Do antidepressants really cause autism?

This study's results bring us no closer to the answer to that question. Although the authors did evaluate more than 900,000 person-years of follow-up and did conclude that, "use of antidepressants, specifically selective serotonin reuptake inhibitors, during the second and/or third trimester increases the risk of autism spectrum disorder in children, even after considering maternal depression," this study is retrospective, with authors evaluating a secondary end point. Several additional study design drawbacks, including that exposure to antidepressant medications was determined by prescriptions filled versus actual drug adherence, provide no correlation with substantive evidence of causation.

Boukhris T, Sheehy O, Mottron L, Bérard A. Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. JAMA Pediatr. 2016;170(2):117–124.

EXPERT COMMENTARY

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Presently it seems that anything a pregnant woman ingests can be correlated with a teratology or an unfortunate neurobehavioral outcome. In an era when up to 15% of pregnant women are taking antidepressant therapy, antidepressants are obvious drugs to be correlated with an untoward fetal outcome, despite the fact that untreated maternal depression itself is significantly worse.[1]

A recent retrospective secondary end point study by Boukhris and colleagues on antidepressant use in pregnancy and the risk of autism spectrum disorder (ASD) in

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

In this registry-based study of an ongoing population-based cohort, the authors suggest a sensational 87% increased risk of ASD with use of antidepressants during pregnancy. While technically correct, the absolute risk (if real) is really less than 1%. Using sound epidemiologic principles, we would advise against speculating on a number needed to harm based on this study design. Such a projection would require a prospective randomized trial.

›› ROBERT P. KAUFFMAN, MD; TERESA BAKER, MD; AND THOMAS W. HALE, PHD

FAST TRACK

Although this study suggests correlation between antidepressant use during pregnancy and autism in children, its inadequate design and lack of key data override the credibility of its conclusions

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children is an example of correlation without substantive evidence of causation. Although this study received media attention,[2] it is a "data-dredge" study. While the authors correctly note that the database is derived from a prospective registry-based population-based cohort study (the Quebec Pregnancy/Children Cohort), their study's design more closely resembles a post hoc nested case-control study.

Details of the study

Researchers evaluated data from 145,456 singleton full-term infants born alive between January 1, 1998, and December 31, 2009, with antidepressant exposure during pregnancy defined according to trimester and specific antidepressant classes. Children were considered as having autism if they had received at least 1 autism diagnosis between their date of birth and the last date of follow-up.

We perceive several problems in the study's design and the authors' conclusions.

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Shortcomings of study design

The study results are based on a post hoc analysis. Autism spectrum disorder was not the primary end point of interest in this database. Accordingly, in a secondary end point study, the risk for bias and confounding is substantial. This study design cannot prove causation.[3–5]

Exposure is defined by number of antidepressant prescriptions filled. No data regarding adherence (true exposure) are provided. Many women will not take antidepressant drugs as prescribed during pregnancy. It has been reported that antidepressants dispensed to pregnant women during the last 2 trimesters of pregnancy were taken by only 55% of the women.[6]

The specific antidepressant agents and dosages used were not identified, and the study provided no good sense of duration of use. Is it biologically plausible, therefore, to suggest that all antidepressants—with their disparate structures and mechanisms, in all doses, and for various durations of use—have a uniform effect on fetal neurodevelopment?

Notably, in another prescription drug study of 668,468 pregnancies in 2013, investigators found no significant association between prenatal exposure to antidepressants and ASD.[7]

Some data suggest that ASD and depression may share preexisting risk factors.[8] The increased risk for ASD proposed by Boukhris and colleagues' study cannot likely be separated from the well-described genetic risk of ASD that might be shared with that of depression.[9,10]

The stated hazard ratios (HRs) are all <2.2. Given this study's design, it is plausible that various biases and confounders account for these findings. True significance of these HRs are suspect unless they exceed 3.0, and there is a greater probability of avoiding a type I error when the risk ratios are greater than 4 to 5.[3,4]

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