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Can non-randomized studies on the safety of antidepressants during pregnancy convincingly beat confounding, chance, and prior beliefs?

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Between 7% and 13% of pregnant women in the United States use antidepressants.¹⁻² As the number of pregnant women taking antidepressants has increased over the last 15-20 years, so has the number of publications on the safety of antidepressant use during pregnancy. Although the evidence is inconsistent, antidepressant use has been associated with a wide variety of adverse outcomes for both infant and mother, including spontaneous abortion, specific congenital malformations, persistent pulmonary hypertension of the newborn, low birth weight, poor neonatal adaptation, and preeclampsia.³

Previous studies have also reported an association between antidepressant use and preterm delivery, but the study by Yonkers and colleagues⁴ in this issue of *EPIDEMIOLOGY* stands out because the authors address potential confounding by depression, depression severity, and psychiatric co-morbidities. Their study benefits from carefully collected clinical information on psychiatric illness history and severity. The reference group consisted of women who did not have depressive illness and did not use SRI (serotonin reuptake inhibitor) antidepressants during pregnancy. A comparison of women who used SRIs but did not have a major depressive episode with the reference group suggests that SRIs are associated with preterm delivery ([odds ratio] 1.5 [95% confidence interval (CI) = 0.9-2.4]). However, these results may reflect residual confounding because it is unclear whether the authors controlled for the SRI indications of women who used SRIs but did not have depression. Further, their results suggest that major depressive disorder is not associated with preterm delivery, based on the comparison between women with a major depressive episode but no SRI treatment and the reference group, although the estimates are imprecise (95% CI = 0.4 - 1.7). Even so, the association for women who had both a major depressive episode and SRI treatment was attenuated after adjustment for age of depression onset, number of prior depressive episodes, number of hospitalizations for depression, post-traumatic stress disorder, generalized anxiety disorder, panic disorder and suicidal ideation

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(from a partially adjusted OR of 2.1 to a fully adjusted OR of 1.5), suggesting that depression severity and psychiatric comorbidities may be associated with preterm delivery.

Preterm delivery is a syndrome with many etiologies.⁵ By focusing on preterm delivery overall, an association between antidepressant use and preterm delivery could be missed if antidepressants affect only certain subtypes of the outcome. By understanding the type of preterm delivery that is affected, we may gain insights into the mechanism by which antidepressants are associated with prematurity. Yonkers et al. ask the appropriate question: which type of preterm delivery is affected by SRI use during pregnancy? However, the number of outcomes in their study was too small to produce stable estimates for subtypes of preterm delivery.

The results from Yonkers et al,⁴ together with previously reported associations, raise a number of questions. Why do women who use antidepressants have an increased risk of such a wide range of perinatal outcomes? Does depression play an etiologic role in the development of these outcomes? Do maternal behaviors that are caused by depression or anxiety increase the risk, or the diagnosis, of the outcomes? Do the associations arise from genetic or environmental factors that cause both psychiatric illness and adverse pregnancy outcomes? Or, are antidepressants so toxic that they actually cause the whole spectrum of adverse outcomes?

There are challenges when studying antidepressant safety during pregnancy. Outcomes of interest are often very rare; specific malformations typically occur in as few as 1-30 per 10,000 live births.⁶ Because different antidepressants may have different adverse effects, it is critical to consider antidepressant classes, and even specific drugs; obtaining enough exposed pregnancies may become difficult. Moreover, findings suggest that the potential increases in risks associated with antidepressants are small to moderate. Consequently, the first challenge in studying rare outcomes, rare exposures, and modest associations is to find large data sources. However, large data sources typically lack detailed clinical information on antidepressant indication and indication severity. This limitation brings us to the second challenge, probably the Achilles' heel of this matter: confounding. Confounding by depression or depression severity is a major concern because it could bias associations away from the null when the reference group contains women without depression or with less severe depression. This is assuming of course that depression or factors associated with it (e.g. use of other psychotropic medications), increases the risk of congenital malformations, persistent pulmonary hypertension, preeclampsia, etc. Although this belief is strong among some investigators, the evidence to support the independent association of depression with these outcomes is weak.

To reduce the potential for confounding by indication, investigators have compared (1) women with depression who are treated with antidepressants during pregnancy with women with depression but no antidepressant treatment during pregnancy; (2) women who continue treatment late in pregnancy (the etiologically relevant period for certain outcomes) with those who discontinue treatment by the end of the first trimester; and (3) women with different types of antidepressant treatment, in a head-to-head, comparative-safety analysis.⁷ Although these analyses may seem to address confounding by indication, they cannot

resolve confounding by indication severity because treated depression, antidepressant continuation and non-SRI antidepressants are likely associated with more severe depression. Other biases, such as misclassification of the exposure (e.g., discontinuation of antidepressant prescriptions) and outcome (e.g., non-validated health insurance claims) are also likely in many published studies but would tend to bias results toward the null. Interestingly, although false negatives are worrisome in safety studies, the discussion in this particular literature has focused primarily on finding non-causal, alternative explanations for the positive findings.

Another challenge in this debate has been strong a priori beliefs either for or against antidepressant safety during pregnancy. Results from non-randomized studies, no matter how large or how valid, may be unable to shift such prior convictions one way or the other. For example, a 1.5-fold increase in cardiac malformations associated with first-trimester use of an SRI was interpreted as evidence of risk in one meta-analysis⁸; while a 1.5-fold increase for the same association in a recent study has been interpreted as evidence of safety because the confidence interval included one.⁹

Considering the wide range of studies on antidepressant safety, it is surprising that very few studies exist on the effectiveness of antidepressants during pregnancy. Cohen et al.¹⁰ found that women with a history of depression who discontinued antidepressant treatment had a higher risk of relapse of major depression during pregnancy compared with pregnant women who continued treatment. However, Yonkers et al.¹¹ found no association between antidepressant use and risk of a major depressive episode among pregnant women with a history of depression. Studies are needed on the effectiveness of antidepressant continuation during pregnancy and withdrawal symptoms among discontinuers. Moreover, these studies should consider the broad range of indications for antidepressant prescription during pregnancy, including anxiety, smoking cessation, insomnia, and chronic pain.

In summary, we have learned from Yonkers et al. that, when assessing the effect of antidepressants on preterm delivery, studies should (1) control not only for the presence of depression but also for its severity; (2) consider specific types of prematurity; and (3) be sufficiently large. To justify the potential risks of antidepressant treatment during pregnancy or to justify spending more resources to define boundaries around safety, we must also demonstrate the benefits of antidepressant continuation during pregnancy. This poses a new question: can non-randomized studies convincingly assess the effectiveness of antidepressants during pregnancy?

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References

1. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol*. 2008; 198(2):194, e191–195. [PubMed: 17905176]

2. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol.* 2007; 196(6):544, e541–545. [PubMed: 17547888]
3. Stewart DE. Clinical practice. Depression during pregnancy. *N Engl J Med.* 2011; 365(17):1605–1611. [PubMed: 22029982]
4. Yonkers KA, Norwitz ER, Smith MV, et al. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology.* 2012; 23:677–685. [PubMed: 22627901]
5. Villar J, Papageorgiou AT, Knight HE, et al. The preterm birth syndrome: a prototype phenotypic classification. *Am J Obstet Gynecol.* 2012; 206(2):119–123. [PubMed: 22177191]
6. Correa A, Cragan JD, Kucik JE, et al. Reporting birth defects surveillance data 1968–2003. *Birth Defects Res A Clin Mol Teratol.* 2007; 79(2):65–186. [PubMed: 17278144]
7. Palmsten K, Setoguchi S, Margulis AV, Patrick AR, Hernández-Díaz S. Elevated risk of preeclampsia in pregnant women with depression: disease vs. antidepressants [abstract]. *Pharmacoepidemiol & Drug Safety.* 2010; 19:S210–S211.
8. Wurst KE, Poole C, Ephross SA, Olshan AF. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol.* 2010; 88(3):159–170. [PubMed: 19739149]
9. Nordeng H, van Gelder MM, Spigset O, Koren G, Einarson A, Eberhard-Gran M. Pregnancy Outcome After Exposure to Antidepressants and the Role of Maternal Depression: Results From the Norwegian Mother and Child Cohort Study. *J Clin Psychopharmacol.* 2012; 32(2):186–194. [PubMed: 22367660]
10. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA.* 2006; 295(5):499–507. [PubMed: 16449615]
11. Yonkers KA, Gotman N, Smith MV, et al. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology.* 2011; 22(6):848–854. [PubMed: 21900825]