Neonatal Abstinence Syndrome After In Utero Exposure to Selective Serotonin Reuptake Inhibitors in Term Infants

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Objective: To compare the prevalence and clinical characteristics of neonatal abstinence syndrome in neonates exposed and not exposed to selective serotonin reuptake inhibitors (SSRIs) in utero.

Design: Cohort study.

Setting: Tertiary care center.

Patients: One hundred twenty term infants, of whom 60 had prolonged in utero exposure to SSRIs, including paroxetine hydrochloride, fluoxetine, citalopram hydrobromide, sertraline hydrochloride, and venlafaxine hydrochloride.

Main Outcome Measures: Neonatal abstinence syndrome was assessed with the Finnegan score as follows: score of 8 or above, severe; score of 4 to 7, mild; and score of 0 to 3, normal. All infants were followed up with a standardized protocol that included repeated Finnegan score assessments and cardiorespiratory monitoring until normalization of the Finnegan score.

Results: Of the 60 neonates exposed to SSRIs in utero, 8 showed severe and 10 showed mild symptoms of a neonatal abstinence syndrome. All nonexposed neonates had a normal Finnegan score. In neonates who developed severe symptoms, the maximum mean daily Finnegan scores were recorded within 2 days after birth, although maximum individual scores were recorded as long as 4 days after birth.

Conclusions: Neonatal abstinence syndrome occurs in 30% of neonates exposed to SSRIs in utero. These neonates should be monitored for at least 48 hours after birth. The long-term effects of prolonged exposure to SSRIs, particularly in neonates who develop severe symptoms, have yet to be determined.


D EPRESSION IS A COMMON disease with a lifetime risk of 10% to 25% in women.1 Furthermore, pregnancy is a stressful state that may aggravate depression and increase the need for medical therapy. The widespread use of selective serotonin reuptake inhibitors (SSRIs), which cross the placenta,2 has prompted investigations of the effects of maternal treatment with SSRIs on the fetus. Fetal exposure to SSRIs has not been associated with an increased incidence of major congenital malformations,3-6 but there is growing evidence that it is associated with a neonatal abstinence syndrome (NAS).7-12 Kallen12 and Costei et al13 showed increased rates of respiratory distress in exposed newborns. Zeskind and Stephens14 observed disruptions in a wide range of neurobehavioral outcomes, and Oberlander et al15 found that 30% of exposed infants had poor neonatal adaptation. In a recent study, 93 cases of suspected SSRI-induced neonatal withdrawal syndrome were reported.16 However, results from large cohort studies of the symptoms of NAS in infants exposed to SSRIs in utero are not yet available. Our aim was to assess the clinical syndrome exhibited by neonates exposed to SSRIs in utero.

METHODS

The objective of the present study was to use a standardized protocol to compare the incidence and clinical characteristics of NAS in neonates exposed and not exposed to SSRIs in utero. This cohort study was performed at Rabin Medical Center in Israel, a tertiary care facility housing a neonatology department that cares for approximately 9000 newborns per year. The study was conducted from January 1, 2002, through August 31, 2004, during which 23,254 consecutive births took place. Maternal intake of SSRIs during pregnancy, including fluoxetine, paroxetine hydrochlo-
ride, citalopram hydrobromide, sertraline hydrochloride, and the serotonin-noradrenaline reuptake inhibitor venlafaxine hydrochloride, was recorded in each case. All full-term infants who had had prolonged exposure to SSRIs during the entire pregnancy or at least during the third trimester were eligible for the study. The infants were identified from the delivery room records as they arrived at the nursery or from a medical history form completed by all mothers at admittance to the nursery. This form included demographic details; maternal and family illnesses; type, dosage, and duration of treatment with SSRIs or other drugs; and use of recreational drugs, tobacco, or alcohol. A control cohort of infants was similarly identified during the final 2 months of the study and included an equal number of healthy non–SSRI-exposed neonates born to healthy mothers and matched for sex, gestational age (±1 week), birth weight (±100 g), and mode of delivery.

Exclusion criteria were known or probable exposure to other medications, illicit drugs, or alcohol, which could have contributed to a NAS, congenital anomalies or conditions affecting the central nervous system. Infants who were exposed to SSRIs or who met any of the exclusion criteria were excluded from the control cohort. Preterm infants also were excluded owing to the difficulty of assessing the Finnegan score in this population.

The nurses and physicians in our center are trained to identify and record NAS symptoms. The SSRI-exposed infants in the present study were followed up after birth according to a protocol introduced in the neonatal department in 1998; it included cardiorespiratory and temperature monitoring, assessment of the Finnegan score, and blood testing. The Finnegan score is an objective method used to monitor onset, progression, and improvement of NAS symptoms in passively exposed neonates. The score rates 21 symptoms in 11 groups most commonly seen in drug-exposed neonates and is used to assess the need for pharmacologic intervention and the response to treatment. The total score is determined by adding the score assigned to each symptom group. Higher scores represent more severe NAS symptoms with a consequent risk of increased morbidity. A score of 8 or higher in 3 consecutive measurements is considered an indication for pharmacotherapy. Finnegan scores were assessed 2 hours after birth and thereafter every 8 hours after meals for 48 hours or longer if the score had not normalized in 48 hours. More frequent assessments were performed as required by the clinical situation. A severe NAS was defined as a Finnegan score of 8 or higher at 1 or more assessments, and mild NAS was defined as a score of 4 to 7 in at least 2 examinations; infants with scores of 4 or higher were assessed repeatedly until the score decreased below 4. At discharge, the medical records were reviewed, and the Finnegan scores were assessed for possible errors. In only SSRI-exposed infants, complete blood cell count, glucose level, coagulation time, and blood chemistry (urea, creatinine, electrolytes, calcium) were tested.

Findings in the exposed cohort were compared with those in the nonexposed cohort. Data are given as summary measures (mean and standard deviation). The t test was used to compare continuous variables and the Fisher exact test or χ2 test, as appropriate, to compare categorical values. The study was approved by the institutional research ethics board.

### RESULTS

During the study, 78 infants born to 76 women had prolonged in utero exposure to SSRIs. Eighteen were excluded from the study because of prematurity (7 infants, including 2 sets of twins), first-trimester cessation of SSRI treatment (3 infants), or concomitant maternal use of other medications that can cause withdrawal symptoms (8 infants; benzodiazepines in 6 and carbamazepine in 2). The infant of a mother who took fluoxetine until 6 days before delivery was included because of the long half-life of the drug (5-7 days). Of the 60 SSRI-exposed infants, 37 were exposed to paroxetine hydrochloride (dose range, 10-40 mg), 12 to fluoxetine (dose range, 20-60 mg), 8 to citalopram hydrobromide (dose range, 10-40 mg), 2 to venlafaxine hydrochloride (dose range, 37.5-75 mg), and 1 to sertraline hydrochloride (dose, 25 mg). In the control cohort, all families agreed to participate. The characteristics of the study population are presented in Table 1. Three infants exposed to SSRIs for the complete pregnancy duration had major congenital anomalies (ventricular septal defect and cleft palate, ventricular septal defect, and hydrenephrosis with ureteroceles). One infant in the control group had hydrenephrosis. None of the infants with major congenital anomalies had any serious medical complications.

Comparison of the presence of each NAS symptom included in the Finnegan score between the SSRI-exposed infants and the control infants is presented in Table 2. Symptoms of NAS were present in 18 of the 60 SSRI-exposed infants (30%) vs none of the 60 control infants (P < .001). Of the 18 symptomatic SSRI-exposed infants, 8 (13%) had a severe NAS (Finnegan score ≥8), and 10 (17%) had a mild NAS (score, 4-7). Of the 8 infants with severe NAS, 6 neonates were exposed to paroxetine, 1 to fluoxetine, and 1 to citalopram. The characteristics of the study group infants with withdrawal symptoms are shown in Table 3. Maximum mean daily symptoms occurred within the first 48 hours of life, although maximum individual Finnegan scores occurred as long as 4 days after birth. No infant with symptoms required any treatment.

The relationship of SSRI dosage to NAS symptoms was assessed only in infants exposed to paroxetine hydrochloride because of subgroup sample size. Mean drug dose was 19 mg for infants with no symptoms, 23 mg for infants with mild symptoms, and 27 mg for infants with severe symptoms. Comparison of the infants with symptoms (Finnegan score >3) to those without symptoms (Finnegan score 0-3) showed a correlation between higher
drug dosage and NAS (P = .01). Examining the paroxetine hydrochloride dose used, we were unable to identify a specific cutoff point for an increased risk of NAS because most infants were exposed to a similar dose (20 mg). However, no infant exposed to a dose less than 20 mg developed any symptoms.

Laboratory test result abnormalities noted in the group exposed to SSRIs were hypoglycemia (glucose level <40 mg/dL [2.22 mmol/L]) in 3 infants, transient coagulation abnormality in 1 infant, thrombocytopenia (platelet count <150 x 10^3/L; lowest count, 103 x 10^3/L) in 3 infants, and leukopenia (leukocyte count <10,000/µL) in 3 infants. All abnormal test results resolved within a few days.

### Table 3. Characteristics of Neonates Exposed to SSRIs With Those in a Control Group

<table>
<thead>
<tr>
<th>Symptom</th>
<th>SSRI-Exposed Infants (n = 60)</th>
<th>Control Infants (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-pitched cry</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Exaggerated Moro reflex</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>Hypertonicity or myoclonus</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Convulsions</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Autonomic nervous system†</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disturbance‡</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Neonatal abstinence syndrome§</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

*Data are given as number of patients. Some patients had more than 1 symptom.
†Yawning, sneezing, sniffles.
‡Exaggerated sucking, poor feeding, regurgitation, vomiting, loose stools. §Defined as a Finnegan score of 4 or higher.

The increasing use of SSRIs during pregnancy warrants careful examination of their effects on the fetus and newborn infant. Results of the present study show that 30% of infants exposed to SSRIs in utero have symptoms of a NAS and that in 13% of these infants the symptoms are severe enough to meet the definition of a severe NAS.

Exposure to an SSRI during pregnancy has been associated with many neonatal symptoms, including respiratory distress, cyanotic events, feeding difficulties, hypoglycemia, and a wide spectrum of neurologic symptoms, ranging from neurobehavioral disturbance, sleep disturbances, and increased motor activity to a neonatal withdrawal syndrome. A retrospective study of maternal use of fluoxetine showed that poor neonatal adaptation was more common in the SSRI-exposed infants than in controls (relative risk 8.7; 95% confidence interval, 2.9-26.6). Reports of neurologic symptoms severe enough to be characterized as a withdrawal syndrome mostly have been anecdotal, but recently Sanz et al identified 93 cases of suspected SSRI-induced neonatal withdrawal syndrome in a large database survey. The most frequent symptoms observed in the newborns in our study were tremor, gastrointestinal or sleep disturbance, hypertonicity, and high-pitched cry. These findings are consistent with those of Sanz et al who reported more neurologic and gastrointestinal than respiratory symptoms. Tachypnea, a common finding in previous studies, was less frequently observed, probably owing to our exclusion of preterm infants. It is noteworthy that 2 of the infants in our study had seizures, but these were transient. Because of the small size of each SSRI subgroup, it was difficult to assess if there is a specific SSRI that is more likely to cause NAS symptoms. Nevertheless, in the largest subgroup of infants, those exposed to paroxetine, 6 (16%) of 37 had severe symptoms. When we compared the infants with symptoms to those without, we found a dose-response effect. Some symptoms of withdrawal, such as jitteriness, tachypnea, hypertonicity, temperature instability, and diarrhea, also can be attributed to serotoninergic hyperstimulation. Laine et al described such serotoninergic hyperstimulation in infants exposed to SSRIs and its correlation with drug levels. Maximum severity of symptoms would be expected to occur shortly after birth, if serotoninergic hyperstimulation is the cause of symptoms, because drug exposure does not continue after birth. However, for most infants, peak symptoms did not occur on the first day of life, so the observed symptoms were unlikely to be caused by serotoninergic hyperstimulation.

The present study is a large population-based study that includes all infants with reported prolonged exposure to SSRIs, enabling an accurate assessment of the prevalence of NAS in exposed infants. Infants were followed up prospectively from birth to identify all symptoms. The 30% rate of neonatal symptoms in our sample of SSRI-exposed infants is close to that in studies by Oberlander et al (30%) and Chambers et al (31.5%) but higher than the rate reported by Costei et al (22%). However, in the latter study, data were not collected immediately after delivery and may underrepresent the true incidence of neonatal symptoms. Our study is the first of its kind to use the Finnegan score, which is an objective score that permits quantification of NAS symptoms, in SSRI-exposed infants. A different NAS score has been used only in case series. Severe NAS symptoms
were found in 13% of exposed neonates in our study. The study design enabled comparison of infants who were exposed with those who were not and supported the causal role of SSRIs in the observed symptoms. Prospectively following up infants until resolution of symptoms provided new information regarding the time and duration of peak symptoms. Because infants who were severely affected exhibited peak symptoms within the first 48 hours of life, this should be the minimum observation period.

Our study has some limitations. Exposure to SSRIs was determined according to maternal report. Because some mothers may elect not to report SSRI use, our study may not have captured the total exposed population. Our sample size was relatively small for each drug subgroup of exposed newborns. Because the Finnegan score routinely is used only in infants exposed to drugs, the staff was aware of exposure status, and a blinded assessment was not possible. Although the neonatal staff was well trained in the use of the Finnegan score, interobserver variability may have occurred. We tried to minimize this problem by recalculating the Finnegan score according to the symptoms noted in the medical record. Because drug levels were not measured, their correlation with symptoms was not possible.

The long-term effects of uterine exposure to SSRIs have not been demonstrated clearly. Oberlander et al reported symptom resolution in all infants within 48 hours of life and normal findings at 8-month follow-up. Nulman et al studied 55 preschool children exposed to fluoxetine in utero and found no change in global IQ, language development, or behavioral development. However, Casper et al noted subtle effects on motor development in exposed children. The long-term effects on the select group of SSRI-exposed infants who develop symptoms suggestive of a severe NAS have not been evaluated.

The high prevalence of NAS in infants exposed to SSRIs in utero should be brought to the attention of family physicians, psychiatrists, gynecologists, pediatricians, and mothers. Because maternal depression during pregnancy also entails a risk to the newborn, the risk-benefit ratio of continuing SSRI treatment should be assessed. If SSRIs are prescribed during pregnancy, use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA. 1998;279:609-610.