6.6% of pregnancies were exposed to antidepressants, and the prevalence of cardiac defects in the overall pregnant population was 1.2%. Therefore, even studies that start with large cohorts often lack power, leading to inconclusive findings. To improve statistical power, heterogeneous outcomes can be grouped (eg, all major congenital defects); however, this approach may obscure heightened risks for specific outcomes (eg, ventricular septal defects). Additionally, sample sizes are often too small to examine individual medications or patterns of use. Starting with Optum data (covering ~200 million lives), Bandoli et al. identified ~15,000 pregnancies exposed to antidepressants but only 434 with sustained high-dose exposure, too few to draw meaningful conclusions. To solve this problem, we must implement new structures and policies that incentivize collaboration and data sharing. We need bold visions, funding mechanisms, and governance policies to stimulate and support large transnational consortia that can generate data sets of 10 to 20 million pregnancies. Current funding mechanisms encourage individualism (grants obtained as a lead principal investigator and articles published as first author) rather than incentivizing participation in large consortia that are sorely needed to generate definitive evidence to improve the well-being of women and infants.

We also need to improve data quality by using new approaches that can bridge the gap between electronic

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health data and survey interview-based studies. Insurance claims data from medical encounters can be used to achieve large samples, but these data sets lack important variables such as exact gestational age (needed to determine timing of exposure), maternal obesity and substance use, measures of illness severity (eg, severity of hypertension or depression), and validated pregnancy outcomes. Electronic medical records and birth certificate data can supply many of the missing data elements, although both have limitations. In some large studies, researchers have examined medication safety in pregnancy using a case-control design in which they interviewed women whose infants had congenital defects and matched interview-based studies within health care systems with a strong track record of using their electronic health records for research. Linking well-studied electronic health record data with interview data could address many potential sources of bias while improving participant retention and completeness of follow-up compared with mobile app studies.

Although millions of pregnant women are exposed to medications each year, data are scant regarding the safety of these exposures for their infants. Because in utero and early childhood experiences provide the foundation for long-term health, it is imperative that we generate better information about the impact of medication exposures on infant and child outcomes. To do so will require investing in research that fosters new collaborations and innovative approaches, with the potential payoff being new knowledge that will improve the health and well-being of future generations of children.

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