See review article by Rommel et al

Challenges in Determining Outcomes of Prenatal Exposure to Antidepressants

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In the current issue of the *Journal*, Rommel and colleagues[1] present a systematic review examining the long-term effects of prenatal exposure to antidepressants on physical, neurodevelopmental, and psychiatric outcomes in children 4 years of age or older. Determining the long-term neurobehavioral sequelae of fetal exposure to a particular medication presents many challenges. Prospective observational studies have yielded the richest data but are small and therefore underpowered in terms of estimating risk, particularly for potentially subtle outcomes. However, even with studies including larger sample sizes, we are often unable to consider confounding factors that may impact outcomes, including adherence to the treatment regimen, medication dosage and duration, quality of prenatal care, symptom burden during pregnancy, and exposure to tobacco and other substances. Thus, the most we can conclude from this sort of study is that prenatal antidepressant exposure may be associated with a particular outcome; we cannot draw a causative line between antidepressant exposure and a particular outcome.

Thus far, most studies have assessed outcomes, such as risk for congenital malformations, that are evident at birth or soon thereafter. Measuring the sequelae of prenatal antidepressant exposures in older children presents even greater challenges, as outcomes may evolve over the course of many years and are influenced by a myriad of external factors including nutritional status, education level, quality of child care, and adverse childhood experiences, including exposure to poverty, violence, and, importantly, maternal psychiatric illness.

In the current study, the authors identified a total of 34 studies in peer-reviewed, English-language journals that assessed outcomes of older children born to women taking antidepressants during pregnancy. Methodologies varied considerably across the studies; 42.9% of the studies were prospective; the majority were retrospective studies relying on large medical databases. Sample sizes ranged from 36 to over 1.5 million. The authors were not able to perform a meta-analysis of the data because of the heterogeneity of the studies, as many of the outcomes measured in the included studies were too varied and biased to be pooled. The quality of the evidence for the examined outcomes was rated as low to very low (per GRADE guidelines).

One of the greatest challenges in conducting this type of research is estimating the impact of maternal psychiatric illness on child outcomes. We have clear evidence that maternal psychopathology may negatively affect outcomes.[2,3] Because we cannot rely on randomized controlled trials in this setting, we must use various strategies to account for the indication for antidepressant usage (ie, maternal psychiatric illness) or confounding by indication. The most widely used approach to addressing this type of confounding is to compare outcomes in women with psychiatric illness who choose to maintain antidepressant during pregnancy to outcomes in women who discontinue antidepressant or in those who have untreated psychiatric illness.

This systematic review identified statistically significant associations between prenatal exposure to antidepressants and various physical and neurodevelopmental outcomes. However, nearly all of the studies failed to show an association between antidepressants and these outcomes after potential confounders were considered. The 5 studies investigating physical outcomes (asthma, cancer, epilepsy) found no association; however, an association between antidepressant exposure and child body mass index was observed.

Eighteen studies examined neurodevelopmental outcomes (IQ, motor and cognitive development, behavior, speech, language, and scholastic achievement). After taking confounding factors into account, there were no consistent associations between antidepressant exposure and any of the outcomes studied.

The remaining studies examined the association between in utero antidepressant exposure and child psychiatric illness, including autism spectrum disorders (ASDs), attention-deficit/hyperactivity disorder (ADHD), and affective illness. While early studies demonstrated an association between prenatal exposure to antidepressants and ASDs, this association disappeared when exposed children were compared to children born to mothers who discontinued antidepressants prior to pregnancy or to children born to mothers with untreated psychiatric illness or unexposed siblings. Similarly, 4 large cohort studies observed an increased risk for ADHD in children with prenatal exposure to antidepressants; however, this association disappeared when studies attempted to control for confounding by

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J Clin Psychiatry 2020;81(3):20com13269

To cite: Nonacs RM, Cohen LS. Challenges in determining outcomes of prenatal exposure to antidepressants. *J Clin Psychiatry.* 2020;81(3):20com13269.

To share: https://doi.org/10.4088/JCP.20com13269

indication. These findings suggest that the underlying psychiatric illness in the mother, rather than exposure to antidepressant, may be responsible for the association between in utero exposure to antidepressants and childhood psychiatric illness.[4]

Thus far, 2 studies have reported on risk of affective disorders in antidepressant-exposed children. Even after attempting to account for confounding by indication, both of these studies observed that the risk for depression was increased in exposed children. While these studies may raise concerns regarding the long-term effects of prenatal exposure to antidepressants, they also highlight the limitations in our ability to identify and control for confounding factors. Women who choose to maintain antidepressants during pregnancy differ from women who elect to discontinue or avoid treatment with antidepressants. The factors that distinguish these two groups, including severity of illness and comorbidity, may ultimately influence child outcomes. While we may use various strategies to control for these differences, it is likely that there are still unknown or unquantifiable factors that affect outcomes.

As we begin to look more closely at outcomes in older children, we must account for many other types of moderating factors. Mood and anxiety disorders are recurrent, and exposure to maternal psychiatric illness may impact cognitive and socioemotional development far beyond the early years of a child's life. Psychiatric illness in the mother may exert its effects on the child in many different ways: inattentive or inconsistent parenting practices, inadequate social supports, and exposure to financial hardship and violence in the home. Worse outcomes in children have been seen in women with more recurrent or chronic illness.[5] Conversely, treatment of maternal illness is associated with better outcomes in children.[6] While we focus on maternal psychopathology, there is a growing body of evidence that paternal psychology affects outcomes in children as well.[7] Given that parental psychopathology may have such deleterious effects on child outcomes and that treatment can mitigate these effects, it is essential that we direct more attention to preventing and managing psychiatric illness in the mother that, in the most ill women, may require treatment with antidepressants during pregnancy.

Published online: May 12, 2020.

Potential conflicts of interest: In the past 12 months, **Dr Cohen** has received the following research support: National Pregnancy Registry for Atypical Antipsychotics: Alkermes, Forest/Actavis, Otsuka, Sunovion, Teva, and Sage Therapeutics. Other research support: Brain & Behavior Research Foundation, JayMac, National Institute on Aging, National Institutes of Health, Sage Therapeutics, and NeRRe/KaNDy Therapeutics. He has served in an advisory/counseling role for Alkermes (through MGH Clinical Trials Network Initiative) and Praxis Precision Medicines, Inc. **Dr Nonacs** has no potential conflicts of interest.

Funding/support: None.

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