Clinical and Practical **Psychopharmacology**

Offspring Outcomes in Studies of Antidepressant-Treated Pregnancies Depend on the Choice of Control Group

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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

Antenatal depression complicates 14%–23% of pregnancies; if the depression is left untreated, there is an increased risk of a wide range of adverse maternal and offspring outcomes. However, antidepressant use, and, more specifically, selective serotonin reuptake inhibitor (SSRI) use, has also been associated with adverse pregnancy outcomes. Regrettably, SSRIs have received bad press in this context even though the evidence linking them with the adverse outcomes has not disentangled depression effects from drug effects. The most important reason why depression and drug effects cannot be separated is that the evidence is derived mostly from retrospective observational studies and not from randomized controlled trials, which are necessary but which cannot be performed during pregnancy for ethical and practical reasons.

In these observational studies, the control groups are formed from healthy women, depressed women, and/or propensity score–matched women who did not receive antidepressant drugs during pregnancy. A limitation of such control groups is that they cannot control for confounding arising from poorly measured, unmeasured, or unknown variables that influence the pregnancy outcomes being assessed. This article discusses problems involved in such research and illustrates how, when confounding is diminished by using sibling controls discordant for antidepressant exposure during pregnancy, the risks of adverse outcomes associated with antidepressant exposure diminish. However, a discordant sibling control group is associated with its own limitations, and these are also discussed.

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Introduction

Depression is common during pregnancy, with one guideline citing prevalence rates of 14%–23%.[1] A review of 21 studies (N = 19,284) found pooled prevalence rates of 7.4% (95% confidence interval [CI], 2.2%–12.6%), 12.8% (95% CI, 10.7%–14.8%), and 12.0% (95% CI, 7.4%–16.7%) for depression during the first, second, and third trimesters of pregnancy, respectively.[2] A more recent systematic review and meta-analysis of 51 studies (N = 48,904) specifically from low and middle income countries found that the pooled prevalence rate of antepartum depression was 25.3% (95% CI, 21.4%–29.6%).[3]

Depression left untreated during pregnancy is associated with health risks to both mother and child. The risks to the mother include alcohol, nicotine, and other substance use; self-neglect; suicidal ideation and behavior; and medical/obstetric complications, among others; and the risks to the child include premature birth, low birth weight, antenatal and postnatal physiological disturbances, failure to initiate breastfeeding, and poorer health indices in early childhood, among others.[4–7]

Antidepressant Use During Pregnancy and Pregnancy Outcomes

Antidepressant medications are increasingly being prescribed to treat depression during pregnancy, and from 3% to 13% of pregnant women may receive these drugs.[8–11] However, antidepressant use, and, more specifically, selective serotonin reuptake inhibitor (SSRI) use, has itself been associated with adverse pregnancy and neonatal outcomes such as spontaneous abortion, preterm birth, low birth weight, major congenital malformations, poor neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn, and neurodevelopmental disorders in early childhood; the results, though, have not always been consistent.[12–16] A limitation of the studies that demonstrate significant associations (between antidepressant use and adverse outcomes) is that they are compromised by confounding, often from inaccurately measured or unmeasured or even unknown sources that cannot be adjusted for using the data that are available. Examples of such sources of confounding include severity of depression (during pregnancy), severity of stress, level of nutrition, compliance with medical advice, smoking, alcohol intake, illicit substance use, exposure to environmental toxins, genetic factors, and others. Thus, such studies cannot disentangle the effects of drug on the outcomes of interest from the effects of depression and other confounds on these outcomes.

Many articles have pointed out flaws in the research indicting antidepressant use during pregnancy; the implication is that antidepressant use may merely be a marker for adverse outcomes associated with severe depression, and to the extent that the antidepressants attenuate depression, they may actually reduce the risks of depression-related adverse pregnancy outcomes.[17–25] Nevertheless, articles with potentially sensational content tend to be highlighted in the scientific and mass media,[26] and it is not unusual for the mass media, across the world, to carry large headlines that state, for example, that

Clinical Points

- Depression that is left untreated during pregnancy is associated with adverse pregnancy outcomes. Prenatal antidepressant exposure is also associated with adverse pregnancy outcomes; it is not known whether these adverse outcomes are due to the antidepressant medication, the indication for which the medication was prescribed, or other confounding variables.
- In observational studies on the subject (to date, the only kind of studies available), control groups are formed from healthy women, depressed women, or propensity score–matched women who did not receive antidepressants during pregnancy. Analyses are adjusted for confounding variables to the extent that data on these are available. However, such studies with such research designs identify only associations, not cause-effect relationships.
- Siblings discordant for prenatal antidepressant exposure comprise another possible control group. In such a study design, unknown genetic and environmental confounds may be controlled for, but poorly measured or unmeasured confounds may remain. Furthermore, discordant sibling pair analyses may be statistically underpowered. Thus, studies using this research design may also yield inconclusive results.
- All that can be said, based on the nature of the available evidence, is that prenatal antidepressant exposure is a marker for certain adverse pregnancy outcomes. A cause-effect relationship cannot be asserted.

SSRI use during pregnancy increases (implying causation) the risk of autism when all that the cited study found was an association between SSRIs and the adverse outcome.

The Importance of Study Design and Nature of the Control Group

The causal role of a drug in efficacy or adverse event outcomes is best studied in randomized controlled trials (RCTs). However, for ethical reasons, no RCTs have so far been conducted to examine the benefits and risks of antidepressant drugs in the treatment of depression during pregnancy. In any case, given that the adverse pregnancy outcomes attributed to antidepressant medications are rare, very large samples would be required to identify risks should these risks truly exist. For example, if the risk of major congenital malformations is 3% in the general population, 3,000 pregnant women would need to be randomized to antidepressant drug or placebo to be 80% certain (at the $P < .05$ significance level) of detecting an antidepressant-related increase in the risk to 5%. The sample size would need to be even larger to detect a smaller increase in risk.

If RCTs are not feasible, control groups must be formed from the observed samples. In such situations, unfortunately, the antidepressant-exposed and control groups could differ substantially because women would not have been randomized to their respective groups. Therefore, differences in outcomes could be a result of such intergroup differences rather than the presence or absence of antidepressant exposure.

Investigators try to refine the control group in ways such as comparing outcomes not just with healthy women but also with depressed women who have no antidepressant exposure. Another approach involves the undertaking of propensity score matching of women who are discordant for antidepressant exposure. Regression analyses are then run to adjust for (measured) confounding variables that might influence outcomes. However, these approaches fail because they cannot adjust for confounding arising from poorly measured variables (eg, smoking, alcohol intake), unmeasured variables (eg, severity of depression, quality of nutrition), or unknown variables (eg, genetic factors, environmental toxicity) that might influence the outcomes being assessed. These issues were discussed in greater detail in earlier articles in this column and elsewhere.[19–22] This article examines a different approach to the problem: the use of sibling control groups that are discordant for antidepressant exposure. The assumption here is that with sibling controls, a wide range of unmeasured and unknown genetic and environmental confounds will cancel out between exposed and unexposed sibs, thereby diminishing the risk of residual confounding.

SSRI Exposure and Pregnancy Outcomes: A Sibling-Controlled Analysis

Viktorin et al[27] used Swedish national registers to identify a population-based cohort comprising 6,572 children who had been exposed to an SSRI during pregnancy, 1,625 children who had been exposed to maternal depression during pregnancy but not to SSRIs, and 383,832 control children with prenatal exposure to neither SSRIs nor maternal depression. This sample included a subsample of SSRI-exposed (n = 501) and depression- and SSRI-unexposed (n = 506) same-parent sibs. Offspring morphometric outcomes were standardized for gestational age at birth. Analyses were adjusted for potential confounds, including birth order; maternal age, education, and body mass index (BMI); maternal smoking; and previous maternal psychiatric history.

The mean age of the women was about 30 years at the time of delivery. The mean BMI was 24.6. About 7% of women were recorded to be smokers at the first antenatal visit. Nearly 9% of women had a previous psychiatric history (details not provided).

Relative to unexposed controls, offspring exposed to SSRIs had a significant decrease in birth length, head circumference, and gestational age at birth; the odds of preterm birth were significantly increased. There was no significant association between SSRI exposure and birth weight.

Relative to unexposed controls, offspring exposed to maternal depression but not SSRIs had a lower gestational age at birth and increased odds of preterm birth; however, there was no significant association between exposure to maternal depression and birth length, head circumference, or birth weight.

In the within-family analysis, relative to SSRI- and depression-unexposed sibs, offspring exposed to SSRIs had a lower gestational age at birth; there was no significant

relationship between SSRI exposure and the remaining birth outcomes.

All significant effects in all analyses were small. For example, the mean antidepressant-associated reduction in gestational age at birth was by 2–3 days, and increased odds of preterm birth were by 31%–45%. In summary, this study[27] showed that antidepressant-associated adverse gestational outcomes varied by control group and were least in the sibling-controlled analysis.

Other Studies With Sibling-Controlled Analyses

Other investigators have also used discordant sibling pair analysis to examine pregnancy outcomes following prenatal antidepressant exposure. In one study, Nulman et al[28] used data from the Toronto Motherisk prospective database to compare intelligence and behavior of 45 sibling pairs, aged 3–7 years, prenatally exposed and unexposed to serotonin reuptake inhibitors. Maternal intelligence predicted offspring intelligence, and severity of maternal depression predicted disturbances in offspring behavior; antidepressant exposure, including drug dose and duration of exposure, was related to neither outcome.

In another study, Brandlistuen et al[29] identified 20,180 siblings in the population-based Norwegian Mother and Child Cohort Study. After adjusting for maternal familial effects and maternal depression, they found that prenatal antidepressant exposure was associated with increased anxiety at age 3 years; there was no association between antidepressant exposure and emotional reactivity, somatic complaints, sleep problems, attention problems, and aggression.

Limitations of Sibling Control Designs

There are 2 important limitations of sibling control designs. One is that the sample size must necessarily be small because it could be quite difficult to identify sibling pairs that are discordant for antidepressant exposure during pregnancy; this reduces the statistical power of the analyses. The other is that the sib unexposed to antidepressant may be unexposed to depression (or, at least, depression severe enough to warrant antidepressant use), as well; in such a situation, all that the investigators succeed in doing in sibling-controlled analyses is exchange one set of confounds for another set of confounds.

Take-Home Message

In observational studies of the effects of prenatal antidepressant exposure on pregnancy outcomes, in between-subjects research designs, control groups have been formed from unexposed healthy women, depression- (but not drug-) exposed women, and propensity score–matched unexposed women. In within-subjects research designs, controls have been formed from pregnancies in the same women that were discordant for antidepressant exposure. All of these designs are vulnerable to results biased by inadequately measured, unmeasured, or unknown sources of confounding. There is therefore a real possibility that antidepressant medications are blamed for effects that may arise either from depression or from other sources of confounding, implying that adverse pregnancy outcomes following prenatal antidepressant exposure may be less than is generally supposed.

Whereas the RCT remains the gold standard, RCT data on antidepressant treatment of depression during pregnancy are presently unavailable and are unlikely to become available in the foreseeable future. The limitations of observational research should therefore be kept in mind when formulating clinical guidance on the management of depression during pregnancy.

Parting Notes

Readers interested in other articles that explain how to critically examine a research paper are referred to previous articles in this column and elsewhere.[17–20,30,31] Viktorin et al[27] themselves provided an excellent appraisal of the strengths and limitations of their own study.

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