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

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Literature review current through: **Oct 2023.**
This topic last updated: **Sep 18, 2023.**

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 of psychopathology in the offspring from prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) generally appear to be small to nonexistent, the potential risks are uncertain due to the lack of high-quality data on the impact of these drugs. 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 other medications, such as 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 psychopathology (other than autism) in the offspring. Antenatal exposure to SSRIs and SNRIs and neonatal outcomes, as well as the risk of 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 autism 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 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'.)

PSYCHOPATHOLOGY

It is not known whether antenatal antidepressant exposure is associated with psychiatric symptoms and disorders in the offspring. In studying the association, it is difficult to distinguish medication effects from other factors such as antenatal and especially postnatal maternal psychiatric illness. Multiple studies suggest that children of depressed mothers are more likely to exhibit psychiatric disorders; this association is due to genetic factors, environmental effects, or both. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes", section on 'Interpreting the evidence'.)

Emotional and behavioral dysfunction — Emotional and behavioral dysfunction is a composite outcome that includes symptoms of psychiatric disorders such as anxiety disorders, attention deficit hyperactivity disorder (ADHD), conduct disorder, depressive disorders, and oppositional defiant disorder. Due to conflicting results from different observational studies, it is not clear whether antenatal exposure to SSRIs and SNRIs is associated with overall emotional and behavioral dysfunction in children and adolescents. This literature is difficult to interpret when emotional and behavioral disorders are considered as a composite outcome because etiological mechanisms underlying the development of each type of dysfunction are likely to

differ; disaggregated evidence for specific disorders is presented in the subsequent section. (See 'Psychiatric disorders' below.)

Evidence that suggests antenatal exposure to SSRIs is not associated with emotional and behavioral dysfunction includes the following:

- A prospective study evaluated 45 sibling pairs, one of whom was exposed to SSRIs and/or SNRIs during gestation and one of whom was not; this approach accounted for shared genetic and environmental factors [11]. The antidepressants were prescribed for maternal depressive disorders during pregnancy. Maternal report questionnaires were used to assess the children between the age of three to six years for emotional/internalizing problems (eg, depressed affect and social withdrawal), and for behavioral/externalizing problems (eg, aggressive and delinquent behaviors). After controlling for potential confounding factors (eg, child's age, birth order, and severity of maternal depressive episodes during pregnancy and after delivery), the analyses found that emotional and behavioral problems in the exposed and unexposed siblings were comparable. However, severity of maternal depression during pregnancy and at the time of assessment was associated with greater levels of emotional and behavioral problems in the children.

- A prospective nationwide study included three groups: pregnant women (n = 210) treated for depression with antidepressants (primarily SSRIs), pregnant women who were depressed but not treated with antidepressants (n = 231), and pregnant women who were not depressed and did not take antidepressants (n >48,000) [12]. The children of these women were assessed at age seven years for behavioral problems with a questionnaire completed by their parents. The analyses were adjusted for potential confounding maternal factors (eg, age, antenatal mood, and smoking status) and compared each group of children with the other two groups. The analyses found that neither antenatal antidepressant exposure nor untreated depression was associated with emotional problems, peer problems, conduct problems, and hyperactivity/inattention problems in the children.

- A prospective study recruited pregnant women treated for depression with antidepressants (n = 415, treated primarily with SSRIs) and pregnant women with untreated depression (n = 489) [13]. The offspring were assessed at an average age of six months. After adjusting for potential confounding factors (eg, maternal age, birth outcomes, and postnatal depression), the analyses found that social behavior in exposed and unexposed infants was comparable.

A subsequent study from the same sample included children of mothers with antenatal depression who were treated with antidepressants (n = 127) and children of mothers with antenatal depression who were not treated with antidepressants (n = 98); the children were assessed at age four or five years [14]. Emotional symptoms, conduct problems, peer and social relationships, hyperactivity, and inattention were each comparable in the two groups.

Other prospective studies suggest that antenatal exposure to SSRIs may perhaps be associated with an increased risk of emotional and behavioral dysfunction. However, the association found in any particular study often represents a solitary finding among several negative results, or the effect of antenatal exposure is clinically small [15,16]:

- A study included discordant sibling pairs (n = 141), one of whom was exposed to an antidepressant during gestation and one of whom was not; this approach accounted for shared genetic and environmental factors [17]. Most of the antidepressants were SSRIs, and the sibling pairs were assessed at age 18 months and again 36 months. After adjusting for potential confounding factors (eg, maternal lifetime depression and antenatal use of other medications, alcohol, or tobacco), the analyses found that at age 18 months, fetal antidepressant exposure was not associated with anxiety, emotional reactivity, somatic symptoms, sleep problems, attention problems, or aggression. At age 36 months, fetal antidepressant exposure was associated with anxiety, but no other psychiatric symptoms.

- 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 concurrent medications), the analyses found that the 15-year cumulative incidence of emotional and behavioral disorders in the offspring was statistically greater in the continuation group than the discontinuation group, but the clinical effect was marginal (hazard ratio 1.13, 95% CI 1.01-1.27).

- A prospective study included women with anxiety and depressive disorders (n >8000) and their children who were assessed periodically up to age five years [19]. After adjusting for potential confounding factors (eg, maternal body mass index and comedications, and the child's sex), the analyses found that children who were exposed to SSRIs in late pregnancy (>29 weeks gestation) had an increased risk for anxious/depressed behaviors on the Child Behavior Checklist (CBCL) at age five years compared with an unexposed group. However,

this was the only statistically significant emotional or behavioral outcome among a range of SSRI exposure time points during pregnancy (early, middle, and late), a range of outcome time points (child age 1.5, 3, and 5 years), and a range of outcomes, including six additional CBCL subscales and four subscales of the Emotionality, Activity, and Shyness Temperament Questionnaire.

The association between maternal antenatal depression and emotional and behavioral dysfunction in the offspring is discussed separately. (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring", section on 'Emotional and behavioral dysfunction'.)

Psychiatric disorders — This section discusses the association between antenatal exposure to antidepressants and the risk of a psychiatric disorder, that is, all disorders analyzed collectively as a single outcome. However, the etiological mechanisms underlying the development of each type of disorder are likely to differ, and the risk of specific psychiatric disorders is discussed in the subsections below.

Antenatal antidepressants may be associated with a small increased risk of a psychiatric disorder in children and adolescents. A national registry study identified four groups of youth according to maternal use of antidepressants (largely SSRI monotherapy): no antidepressants two years prior to and during pregnancy (unexposed; n >850,000), antidepressant use in the two years before pregnancy but discontinued prior to pregnancy (discontinuation, n >30,000), antidepressant use before and during pregnancy (continuation, n >17,000), and use of antidepressants only during pregnancy (new user, n >3000) [18]. The outcomes included any psychiatric disorder (eg, autism, depressive disorder, or substance use disorder). After adjusting for potential confounding factors (eg, maternal age, parental psychiatric history, and concurrent medications), the analyses found that the 15-year cumulative incidence of a psychiatric disorder in the offspring was as follows:

- Unexposed – 8 percent (95% CI 7.9-8.2)
- Discontinuation – 11.5 percent (95% CI 10.3-12.9)
- Continuation – 13.6 percent (95% CI 11.3-16.3)
- New user – 14.5 percent (95% CI 10.5-19.8)

The risk of a psychiatric disorder was greater in the discontinuation group, continuation group, and new user group, compared with the unexposed group (hazard ratios ranging from 1.3 to 1.6). The elevated risk appeared to be comparable across specific SSRIs.

In addition, the risk of psychiatric disorders was modestly greater in the continuation group than the discontinuation group (hazard ratio 1.3, 95% CI 1.2-1.4). This may be attributable to

both in utero antidepressant exposure and severity of the underlying maternal disorder treated with the antidepressant, because antidepressants are more likely to be continued for pregnant women with more severe symptoms than women with less severe symptoms.

The study also examined the risk of a psychiatric disorder in children and adolescents whose fathers used antidepressants both before and during the pregnancy (n >500), compared with fathers who did not use antidepressants during either period (n >30,000) [18]. After adjusting for additional potential confounding factors (eg, maternal use of antidepressants and paternal age), the analyses found that a psychiatric disorder was more likely to occur in the offspring of fathers who used antidepressants (hazard ratio 1.2, 95% CI 1.1-1.3), suggesting that genetic and/or environmental factors at least partially explain the association between antenatal antidepressants and increased risk of a psychiatric disorder.

Anxiety disorders — Use of SSRIs and SNRIs during pregnancy does not appear to be associated with anxiety disorders in the offspring; however, relatively few studies have examined this outcome. A national registry study identified three groups: pregnant women who used SSRIs (n >15,000), pregnant women with psychiatric disorders who did not use SSRIs during pregnancy (n >9000), and pregnant women who used SSRIs in the year prior to pregnancy but not during pregnancy (n >7000) [20]. The offspring were followed for up to 14 years after birth. After controlling for potential confounding factors (eg, maternal smoking, maternal history of psychiatric disorders, and family socioeconomic status), the analyses found that the cumulative incidence of anxiety disorders in the three groups of offspring was comparable (approximately 2 to 3 percent).

The association between maternal antenatal depression and anxiety disorders in the offspring is discussed separately. (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring", section on 'Anxiety'.)

Attention deficit hyperactivity disorder — Most studies suggest that use of SSRIs and SNRIs during pregnancy is not associated with ADHD in the offspring [20-23]. In a review of eight studies, seven found that antenatal antidepressant exposure was not associated with an increased risk of ADHD [24]. Examples include the following:

- A study using an electronic medical record database included children of mothers who received SSRI monotherapy during pregnancy (n = 425) and children of mothers who did not use SSRIs during pregnancy (n >189,000); the age of the children ranged from 6 to 14 years [25]. After controlling for potential confounding factors (eg, maternal age, psychiatric and general medical disorders, and antenatal use of other psychotropic drugs),

the analyses found that the incidence of ADHD was comparable in the exposed and unexposed children (hazard ratio 1.1, 95% CI 0.8-1.6).

In addition, the study identified sibling pairs, one of whom was exposed to antidepressants during gestation and one of whom was not; this approach accounted for shared genetic and environmental factors. The sibling discordant analysis found that the risk of ADHD was comparable for exposed and unexposed siblings (hazard ratio 0.5, 95% CI 0.2-1.7).

- A national registry study identified differentially exposed siblings, who were either exposed to SSRIs in utero during the first trimester or were not [26]. The sample included more than 24,000 individuals who were followed for 15 years. After adjusting for potential confounding factors (eg, parental age at childbearing, education, and history of psychiatric illness), the analyses found that the risk of ADHD was comparable for the exposed and unexposed siblings (hazard ratio 0.9, 95% CI 0.7-1.2).

  In addition, other analyses compared children of fathers who received SSRIs during the first trimester with children of fathers who did not receive SSRIs before, during, or after pregnancy. The risk of ADHD was greater in offspring of fathers who received SSRIs (hazard ratio 1.7, 95% CI 1.3-2.2). This suggests that genetic and/or environmental factors may at least partially account for results in other studies, which found maternal use of SSRIs during pregnancy was associated with an increased risk of ADHD.

Although there are studies that suggest antidepressant exposure during gestation is associated with an increased risk of ADHD [27], several other studies support the hypothesis that maternal mental illness confounds the observed association [23,24]. If women with depressive disorders or other indications for SSRIs are more likely to have children with ADHD, a false association between SSRI use and ADHD may be observed (confounding by indication). Evidence for this explanation includes a study that performed five meta-analyses of observational cohort studies to examine the association between antidepressants (primarily SSRIs) and ADHD in the offspring; sample sizes were not reported [28]:

- A meta-analysis of six population-wide studies found that the risk of ADHD was greater in youth exposed in utero to antidepressants than unexposed youth (hazard ratio 1.3, 95% CI 1.1-1.6).

- However, a meta-analysis of two studies compared children of mothers with psychiatric disorders who either were or were not treated with antidepressants during pregnancy. The risk of ADHD in the two groups was comparable (hazard ratio 1.0, 95% CI 0.8-1.2).

- In addition, a meta-analysis of three studies compared the offspring of mothers with psychiatric disorders to the offspring of mothers without psychiatric disorders; none of the mothers used antenatal antidepressants. ADHD occurred more often in the offspring of mothers with psychiatric disorders (hazard ratio 1.3, 95% CI 1.2-1.4).

- Moreover, a meta-analysis of three studies found that among children of mothers who received antidepressants before conception but not during pregnancy, and children of mothers who did not receive preconception or antenatal antidepressants, preconception use was associated with an increased risk of ADHD (hazard ratio 1.8, 95% CI 1.5-2.2).

- Furthermore, a meta-analysis of two studies found that the risk of ADHD was comparable in the children of mothers who received antenatal antidepressants and the children of mothers who received antidepressants before conception but not during pregnancy (hazard ratio 0.9, 95% CI 0.7-1.1).

Taken together, these results support the lack of a causal association between SSRIs and ADHD and the importance of choosing the proper control group to account for confounding by indication.

Genetic factors are apparently involved in the pathogenesis of ADHD, and studies have found that genes putatively involved in the pathogenesis of unipolar major depression may also confer risk for ADHD [29]. In addition, multiple observational studies that controlled for genetic vulnerability to autism have found that antenatal exposure to antidepressants was not associated with ADHD. These studies used a discordant sibling design, which compared the risk of ADHD between two siblings born to the same mother, one of whom was exposed to SSRIs in utero and one of whom was not. This design controls for confounding genetic (and environmental) factors. In a meta-analysis of three prospective observational studies (sample size not reported), the risk of ADHD in children exposed in utero to antidepressants and in unexposed siblings was comparable (hazard ratio 0.9, 95% CI 0.7-1.1) [28].

The association between maternal antenatal depression and hyperactivity in the offspring is discussed separately, as is the role of genetic factors in the pathogenesis of ADHD. (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring", section on 'Hyperactivity' and "Attention deficit hyperactivity disorder in children and adolescents: Epidemiology and pathogenesis", section on 'Genetic factors'.)

Depressive disorders — Antenatal use of antidepressants is associated with an increased risk of depression in the offspring:

- A national registry study identified three groups: pregnant women who used SSRIs (n >15,000), pregnant women with psychiatric disorders who did not use SSRIs during pregnancy (n >9000), and pregnant women who used SSRIs in the year prior to pregnancy but not during pregnancy (n >7000) [20]. The offspring were followed for up to 14 years after birth. After controlling for potential confounding factors (eg, maternal smoking and maternal and paternal socioeconomic status and history of psychiatric disorders), the analyses found that the cumulative incidence of depression was greater in offspring exposed to SSRIs during gestation, compared with offspring of women with psychiatric disorders who did not use SSRIs (8 versus 2 percent). In addition, depression occurred in more offspring exposed to SSRIs during gestation, compared with offspring of women who used SSRIs prior to pregnancy but not during pregnancy (8 versus 3 percent).

- 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 mood disorders in the offspring was greater in the continuation group than the discontinuation group, and the clinical effect was large (hazard ratio 3, 95% CI 2-5). However, the incidence of mood disorders in the two groups was small: discontinuation group 26 cases, continuation group 27 cases.

Given that most women with mental illness discontinue antidepressants during pregnancy, continued use of antidepressants in pregnancy may be a marker for greater severity of the underlying mental illness and of other illness characteristics (eg, chronicity or frequent recurrences) [18,30-33]. Severe illness may be associated with risk of depression in the offspring and thus confound the observed associations between gestational exposure to SSRIs and increased risk of depression in the offspring. In addition, the observed associations between SSRI exposure and offspring depression may have been due to residual confounding by unmeasured prognostic variables such as maternal postpartum depression and environmental factors, such as marital strain.

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

Autism — The association between antenatal exposure to SSRIs and SNRIs and the risk of autism in the offspring is discussed separately. (See "Antenatal exposure to selective serotonin

reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of autism 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 of 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. (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 emotional and behavioral dysfunction** – Emotional and behavioral dysfunction is a composite outcome that includes symptoms of psychiatric disorders such as anxiety and depressive disorders, attention deficit hyperactivity disorder (ADHD), and conduct disorder. It is not known whether antenatal exposure to SSRIs and SNRIs is associated with emotional and behavioral dysfunction in children and adolescents due to conflicting results across studies. (See 'Emotional and behavioral dysfunction' above.)

- **Risk of psychiatric disorders associated with SSRIs and SNRIs**

  - **Psychiatric disorders collectively** – A relatively large and well-controlled observational study of children and adolescents found that in utero exposure to antidepressants was associated with a small increased risk of psychiatric disorders analyzed collectively as a single outcome. However, interpreting this finding is difficult because the etiological mechanisms underlying the development of each psychiatric disorder are likely to differ. (See 'Psychiatric disorders' above.)

  - **Anxiety disorders** – Use of SSRIs and SNRIs during pregnancy does not appear to be associated with anxiety disorders in the offspring. (See 'Anxiety disorders' above.)

  - **ADHD** – It appears that use of SSRIs and SNRIs during pregnancy is not associated with ADHD in the offspring, particularly in studies that control for confounding by indication. (See 'Attention deficit hyperactivity disorder' above.)

  - **Depression** – Antenatal use of antidepressants is associated with an increased risk of depression in the offspring. However, this may be due to confounding by severity of the maternal depressive syndrome and residual confounding. (See 'Depressive disorders' above.)

Topic 114320 Version 6.0

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