ORIGINAL ARTICLE

Effects of Exposure to Selective Serotonin Reuptake Inhibitors During Pregnancy on Serotonergic Symptoms in Newborns and Cord Blood Monoamine and Prolactin Concentrations

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Background: Selective serotonin reuptake inhibitors (SSRIs) have gained wide acceptance in the treatment of mental disorders in pregnant women, but there seems to be an increased risk for neonatal adaptation problems after exposure to SSRIs in late pregnancy. We aimed to investigate the perinatal sequelae of infants exposed to SSRIs during their fetal life and the relationship of these symptoms to the cord blood monoamine and prolactin concentrations.

Methods: We conducted a prospective, controlled, follow-up study with 20 mothers taking 20 to 40 mg/d of either citalopram or fluoxetine for depression (n=10) or panic disorder (n=10) and their infants and 20 matched controls not receiving psychotropic medication for confounding obstetric characteristics. Maternal cord blood and infant citalopram, fluoxetine, and norfluoxetine, cord blood monoamine and metabolite, and prolactin concentrations were measured. The newborns underwent standard clinical examination and specific assessment of serotonergic symptoms during the first 4 days of life and at the ages of 2 weeks and 2 months.

Results: There was a statistically significant (P=.008, V=15, n=20 for both groups), 4-fold difference in the serotonergic symptom score during the first 4 days of life between the SSRI group and the control group. The SSRI-exposed infants had significantly lower cord blood 5-hydroxyindoleacetic acid (5-HIAA) concentrations (P=.02, t_{31}=2.57) compared with the control group. A significant inverse correlation (r_s=–0.66, P=.007, n=15) was seen between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the SSRI-exposed but not the control infants.

Conclusions: Infants exposed to SSRIs during late pregnancy are at increased risk for serotonergic central nervous system adverse effects, and the severity of these symptoms is significantly related to cord blood 5-HIAA levels.

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MOOD AND anxiety disorders such as depression, panic disorder, and obsessive-compulsive disorder are common in women during their childbearing years. Several studies[1-3] have indicated that the prevalence of these mental illnesses is similar during pregnancy and higher after delivery than in nonpregnant women of fertile age. For instance, the prevalence of depression has been reported to be between 10% and 16% during pregnancy.[1] Thus, there is a clinical demand for effective and safe treatment of these patients with psychotropic medication, taking into consideration the effects of maternal drug therapy on the developing fetus. In the treatment of mood and anxiety disorders during pregnancy and lactation, the selective serotonin receptor inhibitors (SSRIs) are often preferred over tricyclic antidepressants and benzodiazepines because of good documentation of efficacy, relatively few adverse effects, and safety in overdose.[4]

Although the pharmaceutical industry has not yet promoted the use of SSRI drugs during pregnancy due to lack of safety documentation, the off-label use of these drugs has been common for several years. Although no conclusive data are available, it can be suspected that SSRIs are the most widely used class of antidepressant drugs not only in the general population but also in pregnant women in Western countries. Accordingly, epidemiologic studies of hundreds of women exposed to SSRIs during pregnancy have been published, which indicate that a mother's use of SSRIs during pregnancy does not increase the rate of major fetal malformations.[5-9] However, results from medical record reviews have suggested increased neonatal adaptation problems in infants of mothers exposed to fluoxetine during the

third trimester of pregnancy.[9,10] In the study by Cohen et al,[9] third-trimester exposure to fluoxetine was related to a 3-fold higher rate of newborn complications compared with first- or second-trimester exposure. Furthermore, case reports of proposed neonatal adaptation problems have attempted to characterize newborns' symptoms of SSRI exposure during pregnancy.[11-15] These symptoms include irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties, and even convulsions. However, there is no information on the prevalence of serotonergic sequelae in newborns after maternal intake of SSRIs during pregnancy. Furthermore, there has been debate over whether these symptoms reflect true adaptation problems after abrupt cessation of exposure to SSRIs at delivery or if they are, in fact, simply caused by serotonergic overstimulation due to SSRI exposure during late pregnancy.[16] Nevertheless, to our knowledge, no prospective clinical trial has addressed the effects and risks of SSRI exposure during late pregnancy on the outcome of infants during the perinatal period.

Characteristics of the clinical effects of serotonergic overstimulation and adaptation problems on discontinuation of SSRI drug therapy have been well characterized in adults.[17,18] The analysis by Sternbach[17] of the published case reports characterized the clinical consequences of serotonergic overstimulation as mental state changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. Later, these effects were slightly modified to develop and validate a specific scale for assessment of the presence and severity of symptoms during serotonergic overstimulation by Hegerl et al.[19] The common clinical symptoms, such as dizziness, nausea, tremor, anxiety, and insomnia, of SSRI withdrawal syndrome are largely overlapping with those of serotonergic overstimulation, which sometimes makes the differentiation of these 2 syndromes difficult.[17-19]

In this study, we have prospectively assessed the serotonergic symptoms in newborns exposed to SSRI treatment during fetal life compared with nonexposure, using a scale developed according to definitions by Sternbach[17] and Hegerl et al.[19] In addition, this study aimed to characterize the effects of SSRI exposure on the cord blood monoamine and prolactin concentrations and to study their relationship with the clinical symptoms observed.

METHODS

PATIENTS AND ETHICS

Forty pregnant women were enrolled in this controlled, prospective, follow-up study between January 1, 1997, and August 31, 2000. The patients were referred to the study clinic by primary care physicians. Twenty of these women were taking SSRIs (20- to 40-mg/d of citalopram, n=10, or fluoxetine, n=10) during their pregnancy and lactation. The indication for the SSRI treatment was depression (n=10) or panic disorder (n=10). In the SSRI group, one patient took concomitant thyroxin once daily for hypothyroidism, and 3 patients had occasional use of benzodiazepines (alprazolam or lorazepam). The SSRI treatment was started by psychiatrists who were not part of the study team, and these psychiatrists also followed up the clinical efficacy and need for dose adjustments during the study. This study was designed to characterize the nature of perinatal effects after exposure to SSRIs, and no objective measurement of efficacy of the SSRI treatment was included in the protocol.

Table 1. Demographic Characteristics of the SSRI and Control Groups*

Variable	SSRI Group	Control Group	*P* Value
Age, y	35 (5.2)	30 (4.2)	.002
Gravidity, No. of patients	3 (1-8)	2 (1-6)	.08
Parity, No. of patients	1 (0-5)	1 (0-4)	.11
Smoking, No. of patients	6	4	NA
Light use of alcohol, No. of patients	2	0	NA
Exposure of SSRI before delivery, wk	38 (7-41)	NA	NA
SSRI dose during pregnancy, mg/d†			
Citalopram	20 (20-40)	NA	NA
Fluoxetine	20 (20-40)	NA	NA
Concomitant occasional use, No. of patients			
Benzodiazepines	3	0	NA
Other medication	1	1	NA

Abbreviations: NA, not applicable; SSRI, selective serotonin reuptake inhibitor.

*Data are given as mean (SD) or median (range) for 20 patients in each group. Women in the SSRI group were taking citalopram or fluoxetine.

†During pregnancy 2 mothers received 30 mg/d and another 2 mothers received 40 mg/d of citalopram and 1 mother received 40 mg/d of fluoxetine; otherwise all mothers received 20 mg/d of either citalopram or fluoxetine.

A control group of 20 healthy women who were not taking psychotropic medication was prospectively and individually matched for confounding obstetric characteristics (age, gravidity, parity, duration of pregnancy, and time and mode of delivery) at the time of delivery. This matching was successful for all characteristics but age, for which there was a statistically significant difference between the SSRI group and the control group (**Table 1**). Moreover, 2 (10%) of the women in the SSRI group had a habit of occasional light alcohol use during pregnancy compared with none in the control group. One patient in the control group took thyroxin for hypothyroidism; otherwise, none of the patients in the control group used any medications.

The study protocol was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital, and written informed consent was obtained from all mothers before enrollment in the study.

ASSESSMENTS

Venous blood samples (5 mL) were drawn from mothers taking SSRIs just before drug intake (trough value) during the third trimester (gestational weeks 36-38) of pregnancy. Also, blood samples (5 mL) were drawn at delivery from the umbilical vein for measurement of the following: serum prolactin, plasma noradrenaline, 3,4-dihydroxyphenylglycol (DHPG), dihydroxyphenylacetic acid (DOPAC), whole blood serotonin, 5-hydroxyindolacetic acid (5-HIAA), homovalinic acid (HVA) concentrations, and newborn drug and metabolite concentrations. Samples could not be obtained or were destroyed due to warming in 3 patients in the SSRI group and 2 patients in the control group. In addition, sample volume in 2 patients in the SSRI group was sufficient for the measurement of prolactin only.

Table 2. Pregnancy and Delivery Outcomes of the SSRI and Control Groups*

Variable	SSRI Group	Control Group	*P* Value
Duration of pregnancy, d	274 (251-291)	279 (254-289)	.06
Mode of delivery, No. of patients			
Vaginal	16	17	NA
Cesarean delivery	4	3	NA
Infant sex, No. of patients			
Female	8	9	NA
Male	12	11	NA
Weight at birth, g	3455 (457)	3534 (438)	.48
Body temperature at birth, °C	36.9 (0.6)	37.0 (0.4)	.53
Apgar score			
1 min	8.4 (1.1)	8.5 (1.6)	.63
5 min	8.6 (0.9)	9.0 (1.2)	.07
15 min	8.8 (0.8)	9.4 (0.6)	.02
Full breastfeeding, wk†	9 (0-43)	9 (0-26)	.58
Total breastfeeding, wk†	17 (0-52)	24 (2-52)	.87
Infant weight at 2 mo, g	5423 (476)	5458 (626)	.86

Abbreviations: NA, not applicable; SSRI, selective serotonin reuptake inhibitor.

*Data are given as mean (SD) or median (range) for 20 patients in each group. Women in the SSRI group were taking citalopram or fluoxetine.

†Observed for 52 weeks.

Blood samples (2 mL) were taken from infants 2 days and 2 weeks after delivery in the morning before maternal drug intake and breastfeeding for the measurement of plasma drug and metabolite concentrations.

At delivery, all infants underwent standard clinical examination. On each of the subsequent 4 days and at 2 weeks and 2 months after delivery, the neurologic status of the infants in both study groups was evaluated by pediatricians trained to perform the examinations using a specific scale for symptoms seen in a state of serotonergic overstimulation, as first described by Sternbach[17] and later developed and validated into a scaling system for adults by Hegerl et al.[19] This examination included recordings of systolic and diastolic blood pressure, heart rate, and body temperature, which were taken on each occasion before blood sampling. In addition, each of the serotonergic symptoms, including myoclonus, restlessness, tremor, shivering, hyperreflexia, incoordination (assessed by general movements[20]), and rigidity, were given a score from 0 to 3 according to severity (0 indicates none; 1, mild; 2, moderate; and 3, severe). In addition, nausea during the past 24 hours was assessed with the same scoring system but was not included in the total score count. The assessment of the serotonergic symptoms by a pediatrician was designed to be blinded with regard to the study group, but this blinding was not completely sustained in this clinical setting, which may somewhat affect the results. Brain ultrasound and magnetic resonance imaging (MRI) examinations were performed for the infants in the SSRI group both in the neonatal period (38 to 42 postconceptional weeks) and at the age of 2 months. The MRI could not be assessed in 3 infants in the neonatal period.

BIOANALYTICAL METHODS

The plasma concentrations of citalopram were analyzed using a reversed-phase high-performance liquid chromatography (HPLC) with fluorescence detection after alkaline liquid-liquid extraction.[21,22] The interassay coefficient of variation (CV) was 10% for citalopram at the mean concentration of 250 nmol/L (to convert citalopram to micrograms per liter, multiply by 0.33). The lower limit of quantitation was 3 nmol/L, and for calculations, drug concentrations lower than 3 nmol/L were substituted by the value 1.5 nmol/L. Fluoxetine and norfluoxetine concentrations were measured by HPLC with UV detection according to Kelly et al.[23] The interassay CVs were 2.2% and 3.4% for fluoxetine and norfluoxetine at mean concentrations of 120 and 125 nmol/L, respectively (to convert fluoxetine and norfluoxetine to micrograms per liter, multiply by 0.32 and 0.30, respectively). The lower limit of quantitation was 10 nmol/L for both analytes.

The plasma concentrations of noradrenaline, DHPG, and DOPAC were measured by HPLC with coulometric electrochemical detection[24] with interassay CVs of 5.9%, 3.3%, and 1.8% at mean concentrations of 1.4, 5.2, and 15.2 nmol/L, respectively (to convert noradrenaline, DHPG, DOPAC to micrograms per liter, multiply by 0.17). The corresponding quantitation limits were 0.05, 0.5, and 1.0 nmol/L. The concentrations of serotonin, 5-HIAA, and HVA were measured by HPLC with electrochemical detection.[25] The interassay CVs were 5.5%, 5.5%, and 4.3% for serotonin, 5-HIAA, and HVA at mean concentrations of 440, 43.5, and 91.3 nmol/L, respectively (to convert serotonin, 5-HIAA, and HVA to micrograms per liter, multiply by 0.18, 0.19, and 0.18, respectively). The limits of quantitation were 3.0 nmol/L for serotonin and 5-HIAA and 6.0 nmol/L for HVA. The cord blood serum prolactin was assayed by a noncompetitive immunoradiometric assay kit (Spectria Prolactin IRMA; Orion Diagnostica, Espoo, Finland) with an interassay CV of 3.1% at 3789 mU/L and lower limit of quantification of 50 mU/L.

DATA ANALYSIS

The results are given as means and SDs or medians with ranges. The paired *t* test or Wilcoxon signed rank test (for nonnormal and categorical data) was used for the statistical comparison of demographics, pregnancy and delivery outcomes, and umbilical vein monoamine and prolactin concentrations between the SSRI group and the control group. Because of nonnormal distribution, the monoamine and prolactin concentration data were log transformed before statistical testing. The differences in serotonergic symptom scores between the groups at each time point and the difference in the symptom scores between days 1 and 4 (after dividing the score result by 4, ie, the number of measurements) and 2 weeks after delivery were analyzed using the Wilcoxon signed rank test. Between-group comparison of the likelihood of getting any serotonergic symptom on days 1 to 4 was performed using logistic regression analysis. For all correlation testing, the Spearman rank test was used. The 2-tailed level of statistical significance was set at $\alpha = .05$. All the data were analyzed with SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

PREGNANCY AND DELIVERY OUTCOME

The exposure to SSRI treatment during pregnancy ranged from 7 to 41 weeks. In the SSRI group, 9 women were exposed to citalopram and 6 women to fluoxetine already during the first trimester of pregnancy. No malformations were detected. The duration of pregnancy was similar in the SSRI group and the control group. The Apgar score at 15 minutes was lower in the SSRI group ($P = .02$). No significant difference was observed in breastfeeding or the infant weight at birth or 2 months of age between the groups (**Table 2**).

Table 3. Characterization of Perinatal Serotonergic Symptoms in 20 Infants Exposed to Treatment With 20 to 40 mg/d of Citalopram or Fluoxetine (SSRI) or 20 Infants With No Exposure to Psychotropic Medication (Control) During Pregnancy*

	Days 1 to 4		2 Weeks		2 Months	
Variable	SSRI	Control	SSRI	Control	SSRI	Control
Blood pressure, mm Hg						
Systolic	69 ± 10	70 ± 11	93 ± 8	89 ± 10	98 ± 13	96 ± 11
Diastolic	42 ± 8	40 ± 10	56 ± 8	54 ± 11	67 ± 10	61 ± 12
Heart rate, beats/min	131 ± 8	128 ± 9	153 ± 19†	141 ± 14	145 ± 14	139 ± 20
Body temperature, °C	37.3 ± 0.2	37.3 ± 0.2	36.9 ± 0.2	36.8 ± 0.2	37.0 ± 0.4	37.0 ± 0.3
Serotonergic symptom score						
Myoclonus	4	0	0	0	0	0
Restlessness	29	4	2	1	2	0
Tremor	38	7	2	0	0	0
Shivering	12	7	2	1	0	0
Hyperreflexia	11	3	0	0	0	0
Incoordination	2	0	0	0	0	0
Rigidity	25	9	2	1	3	1
Total	**121†**	**30**	**8**	**3**	**5**	**1**

Abbreviation: SSRI, selective serotonin reuptake inhibitor.
*For vital signs, all data are given as mean ± SD. For days 1 to 4, the data are presented as the mean value of 4 measurements for vital signs or as sum of 4 measurements for serotonergic symptom score for both study groups.
†$P<.05$ compared with control.

Results from brain ultrasound or MRI examinations in the SSRI-treated infants revealed no pathologic or structural abnormality, except for a rather common and benign[26,27] caudothalamic cyst in 6 infants at term. Only one of these cysts could still be seen at the age of 2 months. In addition, 1 infant had a thin subdural hematoma after vacuum extraction as the method of delivery.

PERINATAL SEROTONERGIC EFFECTS

There were no major differences in the vital signs of the infants during the first 2 months of life (**Table 3**). The only difference was significantly higher heart rate in the SSRI group compared with the control group ($P=.049$, $t_{31}=2.039$) at the age of 2 weeks. All effects on vital signs were similar between citalopram and fluoxetine subgroups.

A clear difference was seen in the perinatal clinical serotonergic symptoms between the study groups (Table 3). There was a statistically significant ($P=.008$, V=15, n=20 for both groups), 4-fold difference in the serotonergic symptom score during the first 4 days of life between the SSRI group and the control group. The most prominent symptoms in the newborns included tremor, restlessness, and rigidity (Table 3). One of the newborns in the SSRI (fluoxetine) group had myoclonus, which is considered a specific symptom of serotonergic overstimulation in adults but rarely seen in newborns. On days 1 to 4, 17 infants in the SSRI group vs 9 infants in the control group had at least one serotonergic symptom (odds ratio, 6.9; 95% confidence interval, 1.6-29.2; $P=.008$). Also, the number of days with symptoms per infant was significantly ($P=.01$, V=19.5, n=20) higher in the SSRI-exposed infants compared with controls, whereas the total number of symptoms by infant on any day was only marginally ($P=.055$, V=22, n=20) higher in the SSRI group. However, there was a significant ($P=.02$, V=31.5, n=20) reduction in the symptom score from 1 to 4 days to 2 weeks in the SSRI group, and no significant difference in the symptom scores was evident between the SSRI group and the control group at 2 weeks ($P=.38$, V=5, n=20) or at 2 months ($P=.22$, V=7, n=20). None of the infants in either study group were recorded with nausea or feeding difficulties. Exclusion of the 3 mothers with occasional use of benzodiazepines from analyses did not affect the results.

When the symptom scores during days 1 to 4 were evaluated separately within the infants exposed to either citalopram or fluoxetine, there was no significant difference between citalopram-exposed infants and matched controls ($P=.44$, V=6, n=10), but there was a significantly higher symptom score between fluoxetine-exposed infants than controls ($P=.02$, V=2.5, n=10). However, the difference in the symptom score between fluoxetine-exposed infants and controls was no longer evident at the age of 2 weeks ($P=.13$, V=8, n=10).

MONOAMINE CONCENTRATIONS

Treatment with SSRIs induced a significant (69%) reduction of umbilical vein whole blood serotonin concentrations compared with the control group (**Table 4**). Similarly, significantly lower concentrations of whole blood 5-HIAA (18%) and HVA (23%) were observed in the SSRI-exposed infants compared with the control group. Importantly, a significant inverse correlation ($r_s=-0.66$, $P=.007$, n=15) was seen between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the SSRI-exposed infants (**Figure 1**), whereas no such correlation was evident in the control group ($r_s=0.38$, $P=.12$, n=18). No significant correlations were seen between the serotonin or HVA concentrations or length of citalopram or fluoxetine exposure and serotonergic symptoms.

The mean umbilical vein plasma noradrenaline and DHPG concentrations are given in Table 4. The DHPG

Table 4. Umbilical Vein Monoamine and Metabolite Concentrations in 15 Infants Exposed to SSRIs During Pregnancy and in 18 Infants With No Exposure to Psychotropic Medication During Pregnancy*

Variable	SSRI, nmol/L	Control, nmol/L	Percent Reduction (95% CI)	*P* Value	*t* Test
Serotonin	122 ± 89	387 ± 112	69 (57 to 78)	<.001	7.41
5-HIAA	63 ± 13	77 ± 16	18 (5 to 29)	.02	2.57
HVA	122 ± 26	159 ± 40	23 (8 to 35)	.005	3.01
Noradrenaline	12 ± 19	23 ± 33	46 (0 to 87)	.05	2.04
DHPG	5.8 ± 3.4	9.0 ± 6.8	35 (–2 to 53)	.08	1.80
DOPAC	18 ± 6.0	23 ± 7.6	20 (–17 to 40)	.07	1.85

Abbreviations: CI, confidence interval; DHPG, 3,4-dihydroxyphenylglycol; DOPAC, dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovalinic acid; SSRI, selective serotonin reuptake inhibitor.

SI conversion factors: to convert serotonin to micrograms per liter, multiply by 0.18; 5-HIAA, multiply by 0.19; HVA, multiply by 0.18; noradrenaline, multiply by 0.17; DHPG, multiply by 0.17; DOPAC, multiply by 0.17.

*Data are given as mean ± SD.

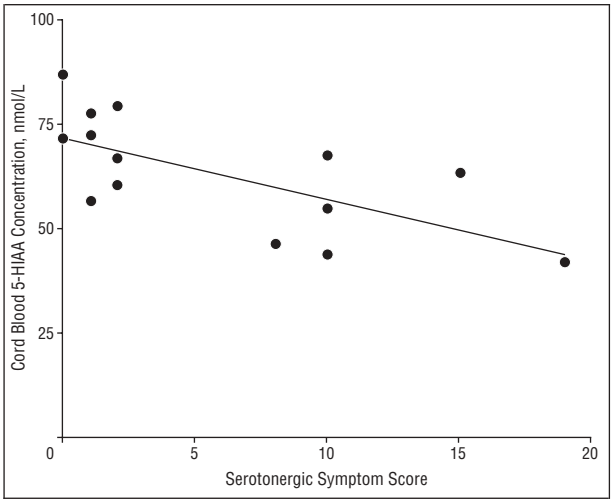

Figure 1. Relationship between the serotonergic symptom score during the first 4 days of life and cord blood 5-hydroxyindoleacetic acid (5-HIAA) concentration in 15 infants exposed to either citalopram or fluoxetine during late pregnancy (r_s=–0.66, *P*=.007, n=15). To convert 5-HIAA to micrograms per liter, multiply by 0.19.

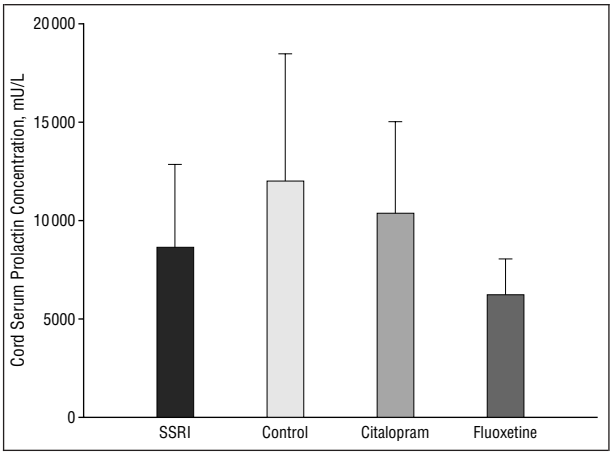

Figure 2. Umbilical cord serum prolactin concentrations in selective serotonin reuptake inhibitor (SSRI)–exposed infants (n=17) and control (n=18) infants and the subgroups exposed to citalopram (n=9) or fluoxetine (n=8). Error bars indicate SDs.

concentrations were significantly (40%) lower in the fluoxetine-exposed subgroup compared with the citalopram-exposed subgroup (*P*=.04, t_{13}=2.29). There was a statistical trend toward lower DOPAC concentrations in the SSRI-exposed group compared with the control group (Table 4). A subgroup analysis revealed significant reduction of cord blood DOPAC concentrations by citalopram vs controls (by 35%; *P*=.001, t_{17}=3.83), but no effect by fluoxetine vs controls was found (5.6% increase; *P*=.81, t_{12}=0.25). This difference was also statistically significant between the citalopram-exposed infants and the fluoxetine-exposed infants (*P*=.03, t_{13}=2.40). The DHPG or DOPAC concentrations, proposed markers for central nervous system noradrenaline and dopamine turnover, respectively, did not show any correlations with the serotonergic symptom score.

PROLACTIN CONCENTRATIONS

The infants exposed to SSRI treatment had 29% lower mean umbilical cord serum prolactin concentrations compared with the control infants at the time of birth (**Figure 2**), but this difference did not reach statistical significance (*P*=.08, t_{33}=1.81). There were no significant correlations between prolactin concentration and the symptom scores in either group. A subgroup analysis indicated that the SSRI-induced decrease in prolactin levels was only 14% for citalopram, whereas it was 49% for fluoxetine (*P*=.04, t_{15}=2.23). Data plots indicated no diurnal rhythm of prolactin secretion in either study group.

DRUG CONCENTRATIONS

Mothers' third-trimester mean (range) trough citalopram concentration was 99.8 nmol/L (58-214 nmol/L), and the sum of fluoxetine and norfluoxetine concentration was 468 nmol/L (317-692 nmol/L). Both SSRIs were also detected in the umbilical vein samples (representing the newborn concentration) at delivery (82 nmol/L [35-217 nmol/L] for citalopram; 278 nmol/L [209-366 nmol/L] for fluoxetine and norfluoxetine). The trough drug concentrations detected in the infants on day 2 were somewhat lower: 50.7 nmol/L (23-95 nmol/L) for citalopram, and 319 nmol/L (151-573 nmol/L) for fluoxetine and norfluoxetine. However, 2 weeks after delivery, the mean infant trough concentrations of citalopram (8.5 nmol/L [0-20 nmol/L]) were significantly (*P*=.003, t_7=4.54) lower compared with the 2-day values. Meanwhile, the reduction of fluoxetine and norfluoxetine con-

centrations was somewhat slower but significant, with the mean infant trough concentration at 2 weeks being 153 nmol/L (58-345 nmol/L) ($P<.001$, $t_9=7.64$, compared with the 2-day value). The drug concentrations at each time of measurement did not show any significant correlations with the serotonergic symptom score.

COMMENT

Prospective clinical examination of the serotonin-related neurologic symptoms revealed a significantly higher score of serotonergic adverse effects during the first 4 days of life in the SSRI-exposed infants compared with infants not exposed to any psychotropic medication during fetal life. The 15-minute Apgar score in the SSRI-exposed infants compared with controls was also significantly lower. The most prominent symptoms observed in the SSRI-exposed infants included tremor, restlessness, and rigidity, typical symptoms seen in a state central nervous system serotonergic overstimulation in adults.[17] Furthermore, hyperreflexia and myoclonus (in 1 infant) were observed as well-defined serotonergic effects. Importantly, clinically relevant structural central nervous system pathologic findings in newborns exposed to SSRIs were excluded by brain ultrasound or MRI. Contradictory to some earlier results, in our material the gastrointestinal symptoms or eating difficulties were not prominent, and the vital signs between the study groups were similar during the first days of life.[15] Accordingly, the weight gain of the infants was similar in both study groups.

Citalopram or fluoxetine and its active metabolite norfluoxetine were detected in all mothers during the third trimester or in samples taken from the umbilical vein at birth. The maternal intake of SSRIs induced significant changes in the cord blood serotonin and metabolite concentrations. Importantly, the cord blood 5-HIAA concentrations had a significant inverse correlation with the clinical serotonergic symptom score in the SSRI group but not in the control group. This finding is in agreement with the large pool of evidence that the lowered cerebrospinal fluid 5-HIAA concentration is a fairly accurate indicator of SSRI treatment–induced increase in central nervous system serotonin activity compared with serotonin and HVA concentrations, which seem to show rather poor correlation to central nervous system serotonin activity.[28,29] Although, because of formation and metabolism of 5-HIAA outside the central nervous system, the cord blood 5-HIAA concentration may be an indicator for serotonergic activity in the whole body of the infant rather than in the central nervous system, our data indicate a significant association between the SSRI-induced central nervous system serotonergic effects and the cord blood 5-HIAA concentration. Indeed, significant correlations have been found between cerebrospinal fluid and peripheral blood serotonin and metabolite concentrations.[30] There is no information on how mood and anxiety diseases would affect the cord blood monoamine levels.

The cord blood noradrenaline and DHPG concentrations were lower in the SSRI-exposed infants compared with the control group. However, the 46% lower noradrenaline levels in the SSRI group only approached statistical significance (power, <30%), whereas the 35% lower DHPG concentrations reached a statistical trend when compared with the control group (power, 30%). Similarly, a statistical trend was udetected with regard to the 20% lower DOPAC concentrations in the cord blood of SSRI-exposed infants (power, 63%). The differences between the 2 SSRIs studied became evident in their different effects on the noradrenaline and dopamine turnover as measured by cord blood DHPG and DOPAC concentrations. Fluoxetine had a significant lowering effect on the DHPG concentrations, whereas no such effect was seen with citalopram. Although this finding is in line with the finding that citalopram has a lower affinity on the noradrenaline reuptake pump compared with fluoxetine,[31] there were no significant differences between the 2 SSRIs in the vital signs of the infants at any time point of measurement. The citalopram-exposed infants had significantly (30%) lower cord blood DOPAC levels compared with those exposed to fluoxetine. We are not aware of any earlier reports on this difference in effects on dopaminergic neurotransmission between citalopram and fluoxetine. In fact, the potency of citalopram to modify dopamine transport is low compared with fluoxetine.[32]

The control group cord blood prolactin concentrations were in the range of those reported earlier (ie, 20- to 50-fold higher compared with nonpregnant women at fertile age).[33] Opposite to earlier findings in healthy volunteers that report an SSRI-induced increase in prolactin concentrations, exposure to SSRIs counteracted the pregnancy-induced increase of the cord blood prolactin concentrations.[34,35] Moreover, the reduction was significantly stronger by fluoxetine (49%) compared with citalopram (14%). This finding may have clinical relevance, since low umbilical cord prolactin levels have been associated with increased risk for infant respiratory distress syndrome.[33]

The clinical relevance of the present results is awareness of the psychiatrists who prescribe SSRIs during pregnancy and the pediatricians who treat the serotonin-related neurologic symptoms of the newborns during the first days of life. Although these effects seem to subside quickly, they may expose the infants to more serious neonatal complications such as convulsions.[15]

The fact that there was a significant correlation between the serotonergic symptom score and serotonin turnover, but not with noradrenaline or dopamine turnover, in the SSRI-exposed infants suggests that the effects seen in the newborns were related to high central nervous system serotonin activity. However, it also provides validation of the scaling method by which the clinical symptoms were assessed. Although no significant relationship was found between the cord blood or infant SSRI concentrations and serotonergic symptoms, the resolution of the symptoms was associated with a quick decline in fetal citalopram and fluoxetine concentrations and not the opposite, which would be expected in the case of withdrawal syndrome. Accordingly, the present data suggest that the symptoms observed could be explained by high central nervous system serotonin activity rather than by withdrawal syndrome. Importantly, this interpretation does not exclude the existence of neonatal SSRI discontinuation syndrome as a separate but obviously more rare entity.

Another clinically relevant question that the present data raise is whether the serotonergic adverse effects in newborns could be prevented by gradual discontinuation of the mother's SSRI treatment during late pregnancy so that, for example, the last 2 weeks (ie, time of resolution of most symptoms in this study) of pregnancy would be drug treatment free. This might, on the other hand, lead to worsening of the mother's disease and would expose the mother to the SSRI discontinuation syndrome. Thus, the decision should be made individually for each patient.

In conclusion, we report increased risk for central nervous system serotonergic adverse effects during the first days of life in newborns of mothers taking the SSRIs citalopram or fluoxetine during the third trimester of pregnancy. The serotonergic nature of the symptoms is supported by the significant inverse correlation between the observed clinical symptoms and cord blood 5-HIAA concentrations. However, these symptoms seem to subside quickly without any need for specific treatment. A timely relationship between declining drug concentrations and resolution of the adverse symptoms suggests that the mechanism behind the symptoms was central nervous system serotonergic overstimulation rather than an SSRI withdrawal syndrome.

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