Maternal Selective Serotonin Reuptake Inhibitor Use During Pregnancy and Newborn Neurobehavior

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ABSTRACT. *Objective.* **This is a prospective study of the effects of maternal use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy on newborn neurobehavioral integrity, including systematic measures of behavioral state, sleep organization, motor activity, heart rate variability (HRV), tremulousness, and startles.**

Methods. **The sample included 17 SSRI-exposed and 17 nonexposed, full-birth-weight newborn infants who had no obvious medical problems and were matched on maternal cigarette use, social class, and maternal age. SSRI exposure was determined by medical records and maternal self-report during a standard interview. Behavioral state, startles, and tremulousness were evaluated for 1 hour between feedings. Automated recordings of motor activity and HRV were also assessed during a 15-minute subset sleep period. HRV was subjected to spectral analysis to detect rhythms in autonomic regulation. Exposed and nonexposed infant groups were compared on measures of neurobehavioral development both before and after adjustment for gestational age as a covariate.**

Results. **SSRI-exposed infants had a shorter mean gestational age; were more motorically active and tremulous; and showed fewer rhythms in HRV, fewer changes in behavioral state, fewer different behavioral states, and a lower peak behavioral state. SSRI-exposed infants also had significantly more rapid eye movement sleep, which was characterized by longer continuous bouts in that state and higher numbers of spontaneous startles or sudden arousals. After effects of gestational age were covaried, significant differences continued to be found in tremulousness and all measures of state and sleep organization, but effects on startles, motor activity, and rhythms in HRV were no longer significant.**

Conclusions. **Results provide the first systematic evidence that women who use SSRIs during pregnancy have healthy, full-birth-weight newborn infants who show disruptions in a wide range of neurobehavioral outcomes. Effects on motor activity, startles, and HRV may be mediated through the effects of SSRI exposure on gestational age. Future research can lead to a better understanding of the effects of SSRI use during pregnancy and an improved public health outcome. *Pediatrics* 2004; 113:368–375; *SSRI, pregnancy, neurobehavior, sleep, heart rate variability, maternal depression.***

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ABBREVIATIONS. SSRI, selective serotonin reuptake inhibitor; HRV, heart rate variability; SES, socioeconomic status; NBAS, Neonatal Behavioral Assessment Scale; REM, rapid eye movement; CPM, cycles per minute; SE, standard error; IUGR, intrauterine growth retardation.

Maternal use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy is of increasing public health concern because of its wide prescriptive base for the treatment of depression and other disorders and its potential teratogenic effects on the developing fetus. Estimates suggest that lifetime risk for depression ranges from 10% to 25% for women with a peak prevalence occurring between the childbearing ages of 25 and 44.[1] Others suggest that 9% to 14% of all pregnant women display signs of depression and/or have illnesses that fulfill research diagnostic criteria for depression[2–4] and that as many as 35% of women use psychotropic medications during pregnancy.[5] SSRIs have become the treatment of choice for depression compared with tricyclic antidepressants because of overall higher efficacy and fewer safety issues.[6,7] Commonly used SSRIs include paroxetine (Paxil), fluoxetine (Prozac), citalopram (Celexa), and sertraline (Zoloft). Although this group of SSRIs varies in such aspects as potency, pharmacokinetic effects, molecular structure, and half-life, the SSRIs similarly act by inhibiting 5-HT reuptake at the presynaptic junction, leading to increased concentrations at the synaptic cleft and potentiating serotonergic neurotransmission.[8,9]

These psychotropic medications readily cross the placental barrier[10] and expose the infant to increased serotonin levels during early development. During embryogenesis, before developing into its role as a neurotransmitter, serotonin regulates the development of γ-aminobutyric acid and monoamine systems that affect cell migration, axon growth, and genesis of synaptic communication.[11,12] Some animal research has shown that higher prenatal levels of serotonin produce adverse neuroanatomic effects, including reduced numbers of β-adrenergic and serotonin receptors and abnormalities in brain serotonin receptor binding.[13–15] Our understanding of the effects of prenatal SSRI exposure on human infants mostly comes from studies of infant physical growth, birth outcome, and surveys of medical records. Reviews of the literature suggest that there is no evidence that use of tricyclics, fluoxetine, or newer SSRIs during pregnancy increases the risk for fetal

death, major birth defects, or fetal growth deficits,[1,16] although a couple of studies have found a gestational age shortened by ~1 week.[17–19]

Despite the widespread use of SSRIs during pregnancy, a paucity of studies have investigated the potential neurobehavioral teratogenicity of these psychotropic medications on the newborn infant. Case reports have described associations between prenatal SSRI exposure and increased motor activity,[20,21] startles,[20] and tremulousness[21–23]; disrupted sleep state organization[20]; and excessive crying.[20,21] Lester et al[24] also found excessive crying in an infant whose mother used fluoxetine during pregnancy and continued to use it during breastfeeding. A recent study of 22 SSRI-exposed and 23 nonexposed infants showed that prenatal exposure is related to attenuated autonomic reactivity to painful stimulation, as measured by spectral analysis of heart rate variability (HRV).[25] These reports suggest that there may be neurobehavioral effects of prenatal SSRI exposure that have not been evidenced in studies of physical growth and birth complications. On the basis of these and other findings, the current policy statement of the American Academy of Pediatrics[26] indicates that conclusions about maternal SSRI use during pregnancy are based on insufficient information and require more research. A review of the literature indicates that a significant gap in information, specifically with regard to the effects of prenatal SSRI exposure on newborn neurobehavioral integrity, needs to be addressed.[1]

The purpose of the present study was to examine systematically the neurobehavior of newborn infants whose mothers used SSRIs during pregnancy. Measures of motor activity, HRV, behavioral state, sleep-state organization, startles, and tremors have been used to assess possible effects of prenatal drug exposure and other adverse prenatal conditions on infant neurobehavioral outcome.[27] We use a combination of these measures to provide some of the first systematic evidence that maternal SSRI use during pregnancy is associated with disrupted neurobehavioral regulation in full-birth-weight, healthy newborn infants.

METHODS

Subjects

The prospective study included 34 postpartum mothers who were 19 to 45 years of age and their 1- to 2-day-old newborns who were recruited at Carolinas Medical Center in Charlotte, North Carolina. The research protocol was approved by the hospital Institutional Review Board. Mothers and infants were studied in the hospital while newborns resided in the term nursery.

Eligibility was determined through a review of medical records followed by an interview of mothers using a standard questionnaire. Exclusion criteria included maternal use of illicit drugs other than marijuana during pregnancy and serious maternal physical illnesses during pregnancy. Marijuana use was not excluded because of its common use. Illicit drug use was determined from medical records and interviews and an infant urine drug screen when the infant or the mother seemed to be at risk for drug use/exposure. Healthy newborns who were in the term nursery and had gestational ages between 37 and 41 weeks were studied except for 1 SSRI-exposed infant who had a gestational age of 36 weeks (mean: 39.2; standard deviation: 1.2). Gestational age in weeks was determined from medical records using the best obstetric estimate. Infants were excluded from study when they showed congenital anomalies, jaundice, or serious medical complications.

A total of 24 mothers who, according to medical records, used SSRIs during pregnancy were approached. Of these, 5 women refused to participate; 2 other mothers were excluded because of use of lithium and Zyprexa for disorders other than depression. The remaining 17 mothers were compared with 17 mothers who did not use SSRIs during pregnancy and were matched on maternal cigarette use ($n = 5$ per group), maternal age (±2 years), and low socioeconomic status (SES), as measured by determined need of public medical insurance (Medicaid; $n = 3$ per group). Mothers reported solitary use of Celexa ($n = 5$), Prozac ($n = 1$), Paxil ($n = 3$), or Zoloft ($n = 5$); a sequential combination of Paxil, Prozac, and Zoloft ($n = 1$) or Paxil ($n = 1$); or Paxil and Zoloft ($n = 1$) in combination with the antidepressant Wellbutrin. All mothers continued taking SSRIs up to labor and delivery, except for 1 mother who reported that she stopped taking Zoloft late in the third trimester. Medical records indicated that dose levels averaged 36.8 mg/day (range: 12.5–100 mg/day) but varied by SSRI class: Paxil (mean: 17.5; range: 12.5–20 mg/day), Celexa (mean: 24; range: 20–40 mg/day), Prozac (30 mg/day, 1 patient), and Zoloft (mean: 56; range: 25–100 mg/day).

Procedures

Infants were studied between feedings when they were between 14 and 39 hours of age (mean: 26.4; standard deviation: 6.9). All infants were placed in a supine position in a temperature-controlled (32°C) isolette, located in a darkened, quiet room in the nursery. Infants were studied for 1 hour during which behavioral state, startles, tremulousness, heart rate, and motor activity were monitored continuously. All neurobehavioral ratings were conducted by an assistant who was trained to criterion and masked to SSRI group membership.

Behavioral State

Assessment of behavioral state has long been integral to the neurologic examination,[28] clinical observation,[29] and standard neurobehavioral assessment of the newborn infant.[30,31] Measures of behavioral state have also been used to study neonatal sleep organization and nervous system integrity[32] and to differentiate infants with prenatal drug exposure.[31] Definitions of behavioral state were based on the 6-point scale used in the Neonatal Behavioral Assessment Scale (NBAS),[30] as described in Table 1. With the use of procedures developed in other studies of prenatal effects on neonatal outcome,[33,34] behavioral state was determined every 30 seconds by the trained and masked observer. The 120 observations of state were reduced to the number of state changes, highest state achieved, and number of different states that infants demonstrated. Because reduction in dosage of SSRIs has been associated with increased rapid eye movement (REM) activity in adults[35,36] we were also interested in the number of epochs (assessed every 30 seconds), number of bouts (contiguous 30-second episodes in the same state), and duration of the longest contiguous bout in active (REM) sleep.

TABLE 1. Descriptions of Behavioral State

1. Quiet sleep: Deep sleep with regular breathing; eyes closed with no eye movements; little spontaneous activity except occasional startles.
2. Active or REM sleep: Light sleep with frequent REMs; eyes closed, but brief eye openings may occur; low activity level; irregular respiration and sucking movements.
3. Drowse: Drowsy or semidozing; dazed look; eyes may be open but dull and heavy-lidded or closed, eyelids fluttering; activity level variable, with occasional mild startles; movements are usually smooth.
4. Alert: Alert, with bright look and minimal motor activity; focused attention.
5. Active alert: Eyes open; considerable motor activity, with thrusting movements of the extremities; brief fussy vocalizations may occur.
6. Crying: Characterized by intense crying; motor activity is high.

Startles and Tremulousness

Assessments of startles and tremors are used in standard neonatal neurobehavioral examinations to asses the integrity of autonomic regulation.[30,31] Higher numbers of startles, or sudden arousals, have been found in term newborns with poor prenatal growth[37] and have been associated with other measures of poor autonomic regulation and neurobehavioral development.[38] Following the definition from the NBAS, a startle was scored when there was a sudden, total body movement for no observable reason other than spontaneous internal stimulation. Similarly, the amount of tremulousness has been part of the NBAS cluster of autonomic stability[39] and the CNS subscale on the Stress/Abstinence scale in the NICU Network Neurobehavioral Scale.[31] For the present study, the number of spontaneous startles that occurred during each 30-second state assessment was determined by the assistant, who was masked to the SSRI exposure history of the infant. At the end of the observation period, the masked assistant rated the amount of tremulousness that the infant demonstrated during the entire hour (1 = very little, 2 = moderate, 3 = high).

Motor Activity

Motor activity has been used in standard neurobehavioral assessment scales[30,31] and to assess the effects of an adverse prenatal metabolic environment on neurobehavioral integrity.[40] In the present study, the amount of motor activity was recorded continuously during a 15-minute subset period during which the infant was observed only in quiet and/or active sleep. Four mercury movement–based motion detectors were attached to the infant's wrists and ankles and connected to a computerized system (Minimitter) that automatically recorded the amount of motor activity within each successive 5-second epoch. A total score of motor activity was determined from a summation of the 180 5-second epochs.

Heart Rate

Spectrum analysis of HRV provides a measure of both the strength and the complexity of rhythms underlying changes in heart rate over time and has been used in the assessment of neurobehavioral integrity and autonomic nervous system regulation[41,42] and effects of prenatal SSRI exposure on newborn infants.[25] Measures of the strength of spectral peaks in HRV, for example, at the frequency of respiratory-sinus arrhythmia—reflecting changes in heart rate associated with the respiratory cycle (20 cycles per minute [cpm])—have been used to assess neural function.[41,43,44] In contrast to measuring the strength of the spectral peaks, we measured the complexity of HRV by determining the number of peaks in the power spectrum. Greater complexity in HRV, reflected in a higher number of spectral peaks, generally increases with gestational age and is typically indicative of healthy development and autonomic regulation.[42] Fewer numbers of spectral peaks of HRV, indicating less complexity and poorer autonomic regulation, have been found in newborn infants with prenatal and early postnatal conditions that disrupt autonomic nervous system regulation and development.[33,34,38] Given similar amounts of HRV, fewer numbers of spectral peaks signify that the infant's maintenance of autonomic homeostasis is more erratic and less energy efficient.[33,34,38,42]

We chose to analyze the frequency band at which the effects of motor activity on heart rate are detected (0.3 cpm).[40] HRV was analyzed via standard spectrum analytic techniques used in previous studies of high-risk newborns. Unlike measures of respiratory-sinus arrhythmia, which require high sampling rates of beat-to-beat variability,[41,43,44] the technique used in the present study uses slower rates to sample mean heart rate over time to capture the rise and fall in generalized infant arousal.[42] Heart rate was sampled every 5 seconds for 15 minutes during the period in which infants were observed only in quiet and/or active sleep. A computerized recording system connected to a Corometric 511 neonatal cardiac monitor generated 180 time samples of heart rate (5-second samples for 15 minutes). Linear, quadratic, and cubic trends in the 180 measures of heart rate were removed before spectra were computed to improve the stationary nature of the time series. The residual variance of each time series was then spectrum analyzed using a Blackman-Tukey window. The number of significant rhythms was determined from the number of peaks in the power spectrum that exceeded the 95% confidence interval determined by a Kolmogorov-Smirnov nonparametric test.[45]

Statistical Analysis

Maternal and infant characteristics and infant neurobehavioral outcomes of the SSRI-exposed and nonexposed groups were compared using t tests on continuous variables and χ^2 tests on noncontinuous variables. Pearson product-moment and Spearman Rho correlation statistical procedures were used to determine the degree of association in parametric and nonparametric data, respectively. Comparisons of neurobehavioral outcomes were repeated with analyses of covariance to adjust for differences in the distribution of gestational age between the 2 groups. Following recommended procedures,[46] a $\log_{10}$ transform of HRV was conducted to compare the amount of overall HRV between groups.

RESULTS

Demographic and Medical Characteristics

Mothers in the 2 groups did not significantly differ in maternal age, cigarette use, SES (the 3 measures on which they were matched), parity, education, or alcohol use during pregnancy (Table 2). Infants in the 2 groups also did not significantly differ in birth weight, birth length, Apgar scores at 1 or 5 minutes, ethnicity, or weight for gestational age. None of the infants who were large for gestational age in the SSRI-exposed group were infants of diabetic mothers; one infant who was large for gestational age in the nonexposed group was an infant of a diabetic mother. In addition to being matched on maternal cigarette use, t tests showed no differences between groups in the number of cigarettes that mothers smoked per day for any of the 3 trimesters (all $P > .63$). Similarly, no differences were found between groups in the number of alcoholic drinks per day for any of the 3 trimesters (all $P > .20$) or in the total amount consumed during pregnancy ($P > .89$). Because SSRI-exposed infants were of lower gestational age than nonexposed infants and showed significant correlations with neurobehavioral outcome, this variable was used as a covariate to adjust for its effects on the neurobehavioral scores described below.

Four mothers in the SSRI-exposed group used marijuana during pregnancy. The t-test comparisons of marijuana-exposed and marijuana-nonexposed infants in the SSRI-exposed group showed no differences in the means or distributions of all neurobehavioral outcome measures ($P > .45$). Spearman Rho correlations also were used to determine the strength of association between maternal marijuana use and newborn neurobehavioral outcome scores within the SSRI-exposed group. All correlations were <0.10 (all $P > .71$), except for low and nonsignificant correlations with the number of rhythms in HRV ($r = -.16$, $P < .55$) and duration of the longest continuous bout in REM sleep ($r = .13$, $P < .62$). Previously established criteria for the selection of possible covariates in analyses of covariance require correlation coefficients >0.10 with neurobehavioral outcome and correlations <0.70 with group membership.[47,48] On the basis of low correlations with neurobehavioral outcomes and high association with group membership and no group differences between marijuana-exposed and -nonexposed SSRI-exposed infants, prena-

TABLE 2. Demographic and Medical Characteristics

	SSRI-Exposed Mean (SE) or *n*	Nonexposed Mean (SE) or *n*	*P*
Maternal demographics			
Parity	2.35 (0.26)	2.71 (0.32)	.39
Age, y	33.18 (1.36)	33.12 (1.28)	.97
Education, y	15.24 (0.48)	14.38 (0.55)	.24
Low SES	3	3	1.00
Alcohol use	12	10	.31
Cigarettes use	5	5	1.00
Marijuana use	4	0	.11
Ethnicity			.18
Anglo-American	16	12	
African-American	1	4	
Hispanic-American	0	1	
Newborn medical characteristics			
Gestational age, wk	38.66 (0.35)	39.65 (0.20)	.019
Birth weight, g	3453.53 (98.87)	3297.35 (88.79)	.25
Length, cm	51.06 (0.65)	50.81 (0.43)	.75
Head circumference, cm	33.87 (0.40)	33.53 (0.40)	.55
Apgar 1	8.06 (0.35)	8.18 (0.15)	.76
Apgar 5	9.00 (0.00)	9.00 (0.00)	1.00
Weight for gestational age			.43
AGA	13	14	
SGA	0	1	
LGA	4	2	

AGA indicates appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age.

tal marijuana exposure was not appropriate for inclusion in subsequent covariate analyses.

Neurobehavioral Outcome

Analyses of the unadjusted mean scores on the measures in Table 3 show that SSRI-exposed and -nonexposed infants demonstrated differences in a wide range of neurobehavioral outcomes. SSRI-exposed infants had significantly more tremors. Whereas the modal score for exposed infants was "3" or "high" ($n = 9$), the modal score for nonexposed infants was "1" or "very little" ($n = 9$). SSRI-exposed infants also had fewer changes in behavioral state and were in fewer different behavioral states during the hour-long observation period than nonexposed infants. Whereas 11 of the 17 nonexposed infants achieved active alert (state 5) and crying (state 6) states, only 2 of the infants in the SSRI group achieved greater than a drowse state (state 3; χ^2 [1] = 10.2, $P < .001$).

Analysis of sleep state patterns showed that SSRI-exposed infants had more active or REM sleep (number of epochs) than nonexposed infants. SSRI-exposed infants averaged ~48 minutes of the 1-hour observation period in REM sleep. REM sleep of SSRI-exposed infants was characterized by fewer numbers of contiguous periods of this state (number of bouts) that were of longer continuous duration (longest bout) and by having a greater occurrence of spontaneous startles, or arousals, than REM sleep of nonexposed infants. No differences were found between groups in the amount of time they were observed in quiet sleep ($P > .69$). The same pattern of effects on behavioral state and sleep state organization were found after effects of gestational age were covaried, except that the effect on number of startles in active sleep was no longer significant.

Measures obtained during the 15-minute continuous sleep period showed that SSRI-exposed infants had a significantly greater amount of motor activity and fewer numbers of significant spectral peaks in the HRV power spectrum than nonexposed infants. Motor activity was significantly related to the number of startles in REM sleep ($r = .67$, $P < .009$) but not tremulousness ($r = .32$, $P < .21$). The first (or basic) rhythm in the power spectrum of HRV occurred at

TABLE 3. Outcome Variables in SSRI-Exposed and Nonexposed Groups

Outcome Variables	SSRI-Exposed Unadjusted Mean (SE)	Nonexposed Unadjusted Mean (SE)	*P*	SSRI-Exposed Adjusted Mean (SE)	Nonexposed Adjusted Mean (SE)	*P*
Tremulousness	2.41 (0.17)	1.71 (0.21)	.006	2.32 (0.20)	1.80 (0.20)	.038
Behavioral states						
Number different	2.53 (0.29)	3.71 (0.32)	.005	2.53 (0.32)	3.71 (0.32)	.009
Number of changes	7.00 (1.90)	16.71 (2.47)	.002	7.15 (2.34)	16.56 (2.34)	.005
Active sleep						
Number of epochs	96.71 (5.99)	81.41 (6.67)	.049	94.66 (6.64)	83.46 (6.64)	.13
Number of bouts	3.24 (0.27)	6.71 (0.53)	.001	3.36 (0.44)	6.58 (0.44)	.001
Longest bout	69.94 (6.13)	48.06 (6.00)	.008	68.20 (6.37)	49.80 (6.37)	.03
Number of startles	15.57 (3.26)	8.93 (1.24)	.037	14.59 (2.70)	9.85 (2.59)	.13
Motor activity	154.24 (25.38)	104.19 (12.40)	.045	152.05 (21.25)	106.51 (21.96)	.08
Number of HRV rhythms	1.94 (0.17)	2.44 (0.18)	.027	1.98 (0.19)	2.39 (0.19)	.07

the known frequency of infant motility (0.3 cpm)[40] or its multiple for 88% of infants in this study. For descriptive purposes, heart rate mean and variability were determined. No differences were found in mean heart rate (SSRI-exposed: mean = 124.3, standard error [SE] = 2.38; nonexposed: mean = 122.5, SE = 9.53; $P > .55$) or the $\log_{10}$ transform of HRV (SSRI-exposed: mean = 1.51, SE = .24; nonexposed: mean = 1.42, SE = 0.26; $P > .31$). The adjusted means of motor activity and spectral peaks in HRV were no longer significant after covarying out the effects of gestational age.

DISCUSSION

Recent evidence suggests that maternal depression during pregnancy is at least as common as postpartum depression,[4] a condition that rightfully has received increased attention in recent years. Clinicians are faced with the difficult cost-benefit consideration of either making a recommendation to treat maternal depression with psychotropic medications, such as SSRIs, or having a mother remain depressed during pregnancy. Not only is maternal depression during pregnancy detrimental to the mother's well-being, but also the biological dysregulation of depression provides a less-than-optimal prenatal context for infant development. Maternal depression, through its action as a stressor, may have an impact on fetal development through its effect on the hypothalamic-pituitary-adrenal axis, adrenocorticotropic hormones, and β-endorphins.[49] Infants of depressed mothers are at risk for physical anomalies and birth complications,[50] delayed habituation of fetal heart rate,[51] higher neonatal cortisol levels,[52] higher levels of indeterminate sleep, and elevated norepinephrine levels, even before infants interact with their mother.[53]

In making an informed recommendation, clinicians have relied on studies that have focused mostly on the effects of prenatal SSRI exposure on physical growth, birth outcome, and complications evident in medical records. Results of these studies are based on comparisons among nonexposed infants and infants who were exposed to tricyclics and/or SSRIs,[17,54,55] between SSRI-exposed and -nonexposed infants,[25,56,57] and between infants who were exposed to SSRIs during different trimesters of pregnancy.[18,19] First-trimester use has been associated with higher rates of >3 minor physical anomalies[19] and miscarriages,[54] thus suggesting possible early effects of SSRI exposure on embryonic development. Third-trimester use has been further associated with lower gestational age, low birth weight, higher rates of neonatal intensive care unit admissions,[19] but no effects on the number of postnatal complications.[56] Others have found effects of SSRI exposure on gestational age and/or birth weight[54,55,57,58] with effects on birth weight disappearing when effects of gestational age were statistically controlled.[17] Furthermore, no studies have found effects of prenatal SSRI exposure on subsequent development of intelligence or language,[58–60] including a recent study that compared SSRI-exposed and -nonexposed 6- to 40-month-old infants/children, all of whom were born to mothers who had major depressive disorder during pregnancy.[61] The 1 significant finding in that study, however, was that SSRI-exposed subjects showed poorer motor development and tremulousness. One other systematic study also showed that prenatal SSRI exposure is associated with an attenuated autonomic response to a heel-stick procedure,[25] thus suggesting effects on neurobehavioral regulation.

The present study provides the first systematic evidence that prenatal SSRI exposure is significantly associated with a wide range of neurobehavioral outcomes among healthy, full-birth-weight infants. Selection and matching criteria resulted in both groups being comparable in SES, maternal age, parity, education, and numbers of mothers who used alcohol or cigarettes during pregnancy. Four SSRI-using mothers also used marijuana during pregnancy, but both correlations and group comparisons showed no effects on neurobehavioral outcome in this sample. SSRI-exposed infants were of similar birth weight, birth length, head circumference, weight for gestational age, and Apgar scores at both 1 and 5 minutes but were, on average, 1 week less in gestational age. Significant effects on several aspects of neurobehavior were found after effects of gestational age were covaried; other aspects of neurobehavior may be mediated through the effects of SSRI exposure on gestational age.

First, as found in case reports of heightened tremulousness and exaggerated startle reflexes in infants who were exposed prenatally to maternal SSRI use,[20–23] SSRI-exposed infants in the present study showed greater global assessments of tremulousness during 1 hour of continuous observation and higher numbers of startles during active sleep (when they occur most frequently).[37] Although milder forms of tremulousness in the extremities are normal during the neonate's first week, heightened tremulousness may reflect central nervous system depression[30] and/or stress/withdrawal from prenatal drug exposure.[48] These findings may be a harbinger of the persisting tremors found in SSRI-exposed infants/children at 6 to 40 months of age.[61] Startles have been described as the sudden discharge of accumulated "neural energy" that occurs when the infant is less available to external stimulation,[29] such as when the infant is in an insulated, nonawake state, as were the SSRI-exposed infants. Higher numbers of spontaneous startles have also been found in studies of full-term, full-birth-weight, healthy newborns who show other signs of poor homeostatic regulation and/or intrauterine growth retardation (IUGR).[37,38]

Differences in behavioral state reflect the infant's inborn ability to regulate arousal and response to both endogenous and exogenous sources of stimulation. Whereas the infant ideally moves smoothly between states and uses a wide range of states in response to these sources of stimulation,[30,42] SSRI-exposed infants showed significantly fewer transitions to different states and exhibited a more narrow range of states than nonexposed infants. SSRI-exposed infants changed state less than half as often as nonexposed infants. The more narrow range

of states included the absence of attaining more than a drowsy state for all but 2 of the SSRI-exposed infants. This lack of lability and flexibility in state organization has previously been found in newborn infants with IUGR[34] and poor autonomic regulation.[38] These characteristics are also similar to the lower arousal and depressed neurobehavior seen in newborns with prenatal polydrug exposure.[47,62–65]

Within the sleep states, SSRI-exposed infants were in REM sleep for a longer overall period of time, averaging 48 of the 60 minutes in which they were systematically observed. With fewer state changes, SSRI-exposed infants remained in continuous, uninterrupted bouts of REM sleep for longer durations than nonexposed infants, averaging 35 minutes at the longest contiguous bout. SSRI-exposed infants had less than half the number of individual bouts in this sleep state than nonexposed infants. Because infants did not differ in the amount of time they were in quiet sleep, the increased time in REM sleep of SSRI-exposed infants was at the expense of wakefulness, as described above. The increased amount of REM sleep is similar to higher rates of REM activity or dream sleep that appear in adults within a few days of stopping or reducing the dosage of antidepressants[35] and have been postulated to result from a sudden decrease in the availability of synaptic serotonin in downregulated serotonin receptors.[66]

The quantity and the quality of motor activity have long been considered part of standard newborn examinations[28,30] but have received increasing clinical attention in recent years as a biobehavioral assessment for the newborn.[67] In the present study, we found that SSRI-exposed infants showed ~50% more overall motor activity, measured during the standard sleep period, than nonexposed infants. With a correlation of 0.67, 45% of the variance in higher motor activity could be attributed to the number of startles occurring in REM sleep; other motor activity seemed to be random movement during REM activity. These results are interesting because of a hypothesized role of serotonin in coordinating sensory and autonomic functions with gross motor activity[68] and support the conclusion that SSRI exposure during fetal development may have subtle effects on motor development and control consistent with the pharmacologic properties of the drugs, persisting at 6 to 40 months of age.[61] Motor activity also reflects differences in maturation and gestational age,[69] thus suggesting a possible basis for the lack of significant effects of prenatal SSRI exposure in the present study when gestational age was statistically controlled.

Similar to findings of previous studies of infants with IUGR and neurobehavioral indices of poor autonomic regulation,[33,34,38] SSRI-exposed infants showed fewer reliable peaks in the power spectrum of HRV. This measure of HRV provides a sensitive window into the integrity of the temporal organization of autonomic regulation in newborn infants and supports other findings of effects of prenatal SSRI exposure on autonomic regulation. Whereas fetal heart rate is initially flat and unchanging until ~28 weeks' gestation, heart rate becomes more variable and rhythmic with development as the effects of oscillations in such systems as motor activity (0.3 cpm), thermoregulation (1.5 cpm), blood pressure (6 cpm), and respiration (20 cpm) become increasingly coordinated with cardiac function.[42,43,70] In the present study, the most powerful rhythm occurred at the frequency of changes in motor activity,[40] with most additional significant spectral peaks occurring at frequencies that represent multiples of the 0.3-cpm ultradian rhythm. Statistically, fewer numbers of reliable peaks in the power spectrum indicate that fewer smooth, sinusoidal waves or rhythms accounted for significant portions of the variance underlying changes in heart rate during the 15-minute sleep period. That is, SSRI-exposed infants showed fewer smooth and predictable changes in the accelerations and decelerations of heart rate that normally occur in newborn infants.

Fewer significant rhythms in the HRV of SSRI-exposed newborns were found in the absence of differences in the mean or variability of heart rate. That is, SSRI-exposed and -nonexposed groups did not differ in the quantity of HRV; they differed in the rhythmic quality of that variability. This difference in the quality of HRV has been described as reflecting an erratic attempt to maintain homeostasis and autonomic regulation. Fewer rhythmic ultradian cycles have been related to poorer metabolic efficiency in newborns[33] and may provide the basis for less predictable feeding and sleeping schedules.[42] Because the number of rhythms increases with gestational age,[42,71] it is interesting that differences between SSRI-exposed and -nonexposed groups were no longer significant when the effects of gestational age were statistically controlled. Differences in HRV may be mediated by the effects of SSRIs on gestational age.

In all, results of the present study call into question the conclusion that SSRI use during pregnancy has little impact on the developing fetus and infant outcome. Among healthy, full-birth-weight infants with no abnormal physical signs, SSRI-exposed newborns showed increased tremulousness, less flexible and dampened state regulation, greater amounts of uninterrupted REM sleep, greater numbers of startles or sudden arousals, more generalized motor activity, and greater autonomic dysregulation than comparable infants in the term nursery. Clinically, the SSRI-exposed infants would be described as tremulous, motorically erratic, underaroused, and in an unchanging REM state. These effects are consistent with findings from a wide range of case studies of adverse effects of prenatal SSRI exposure on infants, as well as findings from the adult literature, and from studies of infants with prenatal conditions that alter autonomic regulation and development.

Although these behaviors have often been attributed to a neonatal withdrawal syndrome,[20,22,23,35] most of these behaviors are also clinical features seen in serotonin toxicity in adults who use SSRIs therapeutically or in overdose and may be evidence of neonatal serotonin syndrome.[21,72,73] Determining whether differences in neurobehavior reflect withdrawal or serotonin toxicity is beyond the scope of

this study but has important implications if SSRIs are used to treat the neonatal condition with the potential of increasing toxicity. At this point, it is also unclear whether these outcomes are transient or provide the basis for subsequent neurobehavioral problems that may be detected with sensitive measures of neurobehavioral development at a later age. That these are not simply transient effects is supported by others' findings of subsequent tremors and poorer motor development in SSRI-exposed infants, even compared with nonexposed infants of depressed mothers. Additional longitudinal examinations of newborn and infant neurobehavior may help to address these issues.

It is interesting that findings of this study point to evidence of both lower arousal (fewer state changes, restricted state range) and higher arousal (increased startles, tremors, motor activity, and REM activity) in SSRI-exposed infants. At this point, we can only speculate that there may be ≥1 mechanisms underlying these underaroused and overaroused neurobehavioral patterns. A single mechanism of arousal regulation has been described as underlying a similar dual neurobehavioral pattern in cocaine-exposed newborns.[74] Another possibility is that these seemingly paradoxic patterns reflect at least 2 underlying mechanisms. Whereas higher arousal and excitability may reflect neurotoxic and/or withdrawal effects of prenatal SSRI exposure, lower arousal and depressed neurobehavior may reflect SSRI effects on increased parasympathetic activity. Effects on parasympathetic activity are consistent with findings of a greater return of parasympathetic cardiac modulation after painful stimulation in infants with prolonged prenatal SSRI exposure.[25] Dual mechanisms of under- and overarousal have also been described in statistical models of neurobehavioral effects of prenatal cocaine exposure on newborn infants.[63] Future work may help to clarify this issue.

In addition to the questions raised by the above issues, there are a number of limitations to the present study that need to be addressed in future work. First, a larger sample size would provide 1) a greater statistical power to detect differences between groups after covariate analyses are conducted, 2) the ability to examine the potentially different effects of different SSRIs on neurobehavior, and 3) a greater generalizability of the findings. A larger sample size would also be helpful in clarifying the potential mediating effects of SSRIs on gestational age. Second, using a record review to determine SSRI use during pregnancy limits our understanding of the effects of SSRIs on neurobehavioral development. Future studies would benefit from determining the timing, duration, and dosage of prenatal exposure, as well as the duration of effects on the infant. Third, adding a comparison group of newborns of untreated, depressed mothers would help to resolve issues regarding the cost-benefit of SSRI use during pregnancy and the possible role of maternal depression on these measures of infant neurobehavior.

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