Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are increasingly used during pregnancy and lactation, with 1.8–2.8% exposed pregnancies. Given the risks of untreated maternal depression for both mother and child, adequate treatment is essential. If pharmacological treatment with SSRIs is indicated, the fetal and neonatal effects of SSRIs have to be considered, as SSRIs cross the placenta and are excreted into breast milk. The overall risk of major congenital malformations during SSRI exposure in the first trimester does not appear to be greatly increased. Depending on the variability in pharmacokinetic properties between the different SSRIs and the individual drug metabolism of mother and child, SSRI exposure during late pregnancy can lead to serotonin reuptake inhibitor–related symptoms in up to 30% of exposed infants postnatally. Symptoms are generally mild and self-limited, but need observation during at least 48 h as some infants develop severe symptoms needing intervention. Limited data are available about the long-term neurodevelopmental outcomes after SSRI exposure during pregnancy and lactation, but currently, cognitive development seems normal, while behavioural abnormalities may be increased.

In this article, the available clinical data are reviewed. Additionally, the authors provide a multidisciplinary guideline for the monitoring and management of neonates exposed to SSRIs during pregnancy and lactation.

INTRODUCTION

Depression is a common mental disorder with a lifetime prevalence rate of 16.2%. Women, especially during their childbearing age, are at increased risk for first onset of major depression and have a lifetime rate of major depression 1.7–2.7 times greater than men.2 During pregnancy, prevalence rates vary widely from 1% to 20%, depending on the classification used.3–7

Besides maternal morbidity and mortality, untreated or undertreated depression is associated with perinatal complications like cesarean delivery, prematurity and low birth weight, lower-quality interactions between mother and child and higher levels of psychiatric disturbances among children.4 5 8 Cohen et al9 described that 68% of women who discontinued antidepressant medication experienced a relapse of major depression during pregnancy, compared with 26% who maintained their medication. Given the potential serious consequences of perinatal depression for both mother and child, adequate treatment is essential. However, only few pregnant women seek treatment and only very few, small studies compare obstetric and neonatal outcomes after treated and untreated depression.5 10–12

Treatment of depression consists of non-pharmacological strategies, like psychotherapy, and pharmacological treatment with antidepressants. Although non-pharmacological interventions can be effective, most studies focus on pharmacological treatment.13 Nowadays, selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for the treatment of both depression and anxiety disorders. They are the most commonly used antidepressant medication in general and during pregnancy,2 with 1.8–2.8% pregnancies exposed to SSRIs.12 14–16 It is also used in anxiety disorders. Recently, Yonkers et al17 developed algorithms for periconceptional and antenatal management of depression. As SSRIs are frequently used during pregnancy, practical recommendations for the management of neonates exposed to SSRIs during the third trimester of pregnancy and during lactation are given.

SSRIS

Serotonin is a neurotransmitter released from serotonergic neurons and dysregulation of serotonergic activity may lead to mood and behaviour problems. SSRIs selectively inhibit the reuptake of serotonin into the presynaptic cell, leading to increased levels of serotonin in the synaptic cleft. Other, increasingly used, antidepressants are venlafaxine, a serotonin-noradrenalin reuptake inhibitor (SNRI) or mirtazapine, a noradrenergic and specific serotonin antidepressant (NaSSA).

Differences are observed with respect to the pharmacokinetic properties among SSRIs (table 1).18 Furthermore, pharmacodynamics are affected by enzyme polymorphism and individual drug metabolism.

Side effects of SSRIs and SNRIs tend to be similar and include gastrointestinal symptoms, headache, insomnia and agitation. Tremors, excessive sweating and weight changes are also reported. Somnolence is seen in patients using mirtazapine, due to its antihistaminergic effect.

FETAL EFFECTS

Initially, small studies on humans observed no increased risk of major congenital malformations after in utero exposure to SSRIs or SNRIs, nor as a class, nor individually.19–23 However, more recent data with larger cohorts suggested an association with congenital heart defects, especially septal defects and, in particular, after exposure to...
paroxetine.\textsuperscript{24, 25} However, after adjustment for potential confounders, there was no significant association with cardiac malformations for paroxetine in the first study.\textsuperscript{26} Källén et al extended their data with more patients resulting in a lower OR (1.66, 95% CI 1.09 to 2.53) for paroxetine and risk of any extended their data with more patients resulting in a lower

## Table 1  Pharmacokinetic properties of SSris, SNRIs and NaSSAs

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Time to peak (hours)</th>
<th>Elimination half-life (hours)</th>
<th>Daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>6–10</td>
<td>15–20</td>
<td>20–50</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6–8</td>
<td>96–144</td>
<td>20–50</td>
</tr>
<tr>
<td>Sertraline</td>
<td>4–8</td>
<td>26</td>
<td>50–200</td>
</tr>
<tr>
<td>Citalopram</td>
<td>3–4</td>
<td>36</td>
<td>20–60</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5</td>
<td>27–32</td>
<td>10–20</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>3–8</td>
<td>15–26</td>
<td>50–100</td>
</tr>
<tr>
<td>SNRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>6–9</td>
<td>5–11</td>
<td>75–375</td>
</tr>
<tr>
<td>NaSSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1–2</td>
<td>37 (Female), 26 (Male)</td>
<td>30–45</td>
</tr>
</tbody>
</table>

NaSSA, noradrenergic and specific serotonergic antidepressant; SNRIs, serotonin-noradrenergic reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

### EFFECTS ON THE NEWBORN

A variety of symptoms have been reported after prenatal exposure to SSRIs and to a lesser extent to SNRIs and NaSSAs. These symptoms include tremors, jitteriness, irritability, muscle tone regulation disorders, excessive crying, sleep disturbances, tachypnoea and feeding problems.\textsuperscript{45–47} Less frequently, lethargy, weak cry and convulsions have been reported.\textsuperscript{45, 46} Symptoms generally occur within 2 days after birth and are usually self-limiting.\textsuperscript{44, 45, 48} Some retrospective cohort studies report an increased OR for hypoglycaemia after in utero SSRI exposure. However, indications (like jitteriness or feeding problems) for glucose measurements are not reported. Therefore, no recommendations can be given on whether routine glucose measurements are indicated.\textsuperscript{28, 49–51}

Although non-specific, these clinical features are similar to the signs seen in adult SSRI discontinuation syndrome and resemble the neonatal withdrawal syndrome. However, the clinical picture is indistinguishable from direct toxicity of SSRIs/SNRIs, leading to overstimulation of the serotoninergic system.\textsuperscript{44} Large pharmacological studies to distinguish withdrawal from toxicity are lacking. It is conceivable that the underlying mechanism might be different between patients and specific SSRIs/SNRIs, reflecting withdrawal in one and toxicity in another individual patient. Therefore, the term serotonin reuptake inhibitor (SRI)-related symptoms is used. The SRI-related symptoms occur in approximately 30% of in utero exposed infants.\textsuperscript{45, 48} Several additional factors, like maternal dose and metabolism, the specific SRI used, the individual drug clearance and possibly genetic predisposition, may be needed for symptoms to develop.\textsuperscript{52} Levinson-Castiel et al\textsuperscript{48} used the Finnegan score to identify and classify SRI-related symptoms in 60 prenatally exposed neonates. In the symptomatic group, 10 showed mild and 8 showed severe SRI-related symptoms. No infant required any specific treatment.

The Finnegan score is an objective method used in the observation of neonatal withdrawal symptoms in neonates exposed to hard drugs to identify the patients needing intervention.\textsuperscript{48, 53} A Finnegan score ≥8 indicates severe symptoms with the need of intensification of the observation and measurements. If Finnegan scores remain high, pharmacological intervention should be considered. Although the Finnegan score is a non-validated tool in antidepressant-exposed infants, until now other objective tools are not available.\textsuperscript{53} One should take into account that most studies focus on SSRIs and that less data about SNRIs and NaSSAs are available.

Persistent pulmonary hypertension of the neonate (PPHN) is a serious and sometimes fatal condition occurring in one or two infants per 1000 live births. A case-control study of risk factors for PPHN, found an association between late prenatal exposure to SSRIs and the occurrence of PPHN. In the PPHN group, 8.7% was exposed to SSRIs after 20 weeks of gestation, adjusted OR 6.1 (95% CI 2.2 to 16.8).\textsuperscript{54} Reis et al found an increased risk of PPHN after 15 cases of SSRI exposure in early pregnancy, RR 2.30 (95% CI 1.29 to 3.80).\textsuperscript{28, 54, 55} Drug use late in pregnancy was not documented unless it was prescribed by the antenatal clinic. Two small retrospective cohort studies found no increased risk. Andrade et al\textsuperscript{56} compared 1104 infants exposed to antidepressants in the third trimester (85% SSRIs) and 1104 controls, no difference in prevalence of PPHN between the two groups were found. In Rochester, 16 cases of PPHN among 25,214 deliveries were observed, not between the 808 SSRI users.\textsuperscript{42} In another case-control study, 577 cases of PPHN were reviewed for possible risk factors. SSRI use was not a risk factor. Wilson et al also did not observe SSRI use as a risk factor for PPHN.\textsuperscript{56, 57}

Based on the available literature to date, no reliable conclusions about associations between PPHN and SSRI exposure can be made. However, it appears that the absolute risk of PPHN after SSRI exposure is not greatly increased.\textsuperscript{58}

### NEUROBEHAVIOURAL DEVELOPMENT

Only few studies examined the effect of exposure to antidepressants on neurobehaviour and cognitive functioning. In a review about long-term effects after prenatal and postnatal exposure to SSRIs, 13 studies with 387 children in total were reviewed. In 11 studies (paroxetine=69, fluoxetine=216, fluvoxamine=1, sertraline=8, citalopram=11), no impairment in neurodevelopment after prenatal or postnatal SSRI exposure is demonstrated. Two studies suggested possible subtle effects on motor development (fluoxetine=27, paroxetine=2, venlafaxine=9).
fluvoxamine=1, sertraline=15, not specified=50). A prospective study conducted by Oberlander et al did not observe a relationship with externalising behaviour of 4-year-old children after prenatal SSRi exposure. Klinget et al assessed the long-term neurodevelopment of children who developed SRI-related symptoms. Infants with SRI-related symptoms had normal cognitive ability, but were at increased risk for social-behavioural abnormalities.

Most studies evaluated neurodevelopmental outcome in the first years, which is a poor predictor for neurodevelopmental and cognitive functioning later in life. Also, the majority of these studies concerned fluoxetine and to a lesser extent paroxetine exposure, so the effects of other SSRIs, SNRIs and NaSSAs are even less established. Due to methodological limitations and the lack of large population-based studies with extended follow-up, so far the long-term neurodevelopmental outcome remains unclear.

**EFFECTS DURING LACTATION**

SSRIs and SNRIs are excreted into breast milk in greater or lesser extent. In general, drug excretion depends on several factors like lipid solubility, maternal dose and metabolism, composition of fore and hind milk and time to milk peak concentration. Also, bioavailability of the drug in newborns and the infant’s individual metabolism play a role in the infant’s exposure to the drug during breastfeeding. Thus, there is a great variability in milk concentrations between breastfed infants as well as between the individual drugs.

Several methods, like the theoretic infant dose (ID) and the milk-to-plasma ratio (M/P ratio) are used to establish the amount of drugs excreted into breast milk and the risks during breastfeeding. The M/P ratio represents the ratio of drug concentration in breast milk to drug concentrations in maternal plasma. The theoretical ID is the multiplication of the drug concentration in milk and the amount of milk taken. The relative ID is the percentage of the theoretic ID/kg/day and the maternal dose/kg/day. A relative ID above 10% is considered to be of potential clinical significance. Table 2 gives the relative ID for and the experience with the specific antidepressants. Note that some SSRIs, venlafaxine and mirtazapine are less well studied during lactation.

Both fluoxetine and its effective metabolite norfluoxetine have a long elimination half-life (4–6 days and 4–16 days, respectively) and a relative ID of 6.5–11%. Due to its long elimination half-life, fluoxetine can accumulate in the newborn, subsequently resulting in an increased relative ID. Several case reports describe short-term complications during exposure to fluoxetine in lactation. To minimise infant exposure, milk peak concentrations can be avoided by ‘pump-and-dump’ breast milk during the time interval when peak concentrations in milk is established, however, the time to peak concentration in milk is individually determined.

There is a debate whether breast feeding can ameliorate SRI-related symptoms, which would be conceivable in the case of a withdrawal mechanism. Until now, no comparative studies are available. Whether chronic exposure during lactation to SSRIs, SNRIs or NaSSA affects the developing human brain remains unanswered.

The benefits of breast feeding are well established. When decisions have to be made concerning lactation during maternal use of antidepressants, these benefits should be taken into consideration, especially in this particular group of patients.

**PRACTICAL RECOMMENDATIONS**

**Preconception and pregnancy**

Management of maternal depression or anxiety disorder is best evaluated and adjusted before conception to ensure proper treatment during pregnancy. Regarding the adverse outcomes of maternal depression, recognising the symptoms and adequate treatment are essential. The different treatment options should be carefully evaluated and if possible, non-pharmacological treatment is preferred. If pharmacological treatment is indicated, several factors are of influence in the choice of antidepressants: prior response to pharmacological treatment, gestation, intention to breast feed and the safety profile based on the available experience.

In patients already receiving SSRIs, clinicians, for example, psychiatrists, should evaluate if pharmacological treatment has to be continued. In general, treatment should be unchanged in patients whose symptoms are well controlled. Some patients may be candidates for medication taper and discontinuation or switching to a more ‘safe’ antidepressant may be considered. Meanwhile, their clinicians should be alert to the relapse of depressive symptoms.

**Postnatal management**

After prenatal SSRi/SNRi exposure during the third trimester, infants should be closely observed for SRI-related symptoms, preferably close to their mothers on the maternity ward.

An observation period of at least 48 h should be sufficient to identify infants with SRI-related symptoms needing intervention. Finnegan scores every 8 h are a useful instrument for an objective observation (Appendix A).

<table>
<thead>
<tr>
<th>Selective serotonin reuptake inhibitor (%)</th>
<th>Available data (n)</th>
<th>Available data (n)</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine 6.5–11</td>
<td>116</td>
<td>200</td>
<td>Discourage</td>
</tr>
<tr>
<td>Paroxetine 1.13–1.25</td>
<td>123</td>
<td>131</td>
<td>Preference</td>
</tr>
<tr>
<td>Sertraline 0.2</td>
<td>146</td>
<td>143</td>
<td>Preference</td>
</tr>
<tr>
<td>Fluvoxamine 1.34–1.38</td>
<td>13</td>
<td>14</td>
<td>Consider</td>
</tr>
<tr>
<td>Citalopram 4.4–5.1</td>
<td>72</td>
<td>76</td>
<td>Consider</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>12</td>
<td>9</td>
<td>Consider</td>
</tr>
<tr>
<td>Serotonin-noradrenaline reuptake inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine 6.5</td>
<td>10</td>
<td>15</td>
<td>Consider</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine ±2</td>
<td>10</td>
<td>9</td>
<td>Consider</td>
</tr>
</tbody>
</table>
Use of SSRIs/SNRIs/NaSSAs during pregnancy and lactation

<table>
<thead>
<tr>
<th>Preconception</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug treatment (still) indicated?</td>
<td>Is medication compatible during pregnancy and lactation?</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Taper medication</td>
<td>Monitor release</td>
<td></td>
</tr>
</tbody>
</table>

Table: SSRIS/SNRIs exposure in third trimester of pregnancy

- Finnegan score <4: no SRI-related symptoms.
- Finnegan score 4–7: mild SRI-related symptoms; symptoms are usually self-limiting and supportive care is usually sufficient.
- Finnegan score ≥8: serious SRI-related symptoms; intensification of Finnegan scores every 2 h. If Finnegan scores remain ≥8 in three subsequent measurements, treatment is indicated, for example, with phenobarbital and reallocation to the neonatal department is advised.

Neurodevelopmental follow-up focusing on behaviour should be considered in infants with significant SRI-related symptoms.

Lactation

Currently, there is no evidence that breast feeding should be actively discouraged in maternal use of sertraline or paroxetine; less is known about other antidepressants. There is one exception: due to the long elimination half-life of fluoxetine and the risk of accumulation, we discourage breast feeding in the case of maternal use of fluoxetine.

A summary of the practical recommendations is provided in figure 1.

Overall, when making a decision on the continuation of SSRIs during pregnancy and lactation, the fetal and neonatal effects of SSRIs have to be balanced out to the risks of untreated depression and/or the benefits of breast feeding. Moreover, both clinicians and parents should be aware of the limited available data about long-term neurodevelopmental outcome after SRI exposure during pregnancy and lactation.

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REFERENCES

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