Clinical and Practical **Psychopharmacology**

Major Congenital Malformations Associated With Exposure to Second-Generation Antipsychotic Drugs During Pregnancy

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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

Major congenital malformations (MCMs) are gestational outcomes that are seen in about 2%–3% of pregnancies in the general population. In this context, many studies have examined the MCM risk associated with gestational antipsychotic exposure. These articles were summarized in a recent meta-analysis. The present article examines the findings of the meta-analysis as well as the findings of 2 recent observational studies that were not included in the meta-analysis; an outcome of specific interest was the risk of MCMs after first-trimester gestational exposure to second-generation antipsychotic (SGA) drugs. In brief, meta-analysis of data from 6 observational studies found that exposure to antipsychotic drugs during pregnancy was not associated with a significantly increased risk of MCMs; this finding was also true of early pregnancy exposure and of SGA exposure alone. A large, retrospective, population-based cohort study from Finland found that first-trimester gestational exposure to SGAs was not associated with a significantly increased MCM risk relative to either no exposure or exposure to first-generation antipsychotics; however, in exploratory analyses, olanzapine was associated with increased risk relative to unexposed pregnancies, and specifically so for musculoskeletal malformations. Prospective data from a US pregnancy registry also found no increase in risk associated with first trimester gestational exposure to SGAs in a cohort of women with psychiatric disorders. In smaller studies that used data from the same registry, neither quetiapine nor aripiprazole were associated with increased MCM risk after first trimester use. It is possible that where risk was identified, such as in unadjusted or exploratory analyses, the significant findings were false positives arising from multiple hypothesis testing, or findings driven by residual confounding. The substantial benefits associated with use of antipsychotics, when indicated, must therefore be weighed against the unsubstantiated risks of MCMs in a shared decision-making process.

J Clin Psychiatry 2021;82(5):21f14252

To cite: Andrade C. Major congenital malformations associated with exposure to second-generation antipsychotic drugs during pregnancy. *J Clin Psychiatry.* 2021;82(5):21f14252.

To share: https://doi.org/10.4088/JCP.21f14252

A large number of adverse gestational and neurodevelopmental outcomes have been associated with exposure to psychotropic drugs during pregnancy.[1] This subject has been well studied in the context of antidepressant drugs, especially the selective serotonin reuptake inhibitors,[2] which do not appear to increase the risk of major congenital malformations (MCMs). During the past 1–2 decades, many studies have examined the risk of MCMs in the context of gestational exposure to antipsychotic drugs. MCMs are perhaps the single most prominent and feared adverse outcome associated with pregnancy; they are external or internal structural abnormalities that may be detected in utero or at or soon after birth; they are cosmetically disfiguring or may compromise functioning or health. MCMs occur with a frequency of about 2%–3% in the general population; sodium valproate is the best known teratogen in neuropsychiatry.

Studies on MCMs associated with antipsychotic exposure during pregnancy were summarized in a recent systematic review and meta-analysis.[3] This article examines the meta-analysis with a focus on findings associated with first-trimester exposure to second-generation antipsychotic (SGA) drugs because SGAs have largely replaced the first-generation antipsychotics (FGAs) in most parts of the world. This article also examines 2 recently published articles that were not included in the meta-analysis; both of these were also observational studies.[4,5]

Results From Meta-Analysis

Wang et al[3] described a systematic review and meta-analysis of observational studies of congenital malformations associated with gestational exposure to antipsychotic drugs. These authors searched electronic databases and other sources and identified 13 studies for systematic review of which 6 could be included in random-effects meta-analyses.

In the main analysis, these authors[3] found that exposure to antipsychotic drugs during pregnancy was not associated with a significantly increased risk of congenital malformations (6 studies; risk ratio [RR], 1.23; 95% confidence interval [CI], 0.96–1.58). In a more specific analysis, they found that exposure to SGAs was not associated with increased risk (3 studies; RR, 1.35; 95% CI, 0.73–2.47). Finally, in the most relevant analysis, they found that antipsychotic exposure during the first or second trimester was not associated with increased risk (4 studies; RR, 1.05; 95% CI, 0.96–1.15). This analysis is important because organogenesis occurs during the first trimester, during which period fetal exposure to a teratogen could result in an MCM.

Limitations of this meta-analysis are chiefly related to the data sources because data were mixed with regard to trimester of exposure, with regard to drug combinations, and with regard to the appropriateness of control groups; additionally, there was no clear differentiation between major and minor congenital malformations. Finally, the meta-analysis was dominated by the results of one study[6] that included nearly 10,000 exposed women; this number was only a few hundred in each of the remaining studies in the meta-analyses. In this study,[6] after adjusting for confounding variables, first-trimester exposure to antipsychotic drugs was not associated with a significantly increased risk of congenital malformations for either FGAs (RR, 0.90; 95% CI, 0.62–1.31) or SGAs (RR, 1.05; 95% CI, 0.96–1.16).

Data From Finland

Ellfolk et al[4] described a retrospective, population-based cohort study of MCMs associated with gestational exposure to antipsychotic drugs. The data were drawn from linked registers in Finland. The sample comprised singleton pregnancies that had ended in live birth or in stillbirth, or that had been terminated due to MCMs, during 1996–2017; pregnancies exposed to known teratogens were excluded. The groups of interest were pregnancies with first trimester exposure to SGAs (n = 3,478), pregnancies with first trimester exposure to FGAs (n = 1,030), and pregnancies unexposed to antipsychotics (n = 22,540). Exposure was defined by purchase of antipsychotic medications between 1 month before pregnancy to the end of the first trimester; nonexposure was defined as no purchase of antipsychotic medications from 3 months before pregnancy to the end of the first trimester. Prochlorperazine was excluded from the FGA group because it may have been prescribed for morning sickness, reducing the effectiveness of controlling for confounding by indication in the SGA vs FGA analyses.

Quetiapine was by far the most commonly used SGA (n = 2,618), followed by olanzapine (n = 413), risperidone (n = 242), aripiprazole (n = 220), and clozapine (n = 106). The authors excluded from analysis MCMs that were clearly due to known genetic disorders. There were 187 (5.4%), 60 (5.9%), and 978 (4.3%) MCMs in the SGA, FGA, and unexposed groups, respectively.

In analyses that adjusted for a large number of confounding variables, SGA exposure was not associated with increased odds of MCMs relative to either FGA exposure (OR, 0.82; 95% CI, 0.56–1.20) or no exposure (OR, 0.92; 95% CI, 0.72–1.19). In exploratory analyses, the study found that (only) olanzapine was associated with an increased risk, but only relative to unexposed pregnancies (OR, 2.12; 95% CI, 1.19–3.76); in further exploratory analyses, the risk appeared to be increased only for musculoskeletal malformations (OR, 3.71; 95% CI, 1.35–10.01). However, the nature of musculoskeletal malformations was diverse, not specific.

A strength of this study is that the number of exposed pregnancies was large. Another strength is that the study also included MCMs associated with termination of pregnancy. A limitation of the study is that the data were retrospectively ascertained and so, for example, there is no assurance that women who bought medications actually took them; if they did not, the findings of the study would be biased toward the null hypothesis. Another limitation is that confounds for adjustment in the final model were identified through univariate analyses; this 2-step procedure is frowned upon because it increases false positive discoveries and overfitting.

Data From a US Pregnancy Registry

Viguera et al[5] presented updated, prospectively collected data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics, established in 2008. The sample comprised women aged 18–45 years who were pregnant, who had a psychiatric disorder, and who were (exposed group) vs were not (comparison group) exposed to oral or long-acting SGAs during the first trimester of pregnancy. These women were interviewed by phone at the time of study enrollment, at 7 months of pregnancy, and at 3 months postpartum. Sociodemographic, clinical, and treatment data were collected during these interviews, as were data on potential confounding variables such as smoking, alcohol intake, and illicit drug use. Finally, data were collected about the pregnancy and its outcomes. In addition to data obtained through interviews, data were collected from medical records. MCMs that were identified were evaluated by a trained dysmorphologist who was blind to medication exposure.

The authors[5] reported results from 640 SGA-exposed infants and 704 comparison group infants. The mean age of the mothers was about 33 years. Mothers exposed to SGAs had a higher body mass index, were more likely to smoke, were overrepresented for bipolar disorder and underrepresented for major depression and anxiety, and were more likely to be taking anticonvulsants but less likely to use selective serotonin reuptake inhibitors.

Very few women in the sample (< 2%, overall) used FGAs. The most commonly used SGAs were quetiapine, aripiprazole, and lurasidone, in that order. Many women in both groups were also receiving treatment with antidepressants, anticonvulsants, and antianxiety medications.

The prevalence of MCMs was 2.50% in the SGA group and 1.99% in the comparison group; the crude odds ratio (OR) was 1.26 (95% CI, 0.61–2.61). In analyses that examined one confound at a time, none of nearly 2 dozen confounds were significantly associated with MCMs. In the final analyses that adjusted for 5 potential confounds, the OR was 1.48 (95% CI, 0.63–3.51); this analysis was perhaps limited because the variables for the final model were selected by a stepwise process and because there were only 30 MCMs in the entire sample, laying the model vulnerable to overfitting. No particular pattern of malformations was apparent in the MCMs in the 2 groups, though with 16 MCMs in the SGA group and 14 in the comparison group, the numbers were perhaps too small for patterns to be detected.

Strengths of the study were the prospective ascertainment of study-related data, including information about a range

of confounding variables; the inclusion of a similarly studied comparison group, also comprising patients with psychiatric disorders, that could reduce confounding by indication; and evaluation of the outcome data that was confirmed by medical records and by a dysmorphologist who was blinded to the exposure status of the patients. A further point, and one that is not usually discussed, is that most observational studies suffer from detection bias because infants of exposed pregnancies are more likely to be closely examined or studied for malformations. Detection bias was less likely to have occurred in this prospective study because all women had psychiatric illness. Limitations of the study were the inability to adjust for diagnosis and severity of illness, the marked underrepresentation (only 4.5%) of schizophrenia in the exposed group, and a sample that had too small a number of malformations to validly accommodate all relevant confounders in the regression model.

Specific Drugs Examined in Other Observational Studies

In a small study of women with psychiatric disorders who were (n = 152) vs were not (n = 205) exposed to quetiapine during the first trimester of pregnancy, the risk of MCMs was 1.3% vs 1.4% in exposed vs unexposed infants, respectively (OR, 0.90; 95% CI, 0.15–5.46).[7] In a slightly larger study from the same group, the risk was 4.29% vs 1.99% in infants with (n = 163) vs without (n = 690) first trimester exposure to aripiprazole. The crude OR was 2.21 (95% CI, 0.88–5.57) and the adjusted OR was 1.35 (95% CI, 0.43–4.20) in this study.[8] Exploratory analyses in other studies have associated olanzapine[4] and risperidone[6] with increased MCM risk.

Comments

It is reassuring that studies of first-trimester exposure to SGAs have so far not identified a clear or consistent risk of MCMs; in fact, because crude risks decreased after adjustment for confounding variables,[4] the evidence suggests that risks, if any, may be due to confounding by indication; that is, due to inadequately measured, unmeasured, and unknown confounds associated with the disorder for which the antipsychotics are prescribed. What is not clear, however, is whether individual SGAs are associated with increased MCM risk. For example, the large study of Huybrechts et al[6] identified an increased risk after first trimester exposure to risperidone, and the large study of Ellfolk et al[4] identified an increased risk after first trimester exposure to olanzapine, but neither study corrected for false positive discovery associated with multiple hypothesis testing, and neither study could rule out residual confounding. Furthermore, neither study confirmed the finding of the other study. These studies would additionally have been exposed to detection bias in exposed infants, to which reference was made in an earlier section. A final noteworthy point is that dosing effects have not been studied.

Concluding Notes

Antipsychotic drugs are used on or off label in monotherapy or as augmentation therapy to treat schizophrenia, mania, major depression, and obsessive-compulsive disorder; they are also but less frequently used to treat anxiety, insomnia, and tic disorders. SGAs may be favored over mood stabilizers (especially valproate) in women because of the risk of MCMs and other adverse outcomes associated with mood stabilizers. In most of the conditions in which SGAs are used, discontinuation of treatment is associated with a high risk of relapse and with a high risk of consequent impairment in multiple domains of mental and physical health and family, social, and occupational functioning. The substantial benefits of necessary initiation or continuation of antipsychotic drugs (especially the SGAs) during pregnancy must therefore be weighed against the small gestational risks, discussed in this article and in another article in this column,[1] that are more likely to be due to confounding by indication than to the drugs themselves. Decision-making should however be shared between the patient and her family, on the one hand, and the treating team, on the other. The process is unlikely to be easy.[9,10]

Published online: October 5, 2021.

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