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Gestational Exposure to Antidepressants and Neurodevelopmental Disorders in Offspring

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Abstract

Untreated depression may adversely affect pregnancy and offspring outcomes through several mechanisms; on the flip side, antidepressants used to treat depression may cross the placenta and affect the developing fetus and its brain. This article examines the research literature on gestational exposure to antidepressants and the risk of neurodevelopmental disorders (NDDs) in offspring. Two recent meta-analyses and 3 subsequently published observational studies, including 1 Asian study, are reviewed with especial focus on autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Despite limitations of the literature, some conclusions can reasonably be drawn. In unadjusted analyses, which assist an understanding of real world risks, gestational exposure to antidepressant drugs is associated with an up to doubled risk of ASD and ADHD. However, in adjusted analyses, which assist an understanding of cause-effect relationships but not real world risks, the risks substantially attenuate and may lose statistical significance. The risks also lose statistical significance in analyses that address confounding by indication by comparing antidepressant-exposed and -unexposed pregnancies in women with psychiatric disorders. The likelihood of confounding by parental genes, parental environment, and parental health-related variables is suggested by findings that antidepressants remain significantly associated with NDDs when the exposure period is outside the pregnancy window (such as before or after but not during pregnancy) or when fathers are exposed to antidepressants during pregnancy. Finally, discordant sibling pair analyses suggest that whether or not a child develops an NDD is related to whether or not its sib has an NDD rather than whether or not the child was exposed to an antidepressant in utero. Discussion points are suggested for the shared decision-making process when counseling women about NDD risks associated with gestational exposure to antidepressant drugs. Take-home messages are summarized.

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The safety of gestational exposure to psychotropic medication is a matter of importance. On the one hand, effective treatment of maternal major mental illness during pregnancy not only alleviates suffering but also attenuates the risk of harm to the pregnancy arising from illness-related risks (Box 1). On the other hand, most psychotropic medications cross the placenta and, in theory, may affect fetal health, including fetal neurodevelopment. Conducting randomized controlled trials (RCTs) during pregnancy could resolve uncertainty, but RCTs in pregnancy are ethically and logistically challenging. When RCTs are unavailable, inferences must necessarily be sought from observational studies.

This article examines studies on gestational exposure to antidepressant medication and the risk of neurodevelopmental disorders (NDDs) in offspring. Five studies are selected for review with especial focus on the most studied outcomes, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). The studies reviewed include 2 recent meta-analyses, 2 observational studies that appeared after the publication of the meta-analyses, and 1 very recent observational study that is the first to be conducted in an Asian sample. This article updates earlier articles in this column.[1,2]

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.

Read the Column

Box 1.

Depression and State-Dependent Factors That May Adversely Affect Pregnancy Outcomes[a]

Depression is associated with many behaviors that can adversely affect gestational and offspring outcomes:

- Poor adherence to medical guidance during pregnancy
- Poor dietary habits, resulting in impaired nutritional status or unhealthy metabolic changes
- Smoking, drinking, and substance use
- Self-neglect and its consequences, including an increased risk of infections
- Self-harm

Depression is associated with physiological changes that can adversely affect gestational and offspring outcomes[b]:

- Neurohormonal changes
- Neuroinflammatory changes
- Changes in the gut microbiome

[a]This list is not exhaustive.

[b]Some of these changes may be a result of depression-related behaviors.

Prelude

In order to provide the reader with a general summary of the literature review and the accompanying discussions, take-home messages and counseling points are provided in Boxes 2 and 3, respectively. Readers might find it useful to peruse the contents of these boxes now, and again after reading this article.

Meta-Analysis: Antidepressants and ASD[3]

Vega et al[3] described a systematic review and meta-analysis of the risk of ASD in offspring following gestational exposure to antidepressant drugs. Their study is important because they conducted additional analyses to indirectly address confounding by indication and confounding by genetic and environmental risk factors.

Their search identified 8 cohort and 6 case-control studies. Important findings, extracted only from forest plots that did not combine data from cohort and case-control studies,[4] are presented in Table 1. The findings and the implications thereof are summarized in Box 4.

Meta-Analysis: Antidepressants, ASD, and ADHD[5]

Leshem et al[5] described a systematic review and meta-analysis of the risk of ASD and ADHD in offspring following gestational exposure to antidepressant drugs. Their study is important because it included 2 studies that Vega et al[3] did not, because it also presented data on ADHD outcomes, and because it presented an analysis that indirectly addressed confounding by maternal risk factors.

There were 16 datasets from 15 studies in the ASD analysis and 8 datasets from 6 studies for the ADHD analysis. Important findings from the meta-analysis are presented in Table 2.

Box 2.

Gestational Exposure to Antidepressant Drugs and Risk of Neurodevelopmental Disorders in Offspring: Overall Impressions[a]

There is strong and almost incontrovertible evidence from unadjusted analyses that gestational exposure to antidepressant drugs is associated with a statistically significant increased risk of ASD and ADHD in offspring. The point estimates suggest that the crude risks are increased by about 50%–100%. That is, at the most, the risks are doubled. Results from unadjusted analyses are important because they indicate what may be seen in the real world. Results from unadjusted analyses *do not have cause-effect implications*.
There is strong evidence that, when analyses are adjusted for covariates and confounds, gestational exposure to antidepressant drugs is associated with an attenuated risk of ASD and ADHD. The point estimates indicate risks that are increased by less than 50% and, in fully adjusted analyses, mostly by much less than 50%. In fact, in many studies the attenuation results in the association losing statistical significance. The adjusted risks do not reflect real world risks; rather, they merely contribute by an unknown extent to causal inference. This is because, in studies in which risks remain significantly increased, residual confounding from illness-related risk factors, genetic risk factors, and familial environmental risk factors remains an important consideration.
The likelihood of confounding by indication cannot be ignored. This conclusion emerges from findings that the association between gestational exposure to antidepressant drugs on the one hand and ASD and ADHD in offspring, on the other, is no longer statistically significant when the comparison group comprises women with psychiatric disorders rather than women from the general population.
The likelihood of confounding by maternal health, maternal genetic, and maternal environmental characteristics cannot be ignored. This conclusion emerges from findings that the association between maternal exposure to antidepressant drugs on the one hand and ASD and ADHD in offspring, on the other, is statistically significant when the exposure period is outside the pregnancy window. Examples are of maternal antidepressant exposure before or after pregnancy but not during pregnancy.
The likelihood of confounding by paternal genetic and family environmental characteristics cannot be ignored. This conclusion emerges from the finding that the association between exposure to antidepressant drugs on the one hand and ASD and ADHD in offspring, on the other, is statistically significant when the father, rather than the mother, uses antidepressants during the pregnancy window.
The likelihood of confounding from maternal and/or paternal genetic and family environmental characteristics cannot be ignored. This conclusion emerges from consistent findings in discordant sibling pair analyses that gestational exposure to antidepressant drugs, among siblings, is not associated with neurodevelopmental disorder risks.

[a]Most of the data address ASD and ADHD, but some studies examined specific learning disorders, intellectual disability, and other developmental delays, as well. The impressions for these disorders are consistent with the impressions stated for ASD and ADHD.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder.

In summary, gestational exposure to antidepressant drugs was associated with a significantly increased risk of ASD as well as ADHD in offspring. However, pre-pregnancy exposure to antidepressants was also associated with an increased risk of both disorders. Because pre-pregnancy exposure does not result in *in utero* exposure, the finding implies that maternal characteristics (genes, environment, and psychiatric illness) rather than antidepressant exposure were responsible for the NDD risk.

There are 2 potentially serious limitations of this meta-analysis.[5] One is that the authors pooled odds

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Box 3.

Points to Consider When Counseling Women About Neurodevelopmental Risks (in offspring) Associated With Gestational Exposure to Antidepressant Drugs

Untreated depression during pregnancy can compromise pregnancy and offspring outcomes through multiple mechanisms. So, a woman who does not wish to expose her pregnancy and fetus to antidepressants and who chooses to experience untreated depression, instead, will expose both pregnancy and fetus to depression-related risk factors (Box 1).

Neurodevelopmental disorder risks associated with gestational exposure to antidepressant drugs may not be a result of the antidepressant exposure. Rather, research findings suggest that at least part if not all of the risk may arise from maternal health characteristics, maternal and paternal genes, and risk factors in the family environment. So, labeling antidepressants as risk factors and avoiding their use when indicated during pregnancy may not serve the intended purpose.

The available research cannot and does not rule out a causal role for antidepressants. However, the adjusted risks, when statistically significant, are small. Given that neurodevelopmental disorders are multifactorial in etiopathogenesis, and given that many dozens of risk factors (some of which are common in the population) have been described for some neurodevelopmental disorders, it is reasonable to consider that removing gestational exposure to antidepressants as a risk factor might merely allow a fuller expression of other risk factors.

The unadjusted risks of neurodevelopmental disorders associated with gestational exposure to antidepressants can be used to estimate what to expect in real world settings, and to then guide post-pregnancy and early childhood health care planning. These risks do not indicate cause and effect.

Table 1.

Gestational Exposure to Antidepressant Drugs and Risk of ASD in Offspring[a]

1. Relative to unexposed controls, gestational exposure to antidepressant drugs was associated with a significantly increased risk of ASD (HR, 1.42; 95% CI, 1.18–1.70; 5 studies).
2. Relative to psychiatric controls, gestational exposure to antidepressant drugs was not associated with a significantly increased risk of ASD (HR, 1.14; 95% CI, 0.84–1.53; 3 studies).
3. In a discordant sibling pair analysis, gestational exposure to antidepressant drugs was not associated with a significantly increased risk of ASD (HR, 0.97; 95% CI, 0.68–1.37; 3 studies).
4. The findings were similar when analyses were restricted to SSRI exposure.
5. The findings were similar in analyses of all antidepressants and of SSRI antidepressants, separately, for any trimester exposure and for first-trimester exposure, separately.

[a]Findings from the meta-analysis by Vega et al.[3] HR values were pooled from the maximally adjusted values presented in individual studies.
Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, HR = hazard ratio, SSRI = selective serotonin reuptake inhibitor.

ratios (ORs) extracted from case-control studies with ORs extracted or computed from cohort studies; this is generally discouraged because ORs obtained from different study designs are conceptually different and possibly numerically different, as well.[4] The other is that the authors did not explain how or even whether they addressed overlapping control groups in forest plots that contained more than 1 dataset from the same study; this is problematic because of double counting of control subjects in the forest plots. The findings of this meta-analysis should therefore be interpreted with caution.

Box 4.

Summary and Implications of the Findings From the Meta-Analysis by Vega et al[3]

In fully adjusted analyses, gestational exposure to antidepressants in general (and to selective serotonin reuptake inhibitors, in particular) was associated with an increased risk of ASD in offspring.

The risk, however, was no longer statistically significant when confounding by indication was addressed; that is, when the comparison group comprised antidepressant-unexposed pregnancies in women with psychiatric illness.

The risk was also no longer statistically significant when confounding by shared genetic and shared environmental risk factors was addressed; that is, in discordant sibling pair analyses.

These findings suggest that the antidepressant-associated risk of ASD arises from confounding rather than from antidepressant exposure.

Abbreviation: ASD = autism spectrum disorder.

Table 2.

Gestational Exposure to Antidepressant Drugs and Risk of ASD and ADHD in Offspring[a]

1. Gestational exposure to antidepressants was associated with a significantly increased risk of ASD (OR, 1.42; 95% CI, 1.23–1.65; 16 datasets from 15 studies).
2. Gestational exposure to antidepressants was associated with a significantly increased risk of ADHD (OR, 1.26; 95% CI, 1.07–1.49; 8 datasets from 6 studies).
3. Gestational exposure to antidepressants *before* pregnancy was also associated with a significantly increased risk of both ASD (OR, 1.39; 95% CI, 1.24–1.56) and ADHD (OR, 1.63; 95% CI, 1.50–1.78).

[a]Findings from the meta-analysis by Leshem et al.[5] OR values were pooled from the adjusted values presented in individual studies.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, CI = confidence interval, OR = odds ratio.

Case-Control Study: Selective Serotonin Reuptake Inhibitors and NDDs[6]

Ames et al[6] described a case-control study of the association between ASD and developmental delays/disorders (DDs; intellectual disability included) on the one hand and gestational exposure to selective serotonin reuptake inhibitors (SSRIs), on the other. The data were drawn from the prospective Study to Explore Early Development, a multicenter study conducted in the US among children born during 2003–2011.

The sample comprised 1,367 children with ASD, 1750 children with DDs, and 1,671 randomly selected general population controls. Preconceptional (3 months before conception; not further defined) and gestational exposure to SSRIs (based on interviews with the mother) were compared between cases and controls in analyses that adjusted for maternal age, race, education, and smoking, and family income.

Important findings from the study are presented in Table 3 and are summarized in Box 5. Of note, in the population control analyses, the study found that, besides

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Table 3.

Preconceptional and Gestational Exposure to SSRIs in Children With Neurodevelopmental Disorders[a]

1.	Relative to population controls, children with ASD were more likely to have mothers diagnosed with 1 or more psychiatric disorders (untreated with SSRIs) during pregnancy. This finding was statistically significant for preconceptional exposure to maternal psychiatric disorder, exposure during each trimester, and exposure anytime during pregnancy. The adjusted ORs lay in the 1.50–1.96 range.
2.	Relative to population controls, children with ASD were more likely to have mothers diagnosed with 1 or more psychiatric disorders (treated with SSRIs) during pregnancy. This finding was statistically significant for preconceptional exposure to maternal psychiatric disorder plus SSRIs, exposure during each trimester, and exposure anytime during pregnancy. The adjusted ORs lay in the 1.98–2.18 range.
3.	In the subset of children with exposure to maternal psychiatric disorders during pregnancy, ASD (relative to population controls) was not significantly associated with exposure to SSRIs. This finding was true for preconceptional exposure, exposure during each trimester, and exposure anytime during pregnancy.
4.	Relative to population controls, children with DDs were more likely to have mothers diagnosed with 1 or more psychiatric disorders (untreated with SSRIs) during pregnancy. This finding was statistically significant for preconceptional exposure to maternal psychiatric disorder, exposure during each trimester, and exposure anytime during pregnancy. The adjusted ORs lay in the 1.28–1.50 range.
5.	Relative to population controls, children with DDs were more likely to have mothers diagnosed with 1 or more psychiatric disorders (treated with SSRIs) during pregnancy. This finding was statistically significant for preconceptional exposure to maternal psychiatric disorder, exposure during each trimester, and exposure anytime during pregnancy. The adjusted ORs lay in the 1.77–2.10 range.
6.	In the subset of children with exposure to maternal psychiatric disorders during pregnancy, DDs (relative to population controls) were not significantly associated with exposure to SSRIs. This finding was true for exposure during each trimester and exposure anytime during pregnancy. However, children with DDs were significantly more likely to have been *preconceptionally* exposed to maternal psychiatric disorder plus SSRIs than to maternal psychiatric disorder untreated with SSRIs (adjusted OR, 1.69; 95% CI, 1.21–2.35).

[a]Findings from the study by Ames et al.[6]
Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, DD = developmental delay/disorder (including intellectual disability), OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

Box 5.

Summary and Implications of the Findings From the Case-Control Study by Ames et al[6]

Gestational exposure to maternal psychiatric disorders untreated with SSRIs and gestational exposure to maternal psychiatric disorders treated with SSRIs were each associated with an increased risk of ASD as well as DDs in offspring.

Relative to gestational exposure to maternal psychiatric disorders untreated with SSRIs, gestational exposure to maternal psychiatric disorders treated with SSRIs was not associated with an increased risk of ASD or DDs in offspring.

These findings suggest that gestational exposure to maternal psychiatric disorders, rather than gestational exposure to SSRIs, is the risk factor for ASD and DDs in offspring.

Abbreviations: ASD = autism spectrum disorder, DD = developmental delay/disorder (including intellectual disability), SSRI = selective serotonin reuptake inhibitor.

gestational exposure, preconceptional exposure to SSRIs was also associated with an increased risk of both ASD and DDs. This seems to suggest that maternal risk factors (genes, environment, health) rather than gestational exposure to SSRIs were responsible for the significant association between prenatal SSRI exposure on the one hand and ASD and DDs, on the other. However, such a conclusion is best not drawn from the study because the authors did not indicate that the analyses of preconceptional and gestational exposure were conducted on non-overlapping samples. The sample sizes presented for these analyses suggested that, in fact, there was likely to have been overlap.

Cohort Study: Antidepressants and NDDs[7]

Suarez et al[7] described a retrospective cohort study of the association between gestational exposure to antidepressant drugs and NDDs in offspring. There were 2 cohorts, drawn from public and private insurance sectors in the US for the years 2000–2015. The pooled sample included 145,702 antidepressant-exposed and 3,032,745 unexposed pregnancies with exposure defined as at least 1 prescription for an antidepressant dispensed between week 19 of gestation and the date of delivery. This exposure window was selected to represent the period of synaptogenesis. Unexposed pregnancies were those in which no antidepressant was dispensed from 90 days before the last menstrual period to the end of pregnancy.

Analyses were conducted for each cohort separately and were adjusted for a wide range of maternal demographic, lifestyle, health, and other covariates and confounds. The findings from the 2 cohorts were pooled using fixed effect meta-analysis. Important findings from the study are presented in Table 4 and summarized in Box 6.

A disconcerting aspect of this study is that the prevalences of NDDs were so high as to cast serious doubt on what exactly was being diagnosed. In the two databases, the cumulative incidence of total NDDs, at age 12 years, was 47% vs 25% in antidepressant-exposed and unexposed offspring in one cohort, and 31% vs 15%, respectively, in the other cohort. The values were a staggering 33% vs 20% and 18% vs 10% for ADHD, but more credible at 4.1% vs 2.1% and 2.9% vs 1.6% for ASD. If diagnostic errors are comparable in exposed and unexposed groups, they may cancel out in statistics such as the hazard ratio. However, such an assumption is fraught with uncertainty, and so the findings of this study must therefore be cautiously interpreted.

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Table 4.

Gestational Exposure to Antidepressants and Neurodevelopmental Disorders in Offspring[a]

1. In crude (unadjusted) analyses, relative to unexposed controls, gestational exposure to antidepressants was associated with a significantly increased risk of ASD, ADHD, SLDs, developmental speech and language disorders, developmental coordination disorders, and ID. The HRs lay in the 1.32–2.02 range.
2. In adjusted analyses, gestational exposure to antidepressants was associated with a significantly increased risk of ADHD, developmental speech and language disorders, and developmental coordination disorders (HRs in the 1.12–1.20 range) but not of ASD, SLD, and ID.
3. When antidepressant-exposed pregnancies were compared with pregnancies in which antidepressants had been discontinued 31–90 days before the last menstrual period, gestational exposure to antidepressants was associated with a significantly increased risk of developmental speech and language disorders (HR, 1.13) and developmental coordination disorders (HR, 1.26) but not of ASD, ADHD, SLDs, and ID.
4. In discordant sibling pair analyses, gestational exposure to antidepressants was not associated with a significantly increased risk of any neurodevelopmental disorder, considered individually or together.
5. The risk of total neurodevelopmental disorders was significantly elevated in unadjusted, adjusted, and exposed vs discontinued analyses for fluoxetine, sertraline, citalopram, escitalopram, all SSRIs combined, all serotonin-norepinephrine reuptake inhibitors combined, and bupropion. For tricyclic antidepressants, the risk was elevated only in crude analysis. Discordant sibling pair analyses could not be performed for individual drugs and drug categories because of inadequate sample size.
6. The findings were generally consistent in a range of sensitivity analyses, including analyses conducted for exposures only in early pregnancy (up to week 19) and only in late pregnancy (week 19 to delivery).

[a]Findings from the study by Suarez et al.[7]

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, HR = hazard ratio, ID = intellectual disability, SLD = specific learning disorder, SSRI = selective serotonin reuptake inhibitor.

Box 6.

Summary and Implications of the Findings From the Retrospective Cohort Study by Suarez et al[7]

Gestational exposure to antidepressants was associated with a small to modestly increased risk of ASD, ADHD, SLDs, developmental speech and language disorders, developmental coordination disorders, and ID.
Many of these associations were no longer statistically significant in adjusted analyses. Where associations remained statistically significant, the HRs were very low (1.20 and lower).
When exposed pregnancies were compared with pregnancies in which antidepressants had been discontinued before pregnancy, almost all of the associations were no longer statistically significant. This suggests that maternal characteristics (genetic, environmental, and health-related risk factors), rather than an exposure to antidepressants, may have been responsible for the neurodevelopmental disorder risk.
In discordant sibling pair analyses, no association was statistically significant. This suggests that shared genetic and environmental risk factors, rather than antidepressant exposure that is not shared, may have been responsible for the neurodevelopmental disorder risk.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, HR = hazard ratio, ID = intellectual disability, SLD = specific learning disorder.

Cohort Study: Antidepressants, ASD, and ADHD[8]

Lee et al[8] described the first Asian study in the field. Using linked registers in Taiwan, they identified all liveborn children (n = 2,301,396) during 2014–2016 and examined neurodevelopmental outcomes across an unstated duration of follow-up.

Gestational exposure to antidepressants, based on drug dispensation, was classified into prepregnancy exposure (90–270 days before conception), first-trimester exposure (0–90 days before conception plus days 0–90 of pregnancy), second-trimester exposure (days 91–180 plus days 0–90), third-trimester exposure (days 181–270 plus days 91–180), and postpregnancy exposure (days 0–180 after delivery). The extra 90 days before each trimester were included in the trimester's exposure window because prescriptions might have been issued for a 90-day supply, and because the supply would enter the trimester window even if dispensation occurred during the previous 90 days. As a result, there was considerable overlap in the samples in the analyses for each exposure classification.

Antidepressant-unexposed status was defined as no antidepressant dispensation from 270 days before pregnancy to 180 days after pregnancy. ASD and ADHD diagnoses were based on *ICD-9* and *ICD-10*, and required a record of at least 1 inpatient or at least 3 outpatient diagnoses. Analyses were adjusted for a very limited range of covariates that included parental age and parental history of bipolar disorder and schizophrenia.

There were 55,707 exposed offspring and 2,245,689 unexposed offspring. ASD was recorded in 1.5% vs 1.0% of exposed vs unexposed offspring, and ADHD in 5.9% vs 4.0%. Important findings from the study are presented in Table 5 and are summarized in Box 7.

A point of interest in this study is that no association lost statistical significance in adjusted analyses; this is likely to be because of the very limited number of covariates included in the adjusted models. A point of concern is that the authors did not clarify whether the definition of pre-pregnancy and post-pregnancy exposure excluded gestational exposure; however, the discordant sibling pair analyses would continue to support the implications stated in Box 7. Another point of concern is that maternal exposure to antidepressants was not included as a covariate in the paternal exposure analyses. The reassuring findings of this study should therefore be viewed with caution.

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Table 5.

Gestational Exposure to Antidepressant Drugs and Risk of ASD and ADHD in Offspring[a]

1. In each of the 3 trimesters of pregnancy, gestational exposure to antidepressant drugs was associated with a significantly increased risk of ASD. The unadjusted HRs lay in the 1.64–1.98 range, and the adjusted HRs, in the 1.35–1.46 range.
2. In each of the 3 trimesters of pregnancy, gestational exposure to antidepressant drugs was associated with a significantly increased risk of ADHD. The unadjusted HRs lay in the 1.62–1.92 range, and the adjusted HRs, in the 1.43–1.49 range.
3. Pre-pregnancy exposure to antidepressant drugs (during days 90–270 before conception) was associated with a significantly increased risk of ASD in both unadjusted (HR, 1.78) and adjusted (HR, 1.56) analyses.
4. Pre-pregnancy exposure to antidepressant drugs (during days 90–270 before conception) was associated with a significantly increased risk of ADHD in both unadjusted (HR, 1.61) and adjusted (HR, 1.46) analyses.
5. Post-pregnancy exposure to antidepressant drugs (during days 0–180 after delivery) was associated with a significantly increased risk of ASD in both unadjusted (HR, 1.61) and adjusted (HR, 1.46) analyses.
6. Post-pregnancy exposure to antidepressant drugs (during days 0–180 after delivery) was associated with a significantly increased risk of ADHD in both unadjusted (HR, 1.53) and adjusted (HR, 1.39) analyses.
7. In discordant sibling pair analyses, in no trimester of pregnancy, nor in pre-pregnancy and post-pregnancy analyses, was exposure to antidepressant drugs associated with an increased risk of either ASD or ADHD.
8. Paternal antidepressant exposure was associated with a significantly increased risk of ASD and ADHD during each of the 3 trimesters of pregnancy; the HRs lay in the 1.37–1.51 range. However, in discordant sibling pair analyses, all associations were not statistically significant.
9. The findings were consistent in subgroup analyses of SSRIs and other antidepressants, separately. The findings were consistent in sensitivity analyses that varied the exposure window definitions.
10. A negative control analysis found that gestational exposure to leukotriene receptor antagonists was not associated with ASD or ADHD in offspring.

[a]Findings from the study by Lee et al.[8]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, HR = hazard ratio, SSRI = selective serotonin reuptake inhibitor.

Box 7.

Summary and Implications of the Findings From the Retrospective Cohort Study by Lee et al[8]

Regardless of trimester of exposure, gestational exposure to antidepressant drugs was associated with an increased risk of both ASD and ADHD in both unadjusted and adjusted analyses.
Paternal exposure, maternal pre-pregnancy exposure, and maternal post-pregnancy exposure to antidepressant drugs were each associated with an increased risk of both ASD and ADHD in both unadjusted and adjusted analyses. Only in post-pregnancy maternal exposure might the offspring also be antidepressant-exposed, such as through breastfeeding; the quantum of exposure, however, is likely to be very small with most antidepressants.
The discordant sibling pair analyses suggested that whether or not a child develops ASD or ADHD depends on whether or not its sib has ASD, rather than on whether or not it was exposed to antidepressants in utero.
The findings of this study suggest that exposure to maternal and paternal characteristics (genes, environment, health), rather than exposure to antidepressants during the narrow window of pregnancy, may be responsible for the risk of ASD and ADHD in offspring.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder.

General Reflections

There are no perfect studies or meta-analyses in the field. Yet, if one tries to make sense of what one reads, conclusions may be drawn, though with varying degrees of certainty. These conclusions were summarized in Box 2.

Concluding Notes

This review is not exhaustive. Other studies have also reported that gestational exposure to antidepressants is not associated with an increased risk of NDDs in offspring.[9–11]

Points to consider when counseling women were presented in Box 3. The final decision about whether or not to use an antidepressant to treat depression during pregnancy should, of course, be based on a shared and documented decision-making process.

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