

Paediatric outcomes following intrauterine exposure to serotonin reuptake inhibitors – a systematic review

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ABSTRACT

The use of serotonin reuptake inhibitors (SRIs) is increasing among Danish pregnant women. This systematic review addresses the potential adverse effects on the foetus and child of maternal SRI medication. The literature indicates a slightly increased risk of cardiovascular malformations and persistent pulmonary hypertension of the new-born, while evidence regarding the risk of preterm labour, low birth weight, low Apgar score, prolonged QT interval and miscarriage is less clear. An estimated 20-30% of infants will have neonatal symptoms following intrauterine SRI exposure. The symptoms may be caused by SRI withdrawal, toxicity or their overlap, but symptom aetiology basically remains controversial. The infants may exhibit neurological, gastrointestinal, autonomic, endocrine or respiratory symptoms. Although the symptoms are self-limited, the families may be seriously affected. In general, studies do not address this important aspect. Evidence concerning long-term effects is surprisingly sparse and many studies have important methodological limitations. However, present evidence does not convincingly indicate detrimental long-term effects. Until sufficient safety studies have been carried out, SRI must be used with caution in pregnancy and every treatment of the pregnant woman should be thoroughly considered.

Pregnant women commonly develop inconvenience or disorders in the depressive spectrum [1-3] and the treatment of choice is often serotonin reuptake inhibitors (SRIs), a group of drugs that can be divided into selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). The SRIs are also prescribed for other conditions such as anxiety, panic attacks or obsessive compulsive disorder. In Denmark, the number of SSRI prescriptions for pregnant women increased tenfold from 1997 to 2006 (Figure 1) [4]. The following years SRI consumption among young Danish women aged from 15 to 44 years increased by another 12%, which indicates that the use of these drugs may still be increasing during pregnancy [5].

It is well known that SRI drugs readily cross the placenta, hereby influencing the foetal serotonin level. Early in pregnancy, serotonin takes part in the morphogenesis and development of the foetal brain [1, 6] and later influence of serotonin has been demonstrated in

relation to the circadian rhythm, the cardiovascular system, the respiration as well as the regulation of appetite, mood, temperature, arousal level and perception of pain [7]. Animal studies have shown that SSRI treatment at certain vulnerable embryonic stages may induce changes in foetal brain circulation resulting in long-lasting behavioural effects [6].

The SRIs have been regarded as relatively safe to use in pregnancy; however, based on the aspects mentioned above, scientific attention has been drawn to potential consequences of in utero foetal SRI exposure. The increased risk of persistent pulmonary hypertension of the new-born (PPHN) and cardiac malformations has recently been thoroughly reviewed [3]. This publication therefore primarily focuses on the neonatal adverse effects and the potential long-term developmental and behavioural effects.

METHODS

Literature in English, Danish, Swedish and Norwegian was searched through PubMed until 1 December 2010 using the search terms:

(SRI OR ssri OR serotonin uptake inhibitors OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR fluoxetine OR paroxetine OR snri OR serotonin norepinephrine reuptake inhibitors OR duloxetine OR venlafaxine) AND (pregnancy OR embryo OR fetus OR neonate OR infant OR preschool child OR child OR in utero OR maternal exposure) AND (neurodevelopment OR epilepsy OR autistic disorder OR cognitive OR IQ OR intelligence OR long-term effects OR prenatal exposure delayed effects OR brain development OR behavioural syndrome OR neonatal abstinence syndrome OR withdrawal OR discontinuation syndrome OR adverse effects).

This search produced 2,199 publications.

Subsequently, included publications were limited to meta-analyses, randomised controlled trials, clinical trials, practice guidelines, reviews, guidelines and controlled clinical trials.

Publications were excluded if:

- the publication did not address infants born of mothers who had been treated with SRI during pregnancy,

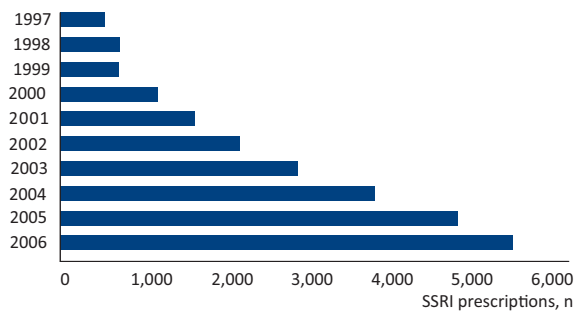
SYSTEMATIC REVIEW

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FIGURE 1

Increase in selective serotonin reuptake inhibitor (SSRI) prescriptions in pregnancy in Denmark 1997-2006.



Several serotonin reuptake inhibitors are commercially available, the consumption is considerable and some of the effects during pregnancy are insufficiently evaluated. Source: [4].

- the publication neither addressed neonatal adverse effects nor long-term effects.

In the remaining 56 publications, the references cited were evaluated, and consequently another 38 potentially relevant publications were identified. Twenty-eight publications were subsequently sorted out: Reviews where better or newer publications had been carried out and publications where thorough reading revealed that they were without relevance.

Three studies were excluded because the data material consisted of less than ten cases, and finally three publications were excluded as they were not accessible.

The Cochrane Library was specifically searched on 2 November 2010, but we found no relevant publication that had not already been identified.

RESULTS

An overview of potential, probable and well-documented effects on the child following in utero SRI exposure is presented in **Table 1** and the results are discussed in detail below.

Cardiac malformations

Several studies have recently emerged documenting that paroxetine treatment during the first trimester will cause a 1% increase of the risk of cardiac malformation (number needed to harm = 100). In addition, a few studies have indicated an increased risk if the foetus had been exposed to fluoxetine and thereby questioned the widespread use of this drug in pregnancy, even though older data did not point to an increased risk. The smallest risk of malformations has been associated with citalopram and sertraline treatment, but rare malformations still cannot be excluded.

There are still very limited data on the teratogenic

safety concerning the newer SSRI drug escitalopram as well as the newer SNRI drugs venlafaxin and duloxetine [3].

Persistent pulmonary hypertension of the new-born

The background incidence of PPHN is reported to be two out of 1,000 new-borns, and the mortality rate may reach 10% [8]. Three studies have shown exposure to SSRI in late pregnancy to increase the incidence of PPHN to 6-12/1,000 [9-11]. Two Swedish register studies [3, 10] have published an adjusted risk ratio and adjusted odds ratio of 3.6 (95% confidence interval (CI) 1.2-8.3) and 3.44 (95% CI 1.49-6.79), respectively. Two studies with limited sample size failed to identify the same association; however, overall the evidence points to an increased risk of PPHN during SSRI treatment in late pregnancy [3].

Preterm labour, low birth weight, miscarriage, low Apgar score, prolonged QT interval

An increased risk of preterm labour and low birth weight have been found in some studies, but the results have not been unequivocal [8]. A large register study where propensity score matching was used to adjust for the confounding effect of maternal depression showed an increased risk of birth weight below the 10% percentile for gestational age [12]. A meta-analysis found the same association [1]. Most studies indicate a small increased risk of lower gestational age and preterm labour [13]. The risk of miscarriage has been addressed in two meta-analyses [14], which found a relative risk of 1.45 (95% CI 1.19-1.77) and an odds ratio of 1.70 (95% CI; 1.28-2.24), respectively.

A review by Tuccori et al from 2009 identified a number of studies indicating the same tendency, but also emphasised important methodological study limitations [2]. Several studies have pointed to increased risk of a low Apgar score, while some studies did not reveal such association [8, 15-19]. A prolonged QT interval has been observed in a few studies, but the clinical relevance of this finding remains unclear, as there seem to be no published cases of SRI-induced arrhythmia associated with QT interval abnormality [2].

Neonatal symptoms

Different definitions of the neonatal symptoms observed following intrauterine SRI exposure have been proposed and terms like "neonatal behavioural syndrome", "serotonin toxicity", "withdrawal", "abstinence syndrome", "serotonin syndrome", "poor neonatal adaptation", "serotonergic excess", "discontinuation syndrome", "transient neonatal symptoms" and "serotonergic central nervous system adverse effects" are widely used. Here we use the neutral term "neonatal symptoms" to avoid



TABLE 1

Overview presenting potential, probable and well-documented effects of in utero serotonin reuptake inhibitor exposure.

Possible complication	Results	Comments
Neonatal symptoms ^a	20-30% display symptoms In general self-limited	Well-documented Cause of symptoms unclear Consequences for families unknown
Long-term effects	No well-documented effects Few studies show light motor development deficit Animal studies show behavioural changes	Few studies Methodological limitations
Miscarriage	Possibly slightly increased risk	Methodological limitations Limited data
Low Apgar score	No clear evidence	
Cardiac malformations	Paroxetine increase risk by about 1% Few studies indicating a slightly increased risk following fluoxetine exposure No observed increased risk regarding citalopram and sertraline	Well-documented regarding paroxetine Some evidence regarding fluoxetine, citalopram and sertraline Lack of evidence regarding escitalopram and serotonin norepinephrine reuptake inhibitors
Pulmonary hypertension of the newborn	Slightly increased risk Absolute risk still low	Methodological problems but results seem consistent
Lower gestational age/preterm labour	Slightly increased risk but results not unequivocal	Methodological limitations
Low birth weight	Slightly increased risk but results not unequivocal	Methodological limitations
Prolonged QT interval	Possibly increased risk	Few studies Clinical relevance unclear

a) See Table 2.

indicating a certain cause (see below). An overview considering typical symptoms is presented in **Table 2**.

The exact causation of these symptoms remains controversial. It is notable that even though the clinical manifestations seem homogenous, the time of symptom appearance may vary considerably [18, 20-23]. Studies of the association between the child's serotonin level/serum level of SRI and appearance or severity of symptoms have not been unequivocal [15, 20, 24]. The adverse effects may be caused by symptoms of withdrawal overlapping effects of serotonin itself. It has also been speculated that the causative factor may be drug influence earlier in pregnancy or the maternal disease itself [25, 26]. However, a study comparing SSRI exposed infants with infants of mothers with untreated depression and a control group without disease seems to limit the possibility of maternal disease itself [22]. There are indications that between 20% and 30% of children who were exposed of SRI in late pregnancy will have neonatal symptoms [9, 16, 20, 23, 27]; a single study even found 77.6% of exposed infants displaying symptoms [22]. A meta-analysis [1] calculated that SSRI exposure late in pregnancy caused an odds ratio of 4.08 ($p = 0.07$) of neonatal symptoms, while a review [21] published an odds ratio of 3.0 (95% CI 2.0-4.4).

Only few studies classified the severity of symptoms by standardised scales [15, 23]. This methodological limitation reduces the validity and makes comparison between the studies difficult. Symptoms are reported to appear within the first three days after birth; however, appearance as late as day 14 has been noted [20, 22,



TABLE 2

Neonatal symptoms		Neonatal symptoms possibly caused by serotonin withdrawal or serotonin toxicity.
Neurological	Tremor, reflex changes, hyper- or hypotonicity, myoclonus, unprovoked movements, jitteriness, convulsions, restlessness, apathy, irritability, tension, abnormal cry, frequent sneezing, abnormal sleep	
Gastrointestinal	Diarrhoea, vomiting, breast feeding problems	
Autonomic	Temperature instability, increased sweating, fever, blood pressure and heart rate changes	
Endocrine	Jaundice, hypoglycaemia	
Respiratory	Respiratory distress, tachypnoea, desaturation while eating	

23]. In general, the symptoms are self-limited and of a duration of between two and three days; still, the effect of symptoms on the involved families may be considerable, but we found no studies specifically addressing this important aspect. Only few reports of more serious complications exist [20, 27]. However, two Danish cases of suspected association between neonatal deaths and intrauterine fluoxetine exposure have recently drawn public attention [3].

Eight studies investigated the need for extraordinary hospitalisation and monitoring. Four studies documented an increased need that was associated with SRI exposure late in pregnancy [9, 13, 17, 28]; two studies showed the same tendency, but did not provide enough power to gain statistical significance [16, 29]; while the last two studies did not find the association likely [18, 20].

Only few studies have investigated the different SRI drugs separately. Paroxetine and fluoxetine are the SRI drugs most often associated with neonatal adverse effects, but the reason for this may just as well be their frequent use in pregnancy as it may be their pharmacological characteristics [21]. A dose-response study specifically found an association between the dose of paroxetine and the risk of transient neonatal symptoms [20]. This dose-response association has not been observed for other SSRI drugs [23]. Interestingly, one study found the infant serotonin transporter (SLC6A4) promoter genotype to be associated with adverse neonatal outcomes after prenatal exposure to SRI [26]. However, the clinical implication of this finding remains unclear.

We only identified one study evaluating SNRI. This study points to an increased risk of neonatal symptoms after intrauterine SNRI exposure, but, in fact, the claimed association was non-significant [19].

In general, many of the studies evaluated have important methodological limitations. There are powerful, unadjusted confounders like smoking, alcohol or other sorts of abuse and very few studies use blinding of investigators. The most powerful of all confounders may be the maternal illness itself and only few studies have tried to adjust for the influence of this confounder on results [12, 13, 18, 25, 30]. In general, no adjustment was made for the severity of illness [12, 13, 18]. However, two recent studies used propensity score matching to adjust for illness severity, and the first study [30] found no difference in neonatal symptoms between early and late SRI exposure, whereas the association between time of exposure and risk of respiratory distress turned out to be significant. The second study [25] showed that withdrawal of SRI treatment 14 days before labour did not affect the risk of neonatal symptoms.

Despite different definitions of symptoms, methodological differences and limitations, there is convincing evidence that 20% to 30% of foetuses exposed to SRI late in pregnancy will have neonatal symptoms post-

natally. In addition, there is a tendency towards augmented hospitalisation and extraordinary monitoring. It is still debatable whether the cause is serotonin withdrawal, serotonin toxicity, the intrauterine exposure or the maternal illness in itself.

Long-term effects

All together, 11 studies of the long-term effects of intrauterine SRI exposure were identified.

Using Bayley Scales of Infant Development (BSID), five publications studied cognitive function, language and motor development in children aged 0-30 months [31-35]. Four of these five studies showed no significant differences between exposed children and a control group [31-34]; further follow-up in three of the studies for up to 86 months still showed no significant differences regarding cognition, language, motor development or mood and behaviour [31-33]. A single study [35] demonstrated significant developmental deficits in the group exposed to intrauterine SRI compared with a group of children exposed of maternal depression without medical treatment.

A recent large Danish study [36] showed that children with second or third trimester exposure to antidepressants were able to sit later than children of women not exposed to antidepressants, but they remained within the normal range of development. At 19 months of age, fewer in the exposed group were able to occupy themselves. However, none of the other developmental milestones measured showed statistically significant associations with antidepressant exposure. In this study, 57 out of the total of 405 cases were treated with other antidepressants than SRI.

Normal neurological development was observed at the age of one year in a small study including 11 children who were exposed to citalopram in utero [37]. Another study found indication of increased stress response three months postnatally [38], and a third publication demonstrated changes in acute pain response both two days and two months after birth [34, 39]. However, follow-up on the latter cohort identified no behavioural changes at the age of four years.

Three studies have addressed the possible association between postnatal maternal mood and long-term children consequences [11, 32, 40]. Two studies demonstrated an association between maternal mood and the risk of aggressive behaviour in the offspring, while SRI exposure seemed to play no role [11, 40]. The last study documented that the severity of the maternal depressive disorder was closely associated with the child's linguistic and cognitive developmental status [32].

Based on the above studies, it is clear that the literature on this subject is surprisingly sparse. Important methodological problems limit the possibility of general-



isation of the study findings. Cognitive and behavioural testing of children are complicated and several different test modes have been carried out; yet, only a single study had sufficient sample size [36]; the rest suffered from limited statistical power. The follow-up period varied among the studies and was in general short-term. Only three studies blinded the investigator [32, 35]; the rest of the studies used methods associated with a serious risk of information bias [36]. Five studies had a risk of recall bias [11, 32, 35, 36, 40]; only two studies tried to adjust for the possible confounding from maternal sickness [35, 36], while none adjusted for the severity of illness. In general, the effect of the individual drugs has not been tested. The best evaluated drug was fluoxetine [31-33], while no long-term safety studies of escitalopram or the SNRI drug group were identified.

In conclusion, the limited literature on this important subject does not convincingly indicate adverse long-term effects on the development of the child, though some evidence of light motor deficits exists. On the contrary, the severity of postnatal maternal depression has been found to have important implications for the development of the child.

DISCUSSION

Severe, untreated depression in pregnancy may itself be detrimental to both the pregnant woman and her child. Some studies indicate that depression in pregnancy increases the risk of preterm labour, low Apgar score, prolonged hospitalisation as well as augmented monitoring, and maternal mood probably has complex long-term influences on infant development [11]. In every case, the risk of untreated depression in pregnancy has to be weighed against the risk of treatment during pregnancy. There is evidence that SRI treatment of the pregnant woman may increase the risk of cardiac malformations, PPHN, low birth weight, preterm labour and spontaneous abortion. Furthermore, some studies found an increased risk of prolonged QT interval, though the clinical significance of this finding remains unclear.

Several studies have estimated that between 20% and 30% of new-borns display neonatal symptoms following intrauterine SRI exposure. Further studies are necessary to reveal if the cause is serotonin withdrawal, serotonin toxicity, long-term intrauterine SRI exposure or if it is induced by the maternal depressive disorder itself. Even though these neonatal symptoms are self-limited there may still be detrimental effects on the families as symptomatic children are often hospitalised while serious diseases like neonatal sepsis or meningitis are suspected, and many of these infants may have unnecessary blood tests performed or receive antibiotic therapy until suspicion of bacterial infection has been ruled out. Neonatal intensive care hospitalisation often

FACTS

Depression and related mood disorders are common in pregnancy.

The prescription number of serotonin reuptake inhibitors (SRI) for pregnant Danish women rose tenfold during the 1997-2006 period.

An estimated 20-30% of infants will have neonatal symptoms following intrauterine SRI exposure. In general, these symptoms are self-limited.

However, the burden on the involved families is unknown and may very well be considerable.

SRI in pregnancy slightly increases the risk of cardiovascular malformations and pulmonary hypertension of the newborn. The evidence regarding long-term effects, preterm labour, low birth-weight, low Apgar score, prolonged QT interval and miscarriage is less unequivocal.

Until more studies are performed, especially concerning long-term effects on behaviour and development, SRI should be used in pregnancy with caution, and every treatment should be thoroughly considered.

causes separation of mothers and babies and the effect of this on breast feeding rates are unknown. This psychological burden for the new vulnerable family may very well be underestimated; however, we found no studies specifically addressing these important aspects.

The long-term effects of intrauterine SRI exposure have not yet been thoroughly investigated. Based on present studies, the evidence of harmful long-term effects are not unequivocal; yet, many studies had serious methodological limitations which must be taken into consideration. There is an urgent need for more studies that adjust for severity of maternal illness and other powerful confounders. Test methods should be standardised and the developmental evaluation of children should be followed into their adolescence. There may be important prognostic differences between the SRI drugs and, ideally, the drugs should be tested separately. In particular, it is crucial to evaluate escitalopram and the newer SNRI if their use in pregnancy should be recommended. Future studies should have the power to detect even moderate effects that may be almost without individual significance as such effects may still have social relevance.

It seems obvious that medical treatment of severe depression in pregnancy is generally indicated; but, on the contrary, there may be milder cases or other treatment indications where risk and adverse effects outweigh possible benefits. Information about side effects should be provided not only regarding the pregnant woman, but also in respect of the risks for the foetus. Until more safety studies have been carried out, especially concerning the long-term consequences, SRI should be used with caution in pregnancy and every treatment should be thoroughly considered.

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CONFLICTS OF INTEREST: none

This review is based on more publications. The total reference list can be ordered from the authors.

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