Are SSRIs safe for pregnant and breastfeeding women?

Shaila Misri, MD, FRCPC Allan Burgmann, MD, FRCPC Demetra Kostaras, MA

abstract

OBJECTIVE To summarize the literature on use of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants for pregnant and breastfeeding women.

DATA SOURCES AND STUDY SELECTION MEDLINE was searched over the past 9 years. An examination of the literature over the last 8 years was included in this review. Primary studies consist of prospective investigations and case studies. Evidence for the safety of SSRIs is limited, but some good studies describe the effects of untreated depression.

SYNTHESIS All studies report that infants are exposed to SSRIs; the drugs can be measured in their plasma and urine. Some evidence shows an increase in minor perinatal complications among infants exposed to SSRIs late in gestation or while nursing. No studies, however, have found an increase in major fetal malformations or pregnancy-related complications. The only investigation of long-term neurodevelopmental outcomes found no negative outcomes among infants exposed to SSRIs during pregnancy. Data are scarce, and readers are cautioned to take into consideration the limitations of the studies reviewed before making definite treatment decisions.

CONCLUSIONS Major fetal malformations and exposure to SSRIs during pregnancy and lactation do not appear to be associated. Some minor perinatal complications have been reported. Data on the long-term developmental outcomes of children exposed to SSRIs in utero and during breastfeeding are limited.

résumé

OBJECTIF Présenter une synthèse des ouvrages scientifiques sur le recours à des antidépresseurs de la catégorie des inhibiteurs spécifiques du recaptage de la sérotonine (ISRS) chez les femmes enceintes et qui allaitent.

SOURCE DES DONNÉES ET SÉLECTION DES ÉTUDES Une recension a été effectuée dans MEDLINE sur une période couvrant les neuf dernières années. La présente étude inclut une analyse des ouvrages publiés au cours des huit dernières années. Les études principales comportent des investigations prospectives et des études de cas. Les données probantes appuyant l'innocuité des ISRS sont limitées, mais certaines études fiables décrivent les effets de dépressions non traitées.

SYNTHÈSE Toutes les études rapportent une exposition chez les nourrissons aux ISRS; la présence du médicament peut être mesurée dans leur plasma et leur urine. Certaines données probantes font valoir une hausse des complications périnatales mineures chez les nourrissons exposés aux ISRS en fin de gestation ou pendant l'allaitement. Par ailleurs, aucune étude n'a constaté une hausse des malformations fœtales majeures ou des complications associées à la grossesse. La seule étude sur l'évolution neurologique n'a relevé aucune répercussion défavorable chez ceux qui avaient été exposés aux ISRS durant la grossesse. Les données se font rares et les lecteurs sont mis en garde de prendre en compte la nature limitée des études passées en revue avant de prendre des décisions thérapeutiques précises.

CONCLUSIONS Les malformations fœtales majeures et l'exposition aux ISRS durant la grossesse et l'allaitement ne semblent pas associées. Certaines complications périnatales mineures ont été rapportées. Les données sur les répercussions à long terme sur le développement des enfants exposés aux ISRS *in utero* et durant l'allaitement sont limitées.

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Treating clinical depression in pregnant and breastfeeding mothers has always required assessing the risk of using a psychotropic medication, which might affect a developing fetus, against the benefits of preventing a mother from becoming incapacitated with depressive symptoms. Increasing experience with the selective serotonin reuptake inhibitor (SSRI) class of antidepressants (eg, fluoxetine [eg, Prozac], sertraline [Zoloft], fluvoxamine [eg, Luvox], and paroxetine [Paxil]) in the peripartum period has made them a feasible option for treating depression during pregnancy and breastfeeding.

This article summarizes current information on using SSRIs during pregnancy and lactation and provides guidelines for physicians, based on the available evidence, to optimize treatment.

Quality of evidence

An extensive literature search over the last 9 years pertaining to use of SSRIs during pregnancy and breastfeeding was conducted using MEDLINE's Ovid database. MeSH words used included selective serotonin reuptake inhibitors, antidepressants, pregnancy, lactation, teratogenicity, and "neurobehaviour."

All articles used in this update were written in English. The update is based on information from scientific, case study, and review articles, looking specifically at each of the SSRIs and their effects on infants during pregnancy and breastfeeding.

There is little conclusive evidence on the effects of SSRI exposure on developing children during gestation and breastfeeding. Detailed information is available, however, on the effects of untreated depression during pregnancy and the postpartum period on mothers, children, and mother-infant relationships.[1,2] Synthesis of these two topics suggests that SSRIs could be a treatment option for women suffering from depression during pregnancy and postpartum.

Dr Misri *is a Clinical Professor in the Departments of Psychiatry and Obstetrics/Gynaecology at the University of British Columbia in Vancouver. She is also Director of Reproductive Psychiatry Programs at St Paul's Hospital and BC Women's Hospital and Health Centre in Vancouver.* **Dr Burgmann** *is a Clinical Instructor in the Department of Psychiatry at the University of British Columbia. He is also Co-director of Consultation Liaison Psychiatry at St Paul's Hospital.* **Ms Kostaras** *is a Research Assistant in Reproductive Psychiatry Programs at St Paul's Hospital and BC Women's Hospital and Health Centre.*

Evolution of depression in pregnancy

As clinical depression evolves, gradual changes in sleep patterns, eating habits, energy level, and concentration slowly start to have a serious effect on progression of pregnancy. Such essential things as managing self-care and maintaining adequate health through regular sleep and eating affect both mothers and developing fetuses. Darkening of mood, social withdrawal, and anhedonia influence the quality of the interaction between women and their families, partners, and social supports. Finally, accumulating feelings of poor self-esteem, hopelessness, and helplessness will make women perceive events and situations as overwhelming, and these feelings could lead to thoughts of self-harm or suicide.

Depression can precede a pregnancy, begin in the 9 months leading up to delivery, or occur postpartum. Women most at risk for developing depression have a psychiatric history of recurrent depressive episodes or prior postpartum depression.[3] The more severe and debilitating the depression, the more important it is to monitor closely for the first signs of an evolving change of mood and to consider prophylactic use of an antidepressant during the pregnancy. If at conception, a woman is just recently recovering from a major depression that required antidepressants, it is crucial that she continue these medications because she is at extremely high risk of relapse. More than 50% of women who discontinue antidepressants need them again later in the pregnancy because of a resurgence of depressive symptoms.[4]

Failing to initiate treatment can lead to progressively worsening depression that greatly compromises maternal-fetal health and can impair bonding and child care in the postpartum period.[5] Studies have found that the children of mothers with untreated postpartum depression are delayed in motor development, have lower intelligence quotients (IQs), and have slower rates of growth when compared with children of mothers whose depression has been successfully treated.[6-8]

The implications of untreated depression during pregnancy and postpartum are so serious that treatment of depression is essential. The vast amount of available research on treating depression during pregnancy and postpartum has focused on the efficacy of antidepressants[9-11] rather than on other treatments, such as cognitive-behavioural therapy. We present evidence on use of SSRIs to help guide physicians on whether to prescribe any of the SSRIs during pregnancy and the postpartum period.

Fluoxetine

The most-studied SSRI with respect to its use in pregnancy and breastfeeding is fluoxetine. No study has found increased rates of major fetal malformations or miscarriages among women treated with fluoxetine when compared with women exposed to tricyclic antidepressants[12] or nonteratogens,[12,13] or historic outcomes reported in surveys of newborns.[14] In the only study comparing first-trimester and third-trimester exposure, an association was found between first-trimester exposure to fluoxetine and increased incidence of three or more minor anomalies, although the nature of these anomalies was not specified.[13]

Fluoxetine use during pregnancy can increase perinatal complications, such as premature delivery, neonatal intensive care unit admissions, poor neonatal adaptation, respiratory difficulty in infants, cyanosis on feeding, jitteriness, lower birth weight, and shorter birth length.[13,15] Evidence also suggests that these perinatal complications are associated with third-trimester exposure to fluoxetine.[13,16] Unfortunately, it cannot be established whether these perinatal complications are wholly or partly due to concomitant use of other psychotropic medications, to alcohol and tobacco consumption, or to degree of severity of depressive symptoms (ie, less weight gain in babies of depressed mothers could be because of the neurovegetative symptom of decreased appetite).

One long-term follow-up study investigating the effect of fluoxetine on fetuses exposed to the drug in utero assessed children up to 86 months old.[17] These children showed no increase in negative effects, compared with unexposed children, with respect to IQ, language, temperament, mood, arousability, activity level, distractibility, or other neurobehavioural areas. In contrast, a substantial effect on the development of children of untreated depressed mothers has been shown.[1,2,4-7,18]

Fluoxetine is present in breast milk at less than 10% of the adult therapeutic dose.[19] Researchers have been able to detect both fluoxetine and its main metabolite, norfluoxetine, in the serum of exposed babies.[20] Two case reports of nursing babies exposed to milk from mothers taking fluoxetine report increased irritability, colic, increased crying, decreased sleep, increased vomiting, and watery stools.[21,22] Another case report found substantial concentrations of both fluoxetine and norfluoxetine in infants' serum and reports of seizurelike activity.[23]

The only published study that has assessed infants exposed to fluoxetine through breastfeeding at a 1-year follow-up examination[20] reported no neurologic or developmental abnormalities. Taken together, these studies cannot directly relate fluoxetine exposure through breast milk to toxicity in infants, but more study is required because only 11 children have been reported on to date.

Sertraline

Case studies of the effects of sertraline on infants exposed in utero report contradictory findings. One case describes a woman who was treated throughout her pregnancy with 200 mg of sertraline.[24] When the medication was stopped in the postpartum period, the infant exhibited signs of withdrawal that included crying, agitation, and restlessness. In a similar case report, however, no such behavioural changes were observed.[25]

Case report data included evidence from one prospective, controlled multicentre study on women counseled during pregnancy after exposure to either fluvoxamine, paroxetine, or sertraline.[26] These women were compared with women counseled after exposure to nonteratogenic agents. Of the 267 women studied, 147 used sertraline at an average dose of 50 mg/d. The authors found no differences between the three drug treatment groups and the control group with respect to rate of major anatomic malformations, stillbirths, miscarriages, prematurity, mean birth weights, and gestation ages.[13]

There are 26 cases of infants exposed to sertraline through breastfeeding, and all find that sertraline and its main metabolite, desmethylsertraline, are present in breast milk at low levels (less than 5 mg/mL).[27] A concentration gradient exists, such that the highest concentration of the drug appears in the hindmilk 7 to 10 hours after maternal dosing.[28] This information can be used to decrease the amount of sertraline to which an infant is exposed. To date, no studies report any adverse short-term effects among infants.[26,27,29] This finding does not suggest, however, that chronic exposure to sertraline will not affect the long-term neurobehavioural development of exposed infants, a topic that has not been investigated thus far.

Paroxetine and fluvoxamine

Pregnancy outcome and perinatal effects of paroxetine and fluvoxamine have been investigated in one study.[26] Of the 267 women taking SSRIs in this study, 97 took paroxetine (at an average dose of 30 mg/d) and 26 took fluvoxamine (at an average dose of 50 mg/d). When compared with a control group exposed to nonteratogenic agents during pregnancy, the women taking paroxetine did not have an

increased risk of major anatomic malformations; higher rates of miscarriage, stillbirths or prematurity; or differences in birth weight or gestational age.[13] In addition to this study, one case report assessed neonatal withdrawal syndrome after maternal use of paroxetine during the third trimester.[30]

Limitations

The number of studies published within the past 9 years is small. Apart from one study of the long-term developmental outcomes of infants exposed to SSRIs during pregnancy,[17] all studies report short-term effects. In addition, most studies are single case reports that are limited in their generalizability. Without long-term and larger studies, effects of SSRI exposure on infants' neurotransmitter systems remain unknown.[31] Thus, implications derived from these studies are limited.

As is true for every drug, determining the fetal safety of SSRIs cannot be ethically tested in clinical trials. It is unethical to test drugs during human pregnancy. Therefore, research proceeds safely and slowly through investigation of cases in which women conceived while taking SSRIs. For treatment clarity, investigation into the safety of SSRIs must answer some more questions. **Table 1** lists areas for future research necessary to increase our understanding of the effects of SSRIs during pregnancy and lactation.

Clinical implications

During pregnancy and breastfeeding, SSRIs should be prescribed when the risk of a depressive episode is greater than the risk of taking the medication. It is strongly recommended that infants be exposed to the minimum amount of medication while still ensuring maternal mental health. **Table 2** provides guidelines for physicians prescribing SSRIs during their patients' pregnancies and lactation.

The US Food and Drug Administration puts fluoxetine, sertraline, and paroxetine in Category B and fluvoxamine in Category C. Fluoxetine could be the best choice; it is the most studied; there have been no reports of increased short-term risk to infants; and it is the only SSRI that has been evaluated, and positive results found, in terms of long-term neurodevelopmental effects.[17] Recent information[14,17] suggests that first-trimester exposure is not associated with increased risk to a developing infant, contradictory to earlier belief.[32] Further research is required to settle this controversy.

Neonatal withdrawal syndrome is repeatedly reported with late-trimester use of fluoxetine,[13,16] sertraline,[24] and paroxetine.[30] Therefore, the dose of the drug should be reduced before delivery to decrease withdrawal symptoms in infants. On the positive side, to date, no studies report an increase in major anatomic abnormalities or miscarriages because of SSRI use during pregnancy, regardless of trimester or length of exposure.[26] Selective serotonin reuptake inhibitors pass through the placental

Table 1. Directions for future research

Undertake larger studies
Control for trimester and length of exposure
Control for dosage and type of SSRI used
Include appropriate control groups, such as mothers not exposed to any teratogens and mothers taking other types of antidepressants. Ensure all participants are matched on maternal age, other medical and psychiatric conditions, degree of depressive symptoms, and abuse of alternative substances, such as tobacco and alcohol
Provide appropriate assessments measuring both short- and long-term neurodevelopmental effects on infants exposed to SSRIs during pregnancy and breastfeeding

Table 2. Guidelines for using SSRIs during pregnancy and lactation

Accurate diagnosis is mandatory; only in cases of moderate to severe major depressive disorder should medication be considered. Comorbid conditions increase the necessity to prescribe medications.
If women conceive while taking SSRIs, discontinuing medication depends on psychiatric history of depression.
History of recurrent episodes of depression predisposes women to relapse during pregnancy and lactation.
Family history of depression increases risk of depression during pregnancy and after delivery.
If discontinuing medication during pregnancy results in relapse of depression, SSRIs might need to be reinstated, as suffering from depression during pregnancy and lactation has negative consequences on mother-infant bonding and children's development.
Levels of medications in milk and infants' serum should be reported to breastfeeding mothers taking SSRIs in order to alleviate anxiety.
Careful monitoring of women who refuse SSRI treatment is necessary; risk of suicide or infanticide can never be overlooked.
Share current research and clinical experience of the pros and cons of SSRI treatment. Always involve family members in the discussion.

Key points

- The literature on the safety of the SSRI antidepressants fluoxetine (eg, Prozac), sertraline (Zoloft), fluvoxamine (eg, Luvox), and paroxetine (Paxil) is limited: mostly case reports and a few prospective studies. Fluoxetine is studied most.
- No studies show an increase in major congenital malformations in infants whose mothers take SSRIs.
- Infants whose mothers take high doses in the third trimester could have some withdrawal symptoms.
- Breastfeeding among mothers taking SSRIs does not seem to be associated with serious problems.
- Women suffering from serious depression, who are not treated during pregnancy or breastfeeding, put themselves and their infants at risk.

Points de repère

- Les ouvrages scientifiques sur l'innocuité des antidépresseurs de la catégorie des inhibiteurs spécifiques du recaptage de la sérotonine (ISRS), comme la fluoxétine (p. ex. Prozac), la sertraline (Zoloft), la fluvoxamine (Luxor) et la paroxétine (Paxil) sont limités (principalement des rapports de cas et quelques études prospectives). La fluoxétine a fait l'objet d'un plus grand nombre d'études.
- Aucune étude ne fait valoir de hausse dans les malformations congénitales majeures chez les nourrissons dont les mères prennent des ISRS.
- Les nourrissons dont les mères prennent de fortes doses durant le troisième trimestre pourraient avoir des symptômes de sevrage.
- L'allaitement par des mères qui prennent des ISRS ne semble pas associé à des problèmes sérieux.
- Les femmes qui souffrent de dépression grave, qui ne sont pas traitées durant la grossesse ou l'allaitement, prennent un risque pour elles-mêmes ainsi que pour leur nourrisson.

barrier and infiltrate breast milk and are consequently passed on to infants. Research thus far shows that use of SSRIs during breastfeeding appears to be safe for newborns who seem to attain their early developmental milestones.

Correspondence to: *Dr Shaila Misri, St Paul's Hospital, Reproductive Psychiatry Program, 2B–250 1081 Burrard St, Vancouver, BC V6Z 1Y6; telephone (604) 806-8589; fax (604) 806-8621*

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