Clinical and Practical **Psychopharmacology**

Paternal Depression as a Risk Factor for Neurodevelopmental Disorders in Offspring: Implications for Maternal Depression and Its Treatment During Pregnancy

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Many but not all studies suggest that gestational exposure to antidepressant drugs is associated with an increased risk of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in offspring. All of these studies have been observational in design, and observational research may suggest but cannot establish cause-effect relationships. In this context, a recent, large, population-based, observational study found that exposure to maternal depression before, during, or after pregnancy was each associated with an increased risk of ASD as well as ADHD. Strikingly, the same finding was obtained for paternal depression, as well, with mostly similar values for risk. If paternal depression before, during, or after pregnancy can increase the risk of ASD and ADHD in the offspring, it suggests that genetic variables, or environmental adversities engendered by behaviors related to paternal depression, may drive the risk for the adverse neurodevelopmental outcomes; some data exist to support this view. An understanding of these possibilities allows greater room for flexibility when considering the prescription of antidepressant drugs to depressed pregnant women.

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A great deal of research has been conducted on the risk of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in offspring after maternal exposure to antidepressant drugs during pregnancy.[1–3] However, there is no clarity, yet, on whether antidepressants contribute to the risk or whether the risk is driven primarily by variables related to maternal depression, the commonest indication for antidepressant use during pregnancy. Interestingly, research has shown that paternal antidepressant use during pregnancy is also associated with an increased risk of ASD in offspring, though the evidence is not consistent.[4,5] A recent study[6] that focused on paternal depression in relation to pregnancy and subsequent risk of ASD and ADHD in offspring is therefore of interest.

Parental Depression and Neurodevelopmental Outcomes in Offspring

Chen et al[6] studied a birth cohort of children (n = 708,515; 52% male) born in Taiwan during 2001–2008 and followed to the end of 2011. The data were drawn from the Taiwan National Health Insurance Research Database, which contains health care data of > 99% of the population of the country. Data were extracted for ASD and ADHD in children and depression in parents; diagnoses were based on *ICD-9* codes. Using Cox regression, the authors studied the effects of paternal and maternal depression on the risk of ASD and ADHD in the offspring, with exposure to parental depression recorded as present before pregnancy, during pregnancy, and < 1, 1–3, and > 3 years after birth. These analyses were adjusted for family income, degree of family urbanization, parental ages, and offspring sex.

The mean age of the mothers was 29 years, and that of the fathers was 32 years. The prevalence of depression before pregnancy was 2.2% in mothers and 1.2% in fathers; these figures were 0.5% and 0.6%, respectively, during pregnancy, and 1.4%–6.6% and 0.8%–3.6%, respectively, in the different time intervals after birth. ASD was diagnosed in 0.6% of the children at a mean age of 4.6 years, and ADHD was diagnosed in 4.0% at a mean age of 6.3 years.

Important findings from the study[6] are presented in Table 1. In summary, maternal and paternal depression were each associated with a statistically significant increase in the risk of each disorder (ASD and ADHD), and in each of the 5 exposure windows studied (before, during, and after pregnancy). When adjacent exposure windows were clubbed together to capture possible increased risks associated with chronic depression, for maternal as well as paternal depression the risks were generally similar for ASD but slightly raised for ADHD, suggesting that chronicity of exposure to depression may be important for the risk of ADHD only. Combined maternal and paternal depression was also associated with generally (modestly) higher values for risk.

Table 1. Parental Depression and ASD/ADHD Risk[a]

1. Maternal depression before pregnancy was associated with an increased risk of ASD (HR, 2.01; 95% CI, 1.70–2.37) and ADHD (HR, 2.25; 95% CI, 2.09–2.41) in the offspring.
2. Maternal depression during pregnancy was associated with an increased risk of ASD (HR, 1.58; 95% CI, 1.11–2.25) and ADHD (HR, 1.88; 95% CI, 1.63–2.17) in the offspring.
3. Maternal depression after childbirth was associated with an increased risk of offspring ASD (HRs, 1.59–1.65) and offspring ADHD (HRs, 1.85–2.10) in each of the 3 postnatal exposure windows studied.
4. Paternal depression before pregnancy was associated with an increased risk of ASD (HR, 1.63; 95% CI, 1.28–2.08) and ADHD (HR, 1.92; 95% CI, 1.73–2.12) in the offspring.
5. Paternal depression during pregnancy was associated with an increased risk of ASD (HR, 1.75; 95% CI, 1.29–2.36) and ADHD (HR, 1.72; 95% CI, 1.51–1.96) in the offspring.
6. Paternal depression after childbirth was associated with an increased risk of offspring ASD (HRs, 1.43–1.55) and offspring ADHD (HRs, 1.42–1.71) in each of the 3 postnatal exposure windows studied.
7. When maternal depression exposure data from adjacent time windows were pooled, as a possible way to capture risks associated with chronicity of maternal depression, there was little change in HR values (range, 1.60–1.95) for ASD, but an impression of slight increase in HR values (range, 1.85–2.33) for ADHD.
8. When paternal depression exposure data from adjacent time windows were pooled, as a possible way to capture risks associated with chronicity of paternal depression, there was little change in HR values (range, 1.43–1.73) for ASD, but an impression of slight increase in HR values (range, 1.42–1.93) for ADHD.
9. Combined maternal and paternal depression was associated with generally increased HR values for ASD (almost all values > 2.00) and ADHD (values between 2.07 and 2.99).
10. Maternal depression was associated with higher risk than paternal depression for both ASD (HR, 1.23; 95% CI, 1.05–1.46) and ADHD (1.35; 95% CI, 1.27–1.45).

[a]Findings from the study by Chen et al.[6]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, CI = confidence interval, HR = hazard ratio.

Critical Appraisal

In general, studies examining neurodevelopmental outcomes after antidepressant exposure during pregnancy adjust analyses for many, even dozens of, confounding variables. In contrast, the study by Chen et al[6] adjusted for very few confounds. As examples, there was no adjustment for maternal comorbidities; maternal medication exposure during pregnancy; maternal use of tobacco, alcohol, and other substances; and exposures to environmental adversities before or after birth, all of which could potentially influence the risk of adverse neurodevelopmental outcomes. However, the authors[6] examined risks associated with exposure to depression in each parent separately and in the context of exposure during different time windows before as well as after birth; the study findings can therefore guide hypotheses on what may drive the risk. In this context, the finding of increased risk associated with paternal depression for each disorder (ASD and ADHD) in each window of exposure assumes importance.

A large number of observational studies have examined the association between antidepressant exposure during pregnancy and the risk of neurodevelopmental disorders, especially ASD, in offspring. Many but not all studies have found that antidepressant exposure is associated with an increase in risk. However, studies specifically with ASD as the outcome of interest have also found increased risks associated with antidepressant exposure limited to the pre-pregnancy period, and studies have found increased risks in gestationally antidepressant-unexposed siblings, as well. The findings of Chen et al[6] are therefore important because if paternal depression is associated with increased risk of ASD and ADHD in offspring, the spotlight moves away from maternal depression and antidepressant use during pregnancy and shifts to unknown and unmeasured confounds.

If paternal as well as maternal depression, occurring in any time window, can increase the risk of ASD and ADHD in offspring, genetic factors are important candidates for the unknown and unmeasured confounds. In this context, a recent, very large genetic study found 20 loci common to major depression and ASD and 10 loci common to major depression and ADHD.[7,8] Besides genetic factors, environmental adversities can also be unknown and unmeasured confounds. For example, behaviors associated with paternal depression may compromise maternal physical and mental health and thereby compromise the future health of an unborn child. Similarly, such behaviors may create environmental adversities during infancy and early childhood, and exposure to these adversities may compromise the health of the developing child.

This does not mean that the experience of maternal depression and gestational exposure to antidepressants are not risk factors; it merely means that the roles of maternal depression and antidepressants, if any, may be even smaller than previously believed. This conclusion is important because health care providers may be reluctant to prescribe an antidepressant during pregnancy because of the studies associating gestational antidepressant exposure with neurodevelopmental risks, and depressed pregnant mothers may be reluctant to use antidepressants, if advised, for the same reason. The understanding that genetic variables or environmental adversity may drive the risk could reduce the guilt associated with the use of antidepressants during pregnancy and reduce the suffering of mothers who respond after initiating the antidepressant. In fact, an expectant mother who is less depressed because she has responded to an antidepressant may have a healthier internal and external environment, and healthier behaviors, than an expectant mother who suffers through her depression out of fear of risks associated with antidepressant use.

Final Notes

The discussion presented in the previous section is not intended to imply that antidepressants are safe during pregnancy; there are many other antenatal, perinatal, and postnatal risks that have been associated with gestational exposure to these drugs, though a causal role can never be established in observational research.[9–15] All decision-making regarding treatment during pregnancy therefore needs to be shared between the health care provider and

the expectant mother. Last, but not least, the findings of studies of outcomes in antidepressant-exposed pregnancies should be considered possibly suspect if they have not been adjusted for exposure to paternal depression.

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