See article by Johnson et al

Adverse Outcomes Following Serotonin Reuptake Inhibitor Exposure During Pregnancy

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In this issue of the *Journal*, Johnson et al[1] describe a study in which they prospectively recruited and carefully followed women through pregnancy, collecting information on variables that have the potential to influence short-term and long-term gestational outcomes. Of 178 women in the sample, 102 received a serotonin reuptake inhibitor (SRI) antidepressant during pregnancy. The sample was reassessed when the offspring were 2.5 to 5.5 years old, and information on a large number of additional variables was collected. Certain neurodevelopmental outcomes were specifically examined in the children because SRI antidepressants, in previous research, had been linked to an increased risk of autism spectrum disorders.[2] The findings were that, relative to unexposed offspring, SRI exposure was associated with a small but significantly increased risk of impairment in expressive language, with slightly but significantly higher ratings of pervasive developmental delay, but with no significant impairment on general cognitive assessment.

This study[1] is notable for its strengths. It was a single-center, prospective study; therefore, issues related to unreliable assessments and unrecorded data were diminished. Such issues are concerns in registry and other retrospective database studies because, for example, there is no assurance that diagnoses would have been made in a standardized manner and that information about important confounding variables would have been asked for, reliably measured, and subsequently recorded. In their study, Johnson et al[1] prospectively obtained information on an impressive number of antenatal and postnatal variables, including use of alcohol, tobacco, caffeine, other substances, and prescription as well as over-the-counter medications.

The study did have its limitations. For example, with regard to antenatal variables, the authors could not or did not record the actual duration of depression during pregnancy, expressed in units of weeks, or the total medication exposure, expressed in defined daily dose units. With regard to the postnatal and early childhood period, there were no data on variables related to child nutrition, infections during infancy and childhood, duration and severity of maternal illness after delivery but before the follow-up assessment, quality of mother-child interactions during infancy and childhood, and so on. All of these variables could have influenced the outcomes examined in the study. To do the authors justice, it could be challenging to even think of, let alone measure, all of the variables that have the potential to influence speech, behavioral, and neurodevelopmental outcomes in childhood.

Retrospective database studies of gestational outcomes are limited to whatever data exist in the records. As already stated, these data would not have been collected in a standardized fashion, and so, for example, one could never be certain whether diagnoses made (or not made) were justified or not; this is a problem of false positives and false negatives. Next, accurate data on important confounds, such as the use of medications and substances during and after pregnancy, would not be available for entry as covariates. Last but not least, data on postnatal and childhood variables would not be available, although these could also influence neurodevelopmental and behavioral outcomes. Therefore, no matter how many database studies show a relationship between (any) medication use during pregnancy and an adverse outcome during childhood or later life, causality cannot be assumed, whether or not a dose-response relationship is identified and no matter how specific the finding is to the medication under study.

Readers may be forgiven for wondering whether a sufficiently large sample will allow the separation of signal from noise. After all, an increase in false positive and false negative diagnoses will certainly weaken the signal and increase the noise, but if the sample is sufficiently large, a real signal will indeed be statistically discernible.[3] The problem, here, is that it is not just the signal that is the issue; it is the confounds.

A moment's reflection will help the reader understand why this is so. Relative to nondepressed persons, depressed persons are more likely to smoke, drink, use caffeine, use prohibited substances, eat unwisely, sleep poorly, exercise less, adhere poorly to medical instructions, and exhibit a variety of other unhealthy and even risky behaviors. Depression is associated with hormonal and other biological changes that can influence the environment in which the fetus develops. Depression can also impair mother-child bonding, communication, maternal care, and child health. There are plenty of other variables through which the depression phenotype can adversely affect fetal, pregnancy, neonatal, and childhood outcomes, and, indeed, such adverse outcomes have been described in association with maternal depression during pregnancy.[4,5] Antidepressant requirement is associated with more severe forms of depression, and antidepressant users and nonusers will therefore differ

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on a number of phenotypic features; so, out of the entire phenotype of severe depressive illness, it does not seem reasonable that antidepressant treatment alone is selected as a possible risk factor for adverse gestational outcomes.

It may be argued that statistical analysis can "control" for the confounding variables that differentiate antidepressant-exposed and -unexposed pregnancies, such as the variables listed in the previous paragraphs. However, in database studies, information on many of the important confounding variables is unavailable, or available only as crude estimates. Do prospective studies with accurate data on a larger number of relevant covariates help to clear an otherwise muddy picture? No. All that such studies do, and this includes the study of Johnson et al,[1] is define the depression phenotype more accurately and in greater detail. This does not solve the problem because, as already pointed out, in such prospective studies, information on many important confounds remains unrecorded if only because it is impossible to list and measure everything in the depression phenotype that can influence the dependent variables under study. So, there is likely to be substantial residual confounding in analyses, regardless of whether the analyses are conducted on information from databases or information from prospective studies.

Due attention must also be paid to the possibility that genetic characteristics may drive both the occurrence of severe depression (which necessitated antidepressant treatment during pregnancy) and the risk for an adverse neurodevelopmental outcome. What the adverse outcome turns out to be may depend on the genes that the offspring inherits and the environmental factors that encourage the expression of these genes. Again, these variables could be hard if not impossible to capture in studies, including prospective studies.

Until randomized controlled studies resolve the controversy, all that can be said is that antidepressant exposure during pregnancy is a marker for adverse pregnancy or early childhood outcomes. Exceptions can be cautiously made when biological plausibility exists, such as in the case of the poor neonatal adaptation syndrome.[6] Until then, some thought must be given to the possibility that if residual confounding is responsible for an adverse outcome, and if the unmeasured variables responsible for the residual confounding are modifiable through antidepressant treatment, then antidepressant use during pregnancy may actually be desirable to the extent that it attenuates the harmful elements in the depression phenotype.

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