Pharmacologic Factors Associated With Transient Neonatal Symptoms Following Prenatal Psychotropic Medication Exposure

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Background: Selective serotonin reuptake inhibitor antidepressants (SSRIs) and benzodiazepines are frequently used to treat maternal depression and anxiety disorders during pregnancy. Recent reports suggest that prenatal SSRI exposure is associated with a neonatal discontinuation syndrome. It remains unclear whether these symptoms are directly related to SSRI exposure alone or are due to concurrent pharmacologic factors. Also, this study explores relationships between neonatal outcomes and medication levels during pregnancy, at delivery, and in the newborn period.

Method: This study sought to compare newborn behavior following second and third trimester exposure to either single-agent SSRIs (group 1) or SSRIs combined with clonazepam (group 2). A prospective cohort of mothers and their infants (N = 46) who had received SSRI medication alone or in combination with clonazepam were studied from June 1996 through June 2000 and compared with a nonexposed control group (N = 23). Infants were assessed in the newborn period for signs suggestive of a "discontinuation syndrome." Maternal drug levels were measured during the pregnancy and at delivery. Infant drug levels from cord blood and at day 2 of life were also obtained.

Results: Overall, 30% of the exposed infants (groups 1 and 2, N = 14) showed symptoms of transient poor neonatal adaptation compared with 9% (N = 2) of control infants. In group 1, 25% had symptoms (fluoxetine N = 3; paroxetine N = 3; sertraline N = 1) and in group 2, 39% of infants had symptoms (paroxetine with clonazepam, N = 7). Symptoms were typically mild respiratory distress and, less commonly, hypotonia. Symptoms were self limited and not associated with other neonatal conditions. When paroxetine was combined with clonazepam, infants with symptoms had significantly elevated paroxetine levels when compared with similarly exposed infants without symptoms ($p < .05$). Among single-agent paroxetine-exposed infants, drug levels did not differ significantly between those with and without symptoms. Maternal dose of clonazepam was significantly higher ($p < .05$) during pregnancy and at delivery among symptomatic infants compared with nonsymptomatic infants. Developmental outcomes at 2 and 8 months of age did not differ between symptomatic and nonsymptomatic infants.

Conclusion: While transient neonatal symptoms were found in infants after single-agent prenatal exposure to SSRIs and when paroxetine was combined with clonazepam, the addition of clonazepam appeared to alter paroxetine metabolism, leading to increased drug levels and risk for transient neonatal symptoms. These data highlight the importance of accounting for a variety of pharmacologic factors beyond single-agent SSRI exposure that may lead to poor neonatal adaptation. Further studies are needed with a larger sample of infants to determine the role of clonazepam and whether similar outcomes occur when exposure includes other SSRIs in combination with clonazepam.

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Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines are widely used to treat maternal depression and anxiety during pregnancy,[1] though our understanding of neonatal behavioral effects following prenatal exposure remains limited.[2] These medications are regarded as safe to use during pregnancy with little or no risk of congenital malformations,[3–7] although large case-controlled prospective studies examining safety have not been conducted to date. However, there are reports of lower birth weight, preterm birth, and altered neurobehavioral adaptation in the newborn period in infants following in utero exposure to fluoxetine.[8–11] Reports of a with-

drawal or "discontinuation" syndrome in newborn infants following third trimester fluoxetine,[11] paroxetine,[12,13] and sertraline[14] exposure have emerged. These include acrocyanosis, tachypnea, temperature instability, irritability, and elevated drug levels[12,15,16] among infants with prenatal fluoxetine exposure.

Cohen et al.[17] reported that among a cohort of 64 infants with late-gestation fluoxetine exposure, there was a greater frequency of poor neonatal adaptation, as quantified by the presence of jitteriness, tachypnea, hypoglycemia, hypothermia, poor tone, and a weak or absent cry in the newborn period. Similarly, in a prospective study of 228 pregnant women taking fluoxetine, Chambers et al.[11] reported that infants with late-gestation exposure had higher rates of premature delivery, admission to special care nurseries, and similar symptoms of poor neonatal adaptation. Neonatal withdrawal symptoms have been reported following third trimester paroxetine.

Dahl et al.[18] reported tachypnea and jitteriness following prenatal exposure and such symptoms disappeared by day 4 of life. Follow-up by week 4 was normal. Similarly, Costei and colleagues[13] in the MotherRisk group reported that by parent report, 12 of 55 neonates with late-gestation paroxetine exposure primarily had transient respiratory distress that disappeared within the first 2 weeks of life.

Nordeng et al.[12] observed 5 infants with withdrawal symptoms following maternal paroxetine, fluoxetine, or citalopram use during pregnancy. Symptoms included poor feeding, lethargy, tachypnea, increased tone, crying, respiratory distress, and irritability. Importantly, many of these studies report only single-agent exposure and do not evaluate the concurrent exposure to other psychotropic medications or assess how neonatal symptoms may be related to polypharmacy.

Compounding prenatal medication exposure, SSRIs are also frequently used in combination with a benzodiazepine. Evidence of adverse effects following prenatal benzodiazepine exposure in humans is also limited, and the best-known example of prenatal effects is the "floppy infant syndrome" seen in babies born to mothers taking diazepam late in their pregnancies.[19] Because of the prolonged half-life of this benzodiazepine, the effects may persist in the neonate for several days to weeks.[20] In addition, prenatal diazepam exposure in humans has been associated with neonatal "withdrawal" symptoms, including hypotonia, hypothermia, respiratory distress, and poor feeding in the newborn period.[21–24] The use of diazepam early in pregnancy has also been reported to be associated with an increased incidence of cleft lip and palate.[25–27]

A single case report following prenatal clonazepam exposure[19] reported apnea, cyanosis, and hypotonia in a 36-week gestational aged infant within a few hours of birth. Maternal and infant drug levels confirmed transplacental transfer, and symptoms resolved within the first 10 days of life. In contrast, a recent report[28] of 27 infants born with prenatal clonazepam exposure (0.25–2.0 mg/day) (15 had concurrent antidepressant medication exposure) stated that such exposure was not related to obstetric complication nor were any signs of a neonatal withdrawal syndrome noted. Therefore, conflicting evidence exists regarding neonatal withdrawal syndrome associated with clonazepam use during pregnancy.

Previous studies[11–18] have described neonatal discontinuation symptoms in small populations. The lack of direct pharmacologic data and the effects of combined prenatal clonazepam with SSRI exposure in neonates have not been previously reported. To further understand neonatal outcomes following prenatal SSRI exposure with or without clonazepam, we prospectively compared outcomes in infants whose mothers were treated with SSRIs alone and SSRIs combined with clonazepam. We also sought to explore relationships between pharmacologic variables and infant outcomes.

METHOD

Subjects

With approval from the University of British Columbia Research Ethics Board, Children's and Women's Health Centre of British Columbia Research Review Committee, and informed parental consent, a consecutive cohort (N = 46) was enrolled, comprising mothers and their infants studied during pregnancy as a part of a larger study of the effects of psychotropic medication use during and following pregnancy. Two groups of medication-exposed infants were studied during the period June 1996 through June 2000: infants with exposure to an SSRI alone (group 1, N = 28: paroxetine, N = 17; fluoxetine, N = 7; sertraline, N = 4) and infants with SSRI exposure combined with the benzodiazepine clonazepam (group 2, N = 18: paroxetine, N = 16; fluoxetine, N = 2). A control group (N = 23) comprising dyads of term-born healthy infants and their mothers were recruited in the newborn period and studied for comparative purposes. Mothers and their infants were included if no psychotropic or antidepressant medications were used during the pregnancy, the pregnancy was term in length (38–42 weeks), and there was no history of maternal mental illness. Infants were excluded if admitted to the neonatal intensive care unit following birth.

Demographic Data

Women with mood and anxiety disorders were recruited prospectively during their pregnancies from British Columbia Women's Hospital (Vancouver, British Columbia, Canada). Healthy control subjects were recruited in the immediate postpartum period. Women were excluded from enrollment if they were also using any psychotropic medications in addition to an SSRI or clonazepam. Maternal age and demographic variables re-

Table 1. Maternal and Delivery Characteristics

Characteristic	Control Group (N = 23)	Group 1 SSRI Alone (N = 28)[a]	Group 2 SSRI + (N = 18)[b]
Age, mean (SD), y	32.9 (4.4)	31.4 (4.4)	31.3 (4.4)
Gravidity 1st/2nd, N	11/9	8/8	2/5
Method of delivery, SVD/CS, N	15/7	22/5	15/3
Analgesia method, epidural/spinal, N	11/4	10/4	10/2
Analgesia medication, meperidine/morphine, N	4/2	7/3	4/0

[a]17 = paroxetine, 7 = fluoxetine, 4 = sertraline.
[b]16 = paroxetine, 2 = fluoxetine.
Abbreviations: CS = cesarean section, SSRI = selective serotonin reuptake inhibitor, SVD = spontaneous vaginal delivery.

garding birth did not vary significantly between subject groups (Table 1).

Infant outcomes of interest included (1) gestational age at birth, (2) growth parameters at birth, (3) Apgar score (1 and 5 minute scores), (4) evidence of transient neonatal symptoms suggesting altered adaptation in the newborn period (jitteriness, respiratory difficulty, hypoglycemia, lethargy, weak or absent cry, or desaturation on feeding [per Chambers[11]]), (5) presence of major anomalies, (6) admission for observational unit or special care nursery, and (7) duration of hospital stay. Concern about respiratory or other symptoms on the part of the family physician, midwife, or obstetrician led to assessment of the infants by the attending pediatrician for symptoms of transient neonatal distress. Physicians who had been asked to assess distressed newborns were, for ethical and practical clinical reasons, partially blinded to the infants' prenatal exposure status. Newborns were referred to the attending pediatrician because of their symptoms, not because they were prenatally exposed to medication. For a complete assessment, the physician had to review the chart and make clinical recommendations, thereby becoming aware of the prenatal status. Poor neonatal outcomes were determined in this study by the presence of symptoms that necessitated a higher level of medical care and observation, no longer allowing infants to remain in the room with their mothers.

Pharmacologic Data

Plasma levels of maternal SSRI medications both during pregnancy and at delivery were obtained, as well as infant levels from cord blood and on day 2 of life. Enantiomers of fluoxetine and norfluoxetine were extracted from plasma using liquid/liquid extraction and subsequently measured employing a rapid, sensitive, and selective chiral assay using gas chromatography (GC) with electron impact ionization mass spectrometry (MS) using the 5890/5971A GC/MSD (Hewlett-Packard, Avondale, Pa.) with selective ion monitoring (mass-to-charge ratio [m/z] 341 and m/z 327 for fluoxetine and norfluoxetine, respectively) developed in our laboratory. Fluoxetine and norfluoxetine enantiomers were converted to their diastereoisomers using (*S*)-(–)-*N*-trifluoroacetylpropyl chloride and were recorded to provide complete resolution of all peaks. The method is linear over a concentration range of 0.5 to 50.0 ng/mL ($r^2 > 0.99$) with intraday and interday precision (CV) and accuracy (relative error) < 10%.

A similar GC/MS (Hewlett Packard 5890/5989A GC/MSD) assay employing either electron impact or negative ion chemical ionization with selective ion monitoring (m/z 525 and m/z 485, respectively) was developed for paroxetine. A heptafluorobutyryl derivative is formed, resulting in improved sample volatility and detector sensitivity. The method is linear over a concentration range of 0.1 to 500.0 ng/mL ($r^2 > 0.99$) with intraday and interday CV and accuracy (relative error) < 15%.

Sertraline and its metabolite desmethylsertraline (norsertraline) were extracted from human plasma by liquid/liquid extraction.[29] The analytes were chromatographically separated on a reverse-phase analytical column, followed by atmospheric pressure electrospray positive ion liquid chromatography/mass spectrometry (LC/MS) analysis using gradient elution with an integrated Hewlett-Packard 1100 LC-MSD system. Quantitation was carried out by monitoring selected ions at m/z 306.1 sertraline and m/z 275.1 norsertraline. The method is linear over concentration ranges of 0.25 ng/mL to 35.03 ng/mL ($r^2 > 0.99$) and 0.50 ng/mL to 25.07 ng/mL ($r^2 > 0.99$) for sertraline and norsertraline, respectively, with respective limits of quantitation (LOQ) of 0.25 and 0.50 ng/mL. Intraday and interday CV and accuracy (relative error) for sertraline and norsertraline were < 4.6% at the LOQ.

Statistical Analysis

Outcomes were tabulated as means and standard deviations. Univariate analyses were undertaken using 2-sample t tests. For categorical variables, chi-squares were tabulated (95% confidence intervals).

RESULTS

Maternal Data

Maternal and delivery characteristics did not vary significantly between exposure groups (Table 1). For most women, the median dose of medications did not vary from any trimester to delivery. Single-agent medication mean dose/day for paroxetine was 21.2 mg (range, 10–40 mg), for fluoxetine was 16.5 mg (range, 10–20 mg), and for sertraline was 68.8 mg (range, 50–100 mg). At delivery, mean dose of paroxetine was 22.2 mg (range, 10–40 mg), fluoxetine was 21.3 mg (range, 10–30 mg), and sertraline was 81.3 mg (range, 50–150 mg). When combined with clonazepam, the mean dose/day during pregnancy of paroxetine was 17.5 mg (range, 5–40 mg) and fluoxetine was 10.0 mg (range, 10–10 mg). At the time of delivery,

Table 2. Background Characteristics of Infants Exposed to Prenatal Psychotropic Medication[a,b]

Characteristic	Exposure Group: Control (N = 23)	Group 1 SSRI Alone (N = 28)[c]	Group 2 SSRI + (N = 18)[d]
Gestational age at birth, wk	39.3 (1.4)	39.4 (1.5)	39.5 (1.1)
Weight, g	3485 (419)	3388 (448)	3553 (432)
Length, cm	51.6 (2.4)	51.9 (3.2)	51.8 (2.2)
Head circumference, cm	35.2 (1.8)	34.2 (1.4)	34.8 (1.0)
Apgar score 1 min, median	8	7	8
Apgar score 5 min, median	9	9	9
Breast fed, %	91	74	72
Length of stay, d	3.4 (0.8)	3.2 (1.1)	3.9 (2.0)
MDI[e] at 2 mo	96.7 (7.8)	97.0 (8.3)	94.0 (5.2)
PDI[e] at 2 mo	102.6 (7.3)	104.8 (6.1)	102.9 (6.2)
MDI[e] at 8 mo	99.4 (5.6)	100.7 (6.4)	97.2 (4.5)
PDI[e] at 8 mo	97.0 (9.1)	91.5 (9.6)	93.1 (8.6)

[a]Differences between groups were not significant for any variables.
[b]Values are mean (SD) unless otherwise specified.
[c]17 = paroxetine, 7 = fluoxetine, 4 = sertraline.
[d]16 = paroxetine, 2 = fluoxetine.
[e]MDI and PDI from Bayley Scales of Infant Development.[30]
Abbreviations: MDI = Mental Developmental Index, PDI = Psychomotor Developmental Index, SSRI = selective serotonin reuptake inhibitor.

Table 3. Characteristics of Prenatal Psychotropic Medication–Exposed Infants With and Without Transient Neonatal Symptoms[a]

Variable	With Symptoms (N = 14)	Without Symptoms (N = 32)
Characteristic		
Gestational age at birth (wk)	38.9 (1.9)	39.7 (1.0)
Weight (g)	3536 (488)	3416 (427)
Length (cm)	51.8 (2.6)	51.9 (3.0)
Head circumference (cm)	34.4 (1.3)	34.5 (1.2)
Apgar score 1 min (median)	6	8
Apgar score 5 min (median)	8	9
MDI[b] at 2 mo	96.6 (7.3)	95.7 (7.6)
PDI[b] at 2 mo	103.1 (6.7)	104.7 (5.9)
MDI[b] at 8 mo	100.1 (4.9)	98.8 (6.3)
PDI[b] at 8 mo	91.1 (8.5)	92.7 (9.5)
No. of days exposure to SSRIs		
Paroxetine	168 (65)	191 (73)
Fluoxetine	123 (80)	155 (97)
Sertraline	158 (0)	252 (53)
Exposure to maternal SSRI dose in 3rd trimester, mg/d		
Paroxetine	22.5 (10.3)	17.9 (7.6)
Fluoxetine	16.7 (5.7)	14.2 (5.3)
Sertraline	75.0 (0)	66.7 (28.8)
Exposure to maternal SSRI dose at delivery, mg/d		
Paroxetine	22.5 (10.3)	20.0 (7.7)
Fluoxetine	16.7 (5.8)	20.0 (5.8)
Sertraline	75.0 (0)	83.3 (57.7)
No. of days exposure to clonazepam	106 (55)	132 (56)
Dose of clonazepam 3rd trimester, mg/d	0.93 (0.53)[c]	0.43 (0.25)
Dose of clonazepam at delivery, mg/d	0.93 (0.53)[c]	0.48 (0.26)

[a]Values are mean (SD) unless otherwise specified.
[b]MDI and PDI from Bayley Scales of Infant Development.[30]
[c]$p < .05$, for difference between infants with and without symptoms.
Abbreviations: MDI = Mental Developmental Index, PDI = Psychomotor Developmental Index, SSRI = selective serotonin reuptake inhibitor.

the mean paroxetine dose was 21.6 mg (range, 5–40 mg) and fluoxetine was 15.0 mg (range, 10–20 mg) per day. The mean dose/day of clonazepam when combined with paroxetine and fluoxetine was 0.67 mg (range, 0.25–1.75 mg) and 0.25 mg (range, 0.25–0.25 mg), respectively, during the pregnancy and 0.67 mg (range, 0.25–1.75 mg) and 0.5 mg (range, 0.25–0.75 mg), respectively, at delivery. The majority of women started antidepressant medication in the first trimester and continued throughout their pregnancy up to delivery (mean number of days of paroxetine = 201 vs. paroxetine + clonazepam = 167, fluoxetine = 160 vs. fluoxetine + clonazepam = 84, and sertraline = 228). Length of clonazepam use did not differ significantly when it was combined with paroxetine (mean = 127 days) or fluoxetine (mean = 81 days).

Neonatal Outcomes

The birth outcomes in the 3 exposure groups are presented in Table 2. No group differences were observed in growth parameters at birth. One infant was found to have a right hydronephrosis. One preterm infant (34 weeks gestation) and 1 term infant went to the neonatal intensive care unit/special care nursery for respiratory distress.

Transient Neonatal Symptoms

Overall, 30.4% (14/46) of infants with SSRI exposure (groups 1 and 2) were found to have symptoms reflecting poor transient neonatal adaptation in the first hours of life requiring admission for observation to a newborn nursery. Nine percent (2/23) of control infants had similar symptoms ($p = .018$; likelihood ratio = 5.64; 95% CI = 1.1 to 25.3). In group 1, 25% (7/28) had symptoms (fluoxetine, N = 3; paroxetine, N = 3; sertraline, N = 1), while in group 2, 39% (7/18) of exposed infants had symptoms (paroxetine + clonazepam, N = 7). Differences in incidence of symptoms between groups 1 and 2 were not significant (95% CI = 0.5 to 6.8). Differences in demographic and birth characteristics between infants with and without symptoms were not significant (Table 3).

Characteristics of individual infants with transient symptoms who went for observation are presented in Table 4. Of this cohort, 1 infant was admitted to the special care nursery for respiratory distress, although symptoms resolved prior to admission. The remaining infants were observed in postpartum nursery observation units. With the exception of 2 infants, 1- and 5-minute Apgar scores were in the normal range. These symptoms were observed to begin within the first few minutes or hours of life and typically had resolved by the end of the first day

Table 4. Characteristics of Individual Symptomatic Infants

Subject	Medication Exposure	SSRI Exposure, d	3rd Trimester SSRI Dose, mg	Maternal Dose at Delivery, mg	Clonazepam Exposure, d	Clonazepam Dose at Birth, mg	Gestational Age at Birth, wk	Birth Weight, g	Apgar Score 1 min	Apgar Score 5 min	Length of Hospital Stay, h	Neonatal Symptoms
1	Paroxetine	188	20	20	NA	NA	37.29	3010	9	9	54.40	Mild respiratory distress, upper airway congestion
2	Paroxetine	50	10	10	NA	NA	41.71	3770	5	9	72.10	Mild respiratory distress
3	Paroxetine	244	40	40	NA	NA	34.71	2560	6	8	347.30	Respiratory distress, TTN, negative blood cultures, hypothermia, preterm birth
4	Paroxetine + clonazepam	139	20	30	137	1.00	39.71	3495	6	6	54.37	Hypotonia, respiratory distress, symptoms resolved in 6 h
5	Paroxetine + clonazepam	260	40	40	48	1.50	37.57	2880	6	7	9 d, then transferred to community hospital	Bradycardia, respiratory distress, hypoglycemia (2.2 mM), hypotonia, head ultrasound normal, blood cultures negative
6	Paroxetine + clonazepam	258	20	20	208	1.00	37.86	4338	7	9	107.75	Cardiac arrhythmia, PVC, respiratory distress, required O_2 by mask
7	Paroxetine + clonazepam	192	20	30	191	1.75	40.43	4170	6	7	79.25	Respiratory distress, hypotonia, grunting, required O_2 for first 18 h, TTN
8	Paroxetine + clonazepam	90	10	10	28	0.25	41.57	3908	3	8	53.75	Respiratory distress, hypotonia and posturing, resolved by admission to SCN
9	Paroxetine + clonazepam	183	20	40	82	0.50	39.43	3439	9	9	48.30	Respiratory distress, grunting, right hydronephrotic kidney
10	Paroxetine + clonazepam	125	20	20	68	0.25	38.29	3780	8	9	38.63	Respiratory distress, TTN
11	Fluoxetine	145	20	20	NA	NA	39.86	3420	6	7	74.82	Grunting, cyanosis, TTN, blood cultures negative, respiratory distress, symptoms resolved in 12 h
12	Fluoxetine	189	20	30	NA	NA	38.57	3350	7	8	74.68	Jittery, mild respiratory distress required CPAP
13	Fluoxetine	33	10	10	NA	NA	38.14	3820	7	8	101.50	Respiratory distress (O_2 required), tremors, hypertonia, septic workup negative, TTN
14	Sertraline	157	75	75	NA	NA	38.43	3570	6	9	25.47	Respiratory distress, given naloxone
15	Control	NA	NA	NA	NA	NA	37.29	3690	9	9	84.65	Respiratory distress, septic workup negative
16	Control	NA	NA	NA	NA	NA	38.71	3160	8	9	123.58	Respiratory distress

Abbreviations: CPAP = continuous positive airway pressure, PVC = premature ventricular contraction, SCN = special care nursery, SSRI = selective serotonin reuptake inhibitor, TTN = transient tachypnea of the newborn.

Table 5. Paroxetine Levels in Infants Exposed to Prenatal Psychotropic Medication With and Without Symptoms of Poor Neonatal Adaptation

	Plasma Paroxetine Levels, ng/mL, Mean (SD)			
	Paroxetine + Clonazepam (N = 16)		Paroxetine Alone (N = 17)	
Measure	With Symptoms (N = 7)	Without Symptoms (N = 9)	With Symptoms (N = 3)	Without Symptoms (N = 14)
Maternal 3rd trimester	30.6 (15.2)*	14.9 (15.6)	19.6 (17.5)	10.0 (12.4)
Maternal level, delivery	33.3* (31.3)	9.1 (8.6)	4.4 (3.3)	8.4 (8.6)
Infant cord level	10.9 (9.8)	3.6 (6.7)	1.5 (1.0)	3.32 (4.6)
Infant level on 2nd day	7.0* (5.3)	1.5 (1.6)	1.6 (0)	1.0 (0.6)

*$p < .05$ for difference between paroxetine + clonazepam–exposed infants with and without symptoms.

of life. All infants with symptoms had some measure of mild respiratory distress, and 3 infants required a short course of supplemental oxygen by mask. As these symptoms were self limited, they were frequently described by the attending pediatrician as symptoms resembling transient tachypnea of the newborn (TTN). Hypotonia was noted in 4 infants, 1 infant was jittery, 1 had tremors and was hypertonic, 1 had cardiac arrhythmia and premature ventricular contractions (PVC), and 1 had bradycardia. Hypoglycemia (2.2 mM) was noted in 1 infant. One infant received naloxone following maternal meperidine exposure during delivery. Birth weight, Apgar scores, and gestational age did not vary significantly between infants with symptoms and those without. By 48 hours of life, symptoms had resolved in all infants. Length of hospital stay did not vary significantly between infants with symptoms and those without. Length of prenatal SSRI exposure or maternal dose did not vary between infants with and without poor adaptation; however, maternal clonazepam dose was significantly higher during pregnancy and at delivery among symptomatic infants.

Medication Levels

Maternal medication levels were determined once a steady state plasma concentration had been achieved (at least 3 weeks following starting medication) during the third trimester, at delivery, from infants at birth (cord blood), and on the second day of the infant's life during the routine phenylketonuria (PKU) heel lance. Medication levels varied between infants with and without transient poor neonatal adaptation. Among infants in the paroxetine + clonazepam exposure group with symptoms, levels of paroxetine were significantly higher ($p < .05$) during pregnancy, at delivery, and on day 2 of life when compared with infants without symptoms (Table 5). Cord paroxetine levels were higher but differences were not significant ($p = .08$). In the single-agent paroxetine group, differences in drug levels between infants with and without symptoms were not significant. Interestingly, even when symptoms were present, medication levels were consistently lower in the paroxetine monotherapy group compared with the paroxetine + clonazepam–exposed infant group. In other medication exposure groups, medication levels did not differ significantly between infants with and without symptoms, though numbers of exposed infants were small. Importantly, maternal dose of paroxetine did not differ significantly between infants with and without symptoms (Table 3).

Developmental Outcomes

Infants' developmental assessments were done at 2 and 8 months of age using the Bayley Scales of Infant Development.[30] No significant differences were noted between medication-exposed and nonexposed infants (Table 2) and those with and without neonatal symptoms (Table 3).

DISCUSSION

Infants with prenatal exposure to SSRI antidepressants alone or in combination with the benzodiazepine clonazepam had an increased incidence of poor neonatal adaptation compared with nonexposed infants. This difference was particularly evident in infants who were exposed to paroxetine combined with clonazepam. Symptomatic infants in the combined therapy group had significantly higher maternal and infant plasma levels of paroxetine compared with symptomatic infants exposed to paroxetine alone. Furthermore, among symptomatic infants, clonazepam dose was also significantly higher during pregnancy and at birth. Respiratory distress was the predominant symptom that warranted admission to a newborn nursery for closer observation. With the exception of 1 exposed infant with hydronephrosis, no major anomalies were present, and, other than 1 exposed infant born at 34 weeks, all infants were term born and healthy at birth. Furthermore, all symptoms of poor neonatal adaptation that appeared in the first 24 hours were short lived and self limited, and length of hospital stay was similar between infants with and without symptoms. Maternal SSRI dose, length of treatment, mode of delivery, and analgesia use did not differ significantly between infants with and without complications. Importantly, the presence of neonatal symptoms did not appear to be related to altered

developmental outcomes on the Bayley developmental assessment at 2 and 8 months.

While these data are consistent with previous reports of neonatal symptoms following maternal SSRI use during pregnancy,[11,12,13,16] our data highlight the importance of accounting for a variety of pharmacologic factors beyond single-agent SSRI exposure that may explain neonatal symptoms. In this study, we prospectively examined these transient symptoms in relation to maternal drug dose and drug levels in mothers and their infants. The addition of clonazepam in combination with paroxetine appeared to increase the risk of poor neonatal adaptation. This increased risk could be due to either pharmacologic toxicity associated with increased levels of paroxetine when combined with clonazepam, an increased dose of maternal clonazepam itself during pregnancy, or possible withdrawal/discontinuation phenomena as previously reported.[11,13] Furthermore, it remains uncertain whether this increased risk also occurs when fluoxetine and sertraline are used in combination with clonazepam. The small size of our study population limited our ability to detect similar outcomes with other SSRI medications. Where indicated, a number of infants were investigated for other identifiable causes of neonatal distress, but these investigations did not yield other perinatal processes (e.g., sepsis) that could have explained our findings.

A variety of factors related to SSRI pharmacology, maternal genotype, or maternal capacity to metabolize these medications might have played a role in our findings and should be considered as possible underlying etiologic mechanisms.[31] Fluoxetine, paroxetine, and sertraline are metabolized by hepatic cytochrome P450 2D6 (CYP2D6).[32] All 3 medications are potent inhibitors of CYP2D6,[33,34] and this inhibition persists long after discontinuation of fluoxetine due to its long half-life.[34] Approximately 5% to 10% of whites lack or have reduced CYP2D6 activity (i.e., poor metabolizer phenotype, PM). Poor metabolizers (i.e., PM CYP2D6 phenotype) may have increased plasma concentrations of paroxetine, which may lead to anticholinergic side effects in infants such as those observed in adults.[35] However, given the relatively low frequency of this PM phenotype, this mechanism may not play a substantial role in increasing paroxetine levels observed in infants with poor adaptation. Future studies in which both mothers and infants are genotyped for CYP2D6 will be of value in confirming this observation.

Paroxetine may also be metabolized by the metabolic enzyme CYP3A4.[36] Importantly, clonazepam also appears to be a substrate for CYP3A4,[35] and thus it is conceivable that competitive interaction of clonazepam and paroxetine for this isoenzyme could explain the significantly higher paroxetine levels observed in infants whose mothers received combined treatment. Moreover, to what extent relative proportions of maternal and/or infant/fetal competitive inhibition contributed to this process remains to be studied, requiring more detailed study in a larger cohort of infants following paroxetine and clonazepam exposure.

The limitation of this study was the small number of infants per medication group, and thus it is unclear whether polypharmacy would have also resulted in similar neonatal symptoms following combined exposure to fluoxetine or sertraline with clonazepam and whether such exposure would have been associated with increased SSRI levels.

The increased dose of clonazepam among symptomatic infants may also reflect increased severity of maternal symptoms, adding another possible prenatal exposure that contributed independently to adverse neonatal outcomes. Beyond pharmacologic influences, the possible influence of maternal mood remains to be studied. The number of other SSRI-exposure groups was limited and thus we cannot generalize our findings from these groups. Further study of polypharmacy in a larger cohort in the newborn period prospectively followed into childhood is required to determine whether neonatal symptoms are related to another adverse outcome.

CONCLUSION

Our findings showed that transient neonatal symptoms were present in infants following prenatal exposure to both fluoxetine monotherapy and paroxetine in combination with clonazepam. In this latter group, levels of paroxetine were higher in mothers and infants when clonazepam was combined with SSRIs. Furthermore, mothers of symptomatic infants had received higher doses of clonazepam. This is the first report of such a relationship between transient neonatal symptoms and elevated medication levels. Respiratory distress was the most prominent symptom. Importantly, these symptoms were not associated with other neonatal conditions, and all symptoms were self limited. It remains unclear how pharmacologic and metabolic factors and maternal mood itself may influence these findings. Larger populations of infants will be required to further assess these pharmacologic effects.

Tentative recommendations based on our findings suggest that, whenever possible, polypharmacy should be avoided in treating prenatal anxiety and depression to reduce the incidence of problematic neonatal symptoms. If clonazepam is required for symptomatic control prior to delivery, an attempt should be made to taper the dose. When a combination of clonazepam and paroxetine is administered, mothers should be monitored closely during pregnancy as well as infants in the newborn period. Our study cohort was small, and therefore it is difficult to determine risk related to a particular SSRI. In spite of the increased incidence of neonatal symptoms following prenatal psychotropic medication exposure, symptoms were

all short lived (all resolved within 48 hours), and typical developmental follow-up was seen at 8 months of age. Therefore, the risk of these symptoms needs to be observed in the context of healthy outcomes observed in our cohort and balanced against the effects of psychiatric illness during pregnancy for mothers and their offspring.

While these results raise concerns about the use of these medications during gestation, the very small sample size and exposure to a limited number of SSRI medications limit the generalizability of our findings. At present, our findings should not prejudice the clinical urgency to treat maternal depression and comorbid anxiety in pregnancy with medications, if warranted. The risk of undertreated psychiatric illness in mothers needs to be balanced against currently known adverse effects of prenatal use of medication to treat anxiety and depression during pregnancy. These findings indicate that maternal drug level during pregnancy and at the time of delivery may help us guide the care of infants in the newborn period, particularly when treatment includes paroxetine combined with clonazepam. Close follow-up and symptomatic treatment in the newborn period are indicated. Further work is needed to study neonatal behavior following prenatal SSRI exposure, both alone and in combination with clonazepam, in larger cohorts. Our findings also need to be replicated with exposure to a variety of SSRI medications to further understand the implications of transient poor neonatal adaptation and psychopharmacotherapy during pregnancy.

Drug names: citalopram (Celexa), clonazepam (Klonopin and others), diazepam (Valium and others), fluoxetine (Prozac and others), meperidine (Demerol), naloxone (Narcan), paroxetine (Paxil and others), sertraline (Zoloft).

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