Selective serotonin reuptake inhibitors in pregnancy and infant outcomes

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Abstract
Adequate treatment of depression during pregnancy is very important for maternal, fetal and neonatal health. Selective serotonin reuptake inhibitors (SSRIs) are commonly used antidepressants. According to one American study, approximately 7% of pregnant women were prescribed an SSRI in 2004-2005. First trimester use of SSRIs, as a group, is likely to increase the risk of congenital malformations. Paroxetine may be associated with a small increased risk of cardiac malformations, but evidence remains inconclusive. Fetal exposure to SSRIs closer to time of birth may result in respiratory, motor, central nervous system and gastrointestinal symptoms in about 10% to 30% of newborns (SSRI neonatal behavioural syndrome). These symptoms are usually mild and transient. Persistent pulmonary hypertension of the newborn is an extremely rare consequence of fetal exposure. This information should be used to make individual risk-benefit decisions when considering the treatment of depression during pregnancy. Newborns with late- pregnancy exposure to SSRIs should be observed in hospital for at least 48 h.

Key Words: Depression in pregnancy; Neonatal abstinence; Neonatal behaviour syndrome; Selective serotonin reuptake inhibitors

Introduction
Selective serotonin reuptake inhibitors (SSRIs: fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine and escitalopram) are probably the most widely used antidepressant medications. It is estimated that up to 7% of women in the US were prescribed these drugs during pregnancy in 2004-2005 [1]. It is important, therefore, that those who care for children be aware of the potential impact of these medications on the fetus and newborn. SSRI use in pregnancy has been linked to congenital malformations, changes in newborn behaviour, intrauterine growth restriction, preterm birth, and altered Apgar scores. The present statement focuses on the most prominent outcomes of congenital malformations and newborn behaviour, and supplements the Canadian Paediatric Society's statement "Maternal depression and child development," published in 2004 [2]. Literature reviews were updated in 2010. The levels of evidence used are taken from the Canadian Task Force on Preventive Health [3] (see Table 1).

Approximately 8% to 20% of all women develop symptoms of depression during their lifetime and women in their childbearing years are at particular risk [4]. Women with a history of a major depression are at high risk of relapse with antidepressant discontinuation during pregnancy [5]. Depression, if untreated, can persist through pregnancy and into the post-partum period [6][7]. Suicide is the most serious complication of untreated maternal depression. Other complications that are independent of antidepressant use include slightly higher risk of miscarriage, preterm birth, low birth weight, respiratory distress and increased length of hospital stay [6][8]. There is a negative relationship between depression and maternal-child bonding as well as cognitive, emotional and behavioural consequences for the child. Adequate treatment of depression in pregnant women is thus important for maternal, fetal, and neonatal health and well-being. Moderate to more severe depression often requires treatment with an antidepressant, typically a SSRI.
SSRI exposure and congenital malformations

A 2005 meta-analysis of prospective comparative studies of first trimester exposure to SSRIs showed no increased risk of major malformations above the baseline risk of 1% to 3% in the general population [8]. Since 2005, several published reports using larger data-sets have suggested teratogenicity, in particular an increased risk of cardiac malformations associated with the use of paroxetine [9]. However, the data are inconsistent and other studies were unable to demonstrate an association between SSRI exposure and congenital malformations, including cardiac defects [10][11]. A Canadian study found an increased risk of both congenital malformations and cardiac malformations only with exposure to maternal paroxetine doses greater than 25 mg/day [12]. A 2007 meta-analysis of six cohort studies and one case-control study concluded that first trimester exposure to paroxetine appeared to be associated with an increased risk of cardiac malformations (odds ratio [OR] 1.72; 95% confidence interval [CI] 1.22 – 2.42) [13]. A subsequent meta-analysis performed by some of the same authors reviewed three case-control studies (n = 30,247) and six cohort studies (n = 66,409) [14]. Data from three of the nine studies were previously included in the 2007 meta-analysis. This updated publication concluded that first trimester exposure to paroxetine did not appear to be associated with an increased rate of cardiac defects. The case-control and cohort studies were analyzed separately, but similar results were obtained from both. For the case-control studies, OR was 1.18; 95% CI 0.88 – 1.59. For the cohort studies, the incidence of cardiac malformations in the exposed and control groups was not significantly different (1.14% and 1.09% respectively), and both were within the range reported for the general population.

The most recent meta-analysis was published in 2010 [15]. This publication included 20 case-control and cohort studies that examined first trimester paroxetine exposure and assessed the outcomes of combined cardiac defects (all types of cardiac malformations), specific cardiac defects, and aggregated congenital malformations (cardiac and non-cardiac malformations). Overall, there was increased likelihood of combined cardiac malformation (OR 1.46; 95% CI 1.17 – 1.82) as well as aggregate congenital malformation (OR 1.24; 95% CI 1.08 – 1.43) following paroxetine exposure. It was not possible to determine whether the latter association resulted from including cardiac lesions with other malformations, or whether the association was related to a specific malformation. Although specific cardiac defects (septal defects, right ventricular outflow tract obstruction defects, conotruncal defects, and left ventricular outflow tract defects) were reported in several individual studies, this meta-analysis could not draw conclusions about association with any specific cardiac defect. The authors speculated that it would be unusual for a teratogen to have an effect on a broad range of congenital malformations.

The dilemma concerning the effects of paroxetine arises from several issues. Studies have used different designs, and control groups vary. Consideration of possible confounders may not have been rigorous. In some studies the number of exposed infants was small, and in others, there was simultaneous presentation of dozens of associations with no adjustment for multiple comparisons. Studies that use administrative databases are hampered by the presence of bias by indication, ie, the tendency for more serious illnesses to be treated with higher doses of medication, thereby confounding the impact of the disease and its treatment on the outcomes being assessed. It is plausible that the neurohormonal changes found in clinical depression have an impact on the fetus. There is evidence from a population-based cohort study using administrative data on 119,547 live births that untreated depression has a clinically insignificant but measurable impact on neonatal outcomes such as birth weight and respiratory distress [16]. Unfortunately, assessment of congenital malformations was beyond the scope of this study. There is no simple means of assessing or controlling for illness severity because this indicator is not routinely captured in administrative databases.

Three review articles summarize the evidence to date on the risks of SSRI use in pregnancy [17][18][19]. Each review provides an excellent summary of at least 25 studies, including study design, main findings and study limitations. Overall, these reviews reach the same conclusion: SSRIs as a group are unlikely to be associated with an increased risk of congenital malformations. Although individual studies report associations with specific defects such as omphalocele [10][11] and craniosynostosis [10], these results are not replicated in other studies. Paroxetine may be associated with a small increased risk of cardiac malformations but the evidence remains inconclusive.
SSRI exposure and newborn adaptation

Information on the effects of SSRIs on newborns is derived from case reports, case series and cohort studies, including population-level data from administrative databases. Most available information concerns paroxetine, fluoxetine and sertraline, as these are the most frequently used SSRIs. A syndrome of respiratory, motor, central nervous system and gastrointestinal symptoms, including tachypnea, cyanosis, jitteriness/tremors, increased muscle tone, and feeding disturbance has been noted in 10% to 30% of babies exposed to SSRIs in utero \(^{[16][18][20][21]}\) \(^{[22]}\). Signs and symptoms usually present within hours, are typically mild, and usually resolve within two weeks. Seizures are reported rarely. Because in utero exposure to an SSRI ceases after birth, these signs and symptoms are often referred to as neonatal abstinence syndrome. However, it is unclear whether they result from neonatal withdrawal, from neonatal toxicity following in utero exposure (serotonergic toxicity), or from a combination of both. This review therefore uses the phrase “SSRI neonatal behavioural syndrome” (SNBS) to describe them.

Several studies have attempted to measure the impact of timing and duration of exposure to SSRIs on SNBS. A review of nine cohort studies reported that exposure to SSRIs late in gestation carried an overall risk ratio of 3.0 (95% CI 2.0 – 4.4) of SNBS compared to exposure early in gestation. Paroxetine and fluoxetine have been implicated more often than other SSRIs \(^{[21]}\).

The most concerning possible post-natal association with SSRI exposure to be reported is persistent pulmonary hypertension of the newborn (PPHN): the persistence of high pulmonary vascular pressures after birth that result in persistent right-to-left shunting of blood through the foramen ovale and ductus arteriosus, diminished pulmonary blood flow, and profound hypoxemia. PPHN is associated with significant morbidity and mortality. In a large case-control study, PPHN was defined as severe respiratory failure (need for intubation and mechanical ventilation) and pulmonary hypertension \(^{[23]}\). Twelve of 377 women whose infants had PPHN had been exposed to an SSRI in the last half of pregnancy, compared with six of 836 controls (OR 4.5; 95% CI 1.6, 14.9). By contrast, neither the use of SSRIs in the first half of pregnancy (<20 weeks) nor the use of a non-SSRI antidepressant at any time during pregnancy was associated with an increased risk of PPHN \(^{[17]}\). Subsequent studies have not been able to confirm this association \(^{[24]}\). It has been postulated that PPHN may be a rare expression of the association between fetal exposure to SSRIs and newborn respiratory problems \(^{[19]}\).

Other possible neonatal effects of fetal exposure to SSRIs include lower birth weight and gestational age, respiratory distress, and admission to the NICU \(^{[16][25]}\). Although SSRIs are excreted in breast milk, there is no evidence of adverse effects on the infant; therefore, SSRIs are considered compatible with breastfeeding \(^{[19]}\). At present, there is no conclusive evidence that prenatal exposure to SSRIs increases the risk of adverse neurodevelopmental outcomes, although further studies in this area are needed \(^{[19]}\).

Conclusions

SSRI use during the first trimester of pregnancy is not found to increase risk of major congenital malformations (level II evidence) overall. Paroxetine use in the first trimester may be associated with increased risk of cardiovascular malformation (level II evidence), but studies have been inconclusive. Other SSRIs may increase the risk of specific birth defects and further, sufficiently powered studies are required to assess this.

SSRI neonatal behavioural syndrome, consisting of central nervous system, respiratory, motor and gastrointestinal symptoms, is seen in 10% to 30% of newborns exposed to SSRIs in late gestation. The syndrome is generally mild and self-limited but may be more severe in up to 10% of infants (level II evidence). The most concerning possible association of exposure to SSRIs during the second half of pregnancy is PPHN, although the absolute rate is likely less than one percent (level II evidence).
Recommendations

Based on available evidence, the Canadian Paediatric Society makes the following recommendations:

• Adequate treatment of depression in pregnancy is very important for the health and well-being of both mother and baby. An individual risk-benefit decision must be made concerning SSRI use in pregnancy, bearing in mind the following:
  – SSRI neonatal behavioural syndrome is common but usually mild and transient,
  – The absolute risk for persistent pulmonary hypertension is negligible,
  – There is no evidence that SSRIs as a group increase the risk of congenital malformation, and
  – The evidence for association of paroxetine and cardiac malformations remains contradictory (Grade A recommendation).

• When women who are taking paroxetine are pregnant or contemplating pregnancy, their care providers may wish to consider switching them to another antidepressant or reducing the dose (Grade B recommendation).

• Babies with late-trimester SSRI exposure should be observed in hospital for neurobehavioural or respiratory symptoms for a minimum of 48 h. Families should receive anticipatory guidance on the possible effects of SSRIs on their infant, including the need for observation after birth (Grade A recommendation).

• Postpartum use of SSRIs is not a contraindication to breastfeeding, and women who choose to breastfeed should be supported (Grade B recommendation).

| TABLE 1 |
| Levels of evidence and strength of recommendations |

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least one properly randomized controlled trial.</td>
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<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed controlled trial without randomization.</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group.</td>
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<tr>
<td>II-3</td>
<td>Evidence obtained from comparisons between times and places, with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category.</td>
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<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.</td>
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<th>Grade</th>
<th>Description</th>
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<tr>
<td>A</td>
<td>There is good evidence to recommend the clinical preventive action.</td>
</tr>
<tr>
<td>B</td>
<td>There is fair evidence to recommend the clinical preventive action.</td>
</tr>
<tr>
<td>C</td>
<td>The existing evidence is conflicting and does not allow a recommendation to be made for or against use of the clinical preventive action; however, other factors may influence decision-making.</td>
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<tr>
<td>D</td>
<td>There is fair evidence to recommend against the clinical preventive action.</td>
</tr>
<tr>
<td>E</td>
<td>There is good evidence to recommend against the clinical preventive action.</td>
</tr>
<tr>
<td>F</td>
<td>There is insufficient evidence to make a recommendation; however, other factors may influence decision-making.</td>
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Acknowledgements

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References

SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PREGNANCY AND INFANT OUTCOMES

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