Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of autism in the offspring

AUTHORS: Donna Stewart, CM, MD, FRCPC, Simone Vigod, MD, MSc, FRCPC
SECTION EDITORS: Peter P Roy-Byrne, MD, Joseph A Garcia-Prats, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

Depressive disorders and anxiety disorders occur in approximately 10 to 15 percent of pregnant women and can have short- and long-term deleterious effects upon the mother, child, and family [1-4]. Although patients with mild to moderate illness may respond to psychotherapy, patients with severe (eg, suicidality or psychosis), chronic, or recurrent syndromes often require pharmacotherapy.

The decision to prescribe antidepressants for pregnant patients requires clinicians to weigh the negative impact of untreated mood and anxiety disorders against the adverse effects of antidepressants. Although the risks to the offspring from in utero exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) often appear to be small to nonexistent, the potential risks are uncertain due to the lack of high-quality data. The complexity of managing pregnant women with mood and anxiety disorders requires coordinated efforts among psychiatrists, primary care clinicians, obstetricians, and pediatricians.

Maternal use of SSRIs and SNRIs during pregnancy is estimated at approximately 8 percent [5]. Indications beyond depressive and anxiety disorders include obsessive-compulsive disorder and posttraumatic stress disorder. In addition, these antidepressants are often combined with

second-generation antipsychotics for treating major depression in pregnant women with bipolar disorder and schizophrenia.

The long-term effects of antenatal antidepressants have been examined in observational studies, which have inherent limitations that make it difficult to disentangle medication effects from genetic and environmental factors, as well as pre-existing and ongoing maternal psychiatric illness. Women with psychiatric symptoms in pregnancy are at high risk for postpartum depression and anxiety, and thus for impaired mother-infant interactions that are associated with emotional and behavioral dysfunction in the offspring [4]. Maternal depression and anxiety can be chronic and recurrent [6], prolonging their impact upon children beyond the immediate postnatal phase. In addition, the evidence suggests that children of depressed mothers are more likely to exhibit psychiatric symptoms and disorders (eg, anxiety disorders, depressive disorders, attention deficit hyperactivity disorder, and oppositional defiant disorder), compared with children of mothers with remitted depression [7-10].

This topic reviews the association between antenatal exposure to SSRIs and SNRIs and the risk of autism in the offspring. Antenatal exposure to SSRIs and SNRIs and neonatal outcomes, as well as the risk of psychopathology (other than autism) and abnormalities in growth, motor skills, and cognition are discussed separately. The antenatal use of antidepressants and risk of teratogenicity and adverse pregnancy outcomes are also discussed separately, as are the clinical features and choice of treatment for antenatal depression, and the risks of exposure to antenatal depression:

- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)
- (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)
- (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)
- (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)
- (See "Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment".)

- (See "Severe antenatal unipolar major depression: Choosing treatment".)
- (See "Antenatal depression: Pregnancy and neonatal outcomes".)
- (See "Antenatal depression: Risks of abnormal infant and child development".)
- (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring".)

INTERPRETING THE EVIDENCE

The evidence regarding the potential risk of antenatal exposure to SSRIs and SNRIs inhibitors is limited due to several factors. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes", section on 'Interpreting the evidence'.)

AUTISM

Overview — Multiple observational studies of intrauterine exposure to SSRIs and SNRIs, using relatively rigorous methods, have found that the risk for autism spectrum disorders in children is likely nonexistent [11-17]. The consensus among many experts is that the study results are reassuring for both parents and clinicians. Although other studies have found that antenatal exposure to SSRIs or SNRIs is associated with a small increased risk for autism spectrum disorders [12,18-21], problems with methodologic bias in the study designs suggest that the results are less robust than those of the more reassuring studies. In addition, all studies agree that antenatal SSRI exposure is highly unlikely to be a major risk factor for autism [18,22-24].

Observed associations between antenatal SSRI exposure and autism are apparently due at least in part to confounding by indication and other sources of methodologic bias such as measurement error and residual confounding [16,25-28]. Confounding by indication is based upon findings that women with depressive disorders, anxiety disorders, or other psychiatric disorders are more likely to have children with autism spectrum disorder; however, these maternal disorders are indications for prescribing SSRIs, which can lead to observing an ostensible but false association between SSRI use and autism [27-29]. The mechanisms by which maternal psychiatric disorders are associated with autism in the offspring may include genetic and environmental factors and dysfunctional behavior.

The general consensus is that autism spectrum disorder is caused by genetic factors that alter brain development. In addition, studies have found that genes putatively involved in the pathogenesis of unipolar major depression may also confer risk for autism. (See "Autism

spectrum disorder in children and adolescents: Terminology, epidemiology, and pathogenesis", section on 'Genetic factors' and "Unipolar depression: Genetics", section on 'Genetic overlap with other mental disorders'.)

Evidence of no risk — Meta-analyses of observational studies suggest that suggest that antenatal SSRI exposure is not associated with autism:

- A meta-analysis of three studies identified cases with autism (total n >3000) and controls (total n >22,000) without autism, and compared exposure with SSRIs during pregnancy in the two groups [14]. Each study controlled for various potential confounding factors, including maternal mental illness. Antenatal use of SSRIs was comparable for the cases and controls (odds ratio 1.4, 95% CI 0.9-2.2).

  Other analyses further controlled for maternal mental illness by restricting the samples to mothers with a psychiatric diagnosis (ie, both the cases with autism and the controls without autism were the offspring of women with a mental illness). Again, exposure to SSRIs was not associated with an increased risk of autism.

- A meta-analysis pooled two retrospective cohort studies; the studies identified individuals exposed in utero to SSRIs (total n >7000) and controls who were not exposed (n >700,000), and then compared the incidence of autism in the two groups [14]. Each study controlled for various potential confounding factors, including maternal mental illness. The rate of autism was comparable among individuals who were exposed to SSRIs and individuals not exposed (odds ratio 1.5, 95% CI 0.9-2.7). A meta-analysis from a different study pooled the same two cohort studies and also found that antenatal SSRI exposure was not associated with autism (hazard ratio 1.3, 95% CI 0.9-1.7) [12].

In addition, studies published after the meta-analyses found that gestational exposure to antidepressants is not associated with an elevated risk of autism spectrum disorders [30]. As an example:

- A national registry study compared children (n >13,000) of fathers who received antidepressants during the child's first trimester of intrauterine development with children (n >680,000) of fathers who did not receive SSRIs before, during, or after pregnancy [31]. The risk of autism spectrum disorder was greater in offspring of fathers who received SSRIs (hazard ratio 1.3, 95% CI 1.1-1.6). This suggests that genetic and/or environmental factors may at least partially account for results in studies that found maternal use of SSRIs during pregnancy was associated with an increased risk of autism.

- Another study used an administrative health claims database to examine the incidence of autism spectrum disorder in children who were followed for an average of five years following birth (n >35,000); the sample included children exposed in utero to SSRIs or SNRIs (n >2800) [25]. After adjusting for the probability (propensity) to receive an antidepressant, based upon 500 potential confounding factors such as maternal age, general medical and psychiatric diagnoses, and use of concomitant medications, the analyses found that antenatal exposure was not associated with autism spectrum disorder (hazard ratio 1.61, 95% CI 0.997-2.59).

Furthermore, multiple observational studies that controlled for genetic vulnerability to autism have found that antenatal exposure to antidepressants was not associated with autism. These studies used a discordant sibling design, which compared the risk of autism spectrum disorder between two siblings born to the same mother, one of whom was exposed to SSRIs in utero and one who was not. This approach controls for confounding genetic (and environmental) factors. In a meta-analysis of four observational studies (sample size not reported), the risk of autism spectrum disorder in children exposed in utero to antidepressants and in siblings not exposed was comparable (odds ratio 0.9, 95% CI 0.5-1.4) [15]. As an example, a national registry study, which included more than 24,000 individuals who were followed for 15 years, found that after adjusting for potential confounding factors (eg, parental age, education, and history of severe psychiatric illness such as schizophrenia), the risk of autism was comparable for the exposed and unexposed siblings (hazard ratio 0.8, 95% CI 0.6-1.1) [31].

Confounding by indication — Associations between antenatal SSRIs and increased risk of autism spectrum disorder may be observed due to confounding by indication, which is a type of methodologic bias. Unipolar major depression is often an indication for SSRIs, and the genetic and environmental factors and dysfunctional behaviors related to the depressive syndrome may account for the risk of autism, rather than the SSRI [28]. The results of the studies reviewed below in this section support the lack of a causal association between SSRIs and autism, as well as the caution that must be taken in interpreting results with population (nonpsychiatric) controls due to the potential for confounding by indication [15].

Evidence for confounding by indication as a source of bias includes a study that examined the risk of autism spectrum disorder in the offspring of mothers who were treated with SSRIs during pregnancy, mothers from the general population not treated with SSRIs, and mothers with depression during pregnancy who were not treated with SSRIs [15]:

- A meta-analysis of eight observational studies (sample size not reported) found that autism occurred more often in children exposed in utero to SSRIs than unexposed children

of mothers from the general population not treated with SSRIs (odds ratio 1.5, 95% CI 1.2-2.0).

- However, a second meta-analysis of four observational studies (sample size not reported) compared children exposed in utero to SSRIs with unexposed children of depressed mothers, which controlled for confounding due to the underlying condition; the risk of autism in the two groups was comparable (odds ratio 1.3, 95% CI 0.9-1.8).

  As an example, a national registry study identified a cohort of children who were born to mothers with a lifetime diagnosis of a depressive or anxiety disorder and were followed from birth until age seven or eight years; the children were either exposed to antidepressants in utero (n >2600) or not exposed (n >14,000) [32]. The primary findings included the following:

  - After adjusting for potential confounding factors such as parental age, maternal use of other psychotropic medications during pregnancy, and paternal lifetime diagnosis of mental illness, the incidence of autism spectrum disorder in the exposed and nonexposed offspring was comparable (2.4 and 1.9 percent; relative risk 1.1, 95% CI 0.8-1.4).

  - The risk of autism was lower in children of mothers who used antidepressants during pregnancy, compared with children of mothers who did not use antidepressants during pregnancy, but had a lifetime diagnosis of at least three different mental disorders (relative risk 0.70, 95% CI 0.50-0.98).

  - Analyses that separately examined in utero exposure to SSRIs, non-SSRI antidepressants, or nonantidepressant psychotropic medications found similar results: for each drug class, the risk of autism spectrum disorder was comparable for exposed and unexposed children.

  Additional evidence that confounding by indication explains observed associations between antenatal SSRI exposure and autism includes the following:

- Multiple observational studies have found that use of antidepressants prior to pregnancy, but not during pregnancy, was associated with an elevated risk of autism spectrum disorder. Specifically, the risk of autism spectrum disorder was greater in children of women who received antidepressants prior to but not during pregnancy, compared with children of women who did not receive antidepressants prior to or during pregnancy. This elevated risk was consistent across studies (sample sizes not reported):

- Meta-analysis of four studies (odds ratio 1.8, 95% CI 1.5-2.1) [12]
- Meta-analysis of three studies (odds ratio 1.8, 95% CI 1.5-2.3) [19]

- Multiple studies have found higher rates of depression in mothers of children with autism than mothers of controls [33,34].

Another aspect of confounding by indication is severity of the depressive syndrome. Most women discontinue antidepressants during pregnancy, which suggests that continued use of antidepressants in pregnancy may be a marker of the severity of the underlying depressive illness and of other characteristics associated with depression (eg, chronicity or frequent recurrences) [11,35,36]. Increased severity of depression may reflect increased dysregulation of maternal hypothalamic-pituitary-adrenal axis hormones and increased fetal exposure to cortisol.

Additional information about the association between maternal antenatal depression and autism in the offspring is discussed separately. (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring", section on 'Autism'.)

Evidence of increased risk — Evidence that antenatal antidepressants are associated with a small increased risk of autism spectrum disorders includes meta-analyses of observational studies. However, the results included findings that suggested confounding by indication (see 'Confounding by indication' above) may account for the association [28]:

- A meta-analysis included five studies (total n >100,000) that compared in utero exposure to antidepressants (primarily SSRIs) in cases with autism spectrum disorder and controls without autism [12]. After adjusting for a history of maternal psychiatric disorders, the analyses found that antenatal use of antidepressants was greater in the cases than controls (odds ratio 1.5, 95% CI 1.1-2.1). However, heterogeneity across studies was moderate to large. In addition, other adjusted analyses found that preconception use of antidepressants was greater in cases than controls (odds ratio 1.8, 95% CI 1.5-2.1), and the authors concluded that the association between antenatal antidepressants and autism could well be due to maternal psychiatric disorders rather than antidepressants (confounding by indication).

- A second meta-analysis pooled odds ratios from an overlapping but not identical set of five studies, which included cases with autism (total n >9000) and controls without autism (total n >74,000) [19]. In utero exposure to SSRIs was greater in the cases than controls (odds ratio 1.7, 95% CI 1.2-2.2). However, other analyses examined use of SSRIs that occurred only during the three months prior to conception and found that SSRI exposure was greater in the cases than controls (odds ratio 1.8, 95% CI 1.5-2.3). Again, this suggests

that the risk of autism is driven at least in part by the underlying psychiatric disorder, rather than the SSRI indicated for the disorder.

- Subsequently, a national registry study identified two groups of youth according to maternal use of antidepressants (largely SSRI monotherapy): antidepressant use in the two years before pregnancy but discontinued prior to pregnancy (discontinuation, n >30,000), and antidepressant use before and during pregnancy (continuation, n >17,000) [18]. After adjusting for potential confounding factors (eg, maternal age, parental psychiatric history, and other medications), the analyses found that the 15-year cumulative incidence of autism in the offspring was modestly greater in the continuation group than the discontinuation group (hazard ratio 1.23, 95% CI 1.01-1.51). However, this association may have been related to greater severity of the underlying maternal psychiatric disorders, because antidepressants are more likely to be continued for pregnant women with more severe symptoms than less severely ill women.

PSYCHOPATHOLOGY OTHER THAN AUTISM

A separate topic discusses the association between antenatal exposure to SSRIs and SNRIs and the risk in offspring for psychopathology other than autism. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)

TERATOGENICITY

The teratogenicity of SSRIs and SNRIs is discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)

PREGNANCY OUTCOMES

The effects of SSRIs and SNRIs on pregnancy outcomes, including spontaneous abortion, stillbirth, length of gestation, fetal growth, and neonatal mortality are discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)

NEONATAL EFFECTS

The neonatal effects of antenatal exposure to SSRIs and SNRIs are discussed separately. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)

ABNORMALITIES IN GROWTH, MOTOR SKILLS, AND COGNITION

Antenatal exposure to SSRIs and SNRIs and the risk in offspring for abnormalities in growth, motor skills, and cognition are discussed separately. (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)

SUMMARY

- **Limitations of the data** – For children who are exposed in utero to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), the risks of adverse outcomes are not clear due to the lack of high-quality studies. Rather, the long-term effects of antenatal antidepressants have been examined in observational studies, which have inherent limitations that make it difficult to disentangle medication effects from genetic and environmental factors, as well as pre-existing and ongoing maternal psychiatric illness. (See 'Introduction' above and "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes", section on 'Interpreting the evidence'.)

- **Risk of autism associated with SSRIs and SNRIs**

  - **Evidence of no risk** – Multiple observational studies of in utero exposure to SSRIs and SNRIs, including studies that controlled for genetic and environmental factors, have found that the risk for autism spectrum disorders in children is likely nonexistent. The consensus among many experts is that the study results are reassuring for both parents and clinicians. Although other studies have found that antenatal exposure to SSRIs or SNRIs is associated with a small increased risk for autism spectrum disorders, problems with methodologic bias in the study designs suggest that the results are less robust than those of the more reassuring studies. In addition, all studies agree that antenatal SSRI exposure is highly unlikely to be a major risk factor for autism. (See 'Overview' above and 'Evidence of no risk' above.)

    Observed associations between antenatal SSRI exposure and autism are apparently due at least in part to confounding by indication, as well as other sources of

methodologic bias such as measurement error and residual confounding. Confounding by indication is based upon findings that women with depressive disorders are more likely to have children with autism spectrum disorder; however, these disorders are indications for prescribing SSRIs, which can lead to observing an ostensible but false association between SSRI use and autism. (See 'Confounding by indication' above.)

- **Evidence of a small risk** – Evidence that antenatal antidepressants are associated with a small increased risk of autism spectrum disorders includes meta-analyses of observational studies. However, the results included findings that suggested confounding by indication may account for the association. (See 'Evidence of increased risk' above.)

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