Clinical and Practical **Psychopharmacology**

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Antidepressant Prescription in Pregnancy:
The Importance of Prenatal Maternal Anemia as a Potential Confound in Studies on Neurodevelopmental and Other Outcomes

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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 observational studies have found an association between antidepressant drug prescription during pregnancy and neurodevelopmental disorders such as autism spectrum disorder, attention-deficit/hyperactivity disorder, and intellectual disability. The results of such studies cannot be considered conclusive because of the possible presence of inadequately measured, unmeasured, and unknown confounds. In this context, maternal anemia before or at but not after 30 weeks of gestation was recently associated with an increased risk of all 3 of these neurodevelopmental disorders. Additionally, meta-analysis has shown that maternal anemia during pregnancy is associated with other adverse gestational outcomes, as well. Given that anemia is common during pregnancy, and that iron deficiency during pregnancy can compromise neurodevelopment in the offspring, it is clear that maternal anemia during pregnancy should be included as a confound that is adjusted for in analyses in studies of psychotropic drugs in pregnancy. However, many studies that significantly associated gestational exposure to antidepressants with adverse pregnancy outcomes did not adjust for maternal anemia during pregnancy. This issue is not merely academic because studies with such "significant" findings discourage depressed pregnant women from accepting antidepressants; therefore, women and their unborn children may risk experiencing the known harms associated with untreated depression during pregnancy. Additionally, such "significant" findings may provoke unjustified guilt in women who do use antidepressants during pregnancy, especially if the pregnancy is associated with an adverse outcome. Whereas this is not an endorsement of the unquestioning use of antidepressants during pregnancy, it does imply that those who argue against medication use during pregnancy should re-examine the science on which their views are based.

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Many studies, in unadjusted or adjusted analyses, have found a statistically significant association between antidepressant prescription during pregnancy and neurodevelopment disorders such as autism spectrum disorder (ASD),[1–3] attention-deficit/hyperactivity disorder (ADHD),[4,5] and intellectual disability (ID)[6] in the offspring. All the studies were observational studies; there are ethical challenges related to conducting randomized clinical trials (RCTs) of antidepressant drugs during pregnancy. Therefore, the statistically significant associations identified in these observational studies could have been due to confounding. The potential influence of inadequately measured, unmeasured, and unknown confounds in such studies has repeatedly been stated in critical commentaries,[2,7] and such criticism is now almost becoming clichéd. It is therefore educative to find research that actually identifies potential confounds. In this context, a study[8] of prenatal maternal anemia and its association with neurodevelopmental disorders in the offspring is of relevance.

Why the Study Was Performed

Anemia is common during pregnancy; this is especially so in developing countries, where rates of 20%–50% have been reported.[9–13] Maternal anemia during pregnancy has long been associated with a large number of adverse gestational outcomes. For example, in a systematic review and meta-analysis of 117 studies with 4,127,430 pregnancies, Jung et al[14] found that maternal anemia was associated with an increased risk of low birth weight (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.45–1.87), preterm birth (OR, 2.11; 95% CI, 1.76–2.53), stillbirth (OR, 1.95; 95% CI, 1.15–3.31), perinatal mortality (OR, 3.01; 95% CI, 1.92–4.73), and maternal mortality (OR, 3.20; 95% CI, 1.16–8.85).

Anemia during pregnancy is also associated with an increased risk of ID in the offspring.[15,16] Iron deficiency is the commonest cause of anemia; this is of concern because iron plays an important role in neurocognitive development.[17,18] It is therefore reasonable to examine the impact of antenatal anemia on neurodevelopmental outcomes in offspring.

What the Study Did

The authors[8] extracted data from linked registers for subjects in the Stockholm Youth Cohort, which comprises persons resident in Stockholm County and born between 1984 and 2011. Subjects were specifically excluded if they had a congenital disorder, such as Down's syndrome, that was known to be associated with ID. The diagnosis of anemia was based on *ICD* codes, as entered in the medical registers.

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Subjects with anemia during the periconceptual period were included because such anemia was very likely to continue into early gestation. The earliest diagnosis of anemia during pregnancy was recorded for the purpose of the study.

The sample comprised 299,768 mothers with 532,232 offspring (51.3% male) aged 6–29 (mean, 17.6) years. There were 31,018 pregnancies with anemia, of which 1,534 were diagnosed early (at ≤ 30 weeks of gestation) and 28,198 were diagnosed late (at > 30 week of gestation); data for time at diagnosis were missing for the remaining 1,286 pregnancies. There were 313 offspring with ASD, 634 with ADHD, and 128 with ID; these numbers included persons with shared diagnoses, such as ASD with ID and ASD with ADHD.

The association of early or late antenatal anemia exposure with neurodevelopmental disorders in offspring was studied in models that adjusted for confounding variables. These confounders included offspring sex, birth year, parental education and income, maternal country of origin, maternal age and body mass index, maternal psychiatric history, history of infection during pregnancy, and multiple pregnancy and interpregnancy interval. In these analyses, the reference group comprised offspring with no antenatal anemia exposure.

A discordant sibling pair analysis was also conducted; that is, between sibs who were and were not exposed to antenatal anemia. This analysis potentially controlled for shared genetic and environmental variables that could represent inadequately measured, unmeasured, and unknown confounds.

What the Study Found

In this study,[8] in almost all analyses, relative to no exposure to gestational anemia, exposure to early gestational anemia was associated with a statistically significant increased risk of ASD, ADHD, ID, and combinations thereof; where the ORs were not statistically significant, the 95% CIs, viewed as compatibility intervals,[19,20] appeared compatible with an increased risk. The highest ORs were for ID, with and without ASD/ADHD comorbidity.

In discordant sibling pair analyses, exposure to early gestational anemia was associated with a significantly increased risk of ASD and ID but not ADHD; the OR was higher for ID than for ASD.

In all continuous analyses, except the analysis of data for ASD with comorbid ADHD, a later week of diagnosis of anemia during gestation was associated with a lower risk of neurodevelopmental disorder.

In all analyses, including discordant sibling pair analyses, exposure to late gestational anemia was not associated with a significantly increased risk of ASD, ADHD, ID, or combinations thereof.

In mediation analysis, preterm birth was identified as the strongest mediator between early antenatal exposure to anemia and neurodevelopmental disorders in offspring. Preterm birth accounted for nearly one-third of the association between anemia and each of the 3 disorders: ASD, ADHD, and ID.

Implications for Research on the Psychopharmacology of Pregnancy

This study[8] was observational; offspring were not randomized to anemia-exposed and anemia-unexposed groups. Therefore, despite the adjustments for confounders in the analyses, and despite the additional discordant sibling pair analyses, it is possible that the association between early antenatal anemia exposure and neurodevelopmental disorders is not cause and effect. What cannot be denied, however, is that early antenatal anemia exposure appears to be a marker for neurodevelopmental disorders. This means that, in observational studies of the association between antidepressant exposure during pregnancy and neurodevelopmental disorders in offspring, analyses should adjust for anemia in addition to other confounds. Such analyses would either adjust for the confounding effect of anemia, or, to the extent possible, for the confounding effect of whatever anemia is a marker of.

Regrettably, such adjustment was not performed in many studies that highlighted an association between gestational exposure to antidepressants and neurodevelopmental disorders in offspring. As an example, Boukhris et al[21] found a significant association between antidepressant exposure during pregnancy and the risk of ASD in the offspring; the authors adjusted their analyses for many important confounds, including maternal psychiatric and physical illnesses, but did not adjust for anemia. There are other notable examples as well, of similar studies with "positive" findings for both ASD[22] and ADHD.[23]

Digressions

In a meta-analysis, anemia was associated with an increased risk of maternal antepartum (OR, 1.36; 95% CI, 1.07–1.72) as well as postpartum (OR, 1.53; 95% CI, 1.32–1.78) depression.[24] The findings were observed to be consistent across definitions of anemia, definitions of depression, and study quality. Whereas the direction of causality cannot be confirmed from the observational studies from which the findings were obtained, it is more reasonable to expect that anemia is the result of behavioral changes that characterize depression than to expect that anemia is the cause of depression. Given that depression (discussed in the next section) and anemia[8,14] are both associated with adverse gestational outcomes, the coexistence of the two conditions could be a double whammy.

Women should ideally have anemia corrected before conceiving. This is because correction of anemia that is discovered during pregnancy will not happen instantly; therefore, even if immediate corrective measures are instituted, there would be substantial early gestational exposure to anemia.

Academic and Clinical Importance

Given the large number of adverse gestational and post-gestational outcomes associated with maternal anemia during pregnancy,[8,14] it is important for studies of *all* potential adverse effects of antidepressant drug use during

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pregnancy to adjust for maternal hemoglobin levels in pregnancy. Unfortunately, for whatever reason, including unavailability of the data or lack of awareness of anemia as a potential confound, such adjustment is not commonly performed. The challenge of this and other inadequately measured, unmeasured, and unknown confounds in observational studies in pregnancy will therefore continue to plague the interpretation of psychopharmacology research results in the field.

A related point is that what is stated in this article with regard to studies of antidepressant drug prescription during pregnancy applies to the study of the prescription of any neuropsychiatric drug or drug category during pregnancy.

Readers may note that it is much more than an academic issue that is at stake. Mothers who are discouraged by medical professionals from taking antidepressants to treat depression during pregnancy, and mothers who feel that taking an antidepressant may place their unborn child at risk would suffer the symptoms of depression because of fears that are not adequately grounded in hard science. Worse, suffering untreated depression during pregnancy could place both mother and unborn child at risk of adverse maternal and fetal outcomes.[25–30] Last but not least, mothers of children with adverse pregnancy or neurodevelopmental outcomes after use of an antidepressant during pregnancy may experience guilt or be blamed for the antidepressant use. The justification for such guilt or blame is also not grounded in hard science.

Parting Notes: There Are Other Important Confounds, Too

This article focused on early pregnancy maternal anemia as an important confound in research on antidepressant use during pregnancy. Anemia is not the only important confound. Recent research has uncovered a considerable overlap in the genes implicated in different neuropsychiatric disorders, with overlap identified even, specifically, for major depression, ASD, and ADHD.[31,32] This suggests that maternal depression may be linked to offspring ASD and ADHD through genes, and not necessarily through antidepressant use during pregnancy. Genetic relationships exemplify the unmeasured and unknown confounds, referred to in the first section of this article.

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