REVIEW ARTICLE

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Treatment with Selective Serotonin Reuptake Inhibitors in the Third Trimester of Pregnancy

Effects on the Infant

Hedvig Nordeng[1] and *Olav Spigset*[2,3]

1 Department of Pharmacotherapeutics, University of Oslo, Oslo, Norway
2 Department of Clinical Pharmacology, St Olav University Hospital, Trondheim, Norway
3 Department of Laboratory Medicine, Children's and Women's Disease, Norwegian University of Science and Technology, Trondheim, Norway

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Abstract

Pharmacotherapy in pregnant women is often necessary to treat chronic or relapsing depression or anxiety disorders. Studies that have evaluated the safety of selective serotonin reuptake inhibitors (SSRIs) in early pregnancy have not shown an enhanced risk of major congenital malformations and these results may have contributed to the increasing use of these agents during pregnancy. Fewer studies have assessed the safety of SSRIs in the third trimester of pregnancy. This article reviews available human data on the safety of SSRI treatment in the third trimester. The main purpose is to present and discuss the existing literature on the risks to the infant and to suggest treatment guidelines for the use of SSRIs in late pregnancy. The use of SSRIs in the third trimester has shown various perinatal complications, most frequently respiratory distress, irritability and feeding

problems. Further studies are needed to evaluate the frequency of these complications and to elucidate whether the symptoms represent a direct serotonergic effect or are a drug withdrawal effect. Studies have shown conflicting results with respect to whether SSRI exposure decreases birthweight and increases the risk of premature delivery. A few case reports have described intracerebral haemorrhage in neonates after maternal SSRI treatment, but it is not known whether the frequency of such complications is higher than in unexposed neonates. Data on possible long-term effects of prenatal SSRI exposure on psychomotor and behavioural development are very sparse. Our interpretation of the current literature suggests that the risk of not receiving adequate antidepressant treatment in the third trimester when indicated outweighs the risks of adverse events in the infant. Thus, adequate pharmacological treatment should not be withheld from a depressed pregnant woman in late pregnancy. However, the neonate should be monitored for possible adverse effects after maternal use of an SSRI in the third trimester.

Depression is a common disorder, both during pregnancy and in the postpartum period. Recently published studies report a prevalence of depression during pregnancy between 9% and 16%.[1-4] The consequences of untreated depression in these periods can be most severe, not only for the mother but also for the infant. Several studies have found maternal depression and anxiety to be risk factors for preterm delivery, low birthweight, operative delivery and admission to neonatal intensive care units.[5-12] However, in some studies, no differences in neonatal outcomes were found, but in these studies all women received very close antenatal follow-up.[13-15] Discontinuation of maintenance pharmacological treatment can lead to therapeutic failure with a high risk of relapse of depression, which again puts the mother and infant at risk.[16] In current guidelines from the American Academy of Pediatrics for the use of psychotropic drugs during pregnancy, it is recommended to prescribe the lowest dose that will provide adequate control of the woman's illness.[17]

Selective serotonin reuptake inhibitors (SSRIs) have gained wide acceptance in the treatment of depression. Reassuring pregnancy data exist for SSRIs used in early pregnancy, particularly for fluoxetine. Four prospective studies of SSRI use in more than 1500 pregnant women have failed to show an increase in major congenital malformations in newborn infants.[18-21] These observations may have contributed to the increasing use of these agents among depressed pregnant women. However, some concern has been raised about the use of SSRIs in the third trimester of pregnancy and the effects on the infant, and reports of increased rates of admission to special care nurseries, poor neonatal adaptation, decreased birthweight and increased rates of premature delivery after third trimester SSRI exposure have been published.

This review is based upon published literature on SSRI treatment in the third trimester in humans and the effects on the newborn infant. The main purpose of the article is to present available data on the safety of SSRI use in late pregnancy with respect to the infant and to discuss the risk-benefit balance of such treatment.

A MEDLINE search of the literature from the past 20 years was conducted. Search items included each of the SSRIs 'citalopram', 'escitalopram', 'fluoxetine', 'fluvoxamine', 'paroxetine' and 'sertraline', in association with 'depression', 'pregnancy', 'third trimester exposure', 'prenatal exposure', 'adverse events' and 'neonatal complications'. References from relevant articles were further scrutinised to ensure that all potential eligible articles were identified.

Assessments of risk to the newborn after third-trimester SSRI exposure are largely derived from case reports or cohort studies, all of which have inherent methodological limitations. The limitations most often involved include the lack of control groups, selection bias, non-blinded evaluation of

outcome variables and failing to control for important confounding factors. The severity of the depression, maternal age, concurrent illnesses, drug compliance, concomitant use of other drugs, use of illegal drugs or alcohol, tobacco smoking and a history of negative events in previous pregnancies (such as stillbirths and preterm or small-for-gestational-age deliveries) may well influence the outcome in the infants and should ideally be controlled for. When interpreting the existing literature these potential pitfalls should be borne in mind.

1. Perinatal Complications

1.1 Case Reports

Table I[22-35] summarises the published case reports and case series of neonatal adverse events after prenatal SSRI exposure. These reports include information on a total of 22 infants with symptoms indicative of either a SSRI withdrawal effect or serotonin toxicity. The most common symptoms include irritability, jitteriness, increased muscle tone, hyperactive reflexes, agitation, restlessness, continuous crying and feeding problems. More severe reactions, such as respiratory distress and convulsions, were infrequently reported. The onset was most often at the day of birth, but ranged from 0 to 5 days after delivery. The symptoms resolved within 1 week in most cases, but lasted for ≥3 weeks in some infants. Plasma concentration measurements were reported for nine infants: five exposed to paroxetine and four exposed to fluoxetine (table I). The concentrations in the infants were in the same range as was seen after therapeutic use in adults[36] in three of the five cases after paroxetine exposure and two of the four cases after fluoxetine exposure. In addition to these case reports, the Australian Adverse Drug Reaction Committee has published information about 26 reports of neonates with symptoms attributed to third-trimester exposure of paroxetine (n = 10), sertraline (n = 7), fluoxetine (n = 7) and citalopram (n = 2). The most frequent symptoms were agitation, jitteriness, hypotonia and feeding problems, but convulsions, tremor, fever and respiratory distress were also reported. The symptoms generally appeared between the day of birth and day 4 of age and lasted 2–3 days in most cases.[37]

1.2 Studies on Fluoxetine

Fluoxetine plus its active metabolite norfluoxetine have been found in umbilical cord blood in mean concentrations varying from 82 to 147 ng/mL in three studies.[38-40] The total concentration range in the studies was 25–383 ng/mL. These concentrations are below or in the lower part of the concentration ranges that are usually reported after therapeutic use in adults (60–1100 ng/mL).[36] Moreover, norfluoxetine has been found in low concentrations in infant plasma up to the age of 2 months.[40] The slow elimination in infants is not surprising given its elimination half-life of 7–14 days in adults, which would be expected to be even longer in neonates.

Several studies that included more than 350 women taking SSRIs have specifically assessed SSRI use during the third trimester in relation to pregnancy outcome (table II) and most of these included fluoxetine.[19,41-44] In a study of 228 pregnant women taking fluoxetine during various trimesters, the authors' primary concern was related to the infants who were exposed in the third trimester.[19] Compared with the infants of women who took fluoxetine only in early pregnancy, the adjusted relative risk of admission to special-care nurseries was 2.6 (95% CI 1.1, 6.9) and the adjusted relative risk of poor neonatal adaptation was 8.7 (95% CI 2.9, 26.6). However, limitations of the study included that the occurrence of other maternal diseases and the severity of depression were not taken into consideration, that 30% of the women took other psychoactive drugs and that there were more smokers in the third-trimester group. Similar results on neonatal outcome were found in another study.[42] In this study, obstetric and neonatal records were reviewed with respect to adverse neonatal outcome for 53 women taking fluoxetine during the third trimester at least and for 11 women taking fluoxetine in the first and/or second trimesters only. In the third-trimester group, there was a non-significant increase in the frequency of neonatal complications (30.2% vs 9.1%) and admission to special-care nurseries (18.9% vs 9.1%). There was also a non-significant trend towards longer fluoxetine exposure among the infants admitted to special-care nurseries. All but two infants were discharged with their mothers, which led the authors to conclude that the clinical significance of the neona-

Table I. Summary of existing case reports of adverse neonatal reactions after *in utero* selective serotonin reuptake inhibitor (SSRI) exposure

Medication	SSRI dosage (mg/day)	Birthweight (g)/ gestational age (wk)	Start of symptoms after delivery	Main symptoms	Infant serum concentrations measured (ng/mL)[a]	Duration of symptoms	Reference
Paroxetine	30	4160/39	12h	Jitteriness, tremor Increased muscle tonus Increased respiratory rate	Day 1: P 22 Day 2: P 25 Day 3: P 7.6	4 days	22
Paroxetine	10	3100/41	Day 2	Jitteriness Increased muscle tonus Insomnia Feeding problems	No	2 days	23
Paroxetine	40	2690/35	Several days	Irritability, jitteriness Lethargy Increased muscle tonus Feeding problems	No	13 days	24
Paroxetine	20	NR/39	3h	Lethargy Decreased muscle tonus Hypoglycaemia Feeding problems	No	3wk	25
Paroxetine	40 until day 4 before delivery	3500/term	Day 5	Irritability Feeding problems Sleeping problems	No	2wk	26
Paroxetine	10	3330/term	At delivery	Tachycardia Increased muscle tonus Increased reflexes Shivering	No	1.5wk	26
Paroxetine	40 until day 4 before delivery	3500/term	Day 5	Irritability Continuous crying Increased muscle tonus	No	3wk	26
Paroxetine	10	1900/38	At delivery	Jitteriness Increased muscle tonus Feeding problems	No	Several days	27
Paroxetine, desipramine	60, increased to 120 at wk 35	2600/37	Day 4	Hypothermia Irritability, jitteriness Lethargy Feeding problems Necrotizing enterocolitis	Day 5: P 45 Day 15: P 70	3wk	27
Paroxetine, buspirone	20	3500/38	At delivery	Irritability Lethargy Feeding problems Necrotizing enterocolitis	No	3wk	27
Paroxetine, trazodone, diphenhydramine	20	3200/38	40h	Hypoglycaemia Lethargy Irritability Decreased muscle tonus	40h: P 66	5 days	27

Continued next page

Table I. Contd

Medication	SSRI dosage (mg/day)	Birthweight (g)/ gestational age (wk)	Start of symptoms after delivery	Main symptoms	Infant serum concentrations measured (ng/mL)[a]	Duration of symptoms	Reference
Paroxetine, olanzapine	40 until 48h before delivery	3370/term	At delivery	Jitteriness Increased muscle tonus Hypoglycaemia	44h: P <25	8 days	28
Paroxetine	NR	3010/37	12h	Convulsions Respiratory distress Bradycardia Decreased muscle tonus	Day 4: P 220	10 days	29
Fluoxetine	20	3580/38	4h	Irritability, jitteriness Tachycardia Increased muscle tonus Increased reflexes Continuous crying Feeding problems	Cord blood: F 26, NF 54 Day 4: F <25, NF 55	4 days	30
Fluoxetine	0.94 mg/kg	NR/NR	NR	Irritability Continuous crying Feeding problems	Wk 6: F <10, NF 187	NR	31
Fluoxetine, methadone	0.90 mg/kg	NR/NR	NR	Irritability Continuous crying Feeding problems	Day 12: F 252, NF 185	NR	31
Fluoxetine	40	3270/35	4h	Petechiae and erythematous rash Convulsions Jitteriness Tachycardia Increased muscle tonus Increased reflexes	Day 4: F 92	1wk	32
Fluoxetine	20	870/27	Day 2	Irritability Agitation	No	1wk	26
Fluoxetine	≤30 from wk 28 until 5 days before delivery	2700/38	At delivery	Cardiac arrhythmia	No	1mo	33
Sertraline	200	NR/NR	48h after cessation of drug while breast feeding at 3wk after delivery	Agitation, restlessness Insomnia Enhanced startle reaction Continuous crying Feeding problems	No	Several days	34
Sertraline	50 the last 2wk before delivery	2520/35	At delivery	Nystagmus Disorganised breathing	No	3–7 days	35
Citalopram	20–30 from mo 5	4230/term	At delivery	Jitteriness Increased muscle tonus	No	1wk	26

a Suggested reference ranges after therapeutic use in adults (median values from several therapeutic drug monitoring laboratories): fluoxetine + norfluoxetine 60–1100 ng/mL, paroxetine 10–220 ng/mL.[36]

F = fluoxetine; **NF** = norfluoxetine; **NR** = not reported; **P** = paroxetine.

Table II. Systematic studies where separate analyses of selective serotonin reuptake inhibitor (SSRI) exposure in the third trimester have been performed

Medication	Number of cases and controls	Study design	Results	Limitations/comments	Reference
Fluoxetine	Third-trimester exposure, n = 115	Reports to the manufacturer, historical controls	13.0% of the infants exposed during the third trimester had neonatal complications Prematurity (6.0% vs 3.1%) and 'sleep syndrome' (2.7% vs 1.4%) occurred twice as often in infants exposed during the third trimester compared with historical controls, but these differences did not reach statistical significance	Lack of information about outcome for 33% of pregnancies prospectively collected	41
Fluoxetine	Third-trimester exposure, n = 74 First- and/or second-trimester exposure, n = 154 Controls exposed to non-teratogens, n = 254	Prospective controlled cohort study	Infants exposed during the third trimester had significantly higher rates of admission to special-care nurseries (31.5% vs 11.9%), poor neonatal adaptation (31.5% vs 8.9%) and premature delivery (14.3% vs 4.1%) than infants exposed only early in pregnancy Birthweight of full-term neonates exposed during the third trimester was significantly decreased (mean –188g adjusted for confounding factors) compared with infants exposed only early in pregnancy	No control for severity of depression or concurrent disease Clinicians observing the infants were not blinded to infant exposure	19
Fluoxetine	Third-trimester exposure, n = 53 First- and/or second-trimester exposure, n = 11	Retrospective controlled cohort study	Infants exposed during the third trimester had non-significantly higher rates of neonatal complications (30.2% vs 9.1%) and admission to special-care nurseries (18.9% vs 9.1%) than infants exposed only early in pregnancy No significant differences were found between late- and early-exposed infants with respect to gestational age, birthweight, Apgar scores at 5min or timing of maternal-infant discharge	Lack of unexposed control group No control for severity of depression or concurrent disease High concomitant use of other psychotropic drugs (39%)	42
Paroxetine	Third-trimester exposure, n = 55 First- and/or second-trimester exposure, n = 27 Controls exposed to non-teratogens, n = 27	Prospective controlled cohort study	Infants exposed during the third trimester had significantly higher rates of neonatal complications (21.8% vs 5.6%) and prematurity (20.0% vs 3.7%) than the joint group of matched unexposed or early-exposed controls	No control for severity of depression or concurrent disease Controls matched for maternal age, gravidity, parity, smoking, use of alcohol and other non-teratogenic drugs	43
Fluoxetine, sertraline, paroxetine	Third-trimester exposure only, n = 84 Unexposed controls for third-trimester exposure, n = 84	Blinded review of medical records within a Health Maintenance Organisation	Infants only exposed during the third trimester had significantly lower Apgar scores at 1min (6.9 vs 7.7) and 5min (8.4 vs 8.9) and lower gestational ages (38.4 vs 39.2 wks) than matched unexposed controls. There was no significant difference in birthweight among infants only exposed during the third trimester compared with unexposed controls	Controls matched for year of birth, maternal age, mental health and life-time duration of SSRI use	44

tal complications was limited.[42] The authors did not state whether the women in the third-trimester group had a higher concurrent use of psychotropics or not.

No significant difference in birthweight, gestational age or Apgar score at 1, 5 and 15 minutes was reported in a clinical study of fluoxetine use throughout pregnancy compared with unexposed controls.[40] However, no trimester-specific analyses were conducted. In addition, no increased risk of perinatal complications after third-trimester fluoxetine exposure was reported in an early study based upon spontaneous reports to the manufacturer.[41]

1.3 Studies on Paroxetine

In a study of eight women receiving paroxetine 10–40 mg/day, there was no clear association between maternal dose, maternal plasma concentrations and umbilical cord blood concentrations.[38] The umbilical cord concentrations were <1 ng/mL in three of the eight women, whereas the remaining five women had concentrations ranging from 3 ng/mL to 14 ng/mL. These concentrations are below or close to the lower limit of the concentration ranges usually reported after therapeutic use in adults (10–220 ng/mL).[36] One prospective study found that 12 of 55 neonates (21.8%) exposed to maternal paroxetine in the third trimester required prolonged hospitalisation for neonatal complications.[43] In logistic regression analyses controlling for gestational age, maternal smoking and mode of delivery, the odds ratio for respiratory distress was 9.53 (95% CI 1.14, 79.30) after third-trimester paroxetine use compared with a control group of women exposed to non-teratogenic drugs. Other symptoms such as hypoglycaemia, bradycardia, tachycardia, jaundice and feeding problems were also reported, but less frequently. All of the infants recovered following a brief period of intensive care and the symptoms disappeared completely within 2 weeks. The authors concluded that the increased rates of neonatal complications after paroxetine use close to delivery was biologically consistent with the high rates of discontinuation syndrome seen in adults with this particular SSRI.[43]

1.4 Studies on Sertraline

Sertraline has been found in umbilical cord blood after maternal use up to delivery in concentrations ranging from <1 ng/mL to 10 ng/mL.[38] These concentrations are generally below the concentration ranges usually reported after therapeutic use in adults (10–100 ng/mL).[36] No studies specifically present neonatal outcomes after exposure to sertraline in the third trimester. However, two studies with a total of 68 women included the use of sertraline during the third trimester, which represented 17%[44] and 26%[45] of the total study populations using various SSRIs, respectively. The authors of one of these studies[44] stated that the sample size (n = 32 exposed to sertraline) was too small for the detection of drug-specific effects, but that the results were similar with respect to perinatal outcome after prenatal exposure to fluoxetine, sertraline or paroxetine.

1.5 Studies on Citalopram

In two studies including a total of 20 women, citalopram was found in umbilical cord blood in mean concentrations of 27 ng/mL and 41 ng/mL, respectively.[39,46] These concentrations are in the lower part of the concentration ranges usually reported after therapeutic use in adults (15–250 ng/mL).[36] Thereafter, citalopram was detected in infant plasma up to the age of 2 months.[46] No published data have been found for the active S-enantiomer of citalopram, escitalopram.

1.6 Studies on Fluvoxamine

Among studies that evaluated the safety of prenatal SSRI exposure to the infant, only one study has included a single woman using fluvoxamine.[47] No trimester-specific or drug-specific analyses were carried out in this study. Because of the lack of data, no separate analysis can be performed for fluvoxamine.

1.7 Studies on Selective Serotonin Reuptake Inhibitors in General

Studies on the effect of third-trimester SSRI exposure to the infant have reported increased rates of a wide range of perinatal symptoms. In a recently

published study, infants exposed to SSRIs at any time during pregnancy had significantly higher rates of respiratory distress (5.5% vs 2.8%), low Apgar scores (2.2% vs 0.9%), convulsions (0.7% vs 0.2%), prematurity (10.9% vs 5.1%) and low birthweights (7.3% vs 3.3%) than the total birth population in Sweden.[48] In this study, separate analyses of third-trimester SSRI exposure on neonatal outcome were not presented. Also, results from joint analyses of exposure after the 24th gestational week to all kinds of antidepressants (e.g. SSRIs and tricyclics) showed significant associations between the use of antidepressants and respiratory distress, low Apgar scores, convulsions, prematurity and low birthweights.[48] Limitations of this study included a lack of information about indication of use, drug doses and duration of treatment in pregnancy.

In another recent study, newborns <2 days of age exposed to SSRIs up to birth were significantly more tremulous and had a higher degree of sleep and behavioural disturbances than the unexposed control group, after adjustment for gestational age.[49] Early neurobehavioural disturbances were also reported in a study in which SSRI-exposed infants had an attenuated autonomic response to acute pain inflicted by a heel-stick procedure.[50]

In an additional study, infants exposed to SSRIs throughout pregnancy had a significantly higher risk of neuromuscular effects.[39] Between the day of birth and 4 days of age, 20 infants exposed to either fluoxetine or citalopram (maternal dosages of 20–40 mg/day) throughout pregnancy and their unexposed controls were scored for tremor, restlessness, rigidity, shivering, hyper-reflexia, myoclonus and incoordination. Of these symptoms, tremor, restlessness and rigidity were the most common. The exposed infants had a 4-fold increase in the total score compared with unexposed controls. Moreover, 85% of the infants exposed to SSRIs had at least one serotonergic symptom compared with 45% of the unexposed controls. The severity of the symptoms was positively correlated to the concentrations of the serotonin metabolite 5-hydroxyindole acetic acid, but not to the SSRI concentrations, in the umbilical cord blood. The symptoms resolved during the first 2 weeks.[39] In contrast, in a review of obstetric and paediatric records of 138 non-smoking women using SSRIs in pregnancy and their infants, neonatal complications were noted in 20% of the infants. The predominant symptoms were respiratory distress and muscular hypotonia. The authors stated that the neonatal complications in their study did not differ between the specific SSRIs and that the rates for the individual symptoms were comparable to that of an unexposed population.[45]

Studies have shown contradictory results with respect to third-trimester exposure to SSRIs and lowered Apgar scores. The Apgar score rates each of the items (colour of trunk, heart rate, respiration, muscle tone and grimace activity as a response to stimulation) with a score from 0 to 2, giving a top score of 10. In one study, infants exposed to SSRIs during the third trimester had a significantly lower mean Apgar score than unexposed controls both at 1 minute (6.9 vs 7.7) and at 5 minutes (8.4 vs 8.9).[44] This effect was not found in infants only exposed to SSRIs in the first and/or second trimesters or in infants exposed to tricyclic antidepressants.[44] In a second study with medication-free depressed controls, SSRI-exposed infants also had a significantly lower mean Apgar score at 1 minute (7.0 vs 8.2) and 5 minutes (8.4 vs 9.0).[47] On the other hand, in a third study[42] no significant differences in Apgar scores at 5 minutes were found between newborns exposed early or late in pregnancy. Other studies without trimester-specific analyses have reported no significant difference in Apgar scores at 1 minute or 5 minutes between SSRI-exposed infants and unexposed control infants,[39,47] but this does not apply to all of the studies.[48]

1.8 Withdrawal Reactions or Neonatal Toxicity?

The observed symptoms could be caused by either a toxic serotonergic effect, abrupt drug withdrawal or a combination of both. Several researchers have suggested that both serotonergic overstimulation with poor neonatal adaptation and withdrawal problems may occur and that they are difficult to distinguish clinically.[29,39,51] The measurement of drug concentrations in plasma or serum from the neonate and from the umbilical cord may help to determine whether toxicity or withdrawal is present.[29] If drug concentrations are low or undetectable, the clinical effects are more likely to represent withdrawal. In contrast, if a drug is found in plasma

in a concentration at which a pharmacological effect could be expected and then declines, it is more likely to represent toxicity. In three of the studies that evaluated the effects of prenatal SSRI exposure, infant plasma concentrations were measured.[39,40,46] In these studies, the mean infant plasma SSRI concentrations were below or in the lower part of the concentration ranges seen after therapeutic use in adults and no association was found between infant plasma concentrations and adverse effects.[40,46] However, in one study the resolution of symptoms was associated with a rapid decline in neonatal blood concentrations.[39]

In theory, if the symptoms are caused by a withdrawal reaction, earlier relief could be expected in breast-fed infants (as long as the mother is still treated with the antidepressant). In contrast, if the symptoms represent toxic effects, the symptoms could be expected to worsen, or at least not decline, by breast feeding. It has also been suggested that breast milk transfer of SSRIs could interfere with intrauterine exposure, thus making it difficult to distinguish which exposure was responsible for the symptoms.[35] However, because the amounts of SSRIs transferred via breast milk are small, particularly when compared with intrauterine exposure, this factor is most likely insufficient to affect the symptoms caused by intrauterine exposure.[32]

The time interval from delivery to symptom appearance may also be of some help in the determination of the underlying mechanism. In adults, SSRIs have long elimination half-lives (30–40 hours for citalopram and escitalopram, 2–3 days for fluoxetine [7–14 days for the active metabolite norfluoxetine], 15–20 hours for fluvoxamine and 20–30 hours for paroxetine and sertraline). In neonates, the half-lives are most likely even longer than in adults. Therefore, it would be expected that symptoms related to withdrawal would develop later than the symptoms related to toxicity and that it would take at least several days before the infant concentrations were low enough for withdrawal symptoms to develop. If so, possible withdrawal symptoms may be overlooked in patients who leave the hospital early after delivery.

1.9 Are There Drug Differences?

Studies investigating the effect of the various SSRIs in neonates have generally evaluated the drugs together as a group and the limited sample sizes have not allowed subgroup analyses on the specific SSRIs. Consequently, it has not been possible to determine whether some drug-specific effects exist or whether there are differences in the frequency of neonatal symptoms between the various SSRIs. Some researchers have suggested that there might be drug differences in the potential for causing adverse events in neonates within the SSRI group because of the differences in pharmacokinetics.[43] It has been suggested[43] that an increased risk of neonatal complications after third-trimester exposure to paroxetine could be in accordance with an increased risk of discontinuation reactions after paroxetine use in adults compared with the other SSRIs.[52] However, in a recently published study paroxetine did not increase the risk of respiratory distress, convulsions or hypoglycaemia when it was compared with other SSRIs.[48]

As the numbers of pregnant women using each of the SSRIs in the population are unknown and there is certainly an under-reporting of neonatal symptoms, it is not possible to determine drug-specific risks without conducting studies that make direct comparisons between individual drugs. Fluoxetine has generally been more widely used than other SSRIs and more clinical data are thus available. Accordingly, one might speculate that depressed pregnant women have been prescribed fluoxetine relatively more often than other SSRIs. In 13 of the 22 case reports of adverse neonatal effects (59%) paroxetine was the drug prescribed (table I). With regard to withdrawal symptoms, the longer half-life of fluoxetine and its metabolite may, at least theoretically, reduce the risk of symptoms as the drug concentrations decrease more gradually. However, this is yet to be demonstrated in comparative studies and it might be turned to a disadvantage if the mechanism is drug toxicity. In fact, separate analyses for citalopram and fluoxetine revealed significantly higher scores on serotonergic symptoms among infants exposed to fluoxetine at the time of delivery than for the control group, but not for infants exposed to citalopram compared with the

healthy controls matched for confounding obstetric factors.[39]

2. Effect on Birthweight and Gestational Age

Several studies have evaluated the effects of SSRI use in the third trimester in relation to birthweight and prematurity, with some conflicting results. In one study, birthweight of full-term neonates exposed to fluoxetine during the third trimester was significantly decreased (by an average of 188g when controlled for confounding factors) compared with infants exposed to fluoxetine in early pregnancy.[19] In addition, maternal weight gain was an average of 3kg lower in the third-trimester exposure group and may have contributed to the observed decrease in birthweight. A methodological limitation of this study is the lack of adjustment for severity of depression. In a recently published study, infants exposed to SSRIs had a higher risk of preterm delivery (<37 weeks; odds ratio 2.06 [95% CI 1.58, 2.69]) and low birthweight (<2500g; odds ratio 1.98 [95% CI 1.42, 2.76]) than the control group consisting of the total Swedish birth population.[48] Other studies have not found associations between third-trimester SSRI exposure and decreased birthweight.[42,44] However, these studies also have methodological shortcomings, such as the lack of an unexposed control group[42] and the lack of a control for the severity of depression.[42,44] In addition, full-term infants exposed to fluoxetine in the third trimester weighed an average of 200g less than infants exposed in the first or second trimester in a retrospective review of obstetric and neonatal hospital records.[42] However, these findings did not reach statistical significance. In another study, premature birth occurred in 14.3% of infants exposed to fluoxetine in the third trimester, compared with 4.1% of infants exposed early in pregnancy and 5.9% in the unexposed control group. The adjusted relative risk of prematurity after fluoxetine exposure in late pregnancy was 4.8 (95% CI 1.1, 20.8).[19] Similar results were found in a study that compared exposure to paroxetine in the third trimester to a joint group of unexposed and early-exposed controls.[43] In this study, 20.0% of the late-exposed infants were premature compared with 3.7% of the infants with early exposure or non-exposure ($p = 0.02$).

A major difficulty in these studies has been to separate the effect of drug exposure from the effect of the underlying depression or from other factors associated with the depression. As bodyweight loss is common in depression, the depression *per se* could be the factor affecting the normal fetal weight gain. Depression has also been shown to increase the risk of premature delivery and of infants being born small-for-gestational age.[6] In addition, as an adverse drug reaction, SSRIs may cause maternal weight loss, thereby possibly indirectly affecting fetal weight gain. Additional methodological limitations in the published studies were the lack of a control for maternal smoking, gestational age and parity when birthweights were compared. Thus, studies with optimum adjustment for possible confounding factors, with carefully selected control groups and with dose- and trimester-specific analyses, are required to provide conclusive documentation as to whether maternal use of SSRIs may affect fetal growth.

3. Effect on Bleeding

The SSRIs inhibit the uptake of serotonin not only in the central nervous system, but also in platelets and this results in decreased platelet aggregation.[53] After therapeutic use in adults, an increased bleeding tendency has been reported.[54,55] Results from an animal study showed that the offspring of rats given fluoxetine 5.6 mg/kg throughout gestation showed a significantly higher frequency of skin haematomas than unexposed control animals.[56] Although the dose given was approximately 10 times the usual therapeutic dose per kg of bodyweight in humans, the plasma concentrations in the rats were not necessarily correspondingly higher as the rate of drug metabolism is generally considerably higher in rats than in humans.

Four case reports describe intraventricular haemorrhage in the neonate after being exposed to an SSRI during late pregnancy (table III).[57-60] Subarachnoid haemorrhage was reported in two cases, intraventricular haemorrhage was reported in one case and a combination of these was reported in one case. Three of the mothers were treated with paroxetine and one with fluoxetine. In general,

Table III. Summary of existing case reports of intracranial haemorrhage in newborns after *in utero* selective serotonin reuptake inhibitor (SSRI) exposure

Medication	SSRI dosage (mg/day)	Birthweight (g)/ gestational age (wk)	Start of symptoms after delivery	Main symptoms and findings	Reference
Fluoxetine	60	3020/NR	At delivery	Subdural haemorrhage Jitteriness Increased muscle tonus	57
Paroxetine	NR	NR/35	At delivery	Intraventricular and subarachnoid haemorrhage	58
Paroxetine	20	4200/40	6h	Intraventricular haemorrhage Convulsions Lethargy Irritability Apnoea	59
Paroxetine	20	3310/41	3–5h	Subarachnoid haemorrhage Convulsions	60

NR = not reported.

predisposing factors for intracranial haemorrhage in neonates include, among others, prematurity, respiratory distress syndrome, hypoxic injuries, reperfusion of damaged vessels, increased or decreased cerebral blood flow and a large fetal head compared with the maternal pelvic outlet.[61] The incidence of intracranial haemorrhage is reported to be 60–70% in neonates weighing 500–750g and 10–20% in neonates weighing 1000–1500g, indicating that this is not an uncommon complication, at least not in extremely premature newborns.[61] Although data on bodyweight and gestational age were not complete among the SSRI cases, the information that is available indicates that none of the infants were premature. The possible small average decrease in infant weight and gestational length at delivery caused by SSRIs (see section 2) would not be expected to have a clinically significant impact on the risk for neonatal bleeding. In one case report,[59] the authors had tried to exclude other causes of bleeding as thoroughly as possible, but the information in the other reports is insufficient to make it possible to reach a conclusion.

Based upon the current data, it is impossible to state whether the frequency of intracranial haemorrhage in SSRI-exposed infants is higher than would be expected. Thus, the question remains to be resolved as to whether neonatal haemorrhage could be a complication caused by maternal SSRI treatment or not. For the moment, it seems advisable to use SSRIs with caution or alternatively to avoid SSRIs in the third trimester in women with concurrent diseases or other conditions that may increase the risk of bleeding.

4. Effects on Cognitive, Psychomotor and Behavioural Development

Five studies have been performed that evaluated the long-term developmental effects of SSRIs after exposure during pregnancy (table IV).[20,40,46,47,62] The percentages of women using these drugs in the third trimester ranged from 48%[20] to 100%.[40,46,62] Although trimester-specific analyses were not presented in any of the publications, these studies are included here because the majority of infants were exposed during late pregnancy.

In the first study,[20] there were no significant differences in cognitive, language and behavioural development at the age of 16–86 months among children exposed to antidepressants compared with unexposed controls. The multiple regression analysis carried out controlled for trimester of exposure, infant's age, maternal IQ, maternal depression and maternal overall health and socioeconomic status. In a second study,[62] neurodevelopment at the age of 15–71 months was investigated. No significant differences in IQ, temperament, behaviour, reactivity, mood, distractibility or activity level were revealed between exposed children and unexposed controls. In contrast, in a third study,[47] prenatal exposure to SSRIs was associated with lower scores on psychomotor and behavioural development when tested with the Bayley's Scales of Infant Development (BSID-II) at the age of between 6 and 40 months

Table IV. Summary of studies evaluating long-term cognitive, psychomotor development and behavioural effects after exposure to selective serotonin reuptake inhibitors (SSRIs) during pregnancy

Medication	Cases	Study design	Outcome	Limitations/comments	Reference
Fluoxetine or TCA	Exposure to fluoxetine, n = 55 (33% with third-trimester exposure) Exposure to TCA, n = 80 (48% with third-trimester exposure) Controls exposed to non-teratogens, n = 84	Prospective controlled study Blinded assessment of IQ, language and behaviour between the ages of 16mo and 86mo	No significant differences in cognitive, language and behavioural development among children exposed to fluoxetine or TCA compared with unexposed controls	No control for breast feeding. Trimester-specific analyses were not conducted	20
Fluoxetine	Exposure to fluoxetine throughout pregnancy, n = 40 Exposure to TCA throughout pregnancy, n = 46 Non-exposed, non-depressed controls, n = 36	Prospective controlled study Blinded assessment of IQ, language and behaviour between the ages of 15mo and 71mo	There were no significant differences in cognitive, language, psychomotor and behavioural development among children exposed throughout pregnancy to fluoxetine or TCA compared with unexposed controls. The maternal level of depression was negatively associated with the children's IQ and language development	Trimester-specific analyses were not conducted	62
Fluoxetine, sertraline, paroxetine, fluvoxamine	Major depressive disorder and SSRI use, n = 31 (74% with third-trimester exposure) Major depressive disorder, no SSRI use, n = 13	Prospective blinded controlled study. Review of hospital records for information on pregnancy outcome Blinded assessment of cognitive, psychomotor and behavioural development at the age of 6mo to 40mo	Children exposed to SSRIs during pregnancy scored significantly lower on psychomotor and behavioural tests. No difference was found with respect to mental development	Drug- and trimester-specific analyses were not conducted. No unexposed control group Infants were not age-matched when assessing developmental outcome	47
Fluoxetine	At least third-trimester exposure, n = 11 Unexposed matched control group, n = 10	Prospective controlled clinical study	Growth and neurological development of all infants was within normal range at the age of 1y	Long-term outcome data were not presented. Trimester-specific analyses were not conducted. Controls matched for age, parity, time and mode of delivery	40
Citalopram	At least third-trimester exposure, n = 11 Unexposed matched control group, n = 10	Prospective controlled clinical study	Growth and neurological development of all infants was within normal range at the age of 1y	Long-term outcome data were not presented. Trimester-specific analyses were not conducted. Controls matched for age, gravidity, parity, time and mode of delivery	46

TCA = tricyclic antidepressants.

than for infants of unmedicated depressed mothers. Trimester- or drug-specific analyses were not presented. After adjusting for Apgar scores at birth the effect diminished, but the motor developmental scores were still significantly lower than in the unmedicated depressed control group. These findings may imply that prenatal SSRI exposure could have long-term effects on psychomotor development. However, although the level of depression did not differ significantly among the two groups of women, a negative effect of the underlying depression cannot be ruled out. It is possible that women receiving medication had a more severe depression *per se*, but that when receiving medication they maintained a similar level of depression as the untreated control group. Moreover, the infants in the SSRI-exposed group were somewhat younger at the time of testing than the infants in the control group (12.9 months vs 17.7 months, $p = 0.12$). In the last two studies,[40,46] growth and neurological development were within the normal range at the age of 1 year. However, the number of patients included in these studies was low and, as no formal rating scales were used, the methodology might have been too crude to detect minor alterations.

In conclusion, four studies that included nearly 100 mother/infant pairs exposed to SSRIs in the third trimester have not revealed any long-term effects, whereas one study[47] has found some rather subtle effects on motor movement control when SSRI-exposed infants were compared with infants of depressed unexposed controls. The clinical implications of the findings in this study are unknown and the results need further confirmation before firm conclusions can be drawn. Nevertheless, it is reassuring that none of the studies found any influence on cognitive, emotional or behavioural development.

5. Clinical Implications

Having depression or poor emotional health *per se* may have negative effects on pregnancy outcome and on the neurobehavioural development of the infant.[5-12] It has also been shown that discontinuation of SSRIs and other psychotropic drugs during pregnancy can lead to substantial morbidity.[16] In addition, abrupt discontinuation of the antidepressant may cause a withdrawal syndrome with troublesome physical and psychological symptoms.[63] Reinstitution of the antidepressant quickly abolishes the symptoms, but it may take several weeks before the antidepressant effect reappears.

To date, no studies have compared the risk of neonatal complications between depressed women using SSRIs, depressed women not using medication and unexposed healthy women. Such studies would separate the effect of depression from the direct drug effects and could hopefully solve these methodological issues.

5.1 Choice of Drug

When considering starting treatment with an SSRI in the third trimester, prior maternal SSRI use, prior maternal adverse drug reactions to particular SSRIs and possible drug interactions with concurrent medications have to be taken into account. In addition, the best choice for the infant should be considered. Ideally, the benefit-risk assessment in the infant should be based upon adequate data on fetal safety. In a recent study, it was stated that sertraline was transferred to the fetus to a lower degree than the other SSRIs (expressed as the ratio of fetal cord serum concentration to maternal serum concentration), whereas the exposure was highest with fluoxetine and citalopram.[38] However, it is not known whether these differences have any clinical impact. To date, most of the published information is on the use of fluoxetine in pregnancy, thus possibly making this a preferred choice for some women without other prior antidepressant use. The drugs with the least information on use in pregnancy are citalopram, escitalopram, fluvoxamine and sertraline. Paroxetine is possibly not the first-choice drug because of a higher number of adverse case reports than for the other SSRIs and a suggested higher rate of withdrawal symptoms in adults.[52] However, if a woman is already using an SSRI it seems wise to continue treatment with the same drug after the second trimester.

5.2 Maternal Dose

Physiological changes in pregnancy affect the pharmacokinetics of many drugs and may, therefore, introduce the need for dose adjustments. In fact, in a recent study two-thirds of the women using

SSRIs during pregnancy required an increase in their daily dose.[64] Despite the need for sufficiently high maternal doses during pregnancy, both the lack of dose adjustments and the existence of plasma concentrations below the adult therapeutic concentration have been reported in several studies,[38-40,46] thus putting the women at risk of relapse. If available, maternal therapeutic drug monitoring should be used both to minimise fetal exposure and to assure adequate maternal plasma concentrations during pregnancy.

When working with women who are planning to become pregnant, it may be helpful to measure the plasma concentration of the drug before pregnancy, or at least in the first trimester, in order to document the concentration that corresponds to an adequate therapeutic response for the specific individual. If the dose has to be increased because of an increased metabolic rate during pregnancy, the dose should probably be decreased again soon after delivery, guided by further therapeutic drug monitoring if possible. Tapering psychoactive drugs approximately 2 weeks before estimated delivery has been suggested to reduce the risk of neonatal complications.[17] However, the risk of relapse is high in pregnant women with severe depression in pregnancy. Moreover, delivery might take place before the estimated date of delivery, thus reducing the utility of such a recommendation, or it might take place after the estimated date of delivery, thus putting the woman at increased risk of relapse. Thus, in our view, the advantages of such a procedure seem to be outweighed by the disadvantages.

5.3 Follow-Up of the Newborn

Neonates of women using SSRIs at delivery should be closely followed up, if possible by a paediatrician at birth and during the first days after delivery, as most adverse reactions reported have occurred during this time period. The most common clinical signs and symptoms are listed in table V and these should be particularly monitored. It is also important to be aware of other potential signs and symptoms that may need specific treatment. However, few studies state how the infants have been managed and there is no consensus on the treatment of affected infants. Some authors[26] have used the Neonatal Abstinence Score[65] to determine whether pharmacological treatment was necessary in addition to supportive treatment. Supportive care includes swaddling to decrease sensory stimulation, frequent small feedings and observation of sleeping habits, temperature stability, weight gain or loss, or changes in clinical status that might suggest another disease process.[66] Symptomatic treatment with phenobarbital has been suggested,[67] but this therapy has never been systematically evaluated. Obviously, specific pharmacological therapy is indicated if neonatal seizures occur.[65] The parents should be educated about possible signs of neonatal adverse events and, if necessary, they should keep a diary that describes the time and intensity of symptoms. Drug serum concentrations could be measured in the infant when adverse reactions are suspected. As the transfer of SSRIs is low and adverse effects are rare, breast feeding could generally be allowed after an individual benefit-risk assessment if the woman desires to do so.[68-70]

Table V. Clinical signs regularly observed in newborns exposed to selective serotonin reuptake inhibitors in late pregnancy

Most common	Less common
Irritability	Incoordination
Restlessness	Hyper-reflexia
Jitteriness	Myoclonus
Tremor	Increased muscle tonus
Muscular hypotonia	Continuous crying
Rigidity	Sleeping problems
Respiratory distress	Convulsions
Feeding problems	

6. Conclusion

Various perinatal complications have been reported after SSRI use in the third trimester (table V). It not known exactly how often such complications appear and it is unknown whether there is a difference in frequency or in symptom pattern between the individual SSRIs. Studies have shown conflicting results as to whether SSRI exposure decreases birthweight and increases the risk of premature delivery. A few case reports have described intracranial haemorrhage in neonates after maternal SSRI treatment, but it is not known whether the frequency of such complications is higher than in unexposed neonates. Controlled studies are urgently needed to investigate whether there is an increased bleeding

tendency in the neonates and also whether the women themselves are at increased risk of blood loss at birth. Data on possible long-term effects of prenatal SSRI exposure on neuro- and psychomotor development are very sparse, but published studies have not demonstrated any detrimental long-term cognitive, emotional or behavioural effects. To date, no studies have compared the risk of neonatal or long-term complications between depressed women using SSRIs, depressed women not using medication and unexposed healthy women. Such studies would separate the effect of depression from the direct drug effects. However, it could be discussed whether it is feasible from an ethical point of view to perform such studies with a randomised design, as current guidelines and reviews state that pharmacological treatment is necessary to manage depression during pregnancy.[17,71,72] Studies to elucidate the most appropriate handling of neonates with SSRI-related symptoms are also clearly needed.

Although adverse effects in the newborn have been described, it should be taken into account that untreated depression may have negative effects on both the fetus and the infant. Moreover, the published literature is ambiguous as to whether some of the symptoms reported are caused by the SSRI exposure *per se* and not by other factors, e.g. related to the maternal disease. Consequently, the risk of not receiving adequate antidepressant treatment in the third trimester when indicated most likely outweighs the risk of adverse reactions in infants. Tapering the SSRI dose before delivery is not recommended, as it will most likely put the woman at risk of relapse of depression.

We suggest that a woman with depression should not be withheld adequate pharmacological treatment in late pregnancy. However, the neonate should be monitored for possible adverse effects. It is also necessary, from a general point of view, to follow depressed women and their infants closely both during pregnancy and in the postpartum period.

7. Note Added in Proof

Very recently, a study on cases of suspected neonatal withdrawal symptoms reported to the WHO adverse drug reaction database was presented.[73] In this database, spontaneously reported suspected adverse drug reactions from more than 70 countries are collected. In total, 93 cases of SSRI-induced neonatal withdrawal syndrome were found, of which 64 cases were associated with paroxetine, 14 with fluoxetine, 9 with sertraline and 7 with citalopram. By using a Bayesian statistical analysis, these numbers were considered to be high enough to confirm a possible causal reaction, with paroxetine emerging as the most likely offending drug.

In an accompanying comment article,[74] it was pointed out that a well defined clinical indication and a clear threshold to prescribe SSRIs during pregnancy are necessary. Moreover, it was stated that we need a better understanding of SSRI effects on the growing brain, including studies investigating a possible genetic vulnerability as well as mechanistic studies in animals.

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Correspondence and offprints: Dr *Hedvig Nordeng*, Department of Pharmacotherapeutics, University of Oslo, PO Box 1065 Blindern, Oslo, No-0316, Norway.
E-mail: h.m.e.nordeng@medisin.uio.no