The Roles of Maternal Depression, Serotonin Reuptake Inhibitor Treatment, and Concomitant Benzodiazepine Use on Infant Neurobehavioral Functioning Over the First Postnatal Month

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Objective: The purpose of this article was to systematically compare the developmental trajectory of neurobehavior over the first postnatal month for infants with prenatal exposure to pharmacologically untreated maternal depression, selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors (collectively: SSRIs), SSRIs with concomitant benzodiazepines (SSRI plus benzodiazepine), and no maternal depression or drug treatment (no exposure).

Method: Women (N=184) were assessed at two prenatal time points to determine psychiatric diagnoses, symptom severity, and prenatal medication usage. Infants were examined with a structured neurobehavioral assessment (Neonatal Intensive Care Unit Network Neurobehavioral Scale) at multiple time points across the first postnatal month. SSRI exposure was confirmed in a subset of participants with plasma SSRI levels. General linear-mixed models were used to examine group differences in neurobehavioral scores over time with adjustment for demographic variables and depression severity.

Results: Infants in the SSRI and SSRI plus benzodiazepine groups had lower motor scores and more CNS stress signs across the first postnatal month, as well as lower self-regulation and higher arousal at day 14. Infants in the depression group had low arousal throughout the newborn period. Infants in all three clinical groups had a widening gap in scores from the no-exposure group at day 30 in their response to visual and auditory stimuli while asleep and awake. Infants in the SSRI plus benzodiazepine group had the least favorable scores on the Neonatal Intensive Care Unit Network Neurobehavioral Scale.

Conclusions: Neonatal adaptation syndrome was not limited to the first 2 weeks postbirth. The profile of neurobehavioral development was different for SSRI exposure than depression alone. Concomitant benzodiazepine use may exacerbate adverse behavioral effects.

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An estimated 8%–12% of pregnant women in the United States suffer from major depressive disorder every year (1). Antenatal major depressive disorder is associated with maternal health and obstetrical risks, as well as adverse outcomes such as preterm birth and lower birth weight (2). Newborns of depressed women compared with nondepressed women display poorer self-regulation and attention, higher arousal levels, and more lethargy and hypotonia (3–5). Long-term emotional, behavioral, and social problems in the children of women with major depressive disorder have also been observed (6–8).

Approximately one-third of depressed pregnant women who seek treatment choose selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor antidepressants (collectively: SSRIs) every year (9, 10). However, more than half discontinue SSRIs before the third trimester due to concerns about fetal exposure (11).

Transient adverse neonatal signs and symptoms (e.g., respiratory distress, tremors, irritability) were found to affect up to 30% of SSRI-exposed newborns; such findings were attributed to poor neonatal adaptation from medication exposure or withdrawal at birth (12–15). A meta-analysis suggested that neonates exposed to antidepressants were five times more likely to experience transient neonatal adaptation symptoms than nonexposed neonates (16).

Furthermore, clinical and preclinical evidence suggest that exposure to SSRIs early in development alters serotonergic

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TABLE 1. Enrollment, Attrition, and Infant Neurobehavioral Assessment Completion by Exposure Group (N=243)[a]

	Total		No-Exposure[b]		Depression[c]		SSRI[d]		SSRI Plus Benzodiazepine[e]	
Variable	N	%	N	%	N	%	N	%	N	%
Total enrolled/met eligibility criteria in pregnancy	243		86		78		65		14	
Withdrew, lost to follow-up, or moved before delivery	17		8		4		5		0	
Anxiety disorder diagnosis only	4		4		0		0		0	
Other psychiatric medication without SSRI medication	18		6		12		0		0	
Total eligible through pregnancy (N; % of enrolled)	204	84.0	68	79.1	62	79.5	60	92.3	14	100.0[f]
Preterm birth (N; % of eligible at birth)	20	9.8	2	2.9	6	9.7	8	13.3	4	28.6[g]
Final sample eligible for standardized newborn assessment (N; % enrolled)	184	90.2	66	97.1	56	90.3	52	86.7	10	71.4
Completed all five assessments (N; % of eligible)	104	56.5	39	59.1	31	55.4	29	55.8	5	50.0
Completed 2–4 assessments (N; % of eligible)	70	38.0	25	37.9	19	33.9	23	44.2	3	30.0
Completed one assessment (N; % of eligible)	10	5.4	2	3.0	6	10.7	0	0.0	2	20.0

[a] Standardized newborn assessments were completed with the Neonatal Intensive Care Unit Network Neurobehavioral Scale; oversampling was conducted to obtain a final sample size of at least 50 women in the no-exposure, depressed, and SSRI [selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor antidepressant] groups.
[b] Fetal exposure status in utero was no exposure to maternal depression or antidepressant medications.
[c] Fetal exposure status in utero was maternal depression/no antidepressant treatment.
[d] Fetal exposure status in utero was maternal history or current depression with SSRI use.
[e] Fetal exposure status in utero was SSRI use with concomitant benzodiazepine use.
[f] Data indicate the group difference in attrition prior to delivery (χ^2=3.86, df=3, p<0.277).
[g] Data indicate the group difference in preterm birth (χ^2=8.16, df=3, p<0.05); pairwise comparisons were tested using the false discovery approach of the Benjamini-Hochberg procedure (36), the differences between groups were not statistically significant.

functioning and may have long-term impact on multiple systems, including motor, circadian, and emotional (17, 18). Despite the indications of more varied and potential long-term effects, only a handful of studies have utilized standardized examinations to assess neurobehavioral functioning beyond symptoms of withdrawal or adverse effects in SSRI-exposed newborns (4, 15, 19–21). All but one study (20) reported poorer quality of movement in SSRI-exposed neonates compared with nonexposed neonates. Repeated measurement of infant neurobehavior has been used successfully to examine the clinical course of newborn opiate withdrawal, as well as the response to treatment (22). Despite the widely accepted notion that these early behavioral signs indicated a degree of withdrawal from SSRI exposure in utero, this repeated measurement paradigm has not been used to examine the trajectory of neurobehavioral indicators (e.g., quality of movement, self-regulation, stress-abstinence signs) in SSRI-exposed newborns. Prior studies examined infants in the first week after delivery, and/or at 6–8 weeks after delivery, with no repeated assessment of neurobehavior across the first postnatal month, when adaptation to withdrawal of medication is most likely to occur.

Concomitant SSRI and other psychotropic medication use is common in clinical practice yet has not been extensively studied. The limited available data suggest that combined use of SSRIs and benzodiazepines may exacerbate behavioral effects in the newborn (23, 24).

The purpose of the present study was to systematically compare the developmental trajectory of neurobehavior over the first postnatal month in infants with prenatal exposure to 1) pharmacologically untreated maternal depression (depression group), 2) prenatal SSRI exposure (SSRI group), 3) SSRI exposure with concomitant benzodiazepine exposure (SSRI plus benzodiazepine group), and 4) no maternal depression or prenatal drug exposure (no-exposure group).

We hypothesized that 1) SSRI-exposed infants compared with nonexposed infants would have more stress-abstinence signs in the first postnatal week, resolving thereafter, consistent with neonatal adaptation symptoms (16), and less optimal movement quality throughout the first postnatal month (4, 19); 2) infants with exposure to both SSRIs and benzodiazepines would have worse neurobehavioral scores compared with infants with SSRI-exposure alone (24); and 3) newborns of women in the depression group would have worse attention and arousal scores throughout the first postnatal month than the no-exposure group and both groups of SSRI-exposed infants (4).

METHOD

Participants

Women were telephone-screened for eligibility for a prospective, naturalistic cohort study. They were invited to participate if they spoke English or Spanish and were between 18 and 40 years old, 23–34 weeks gestation with a healthy, singleton pregnancy (confirmed by routine medical ultrasound), not using illicit drugs, not experiencing medication-dependent hypertension or diabetes, drinking less than one-half of a U.S. standard drink equivalent of alcohol per day (one standard drink=14 grams of alcohol), and smoking less than 5 cigarettes per day in the first trimester with no smoking in the second or third trimesters (N=243). Participants provided urine samples at prenatal visits, and the samples were tested with a

TABLE 2. Maternal and Infant Characteristics for the Total Sample and by Group (N=184)

Characteristic	Total (N=184)		A: No Exposure (N=66)[a]		B: Depression (N=56)[b]		C: SSRI (N=52)[c]		D: SSRI Plus Benzodiazepine (N=10)[d]		Test Statistic[e]		Pairwise Comparisons[f]
Mothers													
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	
Maternal age (years)	28.3	5.9	27.3	5.9	27.1	6.0	30.4	5.1	30.8	4.9	4.44	**0.005**	C>A** & B**
Number of pregnancies	2.3	1.5	1.9	1.1	2.4	1.4	2.6	1.4	4.1	2.3	8.57	**0.001**	A<C* & D***; D>B*** & C**
Number of living children	0.8	1.1	0.5	0.7	0.9	1.2	1.0	0.9	1.9	1.9	6.27	**0.001**	A<C* & D***; D>B*** & C*
Maternal body mass index prepregnancy[g]	27.0	6.4	25.5	6.2	27.2	6.5	28.2	6.3	29.9	6.1	2.48	0.063	
Gestational weeks at first prenatal visit[h]	7.8	3.4	8.1	3.9	7.6	3.9	7.6	2.5	7.1	3.0	0.38	0.765	
Anxiety severity-pregnancy[i]	10.0	7.2	4.8	3.2	11.6	5.8	14.0	8.4	15.4	7.3	27.09	**0.001**	B, C, & D>A***; B=C=D
Depression severity-pregnancy[j]	18.7	9.8	11.9	4.7	22.9	7.7	21.1	9.9	28.7	16.7	26.29	**0.001**	B, C, & D>A***; D>C**; B=C & D
Depression severity-postpartum[j]	12.6	9.8	7.4	4.3	14.6	7.7	15.3	11.0	24.8	19.3	15.91	**0.001**	B, C, & D>A***; D>B** & C**
	N	%	N	%	N	%	N	%	N	%	χ^2	p	
Depression severity category[j]													
None	74	40.4	50	75.8	5	8.9	17	33.3	2	20.0	42.46	**0.001**	B, C, & D>A***; B=C=D
Mild	69	37.7	16	24.2	30	53.6	21	40.4	3	30.0			
Moderate	32	17.5	0	0.0	19	33.9	12	23.5	1	10.0			
Severe	8	4.4	0	0.0	2	3.6	2	3.9	4	40.0			
Any anxiety disorder	48	26.1	0	0.0	15	26.8	23	44.2	10	100	16.11	**0.001**	D>B*** & C***
Not married	83	45.9	25	37.9	34	64.2	18	34.6	6	60.0	11.68	**0.008**	B>A* & C*
Ethnicity													
Hispanic	57	31.0	24	36.4	26	46.4	4	7.7	3	30.0	16.17	**0.001**	C<A*** & B***
Non-White[k]	59	33.0	25	38.5	21	40.4	11	21.2	2	20.0	6.04	0.110	
Lowest socioeconomic status on Hollingshead Four-Factor Index[l]	28	15.8	9	13.6	11	21.2	6	12.0	2	22.2	2.13	0.546	
Infants													
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	
Birth weight (grams)	3.4	0.5	3.6	0.6	3.4	0.4	3.4	0.5	3.3	0.3	2.22	0.088	
Gestational age at birth (weeks)	39.4	1.0	39.5	1.1	39.5	0.9	39.3	1.1	38.6	0.7	2.58	0.055	
	N	%	N	%	N	%	N	%	N	%	χ^2	p	
Male	89	48.4	36	54.5	26	46.4	23	44.2	4	40.0	1.72	0.632	
5-Minute Apgar score <9	20	10.9	6	9.1	6	10.7	7	13.5	1	10.0	0.52	0.914	
Cesarean section delivery	54	29.3	16	24.2	18	32.1	18	34.6	2	20.0	2.13	0.545	
Neonatal intensive care unit admission	13	7.1	4	6.1	1	1.8	6	11.5	2	20.0	5.15	0.161	
Respiratory distress	10	5.4	4	6.1	1	1.8	4	7.7	1	10.0	1.96	0.581	
Breastfeeding at birth	138	75.2	56	85.7	41	73.5	35	67.4	6	60.0	5.84	0.120	

[a] Fetal exposure status in utero was no exposure to maternal depression or antidepressant medications.
[b] Fetal exposure status in utero was maternal depression/no antidepressant treatment.
[c] Fetal exposure status in utero was maternal history or current depression with SSRI [selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor antidepressant] use.
[d] Fetal exposure status in utero was SSRI use with concomitant benzodiazepine use.
[e] For the test statistics, df=3, except for the depression severity category (df=9).
[f] Pairwise comparisons were tested using the false discovery approach of the Benjamini-Hochberg procedure (36).
[g] Prepregnancy weight data were missing for 13 women (no exposure, N=1; depression, N=5; SSRI, N=7).
[h] First prenatal visit data were missing for 11 women (no exposure, N=1; depression, N=5; SSRI, N=5).
[i] Data represent the Hamilton Anxiety Rating Scale score in the third trimester; data were missing for 10 women (no exposure, N=2; depression, N=4; SSRI, N=4).
[j] Data indicate the 30-item Inventory of Depressive Symptomatology-Clinician Rated score or severity category in the third trimester and 1 month postpartum.
[k] Data were missing for five women (no exposure, N=1; depression, N=4).
[l] Data were missing for seven women (depression, N=4; SSRI, N=2; SSRI plus benzodiazepine, N=1).
*p<0.05, **p<0.01, ***p<0.001.

TABLE 3. Serotonin Reuptake Inhibitor and Benzodiazepine Exposure Data (N=62)[a]

Variable	SSRI (N=52)		SSRI Plus Benzodiazepine (N=10)	
	Mean	SD	Mean	SD
Mean daily standard dose equivalent SSRI[b]	1.7	1.0	1.7	0.9
Days of SSRI use in pregnancy	189.7	90.6	167.3	85.3
Days of SSRI use in the first postnatal month	19.5	12.4	27.0	1.1
Maternal plasma SSRI level at delivery (ng/ml)[c]	21.4	24.3	29.6	17.7
Infant cord blood SSRI level at delivery (ng/ml)[d]	12.3	9.9	7.3	4.4
	N	%	N	%
Number using SSRIs in the first trimester	39	75.0	5	50.0
Number using SSRIs in the second trimester	44	86.6	8	80.0
Number using SSRIs in the third trimester	41	78.9	9	90.0
Number using SSRIs in the first postnatal month	41	78.9	10	100.0
Primary SSRI Taken				
Sertraline	32	61.5	6	60.0
Citalopram	7	13.5	3	30.0
Escitalopram	3	5.8	0	
Fluoxetine	5	9.6	1	10.0
Venlafaxine	4	7.7	0	
Duloxetine	1	1.9	0	
Benzodiazepine use in pregnancy				
Benzodiazepine use through delivery	0		9	90.0
Benzodiazepine use in the first postnatal month	0		8	80.0
Clonazepam	0		2	20.0
Lorazepam	0		6	60.0
Alprazolam	0		2	20.0
Other concurrent medications				
Atypical antidepressant (bupropion)	3	5.8	3	30.0
Hypnotic antidepressant (trazodone, amitriptyline)	6	11.5	1	10.0
Hypnotic, non-benzodiazepine	5	9.6	3	30.0
Buspirone	0		1	10.0
Melatonin	1	1.9	0	
Hydroxyzine	0		1	10.0
Zolpidem tartrate	4	7.7	1	10.0
Atypical antipsychotic (quetiapine)	1	1.9	0	

[a] No significant group differences were found for antidepressant medication-related variables. SSRI=selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor antidepressant.
[b] For each SSRI, the mean standard dose was calculated for each trimester and total pregnancy based on the reported dose taken divided by the standard dose defined by the Physicians' Desk Reference.
[c] Data indicate the maternal venous blood for the SSRI drug level obtained from a subset of participants immediately following delivery of the infant (SSRI: N=21, SSRI plus benzodiazepine: N=8).
[d] Data indicate the infant cord blood for the SSRI drug level obtained from a subset of infants (SSRI: N=16, SSRI plus benzodiazepine: N=7).

10-drug screening panel and a nicotine/cotinine strip to rule out confounding drug exposures.

Participants who gave birth to preterm infants <37 weeks gestational age were excluded from analyses to limit potential confounding effects due to prematurity (Table 1). Participants provided written, informed consent before scheduled assessments at 28–30 and 32–36 weeks gestational age, at which time diagnostic and self-report assessments were conducted. Infants were followed repeatedly in the first week after delivery (days 2, 4, and 7) when levels of SSRIs in exposed infants are likely to be changing rapidly, with follow-up assessments at days 14 and 30.

Measures

In addition to demographic information and socioeconomic status (25), we collected data regarding maternal psychiatric diagnoses, depression severity, and treatment for depression at each prenatal visit and 30 days postdelivery using several measures. We utilized the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Non-Patient edition (SCID-I/NP) (26); the Inventory of Depressive Symptomatology-Clinician Rated (27, 28) (continuous total score and severity level range: none=0–11, mild=12–23, moderate=24–36, severe=37–84); the Hamilton Anxiety Rating Scale (29); and the Timeline Follow-back to measure use of prescribed medications, nicotine, alcohol, and other substances for each week of the current pregnancy (30, 31). For a subset of the women reporting prenatal SSRI use, maternal (N=29) and cord blood (N=23) samples were obtained at delivery for determination of plasma drug levels to confirm SSRI exposure (32).

Depression and Antidepressant Group Classification

For all analyses, the no-exposure group consisted of the infants of women who did not meet criteria for any psychiatric disorder or report use of psychotropic medications during their entire pregnancy. Women were categorized as depressed if they were diagnosed by SCID with a unipolar mood disorder during the current pregnancy (33). SSRI exposure was defined as SSRI antidepressant use for at least 4 weeks at any time during pregnancy among women with a current or lifetime diagnosis of a unipolar mood disorder. The SSRI group was further characterized by type of concomitant psychotropic medication use: the SSRI-only subgroup reported one or more SSRI medications with or without additional antidepressant medications, and the SSRI plus benzodiazepine group reported SSRI medication and a benzodiazepine for at least 2 consecutive weeks in the pregnancy.

Infant Measures

Infant medical records were reviewed for Neonatal Intensive Care Unit admission and medical conditions, including respiratory distress, infections, and cardiac or other physical abnormalities. Infants were assessed with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (34), a validated, comprehensive assessment of infant neurobehavior via observation of neurological and behavioral function through elicited responses, reflexes, and social interaction with the

TABLE 4. Model-Estimated Means and Standard Errors of Neonatal Intensive Care Unit Network Neurobehavioral Scale Subscale Scores Over the First Month by Group (N=184)

	Group Main Effect						Model 3 Group-Estimated Means (Standard Errors)								
	Model 1		Model 2		Model 3		A		B		C		D		
	Unadjusted[a]		Adjusted[b]		Adjusted Plus[c]		No Exposure[d]		Depression[e]		SSRI[f]		SSRI Plus Benzodiazepine[g]		Comparison Tests for Significant Models[h]
Variable	χ^2	p	χ^2	p	χ^2	p	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Arousal	1.30	0.729	0.83	0.841	11.06	**0.011**	4.19	0.10	4.00	0.07	4.09	0.07	4.19	0.20	None
Excitability	2.43	0.488	1.94	0.586	7.33	0.062	3.98	0.34	3.72	0.25	4.11	0.23	5.00	0.68	
Handling	1.05	0.790	0.74	0.865	0.33	0.954	0.36	0.04	0.35	0.03	0.36	0.03	0.39	0.08	
Self-regulation	3.00	0.392	2.72	0.438	4.55	0.208	5.30	0.13	5.49	0.09	5.29	0.09	5.00	0.25	
Quality of movement	26.49	**<0.0001**	25.16	**<0.0001**	12.41	**0.006**	4.30	0.09	4.22	0.06	4.04	0.06	3.67	0.17	A>C* & D**; B>C* & D**
Stress-abstinence signs															
CNS	11.27	**0.010**	14.01	**0.003**	9.19	**0.027**	0.19	0.02	0.19	0.01	0.23	0.01	0.27	0.03	A<C* & D*; B<C** & D*
Total	4.79	0.188	3.86	0.278	5.92	0.116	0.16	0.01	0.15	0.01	0.17	0.01	0.16	0.02	
Hypertonia	2.13	0.545	3.03	0.388	2.35	0.503	0.44	0.11	0.44	0.08	0.31	0.08	0.32	0.23	
Hypotonia	10.52	**0.015**	11.59	**0.009**	4.94	0.176	0.27	0.08	0.31	0.06	0.51	0.05	0.46	0.16	Model 2: C>A** & B*
Lethargy	6.47	0.091	5.00	0.172	3.22	0.358	4.74	0.30	5.00	0.23	5.03	0.21	5.99	0.61	
Attention	6.44	0.092	4.63	0.201	3.59	0.309	4.95	0.19	4.84	0.14	4.79	0.13	4.09	0.42	
Habituation	10.63	**0.014**	10.22	**0.017**	2.22	0.528	7.69	0.50	7.02	0.34	6.94	0.30	6.85	0.68	Model 2: A>B* & C**
Non-optimal reflexes	5.76	0.124	5.87	0.118	1.53	0.675	4.27	0.26	4.53	0.20	4.76	0.18	4.95	0.54	
Asymmetry	1.70	0.636	1.87	0.601	1.73	0.630	0.92	0.15	0.95	0.12	1.17	0.11	1.16	0.32	

[a] Unadjusted model (N=184).
[b] Model adjusted for covariates of gestational age at birth, infant sex, and socioeconomic status (N=177 due to missing socioeconomic status data for four subjects in the depression group, two in the SSRI [selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor antidepressant] group, and one in the SSRI plus benzodiazepine group).
[c] Model adjusted for covariates in Model 2 and Inventory of Depressive Symptomatology; numerator df=3 for all variables, denominator df=163–170 for most variables, varying due to behavioral state requirements for individual item completion; habituation df=3,114 because the number of infants included is lower due to requirement of sleeping state at the beginning of the examination for these items.
[d] Fetal exposure status in utero was no exposure to maternal depression or antidepressant medications.
[e] Fetal exposure status in utero was maternal depression/no antidepressant treatment.
[f] Fetal exposure status in utero was maternal history or current depression with SSRI use.
[g] Fetal exposure status in utero was SSRI use with concomitant benzodiazepine use.
[h] Pairwise comparisons were tested using the false discovery approach of the Benjamini-Hochberg procedure (36).
*p<0.05, **p<0.01.

infant. Full details are available in the online supplemental material. Certified examiners, blind to group status, conducted assessments on day 2 (range 0.5–2.5 days) in the hospital and on days 4 (2.8–5.4), 7 (5.5–8.5), 14 (13.0–21.5), and 30 (27.0–38.0) at the infants' homes.

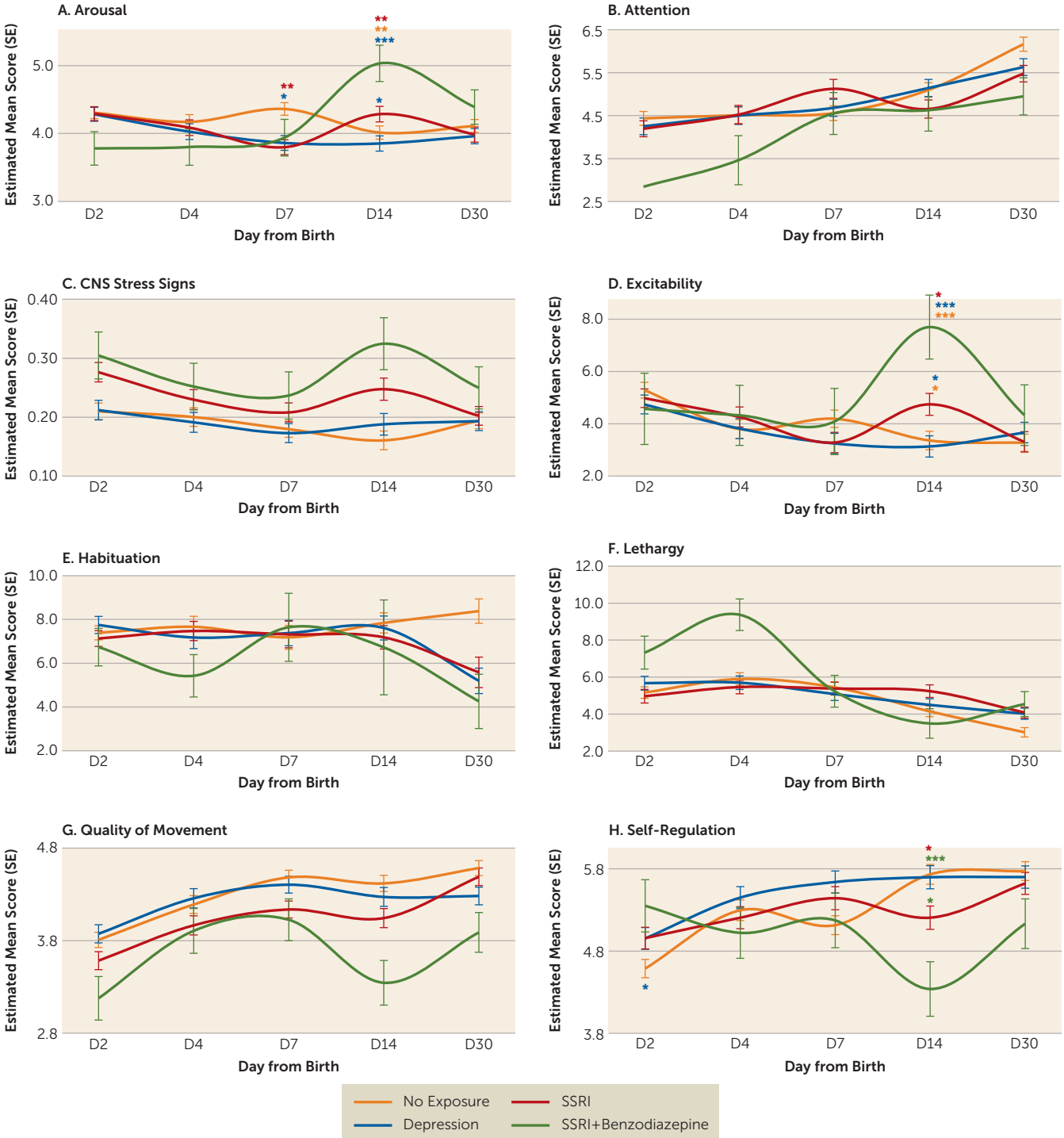
Statistical Analyses

Details of attrition are summarized in Table 1. There were no group differences in attrition due to development of medical conditions or loss to follow-up by time of delivery (χ^2=7.76, df=3, p>0.05). However, there was a significant group difference for preterm birth (χ^2=8.16, df=3, p<0.05). A final sample of 184 infants were assessed using the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Of these, 174 (95.6%) contributed multiple assessments, and 104 (56.5%) completed all five assessments.

Maternal and newborn characteristics, drug levels, and birth outcomes were tested for group differences using one-way analysis of variance for continuous variables. Generalized loglinear models were used to test categorical variable differences between groups. These analyses were conducted using SPSS 21.0 software (IBM, Somers, N.Y.).

Each Neonatal Intensive Care Unit Network Neurobehavioral Scale summary subscale was evaluated as a dependent variable using a general linear mixed model (35) with SAS statistical software (SAS Institute, Cary, N.C.). Three models were tested. Model 1 was a single between-subjects group main effect with four levels (no-exposure [N=66], depression [N=56], SSRI [N=52], and SSRI plus benzodiazepine [N=10]), one within-subject main effect for assessment day (days 2, 4, 7, 14, and 30), and the group-by-day interactions. Model 2 tested model 1 with covariates significantly related to newborn outcomes: socioeconomic status, gestational age at birth, and infant gender. Model 3 tested model 2 with prenatal depression severity as a covariate. Linear, quadratic, cubic, and quartic trends were tested for the assessment day main effect in order to best determine the trajectory of change in scores on the Neonatal Intensive Care Unit Network Neurobehavioral Scale for the neonate over the course of the first 30 days of life. Significant

FIGURE 1. Model 3 Model-Estimated Means of the Significant Neonatal Intensive Care Unit Network Neurobehavioral Scale Summary Scores Over Days From Birth for Each of the Four Groups[a]



[a] The graphs represent the model adjusted for covariates of gestational age at birth, infant sex, socioeconomic status, and depression severity. For A) arousal, the results are: day 7, no exposure > depression; day 14, selective serotonin reuptake inhibitor (SSRI) > depression, SSRI plus benzodiazepine > depression, SSRI, and no exposure; the trajectory is a significant cubic trend for all groups (χ^2=9.59, p<0.002); a quadratic trend is within the no-exposure group (estimate=0.30, SE=0.12, t=2.6, p<0.011) and SSRI plus benzodiazepine group (estimate=−0.75, SE=0.32, t=−2.32, p<0.021); simple slope of the Inventory of Depressive Symptomatology score within group is significant for the depression group (estimate=0.02, SE=0.01, t=2.5, p<0.013) and SSRI group (estimate=−0.02, SE=0.01, t=−2.4, p<0.027). For B) attention, the results are: the trajectory has a significant linear (χ^2=5.6, p<0.02) and quadratic (χ^2=4.5, p<0.04) trend. For C) CNS stress signs, the results are: the trajectory has a significant cubic trend (χ^2=3.8, p<0.05). For D) excitability, the results are: the trajectory has a significant cubic trend for all groups (χ^2=7.9, p<0.005); within the no-exposure group, the trajectory has a significant linear (estimate=−0.19, SE=0.41, t=−2.9, p<0.005) and quadratic (estimate=1.6, SE=0.42, t=2.8, p<0.006) trend. For E) habituation, the results are: the trajectory over time is not statistically significant; however, mean scores at day 30 for the depression, SSRI, and SSRI plus benzodiazepine groups are all lower than the 5th percentile for normative scores at this age, while the no-exposure group is greater than the 50th percentile.

group-by-assessment day interactions were tested for significant trends within groups. Multiple comparison tests were conducted using the Benjamini-Hochberg (36) false discovery rate approach.

RESULTS

Demographic Characteristics

Maternal and infant characteristics of the final sample (N=184) are presented in Table 2. Although several demographic differences were observed across the main subject groups, these were either adjusted for in the data analyses and/or their possible influence discussed.

The mean depression severity rating during the third trimester and 1-month postpartum was significantly lower in the no-exposure group compared with all other groups. The mean depression score for the SSRI plus benzodiazepine group was significantly higher than the score for the SSRI group, while the scores for the SSRI and depression groups were not different (see the data supplement accompanying the online version of this article). Significantly more women in the SSRI plus benzodiazepine group had a comorbid anxiety disorder during pregnancy compared with women in the SSRI and depression groups. However, there were no significant differences between the clinical groups for mean anxiety severity during the third trimester.

Birth Outcomes

There were no significant differences for birth weight, gestational age at birth, infant gender, 5-minute Apgar scores, neonatal intensive care unit admission, respiratory distress, or breastfeeding in the first week postdelivery (Table 2).

Prenatal SSRI Use

The types of medication used during pregnancy in the SSRI-exposure groups, mean standard daily dose, duration and timing of use in pregnancy, and available plasma drug levels are presented in Table 3. There were no differences between the SSRI and SSRI plus benzodiazepine groups on any measure. Most women (81%) took their SSRI through delivery. Sixty-two percent took sertraline, and 16% took citalopram as their primary medication. Eight women (12.5%) reported taking another type of antidepressant or a concomitant medication for sleep during pregnancy. There was a significant correlation between maternal and infant cord blood plasma SSRI levels ($r=0.83$, $df=22$, $p<0.001$).

Main Effects of Exposure Group on Newborn Neurobehavior

The overall adjusted estimated means, standard errors, and results (adjusted and unadjusted values for all three models for the Neonatal Intensive Care Unit Network Neurobehavioral Scale subscales for each group) are presented in Table 4. Significant main effects after adjustment for covariates in model 2 included quality of movement, hypotonia, CNS stress-signs, and habituation. Infants in both the SSRI and SSRI plus benzodiazepine exposure groups had lower quality of movement than those in the no-exposure group ($t=-3.9$, $df=151$, $p<0.001$; $t=-3.7$, $df=156$, $p<0.001$, respectively) and those in the depression group ($t=-2.2$, $df=153$, $p<0.04$; $t=-2.8$, $df=157$, $p<0.006$, respectively). Infants in the SSRI and SSRI plus benzodiazepine groups had more CNS stress-abstinence signs than those in the no-exposure group ($t=3.0$, $df=161$, $p<0.004$; $t=2.3$, $df=169$, $p<0.03$) and those in the depression group ($t=2.7$, $df=163$, $p<0.008$; $t=2.2$, $df=170$, $p<0.03$). SSRI-exposed infants also had higher scores for hypotonia than infants in the no-exposure group ($t=3.1$, $df=161$, $p<0.003$) and in the depression group ($t=2.42$, $df=163$, $p<0.02$). Infants in the depression and SSRI groups had significantly lower habituation scores than those in the no-exposure group ($t=2.9$, $df=87$, $p<0.02$; $t=2.7$, $df=97$, $p<0.01$, respectively). Differences in habituation and hypotonia were no longer significant when including depression severity as a covariate in model 3. Only arousal showed a significant relationship to prenatal depression severity (group-by-severity score: $\chi^2=14.9$, $df=156$, $p<0.002$).

Main Effects of Days From Birth at Infant Neurobehavioral Assessment

Figure 1 presents the trajectories of model 3-estimated means over days from birth for the significant Neonatal Intensive Care Unit Network Neurobehavioral Scale summary variables by group. All but four subscales (habituation, handling, hypertonia, and hypotonia) showed significant differences by assessment day, demonstrating overall significant developmental change over the first month of life: linear trends, increasing for attention and quality of movement and decreasing for lethargy; cubic trends for arousal, excitability, self-regulation, and CNS stress-abstinence signs.

Group-by-Day Interactions

Significant group-by-assessment day interactions were found for arousal, excitability, and self-regulation. Excitability scores were not statistically significant after adjustment for maternal depression severity ($p>0.05$). While all groups showed a significant cubic trend over assessment days for these three variables, the no-exposure group also showed significant linear and quadratic trends over days. Infants in the no-exposure group had higher arousal scores than infants in the depressed and SSRI groups at day 7. However, these infants had decreased arousal with increased self-regulation scores by day 14, while infants in the two groups exposed to

For F) lethargy, the results are: the trajectory has a significant linear ($\chi^2=5.2$, $p<0.02$), cubic ($\chi^2=5.4$, $p<0.021$), and quartic ($\chi^2=5.15$, $p<0.023$) trend. For G) quality of movement, the results are: the trajectory has a significant linear ($\chi^2=8.3$, $p<0.004$) and cubic ($\chi^2=10.2$, $p<0.002$) trend. For H) self-regulation, the results are: day 2, no exposure < depression; day 14, SSRI < no exposure and depression, SSRI plus benzodiazepine < depression and SSRI; the trajectory has a significant cubic trend for all groups ($\chi^2=9.0$, $p<0.003$) and within the no-exposure group, a linear (estimate=6.9, SE=0.14, $t=4.9$, $p<0.0001$) and quadratic (estimate=−0.6, SE=0.14, $t=-4.2$, $p<0.0001$) trend.
*$p<0.05$; **$p<0.01$, ***$p<0.001$.

SSRIs had significantly increased arousal and excitability scores with decreased self-regulation scores at day 14. Infants in the depressed group had a significantly flatter trajectory showing relatively low levels of arousal and higher self-regulation scores across assessment days, resulting in scores more similar to those for the no-exposure group at day 14. It is noteworthy that infants in the three clinical groups had a widening gap from those in the no-exposure group for habituation and attention.

Secondary analyses examined infant neurobehavior in infants exposed to SSRIs through delivery compared with those infants whose mothers discontinued prior to the last month of pregnancy. Only overall attention scores were significantly different between groups ($p<0.02$); all other scores for the Neonatal Intensive Care Unit Network Neurobehavioral Scale subscales, as well as group-by-days interactions, had p values >0.05 (also see the online data supplement). Breastfeeding status was not related to any of the infant neurobehavioral outcomes.

DISCUSSION

The main part of our first hypothesis that SSRI-exposed newborns would show CNS stress-abstinence signs in a pattern consistent with neonatal adaptation symptoms was not supported by the present findings. Rather, evidence for longer-term effects of prenatal SSRI exposure was found across the first postnatal month. The persistence of these signs beyond the first postnatal week is not consistent with a theory of withdrawal. Furthermore, there were no differences seen between infants whose mothers reported discontinuation of the SSRI prior to the last month of pregnancy compared with infants whose mothers continued SSRI use through delivery. This finding is consistent with previous research showing that third-trimester discontinuation of SSRI medication did not prevent neonatal adaption signs (37). Detection of the apparent pattern of longer-term (first postnatal month) versus short-term (before 2 weeks) (12, 13) effects could be due to several reasons. Drug metabolism may be delayed in newborn infants so that medication clearance was longer than anticipated (38). This study had more frequent repeated measurements of neurobehavior in the first postnatal month. In addition, the Neonatal Intensive Care Unit Network Neurobehavioral Scale evaluation provides an expanded standardized assessment of not only the presence or absence of the motor and behavioral signs consistent with neonatal adaptation after SSRI exposure, but also the severity and frequency of these symptoms. Variables measured on the standardized neurobehavioral assessments predicted infant medical and behavioral outcomes at least through early childhood (39, 40).

In addition to higher CNS-stress signs for both SSRI-exposed groups, SSRI-exposed newborns also had poorer self-regulation and higher arousal levels at day 14 than those in the no-exposure and depression groups. These findings remained consistent despite statistical tests of other explanations, such as breastfeeding, early discontinuation, postnatal maternal medication use, and maternal depression severity. This was an unexpected finding given the conclusions of previous studies that these early signs of neonatal adaptation to discontinued exposure were diminished in the first 2 weeks after birth (14). It is noteworthy that Laine et al. (14) found significantly higher blood pressure measurements in SSRI-exposed infants compared with nonexposed infants at 2 weeks postbirth, which may indicate higher stress or irritability. Increased signs of stress at day 14 in SSRI-exposed infants may reflect changing central serotonin functioning over the first weeks after delivery (15) or may be related to other neurodevelopmental effects of early SSRI exposure (41). Areas of potential mechanistic relevance deserving exploration include dose-response relationships, pharmacokinetics, development of circadian rhythms, environmental influences, and biological measures of stress.

The latter part of our first hypothesis was supported by our findings that infants in the SSRI-exposed groups compared with the no-exposure and depression groups had significantly poorer movement quality across the first month. Infants in the SSRI group also had a consistent pattern of lower tone across all measurement days compared with those in the no-exposure and depression groups before depression severity adjustment. Two previous studies also found lower motor scores in SSRI-exposed newborns in the first week after birth (19). In contrast, Suri et al. (20) did not find differences between SSRI-exposed and nonexposed infants at 1 week or 6–8 weeks after birth. The lack of agreement with the present findings may be due to factors such as timing and/or type of assessments, timing of medication exposures, or sample demographic characteristics.

The serotonin system is a key contributor to early motor control, and associated neurochemical, environmental, and experiential factors may contribute to variations in long-term outcomes. Inconsistent findings have been reported for the long-term motor outcomes of prenatally SSRI-exposed infants, with some studies finding a relationship between prenatal SSRI exposure and delayed gross motor development later in childhood, while others either did not or found the effects to be transient after the first year (42–44). Longitudinal study of motor development through later ages is needed to fully examine the potential link between early serotonin alternations and motor development.

Consistent with our second hypothesis, infants with concomitant benzodiazepine exposure had the lowest movement quality scores and highest number of CNS stress signs. Nearly all (90%) of the women using benzodiazepines reported using them through delivery, and 80% used them throughout the first month postpartum. Breastfeeding status did not change these results. The findings regarding concomitant benzodiazepine exposure are limited by the small sample size and the inherent confound with more severe depression and concurrent anxiety disorders in the women in this sample. Although the design controlled for depression severity in model 3, it cannot be conclusively determined whether the findings in this group were due to higher illness severity, lack of remittance, or medication combination. However, these findings are in agreement with previous

studies reporting more problematic outcomes for infants with concomitant psychotropic exposure (24, 45) and suggest a need for more systematic study of the effects of commonly prescribed combinations of medications during pregnancy.

In contrast to our third hypothesis and previous research (4), attention was not found to be significantly different between groups overall. However, all three clinical groups showed a flatter trajectory and a widening gap from the no-exposure group at the day-30 assessment. While attention measures infant response to visual and auditory stimuli while awake, habituation is a measure of how quickly the infant decreases motor responses to visual and auditory stimuli while asleep. There was a significant trend toward more disparate scores at day 30 between the no-exposure group and all three clinical groups. Lower scores indicate difficulty blocking external stimuli and continued arousal from sleep. Maternal depression has been linked to both poor infant and child sleep and long-term behavioral problems in children (46, 47).

Trajectories of arousal were significantly different between groups, and the overall levels were found to be related to maternal depression severity, but that relationship differed by group. Despite the overall low arousal scores in the depression group, higher arousal scores were related to higher depression severity scores within this group. Together, these results suggest a different neurobehavior profile and later emergence of effects attributable to maternal depression rather than medication treatment.

The plasma drug analyses confirmed maternal self-reported SSRI usage. Prior reports indicate that gestational exposure due to maternal SSRI use has a substantial bioeffect on reuptake inhibition in the infant (48).

Limitations

Limitations of the study include the relatively small sample size of the concomitant benzodiazepine group and heterogeneity in depression characteristics and patterns of medication use in the SSRI-exposed groups. Similar to other published studies, there was a difference in the demographic characteristics of women who chose to treat their depression with medication during pregnancy and those that chose not to medicate (49). By design, the sample consisted of full-term healthy infants across all groups, and therefore findings may not generalize to infants born earlier in gestation or to mothers with more varying health conditions. The scope of the present study and lack of variability in SSRI usage patterns did not allow for expanded examination regarding the effect of timing of intrauterine exposure to SSRIs on later infant outcomes.

CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE

While the present findings yield a complex pattern of answers, the results provide data to support informed clinical decision making. The presence of SSRI-specific adverse effects, beyond those stemming from maternal antenatal depression, extends beyond the first 7–10 days postpartum. Furthermore, our data suggest that concomitant use of benzodiazepines in conjunction with SSRIs is associated with more significant problems in infant neurological functioning than SSRI use alone. This may be a result of the underlying disorder and symptom severity or the neonate's inefficiency in metabolizing multiple drugs.

Results of this study have two major clinical implications for prescribers. First, in agreement with the current practice guidelines of the American Psychiatric Association and the American College of Obstetricians and Gynecologists (10), these findings do not support discontinuing SSRI medication in the third trimester of pregnancy for those women who have been successfully managing their depressive symptoms with SSRIs throughout pregnancy. Second, together with other recently published findings (24, 45), results from this study suggest a higher threshold for the use of polytherapy (such as SSRIs plus benzodiazepines) during pregnancy.

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