Title: Selective Serotonin Reuptake Inhibitors for Depression in Pregnancy

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Word Count: 2,987
Condensation: Perinatal depression is associated with significant morbidity and mortality, and understanding the risks and benefits of selective serotonin reuptake inhibitor treatment in pregnancy is important.

Short version of title: SSRIs in Pregnancy
Unstructured Abstract:

Perinatal depression is associated with high risk of morbidity and mortality, and may have long-term consequences on child development. The US Preventive Services Task Force has recently recognized the importance of identifying and treating women with depression in the perinatal period. However, screening and accessing appropriate treatment come with logistical challenges. In many areas, there may not be sufficient access to psychiatric care, and, until these resources develop, the burden may inadvertently fall on obstetricians. As a result, understanding the risks of perinatal depression in comparison to the risks of treatment is important. Many studies of selective serotonin reuptake inhibitors (SSRIs) in pregnancy fail to control for underlying depressive illness, which can lead to misinterpretation of SSRI risk by clinicians. This review discusses the risks and benefits of SSRI treatment in pregnancy within the context of perinatal depression. While SSRIs may be associated with certain risks, the absolute risks are low and may be outweighed by the risks of untreated depression for many women and their offspring.

Key words and phrases:
Antenatal depression
Antenatal exposure to selective serotonin reuptake inhibitor
Antenatal exposure to antidepressant
Antidepressant
Collaborative care
Depression in pregnancy
In utero exposure to antidepressant
In utero exposure to selective serotonin reuptake inhibitor
Perinatal depression
Selective serotonin reuptake inhibitor
Introduction

Recently, the US Preventive Services Task Force (USPSTF) has recommended screening perinatal women for depression. This has followed similar corresponding recommendations from professional associations, including the American Congress of Obstetricians and Gynecologists.\(^1\) Perinatal depression affects nearly 20% of women in pregnancy and in the postpartum. Screening helps identify women who would benefit from psychiatric treatment and reduce depressive symptoms at this vulnerable time.\(^2,3,4\)

Nevertheless, screening comes with challenges. Deciding which type of practitioner should conduct depression screening is not straightforward. Obstetrician-gynecologists (ob-gyns) are often the primary medical providers for women and may be in a unique position to identify women in need of psychiatric treatment during the perinatal period in particular.\(^5\) However, having a system in place for diagnosis and treatment after at risk women are identified is crucial. Recent studies have shown that depression screening accompanied by provider support improves maternal outcomes.\(^6\) Access to general psychiatrists can be difficult and access to psychiatrists with expertise in the perinatal period may be even more difficult. The burden may inadvertently fall on ob-gyns. There are inherent risks to taking on this role, including the risk of misdiagnosis, problematic decisions such as prescribing an antidepressant to a patient with bipolar depression, and the risks of withholding treatment from women who have depression with significant associated morbidity. Consequently, being knowledgeable “gatekeepers” to psychiatric care, especially in regard to depression management in pregnancy, is essential for ob-gyns. This article will discuss the role of selective serotonin reuptake inhibitors (SSRIs) in the treatment of antenatal depression.
The Risk: Risk Analysis

When appropriate, it is important to maximize non-pharmacologic interventions, including psychotherapy, for the treatment of perinatal depression (Table 1). For women with milder depression, a trial off of antidepressant treatment prior to conception may be appropriate. However, women with major depressive disorder are at high risk of relapse in pregnancy with discontinuation of antidepressant treatment. Depending on severity, some women may require pharmacotherapy for treatment of their depression during pregnancy. Antidepressants, especially selective serotonin reuptake inhibitors (SSRI), are considered first line. Treatment decisions in regard to pharmacotherapy must weigh the relative risks of medication exposure against the risks of untreated maternal depression.

Risk of Antenatal and Postpartum Depression

Perinatal depression can have detrimental effects on the fetus and developing child. Antenatal depression has been associated with unhealthy lifestyle choices, including smoking cigarettes, drinking alcohol, and using illicit drugs, variables which have been associated with adverse outcomes, including congenital malformations. In addition, perinatal psychiatric illness and, specifically, perinatal depression are associated with a high risk of suicide.

Fetal exposure to maternal psychiatric illness may increase the risk of poor obstetric outcomes, including preterm birth <32 weeks gestation, admission to a neonatal intensive care unit, prolonged hospital stay, and cesarean section. Prenatal depression is associated with physiologic changes in the offspring and changes in
markers of fetal neurodevelopment. Maternal psychological distress has been associated with epigenetic changes in the placenta, which may have lifelong consequences for exposed offspring. Antenatal maternal depression may adversely affect neurodevelopment and has been associated with behavioral problems and psychiatric illness in the offspring.

Prenatal depression is a major risk factor for postpartum depression, and postpartum depression can have long term detrimental effects on a child’s neurodevelopment and mental health. Postpartum depression may interfere with bonding and attachment with long lasting physiologic effects on offspring. The duration of a mother’s depression has been associated with lower global cognitive index, and the number of maternal depressive episodes after delivery has been negatively associated with language in the child. Children with a depressed parent are three times more likely to develop depression and anxiety, and are four times as likely to have had poor functioning, risks which extend into adulthood. Importantly, there is evidence that treating a mother’s depression can lead to improvement in the child’s depressive symptoms.

Risk of SSRIs Specific to Pregnancy

SSRIs cross the placenta, with cord/maternal concentration ratios ranging from 0.15 (paroxetine) to 0.86 (N-desmethylcitalopram, active metabolite of citalopram). SSRIs are the most commonly prescribed antidepressants in pregnancy, with up to 10.2% of pregnant women filling a prescription. SSRIs include sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram and escitalopram. The term serotonin
reuptake inhibitor (SRI) is a broader category including antidepressants with high affinity for the serotonin transporter, and often includes SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs).

While there are large population-based studies of antenatal SSRI exposure, for ethical reasons, there are not randomized controlled trials (RCTs), and therefore correlations are vulnerable to confounders. Confounding by indication has been a particular problem for this body of literature because the effects of perinatal depression on fetal and infant wellbeing are so profound. Studies that have failed to adequately control for perinatal depression have led to much misinterpretation in regard to risk of SSRI exposure amongst clinicians.

Conception:

Nillni et al. 2016, which controlled for important confounding factors, including confounding by indication, did not find an association between current SSRI use and fecundability. However, current severe depression was associated with decreased fecundability. There does not appear to be a difference in rate of pregnancy via in vitro fertilization with SSRI exposure.

Miscarriage:

Literature on the risk of miscarriage with antenatal SSRI exposure is conflicting. Ban et al. 2012, in a study of 512,574 pregnancies, found an increased risk of miscarriage with SSRI exposure compared to exposure to unmedicated
depression or anxiety in the first trimester (relative risk ratio, RRR, 1.4, 99% CI 1.2-1.7). In addition, women on an SSRI in the first trimester had a marginally statistically significant increased risk of miscarriage compared to women who stopped the SSRI (RRR 1.2, 99% CI 1.0-1.3). However, the study did not control for severity of mental illness, and severity of illness in women who decide to not take or to discontinue an SSRI may differ from the severity of illness in women who decide to continue SSRI treatment in pregnancy.

Other studies have not supported an association between SSRIs and miscarriage. Andersen et al. 2014, in a study of 1,279,840 pregnancies, found no difference in the hazard ratio of miscarriage with exposure to an SSRI in early pregnancy compared to SSRI exposure prior to pregnancy. Johansen et al. 2015, in a study of 1,191,164 pregnancies, found that the hazard ratio for first trimester miscarriage was higher for women who stopped SSRIs prior to pregnancy than for women on SSRIs in pregnancy. In addition, women on an SSRI in pregnancy but without recent maternal diagnosis of depression or anxiety had a lower hazard ratio for miscarriage in the first trimester than women with a diagnosis of depression or anxiety but not on an SSRI. These results highlight the importance of controlling for confounding by indication.

First trimester exposure:

SSRIs do not appear to be teratogens. While findings in the literature have been conflicting, multiple large studies that attempted to control for confounding by indication did not find an association between major congenital malformations and in utero
exposure to SSRIs as a class. Huybrechts et al. 2014 found that, after restricting to women with depression and adjusting, there was no statistically significant association between first trimester exposure to SSRIs and cardiac malformations. Sibling controlled analyses by Furu et al. 2015 did not find a statistically significant association between birth defect in general or cardiac malformation specifically and first trimester exposure to serotonin reuptake inhibitors (SRIs).

Some studies found an association between first trimester exposure to paroxetine and cardiac malformations; however, many of these studies did not control adequately for confounding by indication. Berard et al. 2007 conducted a (nested) case-control study that adjusted for various potential confounders including maternal depression and found a marginally significant association between major cardiac malformations and exposure to >25mg of paroxetine daily (OR 3.07, 95% CI 1.00-9.42). This study did not find an association between paroxetine in general, or paroxetine at lower doses, and major cardiac malformations. Ban et al. 2014 found that, compared to offspring of mothers with a recent diagnosis of depression, first trimester exposure to paroxetine was associated with a marginally statistically significant increased risk of cardiac anomaly (OR 1.67, 95% CI 1.00-2.80). The majority of the cardiac anomalies of offspring exposed in utero to paroxetine were mild. Huybrechts et al. 2014 did not find an association between first trimester exposure to paroxetine and either cardiac malformations in general or specifically right ventricular outflow tract obstruction. Taken together, those data do not support increased ultrasound monitoring in SSRI-exposed fetuses for cardiac malformations such as fetal echocardiography with the possible exception of paroxetine.
Late pregnancy exposure:

In some but not all studies, persistent pulmonary hypertension of the newborn (PPHN) has been associated with late pregnancy exposure to SSRIs. In the general population, persistent pulmonary hypertension occurs in 1-2/1,000 live births.\textsuperscript{50,51,52} The increased rate of PPHN with in utero exposure to SSRIs has ranged from no increased risk to a six fold increased risk.\textsuperscript{16,50,51,52} Huybrechts et al. 2015 found that the risk was attenuated and only marginally statistically significant after attempting to control for confounding factors, including confounding by indication (OR 1.28, 95% CI 1.01-1.64).

Delivery:

Obstetric outcomes after in utero SSRI exposure have been studied. Low birth weight and earlier gestational age at delivery have been associated with in utero exposure to SSRIs in some but not all studies, and there is evidence that at least some of the association may be due to the underlying psychiatric illness.\textsuperscript{16,53,54} Grzeskowiak et al. 2012 found an increased risk of preterm delivery (<37 weeks gestation) and low birth weight (<2,500g) after in utero exposure to an SSRI compared to presence of maternal psychiatric illness in pregnancy; the authors were unable to adjust for severity of psychiatric illness.\textsuperscript{55} Oberlander et al. 2006 found that, with propensity score matching to control for severity of maternal psychiatric illness, depressed mothers on SSRIs had increased risk of having a child with birth weight <10% for gestational age, but did not find a statistically significant difference in risk of delivering prior to 37 weeks gestation. Yonkers et al. 2012 did not show a statistically significant association
between antenatal SRI exposure and preterm birth after controlling for severity of psychiatric illness. This study found an association between late but not early preterm birth and SRI exposure in utero; however, these results were not adjusted for psychiatric illness severity, an adjustment which had attenuated the association between any preterm birth and SRIs. In addition, Nordeng et al. 2012 did not find an association between antenatal maternal SSRI use and preterm birth (<37 weeks gestation) or low birth weight (<2,500g) after adjusting for maternal depression and other important confounding variables, though there had been an association prior to adjusting. Depression itself has also been associated with these obstetric outcomes in some but not all studies. There is limited evidence that SSRIs may even mitigate some of this risk from psychiatric diagnosis as it pertains to preterm birth and cesarean section.

While inconsistent in the literature, multiple large studies that control for confounding by indication did not find an association between cesarean section and antenatal exposure to SSRIs. In a study by Oberlander et al. 2006, using propensity score matched analysis to control for severity of maternal mental illness, exposure to SSRIs + maternal depression was not associated with a statistically significant increased risk of cesarean section compared to exposure to maternal depression alone, though it had been prior to propensity score matching.

SSRIs may increase the risk of bleeding, particularly upper gastrointestinal bleeding. Studies examining whether in utero exposure to antidepressants increases the risk of postpartum hemorrhage have yielded inconsistent findings. When an association was found, the relative risk remained small. Palmsten et al. 2013 found
that women exposed to an SRI at delivery were at increased risk of postpartum hemorrhage (relative risk 1.47, 95% CI 1.33-1.62) compared to the women unexposed after adjusting for confounding variables potentially associated with risk of bleeding. In Grzeskowiak et al. 2015, antidepressant exposure in late pregnancy increased a woman’s risk of primary postpartum hemorrhage (relative risk 1.53, 95% CI 1.25-1.86) and severe primary postpartum hemorrhage (blood loss of at least 1,000mL) (RR 1.84, 95% CI 1.39-2.44) compared to unexposed women. In contrast, Lupattelli et al. 2014 did not find an association between late pregnancy SRI exposure and postpartum hemorrhage (>500mL blood loss).

Post-delivery:

A common adverse effect of antenatal exposure to SRIs is neonatal adaptation syndrome (NAS), which is thought to be transient and not dangerous. Signs of NAS include tremors, jitteriness, restlessness, irritability, changes in muscle tone, or respiratory distress, and are often mild. These symptoms usually begin within the first 24-48 hours after delivery and often resolve within days, though have been reported up to one month. NAS occurs in about one-third of newborns after in utero exposure to SSRIs, compared to around one-tenth of unexposed newborns. SSRI exposure in pregnancy has been associated with lower 5-minute Apgar score and with NICU admission. Further studies are needed to clarify whether NICU admission and lower 5-minute Apgar score are related to the transient symptoms of neonatal abstinence syndrome. In addition, the increased NICU admission rate may be related to bias from increased monitoring of women on psychiatric medications.
Long-term neurodevelopment:

Antenatal exposure to SSRIs does not appear to have a major negative impact on neurodevelopment, though some risks have been identified.

SSRIs have been associated with changes in fetal neurodevelopment, including activity during non-REM sleep and increased motor activity. While offspring exposed in utero to an SRI have been found to have delayed psychomotor skill development, there is evidence that this difference may be transient and still within normal limits. Literature examining antenatal SRI exposure and language or cognition is also reassuring.

Some but not all studies have found an association between internalizing behaviors, such as anxiety, in childhood and in utero exposure to antidepressants after adjusting for maternal psychiatric illness. Antenatal SRI exposure does not appear to confer risk to externalizing problems in the offspring. There is also evidence for an association between maternal depression and behavioral problems in the offspring.

Multiple studies have examined whether antenatal antidepressant exposure is associated with autism spectrum disorders, and current literature is conflicting. El Marroun et al. 2014 found an association between in utero exposure to SSRIs and autistic traits in offspring compared to exposure to depression. When other studies restricted to only women with an affective disorder diagnosis or with a history of anxiety or mood disorder, there was no longer a statistically significant association. This
suggests that the original associations prior to restriction may have been due to confounding factors.

**Limitations of Studying SSRIs in Pregnancy**

Due to the ethical limitations of designing studies of pregnant women, it is difficult to distinguish adverse effects from antenatal SSRI exposure from effects of confounding factors, such as the indication for SSRI prescription (Table 2). Some studies attempt to control for the potential confounding effect of psychiatric illness by either adjusting for psychiatric illness or restricting the study to women with a psychiatric illness. However, most studies do not control for severity of mental illness. The severity of mental illness in women who choose to take an antidepressant in pregnancy may not be the same as in women with a psychiatric illness who choose not to take an antidepressant. In addition, some of the studies that attempt to control for the effect of underlying psychiatric illness adjust for *historical* diagnosis of maternal depression rather than for antenatal exposure to *active* maternal depression.

Other potentially important confounders for which some studies on antenatal exposure to SSRIs do not control include in utero exposure to illicit drugs, other medications, diabetes, hypertension, alcohol, and smoking. Many of these comorbidities have themselves been associated with the adverse outcomes discussed above. It is also important to control for whether women took prenatal vitamins and had prenatal follow up.

Many studies use SSRI prescription as a marker for in utero exposure to an SSRI and were unable to confirm whether a woman who was prescribed an SSRI in the
perinatal period decided to take the medication. Some studies have addressed this methodological problem by either requiring two prescriptions or confirming by interview or blood test whether the medication was taken. Twenty-nine to fifty-three percent of women prescribed an antidepressant stop it when they find out they are pregnant, but over half require restarting the antidepressant during pregnancy, often due to relapse.\textsuperscript{87,88} Methods used to attempt to control for potential confounding factors have their own inherent biases. For example, studies that restrict to only women with depression may lose statistical power to detect an association. In addition, sibling analyses may introduce bias that may weaken the measured association.\textsuperscript{89}

**Conclusion**

Recently, there has been formal recognition for the need to identify perinatal women in need of mental health care. This is an important milestone in providing perinatal women with necessary services and improving outcomes at this vulnerable time in their lives. A challenge is implementing a system that will provide women who screen positive for depression with the appropriate mental health services. Collaborative care, with collocated mental health providers and ob-gyns, is a model that has proven successful.\textsuperscript{90} However, this increasingly popular way to deliver care is not yet available in many settings and is thus not a short term solution. With increased identification of perinatal women in need of psychiatric services, it becomes essential for ob-gyns to have an understanding of depression management in the perinatal period, particularly as it pertains to prescribing SSRIs.
Methodological limitations in studying perinatal depression and its treatments have led to widespread misunderstandings amongst clinicians and significant under treatment of women with depression in the perinatal period. The effect sizes of potential SSRI exposure risks may be small in comparison to the risks of untreated depression for many women. These risks should be evaluated in the context of a woman’s individual psychiatric illness, which should also be considered an exposure. The risk of moderate or severe depression on both the woman and offspring should not been underestimated.
References


57. Nordeng H, van Gelder M, Spigset O et al. Pregnancy Outcome After Exposure to Antidepressants and the Role of Maternal Depression: Results From the


Figure 1: Guiding Principles for Treatment of Antenatal Depression
<table>
<thead>
<tr>
<th>Guiding Principles</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Maximize wellness strategies.</td>
<td>• Engaging in appropriate exercise, reducing stress, optimizing nutrition and sleep, strengthening the family system and other social supports, and assessing partner wellness should be routine interventions in most cases.</td>
</tr>
<tr>
<td>Psychotherapy is often effective, either as monotherapy or in combination with other treatments.</td>
<td>• Interpersonal therapy, cognitive behavior therapy, mindfulness-based intervention, and perinatal dyadic psychotherapy are all evidence-based treatments for the perinatal period.</td>
</tr>
<tr>
<td>Consider complementary treatments.</td>
<td>• Bright light therapy and acupuncture may be helpful in some cases.</td>
</tr>
<tr>
<td>Compare risk of medication vs risk of untreated illness.</td>
<td>• For women who do not adequately respond to non-pharmacologic interventions, risk comparison includes the risk of being potentially well on medication to being unwell off of medication.</td>
</tr>
<tr>
<td></td>
<td>• Being well off of medication may not be an option for some women.</td>
</tr>
<tr>
<td>Limit the number of exposures.</td>
<td>• Both medications and untreated (or undertreated) symptoms should be considered exposures.</td>
</tr>
<tr>
<td></td>
<td>• Maximizing dosing of a single medication is preferred over lower doses of multiple medications, provided this is effective in remitting symptoms.</td>
</tr>
<tr>
<td>Preferentially consider the SSRI that has worked best for the individual woman in the past.</td>
<td>• Individual SSRIs have similar safety profiles, with the possible exception of paroxetine.</td>
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<td></td>
<td>• Despite individual SSRIs having similar efficacy on a population level, efficacy of an individual SSRI for a given individual patient may vary significantly.</td>
</tr>
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<td></td>
<td>• Switching medications from one of known efficacy to one of unknown efficacy for an individual woman increases the risk for relapse.</td>
</tr>
<tr>
<td>Use the lowest effective medication dose.</td>
<td>• It is more important for the dose to be effective than to be low in order to avoid double exposure from unremitted symptoms.</td>
</tr>
<tr>
<td>Pre-pregnancy is the ideal time to consider medication taper in appropriate cases, such as in women with histories of milder depression who are currently well and wish to be off of medication.</td>
<td>• Tapering medication during pregnancy risks relapse and may necessitate restarting medication, conferring risks of both medication and active illness exposure.</td>
</tr>
<tr>
<td>If the decision is made to use an SSRI in pregnancy, this SSRI should be maintained throughout the duration of pregnancy in most cases.</td>
<td>• Tapering the medication in the 3rd trimester places the woman at risk of antenatal relapse and postpartum depression.</td>
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<td></td>
<td>• While risk of neonatal adaptation syndrome is elevated with late pregnancy SSRI exposure, there is evidence that discontinuing the SSRI at the end of pregnancy may not decrease this risk.</td>
</tr>
<tr>
<td>Dose adjustments are frequently necessary in the second and third trimesters due to multiple pharmacokinetic changes in SSRI metabolism.</td>
<td>• SSRI blood levels are expected to drop over the course of a pregnancy and return to pre-pregnancy levels in the postpartum.</td>
</tr>
<tr>
<td></td>
<td>• Dose adjustments should be made based on clinical symptoms.</td>
</tr>
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Figure 2: Confounding Factors
<table>
<thead>
<tr>
<th>Confounding Factors</th>
<th>Examples/Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>- Race, ethnicity, socioeconomic status, country of origin, country of residence, parity, marital status, birth year, maternal age, paternal age, multiple gestation.</td>
</tr>
</tbody>
</table>
| Indication                          | - *Current* symptoms of anxiety and depression, including severity.  
- Controlling for psychiatric histories is not sufficient to control for confounding by indication.  
- Utilizing pharmacy records to define the exposure group without follow-up interview or blood levels is problematic because a significant proportion of women discontinue or do not start medication once they learn they are pregnant. |
| Postnatal environment               | - Most relevant when looking at long-term outcomes, such as neurodevelopment.  
- Includes active maternal *and* paternal psychiatric illness.  
- Includes multiple psychosocial factors.                                                                                                                    |
| Medical/obstetric illness           | - Hypertension, diabetes, body mass index, epilepsy, mode of delivery, infection, autoimmune illness, level of monitoring (i.e. fetal echocardiogram).                                                                                     |
| Comorbid psychiatric illness        | - Bipolar disorder, schizophrenia, eating disorder, substance use disorder, personality disorder, autism spectrum disorder, trauma.                                                                                           |
| Other exposures                     | - Smoking, alcohol use, illicit substance use, concomitant prescribed or over-the-counter medications (class and number).                                                                                                     |
| Family/genetic history              | - For relevant outcomes of interest (e.g. family history of developmental disorders in studies looking at autism).                                                                                                           |
| Health behaviors                    | - Prenatal vitamins, prenatal follow-up, exercise, nutrition.                                                                                                                                                    |