

Impact of Prenatal Exposure to Serotonin Reuptake Inhibitors or Maternal Major Depressive Disorder on Infant Developmental Outcomes

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ABSTRACT

Objective: To examine the impact of prenatal exposure to both serotonin reuptake inhibitors (SRIs; during any trimester) and maternal major depressive disorder (MDD; by *DSM-IV* criteria) on infant functioning. We hypothesized that infants with prenatal exposure to SRIs or MDD would have lower psychomotor, mental, and behavioral scores compared with nonexposed infants.

Method: This longitudinal study included 166 mother-infant dyads: 68 with prenatal MDD/SRI ($n = 41$) or MDD/no SRI exposure ($n = 27$) and 98 nonexposed controls. Maternal depression and SRI exposure assessments were completed at or as near to 20, 30, and 36 prenatal weeks and 12, 26, 52, and 78 weeks postpartum as feasible. Infants were evaluated with the Bayley Scales of Infant Development, Second Edition, including the psychomotor (Psychomotor Development Index; PDI), cognitive (Mental Development Index; MDI), and behavioral (Behavioral Rating Scale; BRS) components. Study assessments occurred between 2003 and 2009.

Results: Neither prenatal exposure to MDD/SRI nor MDD/no SRI significantly impacted overall PDI, MDI, or BRS scores. However, we observed a significant SRI exposure by time interaction for the PDI ($P = .038$). MDD/SRI exposure was associated with lower PDI scores at 26 (mean = 97.0) and 52 weeks (mean = 92.9) compared with nonexposed infants (mean = 101.4 and 100.5). This difference was no longer significant at the 78-week assessment.

Conclusions: Consistent with previous studies, we found no impact of prenatal MDD/SRI exposure on MDI scores. Less favorable PDI scores were observed in the first year; notably, these scores remained well within the normative range. The effects of prenatal MDD/SRI exposure on motor functioning may be transitory. A longitudinal pattern of poor developmental outcomes has not been established.

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Serotonin reuptake inhibitors (SRIs) are the pharmacologic mainstay for treatment of major depressive disorder (MDD) in pregnant women. The SRIs cross the placenta, and fetuses are exposed in utero, with approximately 92,000 exposed infants born yearly in the United States.¹ Although a number of studies have examined the effects of SRI exposure on birth outcomes, few have explored the effects on infant developmental outcomes. Extracellular serotonin (5-HT) plays an important role in cognition, attention, emotion, sleep, and stress responses.² The influence of prenatal serotonergic tone via SRI exposure may affect these processes.

Prenatal maternal mood disturbance and associated psychosocial sequelae also confer risk for infant cognitive and behavioral disturbances. Depressive symptoms often begin or persist during pregnancy,³ and there is ample evidence that prenatal maternal MDD is underrecognized and undertreated.⁴ Maternal MDD impacts birth outcomes.^{5,6} Long-term consequences for infants with prenatal exposure to MDD include increased risk for developmental delay^{7,8} and early childhood mental health problems.⁹ As with prenatal SRI exposure, prenatal MDD exposure also contributes to adverse developmental outcomes.

Although data from animal models suggest a negative impact of prenatal SRI exposure on developmental outcomes,¹⁰ several studies in humans revealed no effect of prenatal SRI exposure on either cognitive development¹¹ or behavioral problems.^{12,13} However, an adverse effect on motor skills has been reported. Compared with infants of mothers with depression, SRI-exposed infants scored lower on the Bayley Scales of Infant Development, Second Edition (BSID-II) Psychomotor Development Index (PDI) and the motor quality factor of the BSID-II Behavioral Rating Scale (BRS),¹⁴ although the neurologic examinations of these children were normal. The same team (Casper et al¹⁵) found that a longer duration of prenatal SRI exposure increased the risk for lower psychomotor functioning in infants (mean age of 14 months).

Delayed motor milestone achievement was also reported in a large ($N = 415$) observational sample¹⁶ in which antidepressant-exposed infants did not meet caregiver-reported motor developmental milestones at the same rate as their peers who were not exposed to depression or antidepressant medication during pregnancy. However, these infants were still within the normative range. No difference in motor skills achievement was observed when these children reached 19 months of age. Hanley and colleagues¹⁷ also found that 10-month-old infants with prenatal SRI exposure had lower gross motor functioning on the BSID than their nonexposed counterparts after controlling for prenatal and postpartum maternal depressed mood. Contrasting findings were reported by Johnson et al,¹⁸ who studied

- The majority of studies on prenatal serotonin reuptake inhibitor (SRI) exposures have examined infant outcomes at 1 time point. A longitudinal pattern of poor developmental outcomes has not been established.
- Consistent with previous studies, we found no impact of prenatal SRI exposure on infant mental development. Less favorable psychomotor development scores were observed in the first year but remained well within the normative range.
- The effects of prenatal SRI exposure on infant motor functioning may be transitory.

6-month-old infants and found no significant differences on a standardized examination (Infant Neurologic International Battery) between those exposed in utero to antidepressants and controls with no psychotropic exposure.

Few studies have examined the relative effects of both prenatal maternal depression and antidepressant use on infant outcomes. Some recent studies have not provided comparison groups with maternal depression when modeling the effects of SRI exposure on infant outcomes¹⁵ or have limited assessment of maternal depression to self-report.¹⁶ Assessment of maternal depression has emerged as a separate predictor from prenatal SRI exposure. Oberlander et al¹⁹ demonstrated that prenatal exposure to both SRIs and maternal depression was associated with internalizing behaviors in early childhood, but only current maternal mood was a predictor of externalizing behaviors.

The aim of this study was to compare developmental outcomes among infants born to pregnant women treated with SRIs for MDD, MDD but no SRI treatment, and neither exposure. We hypothesized that infants with prenatal exposure to MDD treated or untreated with SRIs would have lower scores on the BSID-II scales compared with nonexposed infants.

METHOD

Participants

In this observational study, we enrolled women (aged 17–43 years) at or before week 20 of gestation.²⁰ Women with MDD that was either treated (MDD/SRI) or untreated with SRI medications (MDD/no SRI) and women with neither MDD nor SRI exposure (comparison group) were invited to participate. Women with psychosis, bipolar disorder, substance use, exposure to benzodiazepines or any US Food and Drug Administration pregnancy class D or X drugs, multiple births, or major medical disorders were excluded. Approval was obtained from the Institutional Review Boards at the University of Pittsburgh, and all women provided written informed consent. Study assessments occurred between 2003 and 2009 (ClinicalTrials.gov identifier: NCT00279370).

Procedure

Pregnancy assessments were completed as close to 20, 30, and 36 weeks gestation as possible. Postnatal assessments for

mothers and infants, including the BSID-II, were completed at approximately 12, 26, 52, and 78 weeks.

Definitions of Exposures

We evaluated 3 nonoverlapping groups of subjects according to their pregnancy exposures.

(1) No SRI, no MDD (n=98): No exposure to any SRI or MDD.

(2) MDD/SRI (n=41): Women who have MDD and treatment with SRI. Although they were receiving treatment, these women had varying degrees of depressive symptomatology. The majority of women were treated continuously (n=29, 71%) during gestation. Exposures also included first and/or second trimester, but not the third (n=6, 14.5%), and second and/or third trimester, but not the first (n=6, 14.5%). The SRIs included sertraline (n=15), fluoxetine (n=11), escitalopram (n=7), citalopram (n=5), fluvoxamine (n=1), paroxetine (n=1), and venlafaxine (n=5).

(3) MDD/no SRI (n=27): Presence of syndromal MDD at any point in pregnancy and without any antidepressant exposure. Seven women (26%) were continuously depressed throughout pregnancy; 14 (52%) were depressed in the first and/or second trimester, but not the third; and 6 (22%) were depressed only in the third trimester.

Maternal MDD was evaluated at each assessment with the Structured Clinical Interview for *DSM-IV* (SCID).²¹ To be included in the MDD/no SRI group, the woman had to have depression that met *DSM-IV* criteria for MDD. If she had a history of MDD or depressive symptoms but did not meet criteria for MDD at some point during pregnancy, she was not included in the MDD/no SRI group. Maternal symptoms were measured at each assessment point using the Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms version (SIGH-ADS).²² The Longitudinal Interval Follow-up Evaluation²³ was used in conjunction with the SCID to assess for MDD diagnostic status change. Exposures to alcohol or tobacco also were recorded at each assessment, and urine screens for drugs of abuse were obtained for all subjects at enrollment.

Infant Assessments

At 12, 26, 52, and 78 weeks of age (corrected for prematurity), infants were evaluated with the BSID-II.²⁴ The BSID-II has both good reliability and concurrent validity for infants from 1 to 42 months.²⁴ The BSID-II consists of 3 primary scales: the Mental Development Index (MDI), the PDI, and the BRS. The MDI and PDI assess the infant's cognitive, language, personal-social, and fine and gross motor development. The BRS assesses the infant's behavior during testing. The MDI and PDI scales are age-adjusted and converted to a standardized value (index scores), with a mean of 100 and a standard deviation of 15. The standardized scores for the MDI and PDI were outcome variables in our analyses. The BRS total score is converted to a percentile score ranging from 1 to 100. Given the mixture of dimensions in the BRS

percentage, the 4 factor scales (attention/arousal, orientation/engagement, emotional regulation, and motor quality) were also considered as primary outcomes. Duration of gestation, type of birth, neonatal intensive care unit admission (present or absent), infant sex, birth weight, and length were collected from hospital records by independent evaluators blind to the study hypotheses and design.

Analyses

Descriptive statistics for continuous measures are presented as means and standard deviations and for categorical measures as frequencies and proportions. Tests of association included analysis of variance when continuous measures were normally distributed and Kruskal-Wallis when they were not. Tests of independence included χ^2 when expected cell frequencies were of adequate size and Fisher exact otherwise. Probability values for all post hoc pairwise comparisons were adjusted using the Bonferroni correction.

The effect of exposure on the mental and physical indices was tested using repeated-measures mixed models with a random intercept and an unstructured covariance matrix. Percentile scores for the behavioral subscales were dichotomized at $\geq 75\%$ because their distributions were heavily left skewed. The effect of exposure on the dichotomized subscales was tested using repeated-measures mixed logistic models also with a random intercept and an unstructured covariance matrix. Due to the curvilinear relationship between BSID-II scores and time, a quadratic term (age^2) was added to each model. Interactions between exposure and time and exposure and time squared were also added to each model to test for differential exposure effects across the postpartum period. The attention/arousal factor was not modeled by age since this assessment is made only at 12 weeks.

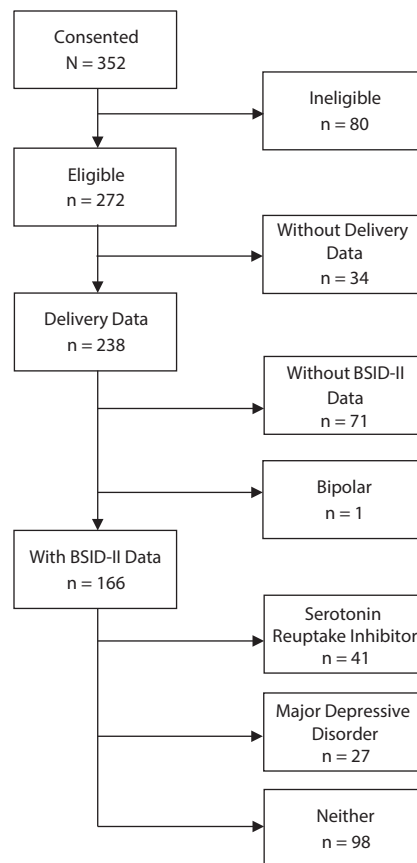
An approach to confounder selection, which estimates effect sizes for each potential variable on both exposure and each BSID-II index (MDI, PDI, BRS) and BRS subscale, was used. Potential confounders were maternal age, race, education, current employment, relationship status, prepregnancy body mass index (BMI), parity, anxiety (lifetime), and use of alcohol or tobacco during pregnancy. An a priori rule was to retain a measure as a potential confounder if it had at least a medium effect on both exposure and BSID-II score (ie, Cohen $d \geq 0.5$).²⁵ No potential confounders met these criteria. Therefore, no adjusted models of BSID-II scores were estimated.

RESULTS

Participants

Of 238 mother-infant pairs included at delivery, 166 (70%) provided infant BSID-II data (Figure 1). Compared with mother-infant pairs from the parent study²⁰ whose infants did not complete BSID-II assessments, the mothers whose infants contributed BSID-II examinations were more likely to complete university or postuniversity education (79% vs 21%, respectively, $P < .001$) and were more likely

Figure 1. Consort Diagram of Participant Recruitment



Abbreviation: BSID-II = Bayley Scales of Infant Development, Second Edition.

to report tobacco use during pregnancy (60% vs 40%, respectively, $P = .026$).

Maternal age, educational status, race, employment, married/cohabiting status, presence of prepregnancy obesity (BMI > 30), parity, baseline SIGH-ADS depression score, and lifetime diagnosis of anxiety disorder were significantly related to exposure (Table 1). Use of alcohol or nicotine during pregnancy was not related to exposure. Post hoc analyses that remained significant after Bonferroni corrections revealed that women in the MDD/no SRI group were more likely to be African American and less likely to have a college education and be married/cohabiting compared to women in both the SRI and no exposure groups (all P values $\leq .003$). Women with untreated MDD were less likely to be employed ($P = .001$) and more likely to be obese ($P = .008$) than women in the unexposed group. Nearly half (44.4%) of the women with MDD/no SRI were obese compared to 26.8% of the SRI and 19.4% of the unexposed groups. Women with MDD/SRI exposure compared to unexposed women had greater parity ($P = .016$), and were more likely to have a lifetime anxiety disorder ($P = .007$).

As expected, the mean \pm SD SIGH-ADS scores of mothers in both the MDD/SRI (14.2 ± 7.4) and MDD/no SRI (17.9 ± 6.5) groups were significantly higher than those of

Table 1. Mothers' Demographic, Clinical, and Behavioral Measures at 20 Weeks' Gestation by Exposure During Pregnancy and Infant Demographic Measures at Birth

Measure	Total (N = 166)	Exposure During Pregnancy			Analyses						
		None (n = 98)	SRI (n = 41)	MDD (n = 27)	Test Statistic	df	P ^a	Pairwise Comparisons			
								None Versus SRI	None Versus MDD	SRI Versus MDD	
Maternal measures											
Age, mean ± SD, y	30.5 ± 5.4	30.7 ± 5.1	31.8 ± 4.5	28.0 ± 6.9	F = 4.13	2,163	.018	.255	.069	.017	
Race, n (%)											
White	133 (80.1)	81 (82.7)	38 (92.7)	14 (51.9)							
Black	29 (17.5)	15 (15.3)	2 (4.9)	12 (44.4)							
Other	4 (2.4)	2 (2.0)	1 (2.4)	1 (3.7)							
White race	133 (80.1)	81 (82.7)	38 (92.7)	14 (51.9)	χ ² = 18.00	2	<.001	.124	<.001*	<.001*	
Education level, n (%)											
<High school	7 (4.2)	2 (2.0)	0 (0.0)	5 (18.5)							
High school	12 (7.2)	7 (7.1)	1 (2.4)	4 (14.8)							
Some university	29 (17.5)	11 (11.2)	9 (22.0)	9 (33.3)							
Completed university	71 (42.8)	47 (48.0)	17 (41.5)	7 (25.9)							
Graduate school	47 (28.3)	31 (31.6)	14 (34.1)	2 (7.4)							
Completed university	118 (71.1)	78 (79.6)	31 (75.6)	9 (33.3)	χ ² = 22.58	2	<.001	.603	<.001*	<.001*	
Employed, n (%)	100 (60.2)	69 (70.4)	21 (51.2)	10 (37.0)	χ ² = 11.69	2	.003	.031	.001*	.251	
Married/cohabiting, n (%)	128 (77.1)	79 (80.6)	35 (85.4)	14 (51.9)	χ ² = 12.02	2	.002	.506	.002*	.003*	
Prepregnancy BMI (kg/m ²), mean ± SD	26.4 ± 7.1	25.4 ± 6.2	26.8 ± 5.7	29.6 ± 10.7	H = 5.29	2	.071				
Prepregnancy BMI ≥ 30, n (%)	42 (25.3)	19 (19.4)	11 (26.8)	12 (44.4)	χ ² = 7.10	2	.029	.331	.008*	.133	
Parity, mean ± SD	2.0 ± 1.1	1.8 ± 1.1	2.2 ± 0.97	2.3 ± 1.2	H = 8.92	2	.012	.016*	.019	.772	
Parity, n (%)					χ ² = 9.30	4	.054				
1	65 (39.2)	47 (48.0)	11 (26.8)	7 (25.9)							
2	60 (36.1)	33 (33.7)	17 (41.5)	10 (37.0)							
≥ 3	41 (24.7)	18 (18.4)	13 (31.7)	10 (37.0)							
SIGH-ADS, mean ± SD	11.1 ± 7.0	8.1 ± 4.9	14.2 ± 7.4	17.9 ± 6.5	H = 46.23	2	<.001	<.001*	<.001*	.038	
Anxiety (lifetime), n (%)	49 (29.5)	21 (21.4)	18 (43.9)	10 (37.0)	χ ² = 7.89	2	.019	.007*	.096	.574	
Smoked during pregnancy, n (%)	15 (9.1)	7 (7.2)	4 (9.8)	4 (14.8)	χ ² = 1.50	2	.471				
Drank during pregnancy, n (%)	50 (30.1)	29 (29.6)	13 (31.7)	8 (29.6)	χ ² = 0.07	2	.968				
Infant measures											
Gestational age (wk), mean ± SD	38.8 ± 1.7	39.0 ± 1.5	38.5 ± 1.9	38.7 ± 2.2	F = 1.33	2,163	.267				
Gestational age < 37 wk, n (%)	18 (10.8)	6 (6.1)	8 (19.5)	4 (14.8)	χ ² = 5.89	2	.053				
Sex, n (%)					χ ² = 11.52	2	.003	<.001*	.562	.041	
Male	94 (56.6)	64 (65.3)	14 (34.1)	16 (59.3)							
Female	72 (43.4)	34 (34.7)	27 (65.9)	11 (40.7)							
Weight (g), mean ± SD	3,463 ± 576	3,552 ± 528	3,369 ± 584	3,278 ± 677	F = 3.21	2,163	.043	.073	.026	.554	
Length (cm), mean ± SD	51.0 ± 2.8	51.3 ± 2.8	50.3 ± 2.8	50.7 ± 2.9	F = 1.98	2,149	.142				
Head circumference (cm), mean ± SD	34.6 ± 1.7	34.8 ± 1.6	34.2 ± 1.7	34.5 ± 1.8	H = 2.44	2	.295				
Ever breastfed, n (%)	123 (78.3)	78 (84.8)	30 (73.2)	15 (62.5)	χ ² = 6.45	2	.040	.113	.022	.368	

^aTest statistic *P* indicates table probability from Fisher exact test.

*Significant after Bonferroni correction.

Abbreviations: BMI = body mass index; MDD = major depressive disorder; SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms version; SRI = serotonin reuptake inhibitor.

mothers in the nonexposure group (8.1 ± 4.9) (Table 1). Both the MDD/no SRI and MDD/SRI groups had significantly higher depressive symptom levels than the unexposed group (both *P* < .001). Although women in the untreated MDD group had higher SIGH-ADS scores than the group treated with SRIs (*P* = .038), the comparison was not significant after Bonferroni correction for multiple comparisons.

The characteristics of infants are shown in Table 1. The BSID-II examinations were administered at 12 weeks (mean ± SD = 15.56 ± 3.16 weeks), 26 weeks (30.63 ± 3.47 weeks), 52 weeks (55.7 ± 3.60 weeks), and 78 weeks (80.67 ± 3.87 weeks). Infants with MDD/SRI exposure were more likely to be female (*P* = .003) and to have a gestational period < 37 weeks (*P* = .053) than their nonexposed counterparts. Infants in the MDD/no SRI group were less likely to be breastfed (*P* = .022) and had a lower birth weight (*P* = .026) than infants of mothers in the nonexposure group.

Missing Data

At each of the postpartum assessments, several mother-infant pairs missed assessments (26 at 12 weeks, 22 at 26 weeks, 34 at 52 weeks, and 57 at 78 weeks). Overall, 76 infants (46%) were missing at least 1 BSID-II assessment. Because attrition appeared to be greater in the MDD/SRI and MDD/no SRI groups versus the nonexposure group (66% and 41% vs 72% retention at the 78-week assessment, respectively), we examined whether baseline characteristics were predictive of study completion.

Lower maternal age, noncompletion of university education, higher baseline SIGH-ADS score, and prenatal exposure were predictive of missing at least 1 BSID-II assessment. Mothers in the MDD/no SRI group were nearly twice as likely to miss at least 1 BSID-II assessment as mothers in the MDD/SRI or nonexposure groups (81.50% vs 46.30% and 35.70%, respectively, *P* < .001). However, missing

Table 2. Probability Values for Exposure, Chronological Age (months), and Their Interaction From Model of BSID-II Subscale Scores

BSID-II Subscale	Exposure	Age	Age ²	Exposure by Age	Exposure by Age ²
Mental Development Index	0.8254	0.0348	0.0022	0.6165	0.4928
Psychomotor Development Index	0.1230	0.0007	0.0011	0.0290	0.0376
Behavioral Rating Scale	0.7442	0.0631	0.0286	0.4156	0.2782
Attention/arousal ^a	0.5254				
Orientation/engagement	0.6318	0.7828	0.9916	0.5022	0.3786
Emotional regulation	0.5345	0.6661	0.9352	0.6621	0.7288
Motor Quality Index	0.9683	0.0982	0.0992	0.9078	0.8877

^aRated at 12-wk assessment only. Time factor cannot be determined.

Abbreviation: BSID-II = Bayley Scales of Infant Development, Second Edition.

at least 1 BSID-II assessment was not predicted by alcohol or tobacco use during pregnancy, race, employment, or infant factors such as gestational age, preterm delivery, weight, head circumference, or length.

Models

Our model tested the main effects of and the interaction between exposure during pregnancy and weeks postpartum on BSID-II measures (Table 2). There was a significant age² by exposure interaction ($P = .038$), with MDD/SRI-exposed infants displaying a decline in PDI scores at 26-week and 52-week assessments, although there were no significant group differences at the 12-week or 78-week assessments (Table 3, Figure 2). Neither exposure nor the interaction of exposure by age² was significant for the MDI factor, although all infants across groups showed a decrease in MDI scores over the 4 assessment time points ($P = .002$) (Table 3, Figure 2). Among the BRS total scores and subscales, which represent proportions of infants with a percentile score ≥ 75 , no significant effects of exposure on BRS total score ($P = .744$), attention/arousal ($P = .525$), orientation/engagement ($P = .632$), motor quality ($P = .968$), and emotional regulation ($P = .535$) were observed (Table 4). The BRS total score and BRS subscale probability values did not show significant change over time (Table 2).

DISCUSSION

Our finding that prenatal MDD/SRI exposure did not impact MDI scores is consistent with published studies.^{14,15,17} The observation that MDD/SRI exposure was associated with lower psychomotor scores during infancy is also consistent with several investigations^{14,15,17} and parallels results of Pedersen and colleagues.¹⁶ We observed that MDD/SRI-exposed infants had a significantly lower PDI score at both 26 (SRI: mean \pm SE = 97.0 ± 2.5 versus nonexposed: 101.4 ± 1.4) and 52 weeks (SRI: 92.9 ± 3.0 versus nonexposed: 100.5 ± 1.4). The MDD/SRI group also showed an early nonsignificant drop in motor quality at the 26-week assessment, with 37.8% (\pm SE = 8.1) of the infants with a score of 75 or greater compared with 51.1% (\pm 5.3) of the nonexposed group. However, these differences in psychomotor functioning were no longer significant by the 78-week assessment. Similarly, Pedersen et al¹⁶ assessed infants at 6 and 19 months of age and found that slight delay

in achieving infant gross motor skills at 6 months of age resolved by 19 months of age. Serotonergic fibers innervate most sensorimotor areas, including the cerebellum, and form early in development.^{26,27} This process suggests a potential mechanism whereby prenatal MDD/SRI exposure may impact early motor skills. If any decrement in these skills resolves over time, as these findings suggest, maturation of the serotonin system or environmental factors that allow an infant to compensate for early slight developmental delay may explain these observations.

Prospective longitudinal designs with multiple points of assessment are important in infant outcome studies. Only by examination of an individual over time can developmental trajectories be observed.^{28,29} Cross-sectional studies are limited to finding decrements at a single time point. Moreover, a number of developmental assessments have poor predictive validity during infancy, and a single assessment time point may provide an inaccurate view of deficiencies within a developmental domain.

Prenatal exposure to maternal MDD/no SRI did not have a significant impact on infant outcomes in our sample. There is a large body of literature that demonstrates that prenatal exposure to maternal MDD impacts early development, often in the domains of temperament and attentional problems,³⁰ and long-term consequences, including risk of early childhood mental health problems.⁹ These behavioral and emotional problems have been found to be independent of maternal depression during the postpartum period.^{31,32} Our finding of no effect of prenatal MDD/no SRI on infant developmental outcome points may be related to the BSID.²⁵ Jacobson and Jacobson²⁵ note that the advantage of the BSID is its sensitivity to a broad range of impairments; however, the disadvantage is that it provides little information about the specificity of the delays. Focused tests that provide a detailed picture of infant development, such as attention, working memory, and emotion regulation, would provide a more detailed picture of the impact of prenatal exposures. In particular, specific measures of functioning such as behavioral measures of emotion regulation³³ or assessments of maternal-infant dyadic interaction³⁴ may be more sensitive to the impact of maternal MDD.

This prospective investigation had several strengths. Depressed women with and without SRI treatment were evaluated,³⁵ which allowed modeling of the hypothesized

Table 3. BSID-II Mental Development Index and Psychomotor Development Index Scores by Exposure During Pregnancy and Postpartum

	None						Serotonin Reuptake Inhibitor						Major Depressive Disorder											
	12 Weeks		26 Weeks		52 Weeks		78 Weeks		12 Weeks		26 Weeks		52 Weeks		78 Weeks		12 Weeks		26 Weeks		52 Weeks		78 Weeks	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
BSID-II Subscale	105.3	0.9	108.4	0.7	105.7	1.2	96.4	1.8	105.4	2.0	107.1	1.2	104.8	2.3	98.1	2.9	105.3	2.0	105.5	2.0	107.3	3.0	100.5	4.8
Mental Development Index	101.4	1.0	101.4	1.4	100.5	1.4	100.5	1.4	102.1	1.9	97.0	2.5	92.9	3.0	99.3	1.7	104.3	2.8	102.5	4.3	99.7	4.7	105.2	3.1

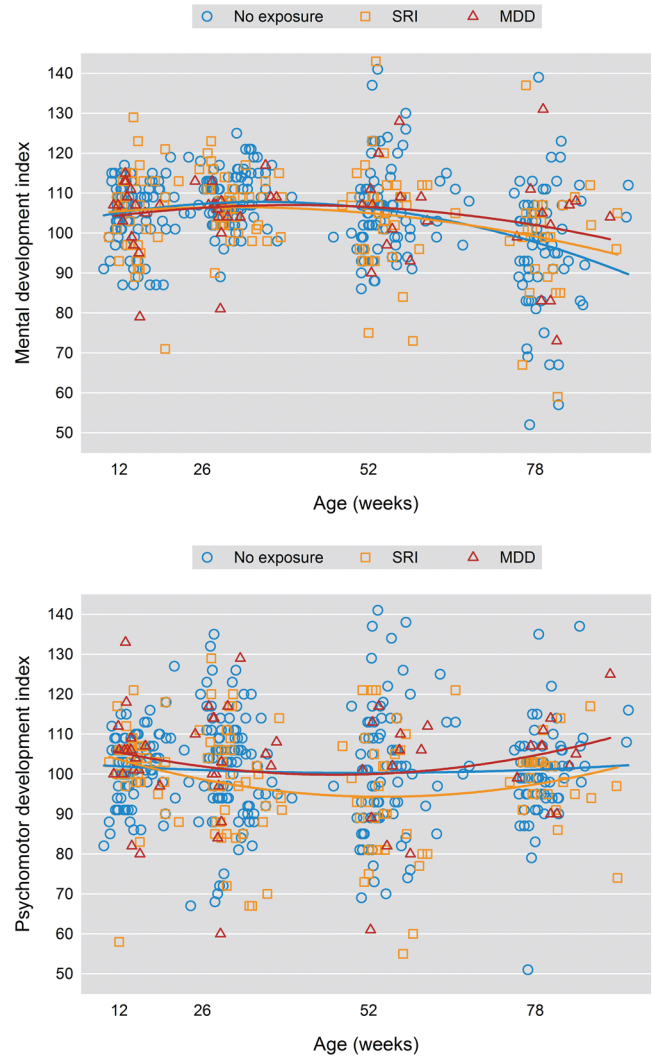
Abbreviation: BSID-II = Bayley Scales of Infant Development, Second Edition.

Table 4. Children With a Percentile Score ≥ 75 on Components of the BSID-II Behavioral Rating Scale by Exposure During Pregnancy and Weeks Postpartum

	None						Serotonin Reuptake Inhibitor						Major Depressive Disorder												
	12 Weeks		26 Weeks		52 Weeks		78 Weeks		12 Weeks		26 Weeks		52 Weeks		78 Weeks		12 Weeks		26 Weeks		52 Weeks		78 Weeks		
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE			
Behavioral Rating Scale	83.7	4.0	91.8	3.0	91.3	3.2	57.1	6.0	81.8	6.8	88.6	5.5	79.3	7.7	72.0	9.2	72.2	10.9	85.7	9.7	75.0	13.1	81.8	12.2	
Total score																									
Attention/arousal																									
Orientation/engagement																									
Emotional regulation																									
Motor quality																									

Abbreviation: BSID-II = Bayley Scales of Infant Development, Second Edition.

Figure 2. Mental Development Index and Psychomotor Development Index Scores Over Time



effects of MDD with and without SRI exposures on infant outcomes. Because SRI use is coupled with the disease that necessitates pharmacotherapy, the adverse developmental outcomes observed in infants may be related to the MDD, the SRI use, or both. The degree to which the disease process is treated is variable. In this study, depressive symptoms were highest in the women with MDD/no SRI but also higher in the MDD/SRI-treated women than the control group. The demographic and clinical characteristics were generally more favorable in the MDD/SRI group than the MDD/no SRI group, which makes the finding of comparatively poorer PDI performance in the offspring noteworthy. Residual confounding by indication severity is a well-known methodological issue in all such observational nonrandomized studies.³⁶

Other notable strengths are outcome raters blind to exposure and urine drug screens to identify substance users. Although other studies excluded mothers with illicit drug use, such use was assessed only by self-report.¹⁵ Exposure

in pregnant women was confirmed by the presence of SRI in maternal serum. Maternal MDD is associated with substance use,³⁷ and pregnant women underreport illicit drug use.³⁸ Because illicit drugs impact infant developmental outcomes,³⁹ screening for substance use in studies of infants with prenatal SRI and MDD exposures is optimal.⁴⁰

Limitations of this study include a small sample size. We are also not able to assess timing of prenatal SRI or depression exposure on later development or the effect of individual SRIs on cognitive, motor, or behavioral development. Although this study provides novel longitudinal data, future studies with assessments that extend into preschool age and beyond are needed.

No studies have found significant cognitive delay attributable to SRI use during pregnancy. However, all prospective studies to date that used direct infant assessment, including the current study, had relatively small sample sizes, with numbers of SRI-exposed infants ranging from 31 to 55. Infant tests are also poor predictors of later cognitive development until 18–24 months of age. Pedersen's¹⁶ sample of 415 SRI-exposed infants is the exception, although this study was limited to maternal report of infant milestone development. Whether the benefits of SRI treatment during pregnancy outweigh the risks remains an important and evolving discussion for women and their physicians.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), and venlafaxine (Effexor and others)

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Author contributions: All listed authors have contributed sufficiently to the project to be included as authors.

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