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COMMENT

Prenatal antidepressant exposure and neurodevelopmental problems in children: to get the right answer, we must ask the right question

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It has been nearly 25 years since the earliest studies of the associations between prenatal antidepressant exposure and child neurodevelopmental disorders were published. Amid a crowded literature examining a dizzying array of outcomes and study populations, in studies of disparate sizes and designs, the question of whether this class of medications causes problems in brain development remains a frustratingly equivocal "perhaps."[1] Differences in conclusions in the literature are often attributed to differences in methods for confounding control.

The new study from Park et al.[2] reports associations between prenatal antidepressant exposure and anxious behaviors, as well as physical independence. Conducted using Canadian population-based healthcare databases linked to a teacher-reported measure of children's school readiness, the study presents multiple effect estimates aimed at better understanding the impact of confounding. Their approaches include a high-dimensional propensity score-matched analysis in all women who gave birth in British Columbia during the study period, and a comparison between women who discontinued, versus continued, their pre-pregnancy antidepressant regimen. Additional sensitivity analyses explore the possible effects of specific classes of antidepressants (i.e., selective serotonin reuptake inhibitors (SSRI) versus non-SSRIs, alone or in combination), as well as extended effects of exposure (i.e., prescription fills covering the second and third trimesters). As in other studies, associations were attenuated but did not disappear after progressively stronger confounding control approaches. But as the authors observe, residual confounding by familial genetic or environmental predisposition and maternal mental illness is a plausible explanation for the results.

However, there is a puzzling disconnect in the interpretation of the complete set of results, and the answers most needed by the beneficiaries of this research: people who are or plan to become pregnant, and who need to make decisions about whether they will make changes to their medication regimen. Bridging this gap requires coupling a satisfactory method for confounding control with a study design that emulates a hypothetical intervention.[3]

THE DRUG OR THE DEPRESSION? CONFOUNDING BY INDICATION

Confounding control is a central challenge in inferring causation from associations in data. Women taking an antidepressant differ in many ways from women who do not require such treatment: among other qualities, they more often carry a diagnosis of depression, anxiety, or a related psychiatric illness. Because these phenotypes have a genetic or otherwise heritable component, confounding by indication is a central and possibly intractable source of bias: we are concerned that any association between antidepressant and child neurodevelopment is in fact due to an inherited susceptibility for mental illness passed from parent to offspring.

Some studies have made use of designs that can mitigate familial confounding, such as sibling comparison[4] or paternal negative control designs.[5] Effect estimates from these studies are generally attenuated and often have confidence intervals that include the null, although direct comparisons are complicated by potential selection bias. However, the underlying message is clear: confounding by indication is a serious threat to validity, and any new contributions to a crowded literature should be rigorous in minimizing this source of confounding.

RANDOMIZED TRIALS AND WELL-DEFINED CAUSAL EFFECTS

To interpret an observed association as causal, we must assume that the treated and untreated groups are exchangeable, meaning that the counterfactual outcome risk under every exposure definition is the same in the treated and untreated groups.[6] The gold standard for determining cause and effect in medicine is the randomized trial: the random assignment of treatment makes the assumption of exchangeability/no uncontrolled confounding palatable. In observational research, we might say that treatment groups are conditionally exchangeable given a set of measured characteristics or study design parameters, but this assumption is much stronger in observational versus experimental data, and therefore harder to justify.

At this point it is common, and accurate, to note that randomized clinical trials of medications typically exclude pregnant women, limiting researchers to using observational studies to learn about associations between prenatal medication exposure and outcomes in children. However, the state of the literature for antidepressants during pregnancy is so balanced that we arguably have equipoise for the risks and benefits of antidepressants. In fact, the uncertainty itself may be causing harm to pregnant women by unnecessarily depriving them of safer treatment options for depression.

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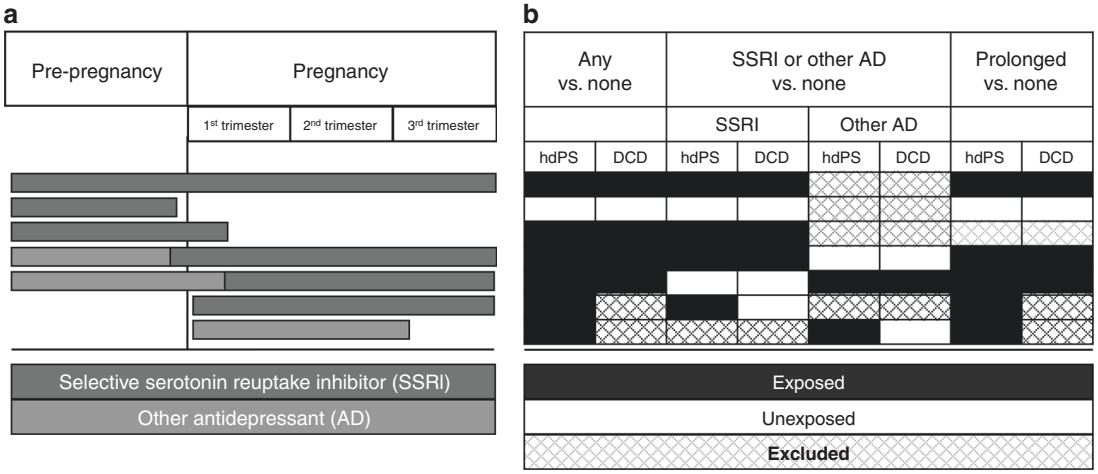

Fig. 1 Multiple patterns of continuation, initiation, and discontinuation of antidepressants before and during pregnancy. Antidepressant exposure during pregnancy can occur through multiple avenues, hypothetical examples of which are illustrated in Panel (**a**). Panel (**b**) shows how categorization into ever versus never exposed (in the hd-PS matched analysis) or continuation versus discontinuation elides many of these avenues, depending on how exposure is defined. Abbreviations: AD: antidepressant; DCD: discontinuer design; hdPS: high dimensional propensity score; SSRI: selective serotonin reuptake inhibitor.

This state of equipoise means we are in the unique position of having two randomized trials underway that address the question of neurodevelopment as either a primary or secondary outcome. While results are not expected for some time, the design of these studies can help us clarify the research question or questions we are truly trying to answer. One protocol enrolls pregnant women with moderate depression not currently on an antidepressant and randomizes them to receive sertraline versus cognitive behavioral therapy, beginning in the second trimester.[7] The "stop or go" trial enrolls pregnant women currently on an antidepressant treatment, and randomizes them to supervised tapering of the medication versus continuation.[8]

TARGET TRIALS FOR ANTIDEPRESSANT USE IN PREGNANCY

With these trial protocols in mind, we are better equipped to define the causal effect(s) of interest.[3] Figure 1 illustrates possible patterns of antidepressant use (Fig. 1A), and their corresponding categorization in the current study from Park et al. (Fig. 1B). The high-dimensional propensity score matching (hdPS) approach categorizes as exposed any individual with any exposure during the relevant time period, whether that exposure is part of a pattern of discontinuation in early pregnancy, continuation of the same treatment throughout the study period, initiation of the treatment in question, or switching from one antidepressant to another. The estimate from the hdPS analysis is likely less biased from confounding but is a mix of multiple possible interventions. Assuming that the hdPS matching approach controlled measured and unmeasured confounding between the treated and untreated groups, and further that other assumptions are met,[6] we could interpret this odds ratio as a causal effect—but a causal effect of what?

The analysis of discontinuation versus continuation of antidepressant treatment before the start of pregnancy corresponds directly to an important potential intervention. However, rather than employing the hdPS approach for confounder control, Park et al. controlled for a handful of covariates in their outcome models, including gestational age at birth, which may be an intermediate. Even assuming that employing the discontinuer analysis controls substantial confounding by design, residual confounding is still plausible, and the inclusion of post-exposure covariates increases the risk of bias.[9] Further, because of differences in confounding control and non-collapsibility of the odds ratio,[10] the estimates are not directly comparable to each other, which limits our ability to learn something new about the impact of confounding bias.

ASKING THE RIGHT QUESTION

No estimate from Park et al. corresponds to the effect of switching from one antidepressant to another, of initiating antidepressant therapy during pregnancy, of discontinuing and resuming treatment during gestation, or of any concomitant treatment with other medication or behavioral therapy. This is not a limitation: we suggest only that studies should seek to estimate a well-defined causal effect, not that they must estimate all possible causal effects. But if the effect estimates from a given study do not correspond to any intervention, how much use can they be for supporting clinical decision making?

As more and more women use medications during pregnancy, it is critical that studies on medication safety carefully define research questions with answers that support clinical and regulatory decision making. Almost invariably, the estimated effect should correspond to an intervention. Epidemiologic research may seek to answer causal questions for which no intervention is possible, even hypothetically.[11] Conversely, associational and descriptive epidemiology remains an important pursuit. But when estimating the effect of medication exposure, the well-defined causal effect is fundamental, and absent that, understanding other biases are secondary concerns.

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ADDITIONAL INFORMATION

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