IMPORTANCE  Several studies have examined the links between prenatal exposure to antidepressants and autism spectrum disorders (ASDs) in children, with inconsistent results, especially regarding the impact of the trimester of exposure.

OBJECTIVE  To perform a systematic review of the literature and a meta-analysis of published studies to assess the association between ASDs and fetal exposure to antidepressants during pregnancy for each trimester of pregnancy and preconception.

DATA SOURCES  PubMed, EMBASE, and PsycINFO databases up to May 2016 were searched in June 2016 for observational studies. For the meta-analyses, data were analyzed on RevMan version 5.2 using a random-effect model. For the review, studies were included if they had been published and were cohort or case-control studies, and for the meta-analysis, studies were included if they were published studies and the data were not derived from the same cohorts.

STUDY SELECTION  We included all the studies that examined the association between ASDs and antenatal exposure to antidepressants.

DATA EXTRACTION AND SYNTHESIS  Three reviewers independently screened titles and abstracts, read full-text articles, and extracted data. The quality of the studies was also assessed.

MAIN OUTCOMES AND MEASURES  Primary outcome was the association between antidepressants during pregnancy and ASDs. Secondary outcomes were the associations between antidepressants in each individual trimester or before pregnancy and ASDs.

RESULTS  Our literature search identified 10 relevant studies with inconsistent results. For prenatal exposure, the meta-analysis on the 6 case-control studies (117,737 patients) evidenced a positive association between antidepressant exposure and ASDs (odds ratio [OR], 1.81; 95% CI, 1.49-2.20). The association was weaker when controlled for past maternal mental illness (OR, 1.52; 95% CI, 1.09-2.12). A similar pattern was found whatever the trimester of exposure considered (first trimester: OR, 2.09, 95% CI, 1.66-2.64; second: OR, 2.00, 95% CI, 1.55-2.59; and third: OR, 1.90, 95% CI, 1.20-3.02). Controlled for past maternal mental illness: first trimester: OR, 1.79; 95% CI, 1.27-2.52, second: OR, 1.67, 95% CI, 1.14-2.45; and third: OR, 1.54, 95% CI, 0.82-2.90). No association was found when the 2 cohort studies were pooled (772,331 patients) for the whole pregnancy (hazard ratio, 1.26; 95% CI, 0.91-1.74) or for the first trimester. In addition, preconception exposure to antidepressants was significantly associated with an increased risk for ASDs (OR controlled for past maternal illness, 1.77; 95% CI, 1.49-2.09).

CONCLUSIONS AND RELEVANCE  There is a significant association between increased ASD risk and maternal use of antidepressants during pregnancy; however, it appears to be more consistent during the preconception period than during each trimester. Maternal psychiatric disorders in treatment before pregnancy rather than antenatal exposure to antidepressants could have a major role in the risk for ASDs. Future studies should address the problem of this potential confounder.

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up to 15% of women have depression during pregnancy. Pregnant women with untreated depression are at increased risk for poor obstetric follow-up and complications, such as gestational diabetes, hypertension, and pre-eclampsia, and postnatal complications have been mainly reported. The impact on the child is also of concern, with a possible increased risk for premature birth and low birth weight. In addition, depression during pregnancy is the main predictor of postpartum depression, which is associated with possible serious impairment in mother-child bonding and child development, behavioral problems and poor scores on social engagement and emotional regulation. Thus, treatment for prenatal depression appears essential for clinicians, with regard to both the mother and the infant.

Antidepressants are the treatment choice for major depressive disorders in the general population. Whereas only 2% of pregnant women were treated with antidepressants in the United States in 1996, more than 5% were receiving treatment by 2013. The rate of exposure increased from 0.2% in 1997 to 3.2% in 2010 in Denmark. The most commonly prescribed drugs are selective serotonin reuptake inhibitors (SSRIs) known for their safety in the general population. Spontaneous abortions, congenital malformations (mainly cardiac defects), prematurity, and low birth weight have been linked to antenatal use of antidepressants. A protective role of SSRIs with respect to preterm birth and cesarean delivery has been also described. Neonatal adaptation syndrome and persistent pulmonary hypertension have also been reported, both being outweighed by the risks of untreated depression.

Animal in utero exposure to SSRIs has been found to induce long-lasting alterations in brain function and behavioral effects. The neurodevelopmental role of serotonin in the fetus has been established and the hypothesis of the role of serotonin in the onset of autism spectrum disorders (ASDs) remains an open question.

First described in 1943, ASDs were reported to affect 1.46% of American children aged 8 years in 2012. Autism spectrum disorders are currently considered a multifactorial disorder resulting from interactions between genetic and nongenetic risk factors. Genetic factors have been found in 10% to 20% of individuals with ASDs. The concordance rate is approximately 70% in monozygotic twins compared with 3% in dizygotic twins. Several genes are thought to be involved. Advanced parental age, maternal diabetes, abnormal melatonin synthesis, zinc deficiency, prenatal viral infection, prenatal and perinatal stress, environmental factors, valproate, and various chemicals have been reported as risk factors.

Morphological brain alterations, biomarkers of oxidative stress, mitochondrial and porphyrin metabolism dysfunctions, and epigenetic alterations have also been reported in ASD populations. In addition, blood and platelet serotonin levels are high in approximately one-third of patients with ASDs, suggesting the implication of serotonin in ASDs. Some authors have suggested that increased serotonergic activity during fetal brain development may play a part in the onset of ASDs.

Given the plausible links between in-utero serotonin dysregulations and ASDs, the question of the impact of antidepressant antenatal exposure on the occurrence of ASDs is crucial.

### Key Points

**Question** Does prenatal antidepressant exposure increase the risk for autism spectrum disorders?

**Findings** This systematic review and meta-analysis suggests an association between increased autism spectrum disorder risk and maternal use of antidepressants during pregnancy; however, it appears to be more consistent during the preconception period than during each trimester. The association was weaker when controlled for past maternal mental illness.

**Meaning** Maternal psychiatric disorders in treatment before pregnancy rather than antenatal exposure to antidepressants could have a major role in the risk for autism spectrum disorders.

Two recent meta-analyses reported a significant association between antenatal antidepressant exposure and ASDs. In addition, recent studies have explored the issue of the trimester of exposure, providing contradictory results.

We present here a systematic review of publications and an up-to-date meta-analysis of studies that have explored associations between fetal exposure to antidepressants and ASDs, focused first on the specific impact of trimester of exposure and second on associations between preconception maternal exposure to antidepressants and ASDs.

### Methods

#### Search Strategies

A systematic literature search was conducted in June 2016 using PubMed, EMBASE, and PsycINFO databases to search for articles published up to May 2016, using the combination of terms: antidepressant or antidepressants and pregnancy or fetal exposure and autism, including MeSH terms (whenever available) found below them in the MeSH hierarchy. References from articles retrieved were also considered. Three reviewers (F. Gressier, P.-A.L., and A.M.) conducted independent searches to identify potentially relevant articles.

#### Inclusion and Exclusion Criteria

For the review, studies were included if they (1) had been published and (2) were cohort or case-control studies that examined the association between fetal antidepressant exposure and ASDs. Articles were excluded if they were case or case series reports. The following information was extracted: first author, publication year, study design, data source, sample size, inclusion/exclusion criteria, potential confounders considered, potential sources of bias, and outcome parameters (hazard ratios [HRs] and odds ratios [ORs]) and their corresponding 95% CIs.

For the meta-analyses, studies were included if (1) they were published studies and (2) the data were not derived from the same cohorts. Studies were excluded if they comprised no control group.

#### Risk of Bias and Quality Assessment of the Studies

The quality of the studies included in the meta-analyses was independently evaluated by the 3 reviewers using the STROBE statement.
Data Analysis
Data were analyzed using the Cochrane Collaboration Review Manager Software (RevMan version 5.3). Both adjusted and nonadjusted results for maternal psychiatric disorders were considered. For each study, the log HR or OR and their SE were calculated on the basis of effect measures provided and their 95% CIs, and then entered into RevMan under the “generic inverse variance” outcome. A random-effect model, which takes into account between-study heterogeneity, if present, was used. Between-study heterogeneity was assessed using the $\chi^2$ test for fit and I². A funnel plot was produced to evidence any selective reporting—the preferential publication of statistically significant results—by plotting the natural logarithms of individual study effect sizes. Finally, we performed sensitivity analyses on the trimester of exposure and on preconception exposure.

Results
Articles Retrieved
The PubMed database yielded 95 records. No additional record was identified from other sources. In all, 12 references were excluded on the basis of the title and abstract. Twenty-three full-text articles were assessed for eligibility (Figure 1). Thirteen were excluded: 3 were literature reviews,36-38 2 were meta-analyses,31,32 7 were editorial letters or commentaries,18,39-44 and 1 analyzed autistic traits.45 Finally, 10 studies were included in the review: 3 were cohort studies18,46,47 and 7 case-control studies (Table 1).13,34,48-53 Three studies from Denmark and 2 from Sweden used the same databases.46,47,49,51,52 In addition, 2 from the United States used the same Partners HealthCare electronic health record over the same period14,48 but used independent data for a replication study.34 All studies explored prenatal antidepressant exposure, but Rai et al51 assessed only antidepressant exposure at the time of the first antenatal interview (median 10 weeks’ gestation). Antidepressant exposure was determined using the available regional prescription databases. Only 1 study50 included both the mother’s self-report and prenatal medical record information. Autism spectrum disorders were determined using the available regional disease registries. Details of the different studies are provided in the eTable in the Supplement and Table 1. The quality of the studies was high (Table 1).

Systematic Review
Boukhris et al33 reported an association between antidepressant exposure during the second and/or third trimester and ASDs. The association persisted after taking into account maternal history of depression. The risk was higher with combined treatments (≥2 antidepressant classes).

Results from the 3 studies on Danish population registries are contrasted.49,51,53 Hvid et al46 showed that ASDs were associated with antidepressant use 2 years to 6 months before pregnancy but not with use during pregnancy. In addition, this study also focused on the use of medication other than SSRIs during pregnancy: antipsychotic agents and mood stabilizer drugs were associated with ASDs. Autism spectrum disorders were also associated with maternal depression; schizophrenia and neurotic, stress-related, or somatoform disorders; adult personality or behavior disorders; eating disorders; and substance abuse, but they were not associated with maternal ASDs. Diagnoses were made in a psychiatric hospital or psychiatric unit.

Exploring the same registries, Sørensen et al47 found a significant association between prenatal antidepressant exposure and ASDs. However, this association did not remain significant when the analysis was restricted to the children of women with a diagnosis of affective disorder. These authors considered the mean dose of antidepressant, and both a low mean dose and a high mean dose increased the risk for ASDs (adjusted HR, 1.3; 95% CI, 1.0-1.8 and adjusted HR, 1.8; 95% CI, 1.3-2.4, respectively) compared with nonexposed patients. When the trimester of pregnancy was considered, exposure during the first trimester was significantly associated with ASDs, but not exposure during the second and third trimesters only.

Gidaya et al49 also performed an analysis on the same registries, but via a case-control study. They reported an association between ASDs and antidepressant exposure, during overall pregnancy and for each trimester, even after adjusting for history of maternal depression. However, SSRI use and the prevalence of depression were lower than reported in other Nordic countries. Assuming a prevalence of depression of 15%, the authors also estimated depression-stratified from simulation-based sensitivity analysis for nondifferential underreporting of SSRIs and depression in the register. The effect did not remain significant among mothers with depression (OR, 1.4; 95% CI, 0.9-2.4).

Croen et al53 showed that antidepressant exposure during pregnancy and in each trimester was associated with an increased risk for ASDs. In this study, no association was seen between ASDs and a history of maternal depression or any other mental health disorder.
### Table 1. Main Adjusted Results of the Included Studies per Trimester and Molecule

<table>
<thead>
<tr>
<th>Study</th>
<th>Antidepressants</th>
<th>Potential Confounders</th>
<th>Adjusted OR or HR (95% CI) Per Trimester</th>
<th>Per Molecule</th>
<th>STROBE Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boukhris et al., 2016</td>
<td>SSRIs, SNRIs, MAOIs, TCAs, others, and COMBI</td>
<td>The infant's sex, year of birth, maternal age at first day of gestation, marital status, education level, social benefit recipient status, maternal psychiatric disorders in the year before or during pregnancy, chronic or gestational diabetes, and chronic or gestational hypertension</td>
<td>First trimester: 0.84 (0.52-1.36)c; second and third trimesters: 1.87 (1.15-3.04)c,d; and second and third trimesters, only considering women with a history of depression: 1.75 (1.03-2.97)c,d</td>
<td>During second and third trimesters: SSRIs: 2.17 (1.20-3.93)c; MAO: NA, TCAs: 1.03 (0.23-4.61)c; others: NA; and COMBI: 4.39 (1.44-13.32)c</td>
<td>20</td>
</tr>
<tr>
<td>Hviid et al., 2013</td>
<td>Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram</td>
<td>Age, calendar period, maternal age, country of origin, place of residence, parity, psychiatric diagnoses before delivery, other drug use during pregnancy, smoking status, employment status, and educational level</td>
<td>Only before pregnancy: 1.46 (1.17-1.81)c; pregnancy: 1.20 (0.90-1.61)b; only during pregnancy: 1.40 (0.92-2.13)c; and first trimester: 1.35 (0.97-1.87)b</td>
<td>No data</td>
<td>16</td>
</tr>
<tr>
<td>Sørensen et al., 2013</td>
<td>SSRIs, SNRIs, and TCAs</td>
<td>Parental age at conception, parental psychiatric history except mother’s affective disorder, gestational age, birth weight, sex, and parity</td>
<td>First trimester: 1.5 (1.2-1.9)b,c; and second and third trimesters: 1.5 (0.8-2.7)b</td>
<td>Antidepressants: 1.5 (1.2-1.9)b,c; SSRIs: 1.6 (1.3-2.0)c,d; SNRIs: 1.7 (0.8-3.5)c; and TCAs: 1.5 (0.8-2.9).c; Statistical significance lost when only women with hospital-diagnosed affective disorders taken into account for antidepressants and SSRIs</td>
<td>19</td>
</tr>
<tr>
<td>Castro et al., 2016</td>
<td>No data</td>
<td>Sex, race/ethnicity, year of birth, maternal insurance, maternal income, maternal major depressive disorder, and proxies for severity of illness (number of psychopharmacological visits, psychotherapy visits, antidepressant in the previous year, and psychiatric disorders or comorbidity)</td>
<td>Prepregnancy: 1.54 (1.02-2.30)c;d; pregnancy: 0.90 (0.50-1.54)c,d; first trimester: 0.89 (0.40-1.78)c; second trimester: 1.11 (0.50-2.26)c; and third trimester: 0.85 (0.38-1.74)c</td>
<td>No data</td>
<td>19</td>
</tr>
<tr>
<td>Clements et al., 2015</td>
<td>Paroxetine, duloxetine, sertraline, citalopram, fluoxetine, citalopram, fluvoxamine, venlafaxine, nefazodone, bupropion, and mirtazapine</td>
<td>Sex, race/ethnicity, birth year, maternal insurance type, maternal age, and median income tertile + maternal major depressive disorder</td>
<td>Prepregnancy: 1.62 (1.17-2.23)c,d; pregnancy: 1.10 (0.70-1.70)c; first trimester: 1.43 (0.85-2.38)c; second trimester: 1.34 (0.77-2.72)c; and third trimester: 1.08 (0.61-1.88)d</td>
<td>No data</td>
<td>18</td>
</tr>
<tr>
<td>Gidaya et al., 2014</td>
<td>Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram</td>
<td>Parental age, child’s sex, history of maternal depression, other SSRI indications, and child’s date of birth (month and year)</td>
<td>Preconception: 1.8 (1.4-2.3)c,d; pregnancy: 1.8 (1.4-2.3)c,d; first and second trimester: 2.0 (1.5-2.6)c,d; and second and third trimester: 2.1 (1.5-3.0)c,d; and third trimester: 2.5 (1.7-3.7)c,d</td>
<td>No data</td>
<td>17</td>
</tr>
<tr>
<td>Harrington et al., 2014</td>
<td>Fluoxetine, paroxetine, sertraline, citalopram, and escitalopram</td>
<td>Center of birth, year of birth, and mother’s birthplace</td>
<td>Pregnancy: 1.55 (0.59-4.08)c,d; first trimester: 1.38 (0.48-4.01)c,d; second trimester: 0.89 (0.24-1.24)c; and third trimester: 1.18 (0.35-4.02).d Still no significance when restricted to anxiety/mood disorder subset</td>
<td>No data</td>
<td>17</td>
</tr>
<tr>
<td>Rai et al., 2013</td>
<td>Fluoxetine, citalopram, paroxetine, sertraline, and NSMRIs</td>
<td>Mother’s age, maternal psychiatric disorder, paternal age, parental income, education, occupation, mother’s birth country, and birth parity</td>
<td>No data</td>
<td>Antidepressants: 1.90 (1.15-3.14)c,d; SSRIs: 1.65 (0.9-3.03)c,d; SNRIs: 2.69 (1.04-6.96)c,d; and maternal depression without antidepressants: 1.49 (1.08-2.08).d</td>
<td>20</td>
</tr>
<tr>
<td>Eriksson et al., 2012</td>
<td>SSRIs</td>
<td>Age, race/ethnicity, maternal education, birth weight, sex, child’s year of birth, and place of birth</td>
<td>Only SSRIs: preconception: 2.3 (1.5-2.6)c,d; first trimester: 4.1 (1.7-9.8)c,d; second trimester: 1.8 (0.5-6.3)c,d; and third trimester: 2.4 (0.7-8.0)c</td>
<td>No data</td>
<td>12</td>
</tr>
<tr>
<td>Croen et al., 2011</td>
<td>Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, nefazodone, trazodone, venlafaxine, and TCAs</td>
<td>Age, race/ethnicity, maternal education, birth weight, sex, child’s year of birth, and place of birth</td>
<td>Only TCAs: preconception: 2.0 (1.2-3.6)c,d; first trimester: 2.0 (1.2-3.6)c,d; and second trimester: 2.6 (1.3-5.4)c,d; and TCAs: 1.6 (0.9-4.5)c</td>
<td>No data</td>
<td>17</td>
</tr>
</tbody>
</table>

**Abbreviations:** COMBI, combination (≥2 antidepressants); HR, hazard ratio; MAOIs, monoamine oxidase inhibitors; NA, not applicable; NSMRIs, nonselective monoamine reuptake inhibitors; OR, odds ratio; SSRIs, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TCAs, tricyclic antidepressants.

*Adjusted on maternal characteristics, potential confounders, and maternal illness if the data were available.

¹HR (95% CI).

²Statistically significant results.

³OR (95% CI).

Rai et al. showed that a history of maternal depression was associated with an increased risk for ASDs (adjusted OR, 1.49; 95% CI, 1.08-2.08). In their subsample with available data on drugs, the association was confined to women reporting...
antidepressant use at the time of the first antenatal interview (median 10 weeks’ gestation) (OR, 3.34; 95% CI, 1.50-7.47). A similar pattern was reported for SSRIs and nonselective monoamine reuptake inhibitors. This association was stronger in cases of autism without intellectual disability. Further, prenatal antidepressant use for psychiatric indications other than depression was not statistically associated with ASDs in offspring. So, the significant association could therefore be due to depression requiring antidepressants rather than to antidepressant exposure. A previous study using the same database reported that antidepressants and the use of other psychoactive drugs (neuroleptics, sedatives, and sleep-inducing medications) during pregnancy in mothers of children with ASDs were more common than among the mothers of control participants (OR, 4.5; 95% CI, 2.19-9.05; P < .001 and OR, 4.4; 95% CI, 2.5-8.0; P = .003, respectively).

Harrington et al reported a highest prevalence of prenatal SSRI exposure in ASDs (5.9%) than in typical development children (3.4%), but with no statistically significant difference. Among boys, prenatal SSRI exposure was associated with ASDs, the strongest association occurring with first-trimester exposure. Findings were similar among mothers with an anxiety or mood disorder history.

Clements et al included a large number of children with ASDs (1377 aged 2 to 19 years matched with 4022 control children). In models adjusted for sociodemographic features, antidepressant exposure during both the first and second trimesters were associated with a higher risk for ASDs, but this association was no longer significant when each trimester was considered and after controlling for history of maternal depression (from electronic medical records). These results suggest that the risk for ASDs observed with prenatal antidepressant exposure is likely to be confounded by the severity of maternal mental illness. Finally, antipsychotic prescription during pregnancy was independently associated with a greater risk for ASDs than antidepressant prescription.

In a replication study, 1245 children with ASDs (aged 2 to 19 years) were matched with 4022 control children. In models adjusted for sociodemographic factors, antidepressant exposure during both the first and second trimesters were associated with a higher risk for ASDs, but this association was no longer significant when each trimester was considered and after controlling for history of maternal depression (from electronic medical records). These results suggest that the risk for ASDs observed with prenatal antidepressant exposure is likely to be confounded by the severity of maternal mental illness. Finally, antipsychotic prescription during pregnancy was independently associated with a greater risk for ASDs than antidepressant prescription.

Regarding antidepressant exposure and the different trimesters, 8 studies analyzed exposure in each trimester and 1 in the first trimester only. For the first trimester, 4 of 9 studies (1 cohort study47 and 3 case-control studies49,51,53) reported an association (adjusted ORs or HRs, even after adjustment for past psychiatric disorders, all studies except that of Sørensen et al49). For the second and third trimesters, 2 of 8 studies (1 cohort study that analyzed the second and third trimesters together33 and 1 case-control study49) reported a significant association, even after adjusting for history of maternal depression. The data analysis of trimester exposure for each class of antidepressant is presented in Table 1, showing contrasted results.

Five studies searched for an association between antidepressant exposure before pregnancy and ASDs, All reported a significant association.

No strong association between prenatal antidepressant exposure during pregnancy and ASDs was found in this review. The association between antidepressants and ASDs appears to be more consistent during the preconception period than during each trimester. Therefore, maternal psychiatric disorders in treatment before pregnancy rather than prenatal antidepressant exposure could have a major role in the onset of ASDs.

Meta-analysis
A summary of all the meta-analyses performed is provided in Table 2. For exposure during pregnancy, the meta-analysis on the 6 case-control studies (117 737 patients)44,48-51,53 showed significant associations between antidepressant exposure and ASDs (OR, 1.81; 95% CI, 1.49-2.20; I² = 11%) (Figure 2). The ORs decreased but remained significant when maternal history was taken into account (OR, 1.52; 95% CI, 1.09-2.12; I² = 61%). No association was found when the 2 cohort studies were pooled (72331 patients: HR, 1.26; 95% CI, 0.91-1.74; I² = 67%).

The meta-analysis on the association between first-trimester exposure and ASDs (6 studies included44,48-51,53) showed an OR of 2.09 (95% CI, 1.66-2.64; I² = 17%) (eFigure 1 in the Supplement). The association was weaker when ORs also adjusted for past psychiatric disorders were considered (OR, 1.79; 95% CI, 1.27-2.52; I² = 55%). No significant result was found for the pooled results of the 2 cohort studies. Similar results were observed for the meta-analysis on antidepressant exposure during the second trimester (5 studies included44,48-50,53; eFigure 2 in the Supplement). Regarding the meta-analysis on the exposure during the third trimester (5 studies included44,48-50,53), a significant association was found, but it did not remain significant when ORs adjusted for past depression were included, with heterogeneity across the study results (I² = 73%) (eFigure 3 in the Supplement).

Four studies were included in the meta-analyses on preconception exposure44,48,49,53 (eFigure 4 in the Supplement). Both reported a significant association (OR, 1.96; 95% CI, 1.65-2.32 and adjusting for past depression, OR, 1.77; 95% CI, 1.49-2.09, with no heterogeneity between studies (I² = 0%). A meta-analysis on results for the whole pregnancy including the same 4 studies showed the following: OR, 1.71; 95% CI, 1.30-2.24; I² = 36% and OR, 1.44; 95% CI, 0.94-2.19; I² = 69%, respectively (data not shown).

Discussion
Results from recent studies have suggested an increased risk for ASDs in children exposed to antidepressants in utero.
These results have been widely reported by the media as a causal link underpinning incentives to discontinue antidepressants during pregnancy. A number of letters has been published in an attempt to address and mitigate this misinterpretation and especially to draw attention to the potentially harmful effects of discontinuing antidepressants in pregnant women. Indeed, inadequately treated prenatal depression can lead to adverse obstetrical and developmental issues, bearing also in mind the risk for maternal suicide. Nevertheless, clinicians are increasingly faced with the question...
of prescriptions to women wishing to quit their treatment during the perinatal period.

Based on our meta-analyses, there is a significant association between ASDs and prenatal maternal use of antidepressants. However, it appears to be more consistent during preconception than each trimester. The association was weaker when controlled for past maternal mental illness. It is also interesting to note that the study with the highest weight reported results that contrasted with those of other studies on the same population. Furthermore, when the results of the 2 cohort studies were pooled, no association was found. Two meta-analyses on SSRI prenatal exposure and ASDs published recently underlined the role of maternal psychiatric condition as a major confounding factor.

The public health implications of the possible risk for ASDs as a result of antidepressant exposure during pregnancy are difficult to assert or to refute, especially as we also observed an association with preconception exposure. The increased risk for ASDs in children exposed in utero could well be related to maternal depression or other psychiatric disorders rather than to antidepressant medications per se.

Limitations

Nevertheless, this review has some major limitations: (1) the small number of eligible studies in the literature; (2) the conflicting results of some studies, evidenced by marked heterogeneity in the meta-analysis on the adjustment for maternal history; and (3) the possibility of a publication bias. Some studies may not have been published because of a lack of results; however, the large registry-based studies should not have been affected by this phenomenon.

Several biases should be mentioned concerning the published studies. First, apart from 1 study, the studies included in our meta-analyses did not adopt a classic case-control design but were based on population registries. In fact, potential confounding effects for ASD detection should be mentioned, especially the fact that children with prenatal antidepressant exposure are possibly more likely to have a higher frequency of pediatric and psychiatric consultations compared with nonexposed children, which could lead to a higher rate of ASD detection. Second, most of the studies defined antidepressant exposure for 1 trimester even if the medication exposure overlapped other trimesters. Only 1 study assessed the duration of exposure for each trimester separately and dichotomized duration into 2 categories: use between 1 and 45 days and use for more than 45 days. In addition, 1 study analyzing preconception exposure considered exposure 2 years to 6 months before pregnancy but not during pregnancy. Third, antidepressant exposure in most of the studies was ascertained from prescription databases. Analyses were carried out on the basis that women had received 1 antidepressant prescription. This does not provide any information as to whether the women actually took the treatments prescribed during pregnancy. Fourth, most studies considered maternal depressive history but not current depression during pregnancy. Several studies also reported that a history of depression was associated with an increased risk for ASDs in children. The effect of maternal depression in itself may be an important confounder. Depression and ASDs have been reported to share risk factors. Genetic overlap has been found and a family history of depression has been associated with the risk for ASDs. Most of the studies considered did not search for autistic traits in the parents. Whereas environmental factors may be influential, the preeminent causes of autism are genetic. Fifth, the indication for the prescription of antidepressants during pregnancy was often missing and the severity of depression was not reported in most studies. Pregnant women who take antidepressants are more likely to have severe depressive disorders than women with less severe depression who often stop taking their antidepressants before pregnancy. Most women using antidepressants during pregnancy are taking maintenance therapy to prevent a possible relapse. The combination of 2 antidepressants seems to increase the risk for ASDs, as does the use of psychotropic drugs other than antidepressants. The use of other psychotropic drugs could explain part of the association, but only 1 study considered this possible confounding factor. All these points suggest the importance of maternal psychiatric disorders in the occurrence of autistic traits in children. Last, accounting for exposures other than prescribed medications, including tobacco, alcohol, and illicit drugs, is missing in most of the studies. The risks for ASDs could increase in the offspring of mothers who used these substances in addition to antidepressants.

Strengths

This article also has certain strengths: (1) its multiple-study approach, based on a systematic literature review complemented with meta-analyses; (2) sensitivity meta-analyses; and (3) the evaluation of the quality of the studies included. The prevention of depression during pregnancy is an important goal. Previous studies reporting an association between fetal antidepressant exposure and ASDs are not sufficient to warrant a discontinuation or avoidance of prescription of antidepressants during pregnancy. Clinicians should always balance the risks of maternal depression against the potential neurodevelopmental risks of antidepressant exposure for the fetus. Each prescription should be evaluated individually. Nevertheless, the risk of untreated depression during pregnancy is considerable. Thus, it seems advisable to reserve psychotropic treatments for women with severe major depression and to promote psychological approaches for others.

Conclusions

Future studies, comprising an assessment of diagnoses, severity of illness, and treatments at different stages in pregnancy and substance abuse, are needed and could help disentangle the role of the mother's psychiatric condition and psychotropic drug use in the risk for ASDs. Further detailed observational data to address these confounding factors are required to investigate the association between antidepressant exposure and ASDs.
ARTICLE INFORMATION

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