ARTICLE

Perinatal Outcome Following Third Trimester Exposure to Paroxetine

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Background: Paroxetine hydrochloride is commonly used for maternal depression, panic disorder, and obsessive-compulsive disorder. The drug readily crosses the human placenta. Although it does not appear to increase teratogenic risk, there have been case reports of neonatal withdrawal. Symptoms were described soon after birth and lasted up to 1 month.

Objective: To investigate whether there is a clinically important discontinuation syndrome in neonates exposed to paroxetine in utero.

Methods: Prospective, controlled cohort study.

Patients: Fifty-five pregnant women counseled prospectively by the Motherisk program in Toronto, Ontario, regarding third-trimester exposure to paroxetine and their infants were included in the study group. Pregnant women who discontinued paroxetine before the third trimester or those receiving other drugs known to cause withdrawal-type symptoms, such as opioids or benzodiazepines, were excluded. A comparison group of 27 women using paroxetine during the first or second trimester and 27 women using nonteratogenic drugs were matched for maternal age, gravity, parity, social drug use, and nonteratogenic drug use.

Results: Of the 55 neonates exposed to paroxetine in late gestation, 12 had complications necessitating intensive treatment and prolonged hospitalization. The most prevalent clinical picture was respiratory distress (n=9), followed by hypoglycemia (n=2), and jaundice (n=1). The symptoms disappeared within 1 to 2 weeks. In the comparison group, only 3 infants experienced complications ($P=.03$). In logistic regression, only third-trimester exposure to paroxetine was associated with neonatal distress (odds ratio, 9.53; 95% confidence interval, 1.14-79.3).

Conclusion: When used near term, paroxetine is associated with a high rate of neonatal complications, possibly caused by its common discontinuation syndrome.

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PAROXETINE HYDROCHLORIDE (Paxil; GlaxoSmithKline, Research Triangle Park, NC) is commonly used for maternal depression, panic disorder, and obsessive-compulsive disorder in pregnant women. Although the drug does not appear to cause major congenital malformations,[1] its perinatal safety when used in late gestation has not been established. The drug readily crosses the human placenta and has a mean elimination half-life of 21 hours.

There have been recently several neonatal case reports of symptoms associated with maternal use of paroxetine,[2-4] including irritability, jitteriness, constant crying, shivering, eating or sleeping difficulties, gastrointestinal symptoms, and seizures. These symptoms were described soon after birth and lasted up to 1 month after birth. Paroxetine has a reported milk-plasma ratio ranging from 0.056 to 1.3, and the maximal daily dosage taken up by the infant is estimated at 0.34% of the maternal dosage per kilogram of body weight.[5-8]

The objective of the present study was to compare the perinatal outcome of infants exposed in utero to paroxetine with that of healthy controls and infants exposed to the drug only during the first and second trimesters of pregnancy.

METHODS

The Motherisk program provides counseling for women and their health care providers on the risk or safety of drugs and chemicals during pregnancy and lactation. Presently, we are counseling as many as 200 patients a day. Between September 1996 and September 1999, we followed all pregnant women who called the Motherisk program about paroxetine exposure during the third trimester of pregnancy. These women were prospectively fol-

Table 1. Maternal Characteristics*

Characteristic	Paroxetine Hydrochloride Exposure in the Third Trimester: Cases (n = 55)	Comparison Group† (n = 54)	*P* Value
Maternal age, mean, y	32.9	32.4	.82
Gravidity			
1	19 (35)	18 (33)	.95
>1	36 (65)	36 (67)	
Parity‡			
0	24 (44)	23 (43)	.94
1	22 (40)	19 (35)	
2	7 (13)	9 (17)	
Social drug use			
Alcohol	4 (7)	9 (17)	.12
Smoking	14 (26)	5 (9)	.05

*Data are presented as the number (percentage) of subjects unless otherwise indicated.

†Comparison group included 27 women who used paroxetine only during the first and/or second trimesters and 27 women who used nonteratogenic drugs.

‡Some women had parity higher than 2.

lowed up by telephone calls after delivery. The interview addressed the course of pregnancy, delivery, and the neonatal period, including malformations, developmental milestones, nutrition, etc. Interviewers did not make any suggestions about potential adverse outcomes. The protocol of the interview has been previously outlined in detail.[9]

The inclusion criterion was exposure to paroxetine throughout the third trimester. Pregnant women who discontinued paroxetine before the third trimester or those receiving other drugs known to cause withdrawal-type symptoms, such as opioids, benzodiazepines, barbiturates, or heavy use of ethanol, were excluded from the study. At the time of counseling, we collected data on reproductive and medical history, detailed exposure data, and information on all other drugs used concomitantly. Details about cigarette, alcohol, and recreational drug use were also collected. After delivery, participants were contacted again to record the pregnancy outcome and neonatal complications, including withdrawal symptoms and breastfeeding.

For each case, we chose a control mother-child pair from the same prospective cohort and matched them for maternal age, gravity, parity, social drug use (alcohol and smoking), and nonteratogenic drug use (eg, acetaminophen, vitamins, and calcium supplements). Two comparison groups were chosen. The first group included women counseled by Motherisk about gestational use of paroxetine only during the first and second trimesters (1-week to 6-months gestational age; median age, 6 weeks). Daily dosage of paroxetine hydrochloride ranged from 10 mg to 40 mg, with a median of 20 mg. The second group included women counseled by Motherisk about first-trimester exposure to nonteratogenic agents (eg, acetaminophen or dental x-rays).

Data were analyzed with Statistical Product and Service Solutions software for Windows, version 10 (SPSS Inc, Chicago, Ill). Descriptive statistics were used to summarize demographic data. The χ^2 test was used to compare categorical variables, and the *t* test or Mann-Whitney test, as appropriate, was used for continuous variables. Backward stepwise logistic regression was used to identify factors that could affect the rates of respiratory distress. Variables found to differ significantly between the study and control groups ($P<.10$) or those that might confound the relationship between other variables and respiratory distress were included in a multivariate analysis. Variables were retained in the multivariate analysis if they met the significance level of $P<.05$ or if they changed the point of estimate of another variable by more than 10%.

RESULTS

Of 291 pregnant women who were counseled by the Motherisk program about paroxetine use, 55 met the inclusion criterion, being exposed to the drug during the third trimester. They used paroxetine for depression (31 women [56%]), anxiety (17 women [31%]), anxiety and depression (7 women [13%]), and panic attacks (5 women [9%]) (some patients had more than 1 indication). The daily dosage ranged from 10 mg to 60 mg (mean, 23 mg; median, 20 mg).

The maternal characteristics of the 2 groups are summarized in **Table 1**. The infants in the 2 comparison subgroups did not differ in any characteristic and therefore were combined for the sake of comparison with the study group.

Of the 55 infants exposed to paroxetine during the third trimester of pregnancy, 12 experienced neonatal complications that necessitated prolonged hospitalizations (**Table 2**). The most prevalent clinical picture was respiratory distress (n=9), followed by hypoglycemia (n=2) and jaundice (n=1). None of the infants had pneumonia, cardiac malformation, respiratory distress syndrome, sepsis, or other causes of respiratory distress. In contrast, only 3 infants in the comparison group had neonatal complications (2 infants with paroxetine exposure in trimesters 1 and 2 had respiratory distress and meconium aspiration, respectively; 1 of the nonteratogenic controls had jaundice). The rate of neonatal complications among neonates exposed to paroxetine in the third trimester (22%) was significantly higher than among controls (6%) ($P=.03$). In the study group, there was a significantly higher rate of prematurity (20% vs 3.7%; $P=.02$) (**Table 3**).

In the third-trimester paroxetine exposure group, 36 women breastfed and continued taking paroxetine after delivery. During breastfeeding, 8 women reported symptoms in their infants, including alertness (n=6), constipation (n=3), sleepiness (n=1), and irritability (n=1). In the comparison group, 44 babies were breastfed, and none of the mothers reported adverse neonatal effects, ($P=.001$).

The following variables were initially included in a backward logistic stepwise regression model: prematurity, maternal smoking, cesarean delivery, and exposure to paroxetine in the third trimester (**Table 4**). The only factor retained in the model and found to be associated with respiratory distress in the newborn was exposure to paroxetine in the third trimester (odds ratio, 9.53; 95% confidence interval, 1.14-79.30).

COMMENT

Paroxetine discontinuation symptoms have been reported at a rate of 0.3 per 1000 perscriptions.[10] This may be partly due to the relatively high potency of parox-

Table 2. Complications Among Neonates Exposed to Paroxetine in the Third Trimester and the Comparison Groups*

Patient No.	Complication	Relevant Details
	Paroxetine Hydrochloride Third Trimester Group (n = 55)	
4	Bradycardia	Term, septic workup was negative, echocardiogram, computed tomographic scan, 4-d hospitalization, no diagnosis
5	Respiratory distress	Term, no sepsis, 1-wk hospitalization
9	Hypoglycemia	Term, no sepsis
15	Respiratory distress, jaundice	Preterm, intubation, phototherapy, 10-d hospitalization
20	Respiratory distress	Term, placenta previa, bleeding, cesarean delivery, 2-wk hospitalization
21	Suckling problems	Term, 2-wk hospitalization, no diagnosis
25	Respiratory distress	Term, intubation
33	Respiratory distress, hypoglycemia	Preterm, problems resolved in first few hours
35	Respiratory distress, tachycardia	Preterm, 1 day in intensive care unit for respiratory distress
36	Respiratory distress	Term
41	Respiratory distress	Term
52	Respiratory distress	Term
	Paroxetine First and Second Trimesters Group (n = 27)	
18	Respiratory distress first few hours	. . .
29	Meconium aspiration, intubation	. . .
	Nonteratogenic Drugs Group (n = 27)	
56	Jaundice	. . .

*Ellipses indicate not applicable.

Table 3. Pregnancy Outcome*

Variable	Paroxetine Hydrochloride Exposure in the Third Trimester: Cases (n = 55)	Paroxetine Hydrochloride Exposure in the Third Trimester: Comparison Group† (n = 54)	*P* Value
Gestational age			
Term	42 (76)	35 (65)	.33
Preterm	11 (20)	2 (4)	.02
Postterm	2 (4)	17 (32)	.001
Birth weight, mean ±SD, g	3394 ± 650	3578 ± 464	.09
Sex			
Female	24 (44)	28 (52)	.45
Male	31 (56)	26 (48)	
Major malformation	0	0	
Breastfed	36 (65)	44 (81)	.85

*Data are presented as the number (percentage) of subjects unless otherwise indicated.

†Comparison group included 27 women who used paroxetine only during the first and/or second trimesters and 27 women who used nonteratogenic drugs.

Table 4. Univariate Analysis of the Association Between Risk Determinants for Respiratory Distress in the Study Group

Variable	Odds Ratio (95% Confidence Interval)
Maternal smoking	
No smoking	1.00 (Reference)
Smoking	2.22 (0.52-9.52)
Maternal use of paroxetine hydrochloride in the third trimester	
Did not use paroxetine	1.00 (Reference)
Used paroxetine	10.35 (1.27-84.67)
Gestational age, wk	
≥37	1.00 (Reference)
<37	3.81 (0.85-17.13)
Mode of delivery	
Vaginal	1.00 (Reference)
Cesarean	0.92 (0.18-4.65)

etine at the serotonin uptake site. In adults, discontinuation of selective serotonin reuptake inhibitors (SSRIs) leads to nonspecific symptoms such as dizziness, paresthesia, tremor, anxiety, nausea, and emesis, which typically occur 2 days after the last dose and continue for an average of 10 days.[10] In a large British study, withdrawal reactions with paroxetine were 10-fold more common than with fluvoxamine maleate, which has a similarly short half-life (fluvoxamine, 15 h; paroxetine, 17 h), and 15-fold more common than with fluoxetine hydrochloride.

In the present study, we detected a high rate of newborns who developed neonatal complications at birth after exposure to paroxetine in the third trimester. They all required intensive treatment for a short period of time, and their conditions improved without further intervention or emergence of other underlying diagnoses.

It may be argued that the high rate of adverse neonatal events, especially during breastfeeding, among infants exposed to paroxetine during the third trimester may, at least in part, be associated with maternal psychiatric morbidity or disorders associated with it. However, half of our comparison group was composed of mothers who had similar conditions and who received the drug only during the first and second trimesters. Infants exposed to the drug only during the first and second trimesters did not exhibit neonatal complications or higher rates of prematurity, as did those exposed in the third trimester. This strongly suggests that paroxetine exposure near term may compromise fetal and neonatal health. The fact that the adverse events were brief and without other underlying abnormalities further supports drug exposure as the mechanism for the adverse effects. Logistic regres-

What This Study Adds

Paroxetine, an SSRI, is commonly used for depression, panic disorder, and obsessive-compulsive disorder. Discontinuation symptoms have been frequently described in adults. Several case reports suggest that infants exposed in utero to paroxetine during the third trimester may have poor neonatal adaptation. The present study is the first to compare the perinatal outcome of women exposed to paroxetine during the third trimester of pregnancy with women who took paroxetine in early pregnancy and women who took nonteratogenic drugs. The incidence of complications (mainly respiratory distress) was significantly higher in neonates exposed to paroxetine in late pregnancy.

sion analysis confirms that paroxetine exposure in the third trimester, and not prematurity, maternal smoking, or other confounders, was associated with neonatal respiratory distress.

Chambers et al[11] reported poor neonatal adaptation in nearly one third of the neonates exposed to fluoxetine. We have recently completed a study comparing pregnancy outcome and child development among children exposed to fluoxetine or tricyclic antidepressants throughout gestation, and they did not exhibit an increase in prenatal complications, compared with unexposed controls.[12] Whether other SSRIs have neonatal toxicity profiles similar to paroxetine's remains to be explored. The unexpected high rates of neonatal complications with paroxetine are biologically consistent with the high rate of discontinuation syndrome with this particular SSRI and also with its being the most pharmacologically specific of the SSRIs. More studies are needed to verify our observations and to better characterize pregnancy outcomes and neonatal response.

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