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Commentary

Influences of medications on the developing fetus: toward deciphering the unknowns

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The developing fetus, when exposed to exogenous chemicals and drugs, is vulnerable, plastic in its remodeling, and is incredibly resilient. Compounds that fetuses are exposed to include licit and illicit drugs, which alter neurotransmitter levels or directly bind to and activate or inhibit specific receptor systems (1). Such influences can alter neuronal division, rates of apoptosis, axonal growth, and synaptic plasticity.

The scope of compounds that fetuses are exposed to is quite broad, including alcohol, cannabis, and nicotine; food and beverage additives such as caffeine; illicit drugs such as opioids, cocaine, amphetamines, and their derivatives; and prescription medications such as anticonvulsants, opioid treatment medications, and antidepressants (1). The important question—what are the long-term consequences of these exposures?—is complex and evolving in its answers.

In this issue of *Pediatric Research*, Galbally *et al.* (2) examined potential effects of prenatal exposure to antidepressant medications on the fetus. The authors present evidence of short-term autonomic dysfunction, as assessed by the Neonatal Abstinence Scoring System (NASS) (2). Abnormal neurologic function in some of the babies is suggested from results of the parent-administered Ages and Stages Questionnaire at 6 months of age (2). The study design, which is not unusual for this type of investigation, highlights the need for additional approaches to examine effects of prenatal drug and chemical exposures, approaches that require exquisitely executed longitudinal studies involving large cohorts, similar to those originally conceived in the National Children's Study.

Effects on the fetus by chemicals or drug exposure may be structural, metabolic, functional, or genomic. Structural abnormalities can be difficult to detect if subtle and missed if the study design does not include evaluation by expert dysmorphologists (3). The classic study of the effects of anticonvulsants on the fetus highlights the importance of such approaches, which identified problems not previously convincingly observed by others (3).

Development of the fetus and specific organ systems, including the brain, involves very specific temporal and spatial patterns of development. Chemical exposure during specific windows of development may result in abnormalities at one point in time, but not at others. As such, frequent routine sampling throughout pregnancy is needed to identify periods of vulnerability. It is thus laudable and extremely important that the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) has initiated a new program—the Environmental influences on Child Health Outcomes (ECHO)—to facilitate these types of longitudinal investigations. This program will support the study of existing populations to investigate environmental exposures, and one of the areas of focus will be neurodevelopment.

Perhaps because it is difficult to assess potential long-term cognitive function in infancy, whereas autonomic function has clear outputs, there is a preponderance of studies of disturbed autonomic function in infants following a variety of neonatal exposures. The widely used NASS assesses autonomic, not cognitive, function. Furthermore, the postnatal treatment of infants following prenatal drug exposure is often guided by this autonomic assessment. The missing link in an autonomic-based approach is that it is not clear that autonomic dysfunction correlates with long-term cognitive or other cortical defects. We also do not know whether treatment of such autonomic instability influences the child long term, either in a favorable or in a potentially adverse manner.

For the drug-exposed infant, we also need to learn more about how best to treat postnatally. We must consider that drugs including alcohol and gamma-aminobutyric acid, which are inhibitory on neurotransmission or neural activity, can trigger waves of neuronal apoptosis in the developing brain (4). One can expect postnatally administered opioids, which can inhibit neuronal activity (4), to behave similarly. It is intriguing that very recent studies show that behavioral, rather than pharmacologic, approaches can be used to treat some opioid-exposed infants (5). Considering the unfortunate and burgeoning opioid epidemic, considerable additional state and federal support will be needed to compare short-term and long-term outcomes of different therapeutic strategies.

The key question for parent and physician following prenatal drug exposure is what are the potential long-term

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effects on intellectual function? As has been shown in a number of long-term studies emanating from the follow-up of preterm infants, it can take many years, sometimes decades, before one can answer such critical queries. Thus, to address these issues, the tincture of time is needed.

From a policy point of view, it remains critical that, before medications go to market and are potentially used during pregnancy, prenatal toxicology testing takes place. Such standard approaches can identify potentially neurotoxic chemicals. As such, it is time to end the systematic exclusion of pregnant women in pharmaceutical research. Safe and effective treatments in pregnancy are not possible without proper studies. Although study designs in pregnancy require careful and creative considerations, it is critical that these studies are carried out. Within NIH there are a few branches that support research activities focusing on effects of therapeutics during pregnancy, such as the Obstetric and Pediatric Pharmacology and Therapeutics Branch of NICHD. Expanded support for federal research activities in this realm is warranted, and we need to further develop funding mechanisms for necessary long-term research studies that involve follow-up that can span a decade or more.

It has been estimated that between 10% and 20% of fetuses are exposed to either licit or illicit drugs or chemicals (1). Considering that ~4,000,000 children are born per year in the United States, a staggering number of infants will be exposed to medications prenatally. As such, it is important that we continue to advocate for rigorous longitudinal studies that are needed to assess the short-term and long-term effects of such prenatal exposure. The establishment and implementation of such studies faces major hurdles, as funding mechanisms typically provide relatively short-term support. Policy considerations need to be given to the drafting of new long-term study support mechanisms that will allow continuity of follow-up spanning from fetus to adulthood. Support for such complex long-term studies may allow us to unravel the consequences of prenatal drug exposure and properly guide treatment.

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