# Antidepressant Use in Pregnancy and Risk of Autism Spectrum Disorders: A Critical Examination of the Evidence

*Chittaranjan Andrade, MD*

Recent epidemiologic studies suggest that autism spectrum disorders (ASD) are far more prevalent than formerly believed; whereas broader definition and better ascertainment may partly be responsible, higher incidence is also a potential explanation. Therefore, given that ASD may have environmental as well as genetic roots, environmental causes need to be explored. Might maternal mental health and use of psychotropics during pregnancy contribute to the environmentally mediated risk? These possibilities were considered in 2 recent studies.[1,2] The studies are summarized here in order to provide an interpretation of the results, but more especially to provide insights on how to critically evaluate literature.

## Antenatal Antidepressant Exposure and ASD Risk

Croen et al[1] described a northern California, population-based, case-control investigation using data extracted from medical records. In case-control studies, cases are subjects who have been identified in the population to have the characteristic of interest; ASD, in the present context. Controls are subjects who are chosen from the population such that each control matches a specific case on important variables. Because cases are usually infrequent in the population, it is often possible to match many controls to a single case.

Two hundred ninety-eight children with ASD were matched (for gender, birth year, and hospital) in a 1:5 ratio with 1,507 controls. ASD was defined to include autism, Asperger syndrome, or pervasive developmental disorder (PDD) not otherwise specified, based on *ICD-9-CM* criteria. Analyses were adjusted for various confounding variables in different models.

Maternal antidepressant use in the year before delivery was found to be associated with a doubled risk of ASD in the offspring (20 cases, 50 controls; odds ratio [OR] = 2.0; 95% CI, 1.2–3.6). This finding was confirmed for selective serotonin reuptake inhibitors (SSRIs) (13 cases, 25 controls; OR = 2.6; 95% CI, 1.3–5.4). The results were nonsignificant for non-SSRI antidepressants, but these analyses were probably underpowered. The strongest effect was observed with first-trimester SSRI exposure (14 cases, 19 controls; OR = 3.5; 95% CI, 1.5–7.9). In the fully adjusted model, SSRI exposure during the second and third trimesters showed nonsignificant though similar trends, but these analyses were also underpowered. Importantly, there was no increase in ASD risk in the offspring of mothers who had a history of treatment for mental health concerns but who had not used SSRIs during pregnancy.

## Parental Depression, Early-Pregnancy Antidepressant Exposure, and ASD Risk

Rai et al[2] presented a large, population-based, nested case-control study that examined whether parental depression or maternal use of antidepressants during early pregnancy influenced the risk of ASD in the offspring. The sample was drawn from a Swedish cohort of 589,114 children and adolescents aged 0–17 years. On the basis of *ICD-9*, *ICD-10*, or *DSM-IV* criteria, there were 4,429 cases of ASD, of whom 1,828 had an intellectual disability and 2,601 did not. These cases were matched by gender and date of birth in a 1:10 ratio with 43,277 controls. There was also a subsample of 1,679 cases with ASD and 16,845 controls for whom data on maternal antidepressant use during early pregnancy (median, week 10) were available.

ASD was defined to include autism, Rett and Asperger disorders, PDD, childhood disintegrative disorder, and other conditions generally classified under this rubric. Intellectual disability was defined as the presence of any diagnosis of mental retardation. The risk of ASD was examined with regard to variables that had been prospectively recorded before the birth of the children. In different models, analyses controlled for different confounding variables. Antidepressant categories other than SSRIs and non-SSRI monoamine reuptake inhibitors were not subjected to analysis because these drugs were used in too few cases. For the same reason, data were not analyzed for individual drugs within a class.

In the main sample (4,429 ASD cases and 43,277 controls), a history of maternal depression was present in 44 cases (1.0%) versus 272 controls (0.6%). After adjusting for covariates and confounding variables, maternal depression was associated with a significantly increased risk of ASD in the offspring (OR = 1.49; 95% CI, 1.08–2.08). Paternal depression was not associated with an increased risk (0.4% vs 0.4% in cases vs controls; OR = 1.21; 95% CI, 0.75–1.96).

In the subsample reporting antidepressant use during early pregnancy (1,679 ASD cases and 16,845 controls), maternal depression and antidepressant use did not increase the risk of ASD with intellectual disability. In contrast, the risk of ASD without intellectual disability was significantly elevated by antidepressants, but only in the context of maternal depression (7 cases and 4 controls; OR = 4.95; 95% CI, 1.85–13.23) and not in the absence of maternal depression (9 cases and 36 controls; OR = 2.10; 95% CI, 0.97–4.57).

The above data notwithstanding, antidepressant use was significantly associated with ASD even after the researchers adjusted for maternal psychiatric disorders and other potential confounders (OR = 2.54; 95% CI, 1.37–4.68). The association between antidepressant exposure and increased risk of ASD was significant with SSRIs as well as with nonselective monoamine reuptake inhibitor antidepressants (but not for ASD with intellectual disability).

The findings were similar in statistical models that progressively increased adjustment for covariates and confounders and in different sensitivity analyses. Importantly, it was estimated that, if antidepressant use during pregnancy is causal for ASD, antidepressants explain the occurrence of only 0.6% of the observed cases.

## Critical Evaluation

Why differentiate risks between ASD with and ASD without intellectual disability? One reason is that the latter category includes high-functioning autism and Asperger syndrome. More importantly, given that diagnoses were only crudely ascertained through register-based identification of *ICD-9*/*ICD-10* or *DSM-IV* codes, ASD without intellectual disability might define the presence of ASD with greater precision; so, if maternal depression or antidepressant use are truly associated (whether causally or not) with ASD risk, the relationship would be more easily identified for ASD without intellectual disability. This is exactly what Rai et al[2] found. An alternate explanation is that ASD with intellectual disability is biologically different from ASD without intellectual disability and that these differences explain why the associations with maternal depression and antidepressant use were significant for one group and not the other.

An important limitation of the Swedish study[2] is that antidepressant use was defined as use at the first antenatal interview

(median, 10 weeks of gestation). Thus, whereas point exposure during the first trimester was recorded, no information was available about ASD risks as a function of duration of exposure at different times during pregnancy. This is important for several reasons. For example, given that the findings of statistical significance were established on the basis of only a few cases and controls, if antidepressant exposure was brief whereas the indication for antidepressants (maternal depression) persisted, one might speculate that it was the maternal depression, really, that was responsible for the increased risk identified. However, if specific timing of exposure was shown to influence risks (eg, first trimester vs last trimester), causality of exposure could be more reasonably concluded.

In the Swedish study,[2] antidepressant use was significantly associated with ASD only in the presence of maternal depression. This suggests that maternal depression rather than antidepressant use may explain the risk. A caveat here is that the relationship between antidepressant exposure and ASD in the absence of maternal depression only narrowly missed statistical significance in what might have been an underpowered analysis.

Both studies[1,2] employed a case-control design, and so neither could establish that antidepressants are causal for ASD. The significant association between antidepressants and ASD could therefore have arisen from confounding by indication[3]: women for whom antidepressants could not be discontinued during pregnancy may have differed systematically from those for whom antidepressants could be discontinued, and such differences may have been responsible for the increased risk of ASD in the offspring. For example, women who required antidepressants may have been more severely depressed, and behaviors or experiences associated with greater severity of depression (rather than use of antidepressant drugs) may have predisposed to ASD. If so, the effective treatment of depression (including through the use of antidepressants) might actually reduce the risk of ASD. Another possibility is that women with more severe depression (who hence needed to use antidepressant drugs) may have been genetically different from those with less severe depression, and these genetic differences, rather than antidepressant use, could have explained the greater risk of ASD. Then, antidepressant need during pregnancy would be a marker of risk, but would not influence the risk of ASD.

Rai et al[2] did control for a number of possible confounds but, as they conducted a register-based investigation, could not vouch for the accurate measurement of these variables or control for all the variables that have been associated with increased ASD risk. Examples of such variables are family history of ASD or major mental illness, maternal infection during pregnancy, maternal childhood abuse, absence of folate supplementation during pregnancy, use of other medications such as valproate, air pollution, and many others. Curiously, the authors controlled for smoking but not for alcohol use or abuse. Thus, residual confounding by unmeasured or improperly measured variables is also a possible explanation for the findings.

Because the Swedish study[2] was register based, depression was almost certainly underascertained (prevalence < 1% in the whole sample). More importantly, the severity and course of illness could not be assessed. In fact, there was no information on whether or not women with a history of depression were depressed during pregnancy—the study merely recorded a history of depression, not the actual presence of depression during pregnancy. So, women with a history of depression who used antidepressants during pregnancy may have actually been depressed, whereas those who did not use antidepressants may have been well during pregnancy; in other words, this is a confounding by indication scenario, as noted earlier. If maternal depression rather than antidepressant use is the real risk factor, then (again, as observed earlier) antidepressant use may actually reduce the risk of ASD in the offspring.

Certain statistical issues in the Swedish study[2] need consideration. On the one hand, several analyses were underpowered (even though this is the largest study on the subject to date), possibly resulting in false-negative (type II) statistical errors. On the other hand, the authors did not correct for multiple hypothesis testing, resulting in possible false-positive (type I) statistical errors.

It must be remembered that if an event (eg, ASD incidence) is rare, then even doubling of the risk of that event may be of small clinical significance. Rai et al[2] estimated that, even if antidepressant exposure is causal for ASD, avoidance of antidepressants during pregnancy would prevent only 0.6% of ASD cases. This finding is reassuring and indicates that there may not be a need for a change in current practice in reproductive psychiatry. An important caveat is that this population attributable risk was calculated in the context of a very low prevalence of maternal depression and antidepressant use.

Lastly, autism is considered to have genetic roots. However, Rai et al[2] found that maternal but not paternal depression was associated with increased risk of ASD in the offspring. Because autism has not so far been linked to maternal transmission alone, this finding suggests that the genes associated with depression do not overlap substantially with those associated with ASD and/or that maternal behavior and experiences related to depression (rather than the genetics of depression) drive the risk for ASD in the offspring of depressed mothers who need antidepressants during pregnancy. In the latter case, as suggested earlier, effective treatment of severe depression during pregnancy might actually reduce the risk of ASD in the offspring.

## Take-Home Message

On the surface, it appears from the literature that antidepressant use during pregnancy, especially during early pregnancy,[1,2] increases the risk of ASD in the offspring. However, a critical examination shows that a causal association has by no means been established and that several other interpretations of the findings are possible. Finally, even if the link is causal, the population attributable risk is very small. Therefore, there does not as yet seem to be a need for a change in current practice in reproductive psychiatry.

***Author affiliations:*** Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India.
***Potential conflicts of interest:*** Full statement is online at www.psychiatrist.com/documents/andrade-financial-disclosure.pdf.
***Funding/support:*** None reported.
***Corresponding author:*** Chittaranjan Andrade, MD, Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka 560 029, India (candrade@psychiatrist.com).

## REFERENCES

1. Croen LA, Grether JK, Yoshida CK, et al. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry*. 2011;68(11):1104–1112.
2. Rai D, Lee BK, Dalman C, et al. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ*. 2013;346:f2059.
3. Andrade C. How to read a research paper: reading between and beyond the lines. *Indian J Psychiatry*. 2011;53(4):362–366.

*J Clin Psychiatry 2013;74(9):940–941 (doi:10.4088/JCP.13ac08607)*


ASCP Corner offerings are not peer reviewed by the *Journal* but are peer reviewed by ASCP. The information contained herein represents the opinion of the author.

**Visit the Society Web site at www.ascpp.org**