Clinical and Practical **Psychopharmacology**

Genes as Unmeasured and Unknown Confounds in Studies of Neurodevelopmental Outcomes After Antidepressant Prescription 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

In observational studies, significant associations have often been identified between antidepressant drug prescription during pregnancy, on the one hand, and autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), on the other. Interpreting these associations is problematic because they are based on analyses that could not adjust for inadequately measured, unmeasured, and unknown confounds. Recent clinical data suggest that a genetic relationship exists between depression and neurodevelopmental disorders. A very recent study identified many genetic loci that were common to depression, ASD, and ADHD. These findings suggest the possibility that depression in a pregnant woman may predispose to neurodevelopmental disorders in offspring through shared genes and not through antidepressant use during pregnancy. Previous studies that significantly associated gestational exposure to antidepressants with adverse pregnancy outcomes could not adjust for genetic factors because they were unknown confounds at the time. Now that common risk loci have been identified, at least some of the unknown (genetic) confounds are no longer unknown; however, unless specifically examined in prospective studies, they will remain as unmeasured confounds that will continue to compromise the interpretation of study results. The possibility of confounding by inadequately measured, unmeasured, and unknown risk factors must therefore be considered before indicting antidepressant use during pregnancy in neurodevelopmental risks. In this context, the importance of genetic factors as unmeasured and unknown confounds must be acknowledged.

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Many observational studies have identified 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. In many of these studies, the association was observed to remain statistically significant even after adjusting for confounding variables such as maternal age, maternal body mass index, indices of socioeconomic status, medical comorbidities, and others.

In all of these studies, because depressed pregnant women had not been randomized to receive antidepressant medication vs treatment as usual, it is very likely that the medicated women differed from unmedicated women in many ways, some of which could explain why they were at higher risk of bearing offspring with neurodevelopmental disorders. The results of these studies are therefore suspect because they did not or could not control for inadequately measured, unmeasured, and unknown confounds.[2,7]

Inadequately Measured, Unmeasured, and Unknown Confounds

The authors of an observational study (with data extracted from health care records) may have adjusted their analyses for past history of depression, past medication history, past history of hospital visits, and so on, as measures of severity of illness. However, these variables inadequately capture the actual severity of depression and the nature of depression-related behaviors during pregnancy, many or all of which might compromise maternal and fetal health. In such studies, therefore, severity of depression is an inadequately measured confound.

Most observational studies do not adjust analyses for use of tobacco, alcohol, and illicit substances because the necessary data are unavailable in the databases from which the information is extracted, so use of these licit and illicit substances during pregnancy is an unmeasured confound. Recent research suggests that preeclampsia,[8] polycystic ovaries,[9] and maternal inflammation during pregnancy[10] are also relevant to neurodevelopment and, therefore, are also examples of unmeasured confounds to the extent that they are not recorded, extracted, and adjusted for in analyses. Other examples of potential unmeasured confounds are listed elsewhere.[11]

In the previous article in this column,[12] maternal anemia during pregnancy was presented as yet another, strongly relevant example of an unmeasured confound that might increase the risk of ASD, ADHD, and ID in the offspring of women who use antidepressant drugs during pregnancy.

What about the unknown confounds? This article examines how genetic factors were and still are unknown confounds in observational studies that associate gestational exposure to antidepressant drugs with the risk of developing neurodevelopmental disorders during childhood.

Genetic Factors as Unknown Confounds

Unknown confounds, by definition, cannot be listed because they are not known. However, recent research has offered clues. In a nationwide, population-based study conducted in Taiwan, Chen et al[13] analyzed data from a national health insurance database and found that the risk of major depressive disorder (MDD) was increased in the first degree relatives of persons with ADHD relative to the first degree relatives of control subjects (rates, 2.11% vs 1.02%; relative risk, 2.08; 95% confidence interval [CI], 2.02–2.13).

In a study based on data from 7,543 adolescents in the Avon Longitudinal Study of Parents and Children, UK, Rice et al[14] found that depression with onset in early adolescence was associated with a polygenic risk score for MDD (odds ratio [OR], 1.24; 95% CI, 1.06–1.46) as well as with a polygenic risk score for ADHD (OR, 1.32; 95% CI, 1.13–1.54). Early onset depression was also associated with childhood ADHD, pragmatic language difficulties, and social communication difficulties; that is, with neurodevelopmental disturbances.

The findings of these 2 studies imply the presence of a genetic relationship between neurodevelopmental disorders and MDD. So a woman with MDD may be at increased risk of having children with neurodevelopmental disorders for reasons related to genes, regardless of whether or not she uses an antidepressant during pregnancy.

Identification of Common Genetic Loci Between Depression and Neurodevelopmental Disorders

Lee et al[15] analyzed data from 232,964 cases and 494,162 controls, all of European ancestry. The data were obtained from genome-wide single nucleotide polymorphism (SNP) studies of 8 neuropsychiatric disorders: anorexia nervosa, ADHD, ASD, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, and Tourette syndrome. They found that major depression was closely correlated with ASD ($r_g = 0.45$) and with ADHD ($r_g = 0.44$); the correlations were lower between major depression and bipolar disorder ($r_g = 0.36$) and between major depression and schizophrenia ($r_g = 0.34$). The relationship of major depression with ASD and ADHD was confirmed in factor analysis.

In further analysis, the authors[15] identified 23 pleiotropic genetic loci that were common to 4 or more of the 8 neuropsychiatric disorders. There were 20 loci common to major depression and ASD, 10 loci common to major depression and ADHD, and 9 loci common to all 3 disorders. Many of the shared loci had obvious importance. For example, one of the loci lay within *DCC*, a gene that is important in the early development of white matter connectivity in the brain, and dysfunction of which is associated with neurodevelopmental syndromes. Lee et al[15] observed that variation in *DCC* would be consistent with effects on the early organization of neural circuits as well as effects on the later maturation of mesolimbic dopaminergic connections with the prefrontal cortex. Other loci of neurodevelopmental significance were also identified. Importantly, the expression of many of the pleiotropic genes peaked during the second trimester of pregnancy and remained overexpressed all through the lifespan.

Academic Importance

The genetic studies described in the previous sections have important implications for research that associates antidepressant drug use during pregnancy with neurodevelopmental disorders in the offspring. In short, the discovery of genetic overlap across major depression, ASD, and ADHD suggests that offspring ASD and ADHD may be linked to maternal depression during pregnancy through gestational antidepressant drug exposure. Thus, genes are examples of the unmeasured and unknown confounds to which reference was made at the beginning of this article. When these confounds cannot be adjusted for, gestational antidepressant drug exposure cannot be considered to causally increase the risk of ASD and ADHD in children.

Clinical Importance

A large number of observational studies have associated antidepressant prescription during pregnancy with the risk of neurodevelopmental disorders in the offspring.[1,2] The results of these studies have repeatedly been widely disseminated in the scientific and lay media. As a result, health care professionals hesitate to advise antidepressant medication to depressed pregnant women; some may even discourage the use of these drugs during pregnancy. Additionally, depressed pregnant women who are aware of such studies may hesitate to accept antidepressant drugs, thereby exposing themselves, the pregnancy, and the unborn child to the risks associated with untreated depression.[16–21] Finally, women with adverse pregnancy outcomes and mothers of children with neurodevelopmental disorders may experience guilt or be blamed had they used antidepressant drugs during pregnancy. It is therefore important for health care professionals and the general public to know that inadequately measured, unmeasured, and unknown confounds, rather than antidepressant drug use, may explain the relationship between gestational exposure to antidepressants and neurodevelopmental disorders in the offspring. As this article points out, genes that are responsible for both depression and neurodevelopmental disorders are important examples of unmeasured and unknown confounds.

Parting Note

Neurodevelopmental disorders have multifactorial origins. Environmental triggers may be required for genes, even "bad" genes, to express themselves. It is theoretically possibly that antidepressant use during pregnancy is one such trigger. However, given that depression is associated with a large range of unhealthy behaviors and with many adverse changes in the internal (physiological) environment, it is more likely that the triggers for gene expression are related to depression or to whatever was responsible for the depression. All said and done, it must be emphasized that all decision-making needs to be shared between clinician and patient.

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