Clinical and Practical **Psychopharmacology**

Gestational and Neurodevelopmental Outcomes Associated With Antipsychotic Drug Exposure 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

Exposure to psychotropic drugs during pregnancy may adversely affect gestational and neurodevelopmental outcomes in many different ways. Much literature on the subject exists for antidepressant drug exposure. In contrast, the literature on antipsychotic drug exposure during pregnancy is relatively thin; this is a situation in which the underlying psychiatric disorder, the context of use, and the associated risks must all be understood. In this context, a large (n = 411,251 mother-child pairs), population-based, retrospective observational cohort study with 8–10 years of follow-up examined pregnancy (preterm birth, small for gestational age) and neurodevelopmental (attention-deficit/hyperactivity disorder [ADHD], autism spectrum disorder [ASD]) outcomes after gestational exposure to antipsychotic medications. The study found that, when exposed vs unexposed pregnancies were compared, gestational exposure to antipsychotics was associated with a small but significantly increased risk of preterm birth; there was no significant increase in the risk of small for gestational age, ADHD, or ASD. When pregnancies with gestational vs (only) pregestational (pre-pregnancy) exposure to antipsychotics were compared, and when exposed vs unexposed siblings were compared, gestational antipsychotic exposure was not associated with a significantly increased risk of any of these adverse outcomes. Pregnancies with only pregestational exposure were associated with all of the adverse outcomes (except ASD) relative to pregnancies in women with no antipsychotic exposure at any time. In antipsychotic-unexposed pregnancies, mothers with psychiatric disorders were more likely to have children with ADHD or ASD (but not preterm birth or small for gestational age) relative to mothers without psychiatric disorders. The findings of the study appear reassuring. However, there are many concerns about the study, some of which are potentially serious. The findings of the study should therefore be interpreted with caution, and decisions about antipsychotic use during pregnancy should continue to be made on a case-by-case basis, in consultation with the patient and her family. In most cases of women with major mental illness, the risk-benefit ratio is likely to favor continuation of antipsychotics during pregnancy.

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Exposure to psychotropic drugs during pregnancy may adversely affect gestational and neurodevelopmental outcomes; examples of possibilities are listed in Table 1. This subject has been extensively studied in the context of antidepressant drugs[1] but not as well for antipsychotic drugs. A recently published systematic review and meta-analysis of 6 observational studies that included 2,515,272 pregnancies found a small increase in the risk of congenital malformations associated with antipsychotic exposure during pregnancy; the risk, however, did not reach statistical significance (risk ratio, 1.23; 95% confidence interval [CI], 0.96–1.58).[2] Two very recent observational studies that were not included in this meta-analysis also suggested reproductive safety for antipsychotic drugs, except for a possible increase in malformation risk associated with olanzapine.[3,4]

Many observational studies have examined the risk of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) after gestational exposure to antidepressant drugs; these studies were discussed in earlier articles in this column and elsewhere.[1,5–7] In this context, Wang et al[8] described a large population-based, retrospective, observational cohort study of pregnancy (preterm birth, small for gestational age) and neurodevelopmental (ADHD, ASD) outcomes after gestational exposure to antipsychotic medications.

The Study by Wang et al[8]

In this study, data were extracted from electronic medical records for children born in Hong Kong during 2001–2015 with follow-up to 2019; children with gestational exposure to antidepressant drugs or lithium were excluded because these drugs have been associated with adverse pregnancy and neurodevelopmental outcomes in some studies. There were 333,749 mother-child pairs for the ADHD analyses, of whom 547 (0.16%) were recorded to have had antipsychotic exposure during pregnancy; and 411,251 pairs (706; 0.17% exposed) for the preterm birth, small for gestational age, and ASD analyses. In these cohorts, the mean age of the mothers was about 31.6 years at the time of delivery. The mean duration of follow-up was about 10.4 years for the ADHD analyses and 8.3 years for the ASD analyses. Readers may note that the ADHD cohort was not an independent cohort. Rather, it was a subset that was carved out of the ASD, preterm birth, and small for gestational age cohort. This subset comprised subjects for whom a longer duration of follow-up (at least 6 years) was available, to allow for a later diagnosis of ADHD.

Preterm birth was defined as birth with < 37 weeks of gestation, and small for gestational age was defined as a birth weight that was 2 standard deviations or more below

Table 1. Possible Adverse Gestational and Neurodevelopmental Outcomes Associated With Exposure to Psychotropic Medications Before or During Pregnancy[a]

1. Impaired fertility
2. Spontaneous or elective abortion
3. Metabolic complications, including excessive weight gain and gestational diabetes
4. Intrauterine growth retardation, small for gestational age, small head circumference
5. Preterm birth
6. Assisted/complicated delivery
7. Postpartum hemorrhage
8. Major or minor congenital malformations
9. Drug toxicity or drug withdrawal in the newborn associated with poor neonatal adaptation syndrome or neonatal seizures
10. Persistent pulmonary hypertension of the newborn
11. Neonatal hyperbilirubinemia
12. Intellectual disability, including low IQ or low scores in specific neurocognitive domains
13. Neurodevelopmental disorders, including autism spectrum disorder and attention-deficit/hyperactivity disorder

[a]This list is not exhaustive.

Table 2. Sets of Analyses Conducted in the Study by Wang et al[8]

1. *Main analysis, gestational exposure vs no gestational nonexposure*
   In this analysis, the authors compared outcomes[a] in pregnancies that were vs were not exposed to antipsychotic drugs.
2. *Gestational exposure vs past exposure*
   In this analysis, the authors compared outcomes in pregnancies with gestational exposure vs pregnancies where women stopped antipsychotics when pregnant (classified as past exposure).
3. *Past exposure vs never exposed*
   In this analysis, the authors compared outcomes in pregnancies with past exposure (as defined above) vs pregnancies in women who were never exposed to antipsychotic drugs either before or during pregnancy.
4. *Never exposed with psychiatric disorders vs never exposed without psychiatric disorders*
   In this analysis, the authors compared pregnancy outcomes in women who had psychiatric disorders but who had never been exposed to antipsychotics vs women who did not have psychiatric disorders and had never been exposed to antipsychotics.In this context, psychiatric disorders were operationalized as *ICD-9-CM* codes of 290–319.
5. *Exposed vs unexposed sibs*
   In the sibling pair analyses, the authors compared pregnancy outcomes in sibs who had vs did not have gestational exposure to antipsychotic drugs.
6. *Subgroup, sensitivity, and other analyses*
   These analyses examined pregnancy outcomes separately after first- and second-generation antipsychotic exposure, in boys and girls, in pregnancies exposed to antipsychotics during different trimesters, etc.

[a]The outcomes studied were attention-deficit/hyperactivity disorder, autism spectrum disorder, preterm birth, and small for gestational age.

the population mean. ADHD and ASD were identified through *ICD-9* codes, though diagnoses were believed to have been made based on *DSM-5* criteria. ADHD was additionally identified through prescriptions for atomoxetine or methylphenidate. Exposed and unexposed groups, variously defined and composed (and hence overlapping, in many comparisons), were compared using Cox proportional hazard regression for the ADHD and ASD outcomes and using logistic regression for the preterm birth and small for gestational age outcomes. The groups being compared differed on a range of important confounding variables, and these were adjusted for using propensity score fine stratification weighting. The confounds included maternal age, socioeconomic status, infant sex, maternal medical and psychiatric illness, gestational and preexisting diabetes, and others.

The sample had 13,196 (3.95%) children with ADHD, 8,715 (2.12%) children with ASD, 33,891 (8.24%) children born preterm, and 7,009 (1.70%) children born small for gestational age. Many sets of analyses were conducted; these are detailed in Table 2.

Important findings from the study are presented in Table 3. In several of the unadjusted analyses, gestational exposure to antipsychotic drugs was significantly associated with many or all of the adverse outcomes. In adjusted analyses, however, most of the significant associations became nonsignificant.

In summary, in this observational, records-based study from Hong Kong, in the main analyses, when antipsychotic-exposed vs unexposed pregnancies were compared, gestational exposure to antipsychotic drugs was associated with a small (odds ratio, 1.40) but statistically significant increase in the risk of preterm birth; there was no significant increase in the risk of small for gestational age, or of ADHD or ASD across 8–10 years of follow-up. When pregnancies with gestational vs (only) pregestational (pre-pregnancy) exposure to antipsychotics were compared, and when exposed vs unexposed siblings were compared, gestational exposure to antipsychotics was not associated with a significant increase in the risk of any of these 4 adverse outcomes. Pregnancies with no gestational but only pregestational exposure were associated with all of the adverse outcomes (except ASD) relative to pregnancies in women who had never had antipsychotic exposure at any time. Mothers with psychiatric disorders were more likely to have children with ADHD or ASD (but not preterm birth or small for gestational age) relative to mothers without psychiatric disorders.

Interpretation of the Findings of the Study[8]

On the surface, the findings of the study are reassuring. Although no primary outcome was stated, and although no correction was made for type I (false-positive) statistical errors arising from multiple hypothesis testing, few analyses found significantly increased risks associated with gestational exposure to antipsychotic drugs. The discordant sibling pair analysis, which offered partial control for unmeasured and unknown genetic and shared environmental confounds, found that none of the 4 adverse outcomes studied were significantly associated with gestational antipsychotic exposure. In fact, it appeared that the risks of adverse outcomes were associated with the psychiatric illness rather than with antipsychotic drugs, as suggested by the findings of the current vs past exposure analyses and the analyses of the psychiatric vs no psychiatric disorders groups in never-exposed women.

The authors[8] wrote that their findings suggest that women who need antipsychotics should not stop their medication during pregnancy because of a fear of the adverse outcomes

Table 3. Important Findings From the Study by Wang et al[8]

1. In exposed vs unexposed cohorts, gestational exposure to antipsychotic drugs was associated with an increased risk of preterm birth (OR, 1.40; 95% CI, 1.13–1.75) but not of small for gestational age (OR, 1.36; 95% CI, 0.86–2.14), ADHD (HR, 1.16; 95% CI, 0.83–1.61) or ASD (HR, 1.06; 95% CI, 0.70–1.60).
   Interpretation: Gestational exposure to antipsychotic drugs was associated with an increased risk of preterm birth, but not of ADHD, ASD, or small for gestational age.
2. In pregnancies with current vs past exposure to antipsychotic drugs, gestational exposure to antipsychotic drugs was not associated with a significantly increased risk of ADHD (HR, 0.99; 95% CI, 0.60–1.61), ASD (HR, 1.10; 95% CI, 0.58–2.08), preterm birth (OR, 0.93; 95% CI, 0.70–1.24), or small for gestational age (OR, 1.21; 95% CI, 0.66–2.20).
   Interpretation: The risks of ADHD, ASD, preterm birth, and small for gestational age were not decreased in women who opted to stop antipsychotic drugs before pregnancy.
3. In pregnancies previously exposed vs never exposed to antipsychotic drugs, previous exposure was associated with an increased risk of ADHD (HR, 2.72; 95% CI, 2.16–3.44), preterm birth (OR, 1.47; 95% CI, 1.23–1.75), and small for gestational age (OR, 1.88; 95% CI, 1.36–2.59) but not ASD (HR, 1.35; 95% CI, 0.92–1.98).
   Interpretation: Women who needed antipsychotic drugs before pregnancy were at increased risk of ADHD (but not ASD) in offspring, and of preterm birth and small for gestational age, relative to women who never received antipsychotic drugs; this, despite stopping antipsychotics before pregnancy.
4. In women who had never been exposed to antipsychotic drugs, relative to pregnancies of women without psychiatric disorders, pregnancies of women with psychiatric disorders were associated with an increased risk of ADHD (HR, 2.08; 95% CI, 1.75–2.48) and ASD (HR, 1.97; 95% CI, 1.60–2.43) but not of preterm birth (OR, 1.08; 95% CI, 0.93–1.24) and small for gestational age (OR, 1.14; 95% CI, 0.85–1.53).
   Interpretation: Among women who had never received antipsychotic drugs, mothers with psychiatric disorders were more likely to have children with ADHD or ASD relative to mothers without psychiatric disorders. The risks of preterm birth and small for gestational age were not increased.
5. When comparing siblings who were vs were not exposed to antipsychotic drugs during pregnancy, gestational exposure to antipsychotic drugs was not associated with a significantly increased risk of ADHD (HR, 0.41; 95% CI, 0.04–4.93), ASD (HR, 0.90; 95% CI, 0.40–2.01), preterm birth (OR, 1.25; 95% CI, 0.85–1.82), and small for gestational age (OR, 0.86; 95% CI, 0.32–2.31).
   Interpretation: Siblings were at a similar risk of ADHD, ASD, preterm birth, and small for gestational age regardless of whether or not they had been exposed to antipsychotic drugs during pregnancy.
6. The findings were generally consistent in subgroup and sensitivity analyses, most of which showed that significant unfavorable outcomes disappeared in analyses that adjusted for confounding. Of special note, there were no differences in outcomes associated with first vs second generation antipsychotic exposure, but boys expectedly had higher risks of ADHD and ASD than girls.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CI = confidence interval; HR = hazard ratio; OR = odds ratio.

examined in the study. These reassurances notwithstanding, there are many concerns about the study, some of which are serious. These concerns are discussed in the sections that follow.

Concerns About the Study[8]

Although the study sample appeared large (411,251 mother-child pairs), only 706 mother-child pairs had gestational antipsychotic drug exposure, and in the sibling-pair analyses, only 215 of 85,257 children were exposed. These numbers are rather small for sweeping generalizations about the safety or risks associated with antipsychotic drug exposure during pregnancy. Contrast these numbers, for example, with the numbers reported by a single pregnancy registry which, by April 2020, could report on 889 women who were prospectively studied for the reproductive safety of second-generation antipsychotic drugs.[3]

In a related context, many of the secondary, subgroup, and sensitivity analyses were probably underpowered. Examples are the trimester-wise analyses, the analyses for first- and second-generation antipsychotics separately, the analyses for boys and girls separately, and others. The authors did not analyze data by diagnosis (eg, for schizophrenia and mood disorders, separately); whereas this analysis would have been informative for clinical practice, it would probably also have been underpowered.

The authors reported that 72% of the exposed mothers had psychiatric disorders. So why were the remaining 28% prescribed antipsychotics; for conditions such as insomnia, tic disorder, or hyperemesis gravidarum? This (28%) is a large proportion of women treated with antipsychotic drugs for supposed nonpsychiatric indications during pregnancy. An even more puzzling finding is that only 0.9% of unexposed mothers had psychiatric disorders. A possible explanation is that women receiving antidepressants or lithium were excluded from the sample; so, for example, women with more severe anxiety or depression (who used these drugs during pregnancy) would have been excluded. However, there should have been a large number of women with milder anxiety and depression, and women with other psychiatric disorders, because the authors defined psychiatric disorders as all disorders with *ICD-9-CM* codes of 290–319; that is, the entire range of mental disorders. If these curiosities in the percentages were errors in the medical records or in the data extraction, then errors could have been present elsewhere in the study findings, as well.

The analyses of pregnancies of never exposed women with vs without psychiatric disorders may have been misleading on 2 counts: the psychiatric disorders in these analyses would very probably have been very different from the psychiatric disorders for which antipsychotic drugs are prescribed; and these women may have been treated for their psychiatric disorders with medications other than antipsychotics, antidepressants, or lithium, for which analyses were unadjusted.

The authors did not provide information about individual antipsychotic drugs. Whereas analyses for individual drugs would almost certainly have been underpowered, it would have been helpful for readers to know at least which antipsychotic drugs had been commonly used in the exposed pregnancies, and in what doses they had been prescribed. The findings of the study would best generalize to these drugs and doses. The authors did, however, indicate that 405 pregnancies had been exposed to first-generation antipsychotics alone, and 199 to second-generation antipsychotics alone. Given that the use of first-generation antipsychotics is declining, it could be difficult to generalize the findings of the study to current practice.

The authors did not adjust their analyses for body mass index, smoking, alcohol intake, illicit substance use, adherence

to antipsychotic medication, and illness status during pregnancy. Certain of these (eg, active illness) could have biased the analyses toward worse outcomes, and certain of these (eg, poor medication adherence) could have biased the analyses toward the null hypothesis, exonerating antipsychotics from risk.

Although the authors adjusted for confounding to the extent possible, there is no way in which they could have adjusted for inadequately measured, unmeasured, and unknown confounds; some examples of these were listed in the previous paragraph. On the one hand, confounding by indication is likely to be associated with worse outcomes; this is because more severely ill women are more likely to continue medications during pregnancy, and greater severity of illness rather than medication use may predispose to adverse pregnancy outcomes. So, the absence of detection of unfavorable outcomes, despite incomplete adjustment for confounding, is reassuring. On the other hand, there could have been unmeasured confounds in the comparison groups that could have biased the findings toward the null hypothesis. For example, the women who discontinued antipsychotic treatment when pregnant (classified as past exposure) could have taken other psychotropic drugs or over the counter medications as medicinal substitutes that would help them better cope with illness-related symptoms during pregnancy. This concern also applies to the sibling-controlled analyses; the unexposed sibs could likewise have been exposed to other medications.

On a final note, coding for neurodevelopmental disorders in administrative databases may miss children who are affected but not diagnosed.

The Elephants in the Room

Women who "used antipsychotics before pregnancy but . . . discontinued receipt of treatment when pregnant"[8] were classified as "past exposure"; additionally, these women may have been included under "gestationally unexposed" because there was overlap across comparison groups. Such classification is debatable because discontinuation of antipsychotic treatment only when pregnancy was discovered implies that there was some antipsychotic exposure during early pregnancy. Therefore, all analyses that included (as controls) women so classified would be biased toward the null hypotheses that suggest an absence of risk associated with gestational antipsychotic exposure. An additional problem is that such women may have taken other psychotropic drugs, or over-the-counter medications, to cope with illness symptoms during pregnancy. If treatments with unknown safety were used during pregnancy, this would also bias the results toward the null hypothesis.

The authors adjusted for gestational diabetes, recorded in 19.2% vs 11.5% of exposed vs unexposed pregnancies. On the surface, this appears to be important and necessary because gestational diabetes has been associated with adverse pregnancy outcomes, and particularly because gestational diabetes is associated with large for gestational age, which may mask the ability of the study analyses to detect an antipsychotic exposure effect on small for gestational age.[9] However, antipsychotic drug exposure during pregnancy increases the risk of gestational diabetes,[10] and gestational diabetes has also been associated with neurodevelopmental disorder[11]; so, to adjust for gestational diabetes would remove a mechanism by which gestational antipsychotic exposure might affect neurodevelopment. This would bias the results of the analyses toward the null hypothesis.

Take-Home Message

What can we conclude? On the one hand, the findings of this study[8] were largely reassuring: unfavorable gestational and neurodevelopmental outcomes were associated with psychiatric disorders rather than with antipsychotic drug exposure during pregnancy. On the other hand, because of the many shortcomings in the analyses, risks associated with gestational antipsychotic exposure cannot be ruled out. The findings of the study should therefore be interpreted with caution and decisions should be made on a case-by-case basis, in consultation with the patient and her family. If antipsychotic medications are stopped, there is a high risk of relapse into major mental illness with potentially serious consequences for mental and physical health and functioning in family, social, and other domains. If antipsychotic medications are continued during pregnancy, there is a small theoretical risk of adverse gestational and neurodevelopmental consequences. The decision to stop or continue is not easy.[12]

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