One-Year Developmental Outcomes for Infants of Mothers With Bipolar Disorder

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ABSTRACT

Objective: Few data about the development of infants born to women with bipolar disorder have been published. We hypothesized that infants of women with bipolar disorder (by *DSM-IV* criteria) treated with psychotropics (BD+) or untreated with psychotropics (BD−) would demonstrate poorer cognitive and behavioral development than infants of controls. On the basis of previous studies, we expected that psychotropic-exposed infants of women in the BD+ group would have poorer neuromotor performance during infancy.

Methods: This longitudinal study included 197 mother-infant dyads recruited to participate between July 2006 and March 2011: 81 with prenatal maternal bipolar disorder without psychotropic treatment (BD−, n = 27) or bipolar disorder with psychotropic exposure (BD+, n = 54) and 116 in which infants were exposed to neither bipolar disorder nor psychotropics. Maternal psychopathology and pharmacotherapy exposure assessments were completed at 20, 30, and 36 prenatal weeks and 12, 26, and 52 weeks postpartum. Infants were evaluated with the Bayley Scales of Infant Development, Second Edition, which included the psychomotor (Psychomotor Development Index [PDI]), cognitive (Mental Development Index [MDI]), and behavioral (Behavioral Rating Scale [BRS]) components.

Results: Neither prenatal exposure to BD− or BD+ significantly impacted overall PDI ($P = .2449$), MDI ($P = .7886$), or BRS ($P = .6072$) scores. However, we observed a significant effect of BD+ exposure-by-time interaction for the BRS Motor Quality index ($F_{245} = 3.16$, $P = .0441$), with BD+ exposed infants less likely to be above the 75th percentile at the 52-week assessment (mean = 11.5%) compared with BD− (mean = 40.0%) and nonexposed infants (mean = 48.4%).

Conclusions: We found no significant impact of prenatal BD− or BD+ exposure on infant PDI, MDI, or overall BRS scores at 12, 26, or 52 weeks of age, with most scores remaining within normal limits. Consistent with previous studies, we found a specific effect of prenatal BD+ exposure on quality of motor functioning at 1 year. However, the majority of infants were within normal limits on this developmental outcome.

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Bipolar disorders are serious psychiatric conditions with a prevalence of nearly 4% in the United States.[1] With typical illness onset in their late teens to early 20s, women are at increased risk for bipolar episodes during their reproductive years.[2] Women with these disorders are more likely to have rapid cycling and depressive symptoms than their male counterparts.[3] Although pharmacotherapy is the mainstay of treatment for bipolar disorder, some women choose to discontinue pharmacotherapy during pregnancy. The risks and benefits of medication must be carefully considered[2] because maternal decompensation can result in psychosis, high-risk behavior, and suicide during pregnancy and the postpartum periods.

Although there are reports that bipolar disorder symptoms improve during pregnancy, the majority of women are at risk for recurrence.[2] For women whose illness is responsive to lithium and who choose to discontinue the medication during pregnancy, the risk for relapse is high. Viguera et al[4] reported that the recurrence risk was 2.3 times greater after discontinuation of mood stabilizer treatment (53 of 62, 85.5%) than with continued treatment (10 of 27, 37.0%). Women with bipolar disorder are also at high risk for symptom exacerbation during the immediate postpartum period, which may result in adverse neonatal outcomes and infant health. Although no studies have explored the risk of untreated maternal bipolar disorder on development of older infants, one investigator found that women with untreated bipolar disorder were at increased risk of having offspring with microcephaly and neonatal hypoglycemia.[5] Bipolar symptom exacerbation during the postpartum period may have consequences for establishment of the developing attachment relationship.[6]

The risk of uncontrolled bipolar disorder must be balanced with consideration of the risks of pharmacologic treatment, the standard of care for bipolar disorder, during pregnancy.[2] Although initial voluntary reports of first-trimester lithium exposure suggested a high risk for Ebstein's anomaly, prospective studies have suggested it is associated with a much lower risk for morphological malformations.[7] Other commonly prescribed antimanic agents include atypical antipsychotics and anticonvulsants. Studies of anticonvulsant use during pregnancy have been published in the neurology literature[8] with increasing attention to valproic acid as a morphological and developmental teratogen. Lamotrigine has emerged as the anticonvulsant with a favorable reproductive risk profile.[9] A number of studies that have specifically examined antipsychotic exposure during pregnancy have

not demonstrated adverse neonatal outcomes.[5,10,11] However, a cross-sectional study by Johnson et al[12] demonstrated significantly lower neuromotor scores among 6-month-old infants with intrauterine antipsychotic exposure. Peng et al[13] found that early differences in multiple domains of development on the Bayley Scales of Infant Development III did not persist through 12 months of age.

Women with bipolar disorder are more vulnerable to mood and psychotic episodes after childbirth than at any other time during their lives,[14] and postpartum psychoses are most commonly manifestations of bipolar disorder.[15,16] The massive, rapid gonadal steroid withdrawal after delivery contributes to destabilization in these neurobiologically[17] and genetically[18–20] vulnerable women. Sleep deprivation and disruption in circadian rhythms during late pregnancy, during labor, and for infant feeding also promote mood symptoms in women with bipolar disorder.[2]

Thus, prenatal exposure may be followed by a postpartum milieu of elevated stress, difficulty establishing routines, and poor self-care. An environment of unpredictability may in itself result in difficulties with behavioral and physiological regulation in infants of women with bipolar disorder. For example, Johnson et al[21] found that 6-month-old infants of mothers with bipolar disorder showed an increase in respiratory sinus arrhythmia, a marker of physiological and affect regulation, in response to a stressor, the opposite pattern of vagal withdrawal that would be expected.[21] Since our sample included women who were both treated and untreated with pharmacotherapy during pregnancy, we examined the potential direct effects of maternal bipolar disorder on infant developmental outcomes.

We examined group differences in infant developmental outcomes at 12, 26, and 52 weeks. Our hypothesis was that infants of women with bipolar disorder (BD+ and BD–) would demonstrate poorer motor, cognitive, and behavioral development than infants of controls. Based on the findings by Johnson et al,[12] we expected that infants of women in the BD+ group would have poorer neuromotor performance during infancy.

METHODS

Participants

A total of 81 women with bipolar disorder were enrolled in this prospective observational study at or prior to 20 weeks gestation (Antimanic Use During Pregnancy: R01 MH 075921; K.L.W., principal investigator; ClinicalTrials.gov identifier: NCT00585702). Comparison data from 116 pregnant women whose infants had Bayley Scales of Infant Development, Second Edition (BSID-II) infant assessments were included from a parallel study (Antidepressant Use During Pregnancy: R01 MH60335) (Figure 1). The women were 18–44 years of age, English-speaking, and recruited in Pittsburgh, Pennsylvania, between July 2006 and March 2011. Recruitment was by self-referral, physician and community health center referral, and/or advertising. Approval was obtained from the University of Pittsburgh Institutional

Clinical Points

- Pharmacotherapy to treat bipolar disorder is the standard of care. During pregnancy, the risks and benefits of medication management must be weighed; however, few studies have explored the developmental outcomes of infants with these exposures.
- Although we found an impact on quality of motor skills in infants whose mothers received pharmacologic treatment for bipolar disorder during pregnancy, the development of these infants was within normal limits.

Review Board. All women provided written informed consent. To be included in this analysis, the women had a *DSM-IV* diagnosis of bipolar I, bipolar II, or bipolar not otherwise specified (NOS), as determined by evaluation with the full Structured Clinical Interview for *DSM-IV*.[22] Decisions about treatment, including risk/benefit discussions, were made by the woman and her treatment provider in the community. The choice to accept or decline treatment or implement the consultation did not dictate entry or retention in the study.

All methods are similar to those previously described in Santucci et al,[23] which includes the women in this cohort who had unipolar depression. History and current use of alcohol, tobacco, and illicit substances were obtained. Women with alcohol or drug dependence during pregnancy or a positive drug screen for illicit drug use were excluded from the population with the exception of marijuana since use in this sample was common and would have impacted both generalizability and sample accrual. Women with exposure to US Food and Drug Administration pregnancy class D or X drugs, multiple births, or major medical disorders were excluded.

Maternal Assessments

Pregnancy assessments were completed as close to 20, 30, and 36 weeks gestation as possible. Postnatal assessments for mothers and infants, including BSID-II,[24] were completed at approximately 12, 26, and 52 weeks. Maternal symptoms were assessed at each assessment point using the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS).[25] Manic symptoms were evaluated with the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia Research Diagnostic Interview.[26] A score of 10 or higher indicated significant symptomatology that warranted a diagnostic interview to assess for hypomania/mania.

We evaluated 3 non-overlapping groups of subjects according to their pregnancy exposures:

1. No bipolar disorder, no pharmacotherapy (n = 116): no exposure to any psychotropic medication or bipolar disorder.
2. Bipolar disorder treated with pharmacotherapy (BD+) (n = 54): we used the general category of pharmacotherapy, which was operationalized as *any psychotropic treatment* because these patients

were treated with a variety of drug types and polypharmacy was present in the majority (n = 35, 65%). Pharmacotherapy included treatment with anticonvulsants (12), antipsychotics (24), benzodiazepines (3), lithium (7), and serotonin reuptake inhibitor (SRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) and non-SRI antidepressants (9). Of the 20 women taking only a single psychotropic medication, antipsychotics were the most common (n = 8), followed by SSRI/SNRIs (n = 6) and lithium (n = 5). The majority of women were treated continuously (n = 33; 61.1%) during gestation. Exposures included first and/or second trimester, but not the third (n = 11; 20.4%), and second and/or third trimester, but not the first (n = 9; 16.7%).

3. Bipolar disorder not treated with pharmacotherapy (BD–) (n = 27; 50%): presence of the diagnosis of bipolar disorder but with no psychotropic exposure.

Infant Assessments

At 12, 26, and 52 weeks of age (corrected for prematurity), infants were evaluated with the BSID-II. The 3 primary scales are the Mental Development Index (MDI), the Psychomotor Development Index (PDI), and the Behavioral Rating Scale (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, which were outcome variables in our analyses. The BRS total score is converted to a percentile score ranging from 1 to 100; percentiles above the 25th are within normal limits. 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 are presented for continuous measures as means and standard deviations and for categorical measures as frequencies and proportions. Tests of association included analysis of variance for normally distributed continuous measures and Kruskal-Wallis otherwise. 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.

We employed the same analytic strategy previously described in Santucci et al.[23] 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

Figure 1. CONSORT Diagram
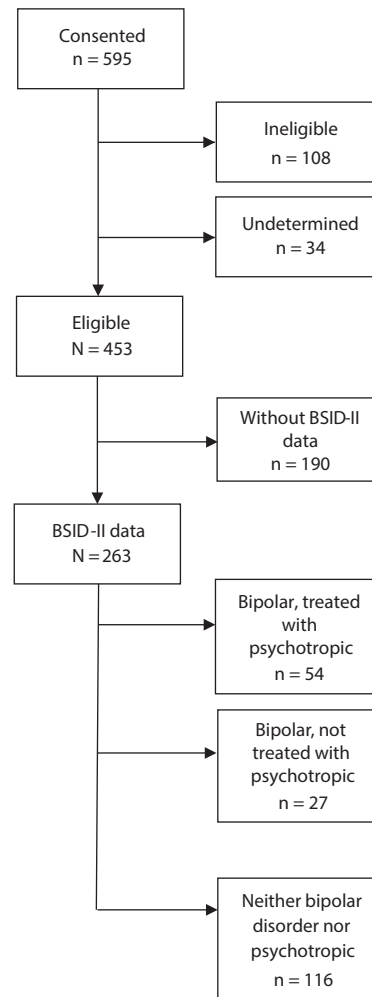
Abbreviation: BSID-II = Bayley Scales of Infant Development, Second Edition.

BRS and behavioral subscales were dichotomized at ≥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 that estimates effect sizes for each potential confounder 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, and use of tobacco or illicit drugs during pregnancy. An a priori rule was to retain a measure as a potential confounder if it had an effect on both exposure and BSID-II score that was in the "medium" range (ie, Cohen $d \geq 0.4$). According to these

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

Measure	Total (N = 197)	Exposure During Pregnancy			Probability Values			
		None (n = 116)	BD+ (n = 54)	BD− (n = 27)	Overall	None vs BD+	None vs BD−	BD+ vs BD−
Maternal measures								
Age, mean ± SD, y	29.0 ± 5.67	30.6 ± 5.06	28.0 ± 5.71	24.0 ± 4.84	<.0001	.004*	<.001*	.002*
Race, n (%)					.0480			
White	146 (74.1)	92 (79.3)	40 (74.1)	14 (51.9)				
Black	42 (21.3)	20 (17.2)	12 (22.2)	10 (37.0)				
Other	9 (4.6)	4 (3.4)	2 (3.7)	3 (11.1)				
White race	146 (74.1)	92 (79.3)	40 (74.1)	14 (51.9)	.0135	.445	.003*	.046
Education level, n (%)					<.0001	<.001*	<.001*	.027
< High school	10 (5.1)	2 (1.7)	3 (5.6)	5 (18.5)				
High school	33 (16.8)	10 (8.6)	12 (22.2)	11 (40.7)				
Some university	52 (26.4)	16 (13.8)	29 (53.7)	7 (25.9)				
University	57 (28.9)	47 (40.5)	6 (11.1)	4 (14.8)				
Graduate school	45 (22.8)	41 (35.3)	4 (7.4)	0 (0.0)				
Completed university	102 (51.8)	88 (75.9)	10 (18.5)	4 (14.8)	<.0001	<.001*	<.001*	.765
Employed, n (%)	106 (55.2)	83 (72.2)	19 (36.5)	4 (16.0)	<.0001	<.001*	<.001*	.065
Married/cohabiting, n (%)	121 (61.4)	92 (79.3)	21 (38.9)	8 (29.6)	<.0001	<.001*	<.001*	.413
Parity, n (%)					.0250	.006*	.658	.188
1	76 (39.2)	51 (44.3)	16 (30.2)	9 (34.6)				
2	67 (34.5)	42 (36.5)	14 (26.4)	11 (42.3)				
3+	51 (26.3)	22 (19.1)	23 (43.4)	6 (23.1)				
Pre-pregnancy BMI (kg/m^2), mean ± SD	26.0 ± 6.51	25.5 ± 6.22	27.6 ± 7.03	25.5 ± 6.59	.1670			
Pre-pregnancy BMI 30+, n (%)	42 (22.7)	21 (18.9)	14 (29.8)	7 (25.9)	.2997			
Smoked tobacco, n (%)	35 (17.9)	7 (6.1)	16 (29.6)	12 (44.4)	<.0001	<.001*	<.001*	.186
Drank alcohol, n (%)	49 (24.9)	33 (28.4)	9 (16.7)	7 (25.9)	.2521			
Lifetime illicit drugs use, n (%)	25 (12.7)	2 (1.7)	12 (22.2)	11 (40.7)	<.0001	<.001*	<.001*	.081
Bipolar subtype, n (%)					.0576			
I	47 (58.0)		35 (64.8)	12 (44.4)				
II	25 (30.9)		12 (22.2)	13 (48.1)				
NOS	9 (11.1)		7 (13.0)	2 (7.47)				
Any psychiatric hospitalization, n (%)	4 (2.0)	0 (0.0)	4 (7.4)	0 (0.0)	.0137	.009*	1.000	.296
MRS, mean ± SD	0.84 ± 2.57	0.18 ± 0.66	1.98 ± 3.68	1.77 ± 4.19	.0016	<.001*	.012*	.810
SIGH-ADS$_{29}$, mean ± SD	11.7 ± 8.17	7.33 ± 4.15	18.5 ± 8.82	18.8 ± 7.09	<.0001	<.001*	<.001*	.864
Infant measures								
Gestational age, mean ± SD, wk	39.0 ± 1.53	39.1 ± 1.49	38.8 ± 1.55	39.1 ± 1.64	.2387			
Gestational age < 37 wk, n (%)	16 (8.1)	8 (6.9)	6 (11.1)	2 (7.4)	.6381			
Sex, n (%)					.0441	.112	.022*	.345
Male	114 (57.9)	75 (64.7)	28 (51.9)	11 (40.7)				
Female	83 (42.1)	41 (35.3)	26 (48.1)	16 (59.3)				
Weight, mean ± SD, g	3,457 ± 545	3,528 ± 520	3,380 ± 550	3,248 ± 606	.0483	.117	.026	.329
Length, mean ± SD, cm	51.1 ± 2.84	51.3 ± 2.67	50.4 ± 3.10	50.9 ± 3.14	.1835			
Head circumference, mean ± SD, cm	34.6 ± 1.70	34.8 ± 1.56	34.6 ± 1.73	33.3 ± 2.01	.0039	.453	<.001*	.030
Ever breastfed, n (%)	132 (69.5)	90 (81.8)	27 (50.0)	15 (57.7)	<.0001	<.001*	.008*	.519

*Significant after Bonferroni correction.
Abbreviations: BD− = maternal bipolar disorder not treated with pharmacotherapy, BD+ = maternal bipolar disorder treated with pharmacotherapy, BMI = body mass index, MRS = Mania Rating Scale, NOS = not otherwise specified, SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement.

criteria, age was included as a potential confounder in the MDI, Orientation/Engagement, and BRS total score models, and education and relationship status were also included in the MDI model.

RESULTS

Participants

Participants included 81 BD+/BD− and 116 control mother-infant pairs for a final sample of n = 197. Compared with the BD+ and BD− mother-infant pairs whose infants completed BSID-II assessments, the 190 mother-infant pairs (Figure 1) who did not participate in BSID-II assessments did not significantly differ on maternal race, education, employment, marital status, parity, alcohol or tobacco use,

lifetime use of illicit drugs, or psychiatric hospitalization or infant outcomes including gestational age, infant sex, length, weight, or head circumference.

Maternal age, race, education, employment, married/cohabiting status, parity, and tobacco and marijuana use were significantly related to exposure (Table 1). Post hoc analyses that remained significant after Bonferroni corrections revealed that women in the nonexposed group were older and more likely to have completed university-level education; in contrast, the untreated bipolar group (BD−) were the youngest and least likely to have completed university-level education of the 3 groups. BD+ and BD− women were less likely to be employed, married or cohabitating, and breastfeeding. They were more likely to smoke or have lifetime history of drug use than their nonexposed counterparts. BD− group mothers

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Table 2. Results of Repeated-Measures Mixed Models of BSID-II Scores

Model I, unadjusted

Measure (df$_{NUM}$)	MDI (df$_{DEN}$=253) F	P	PDI (df$_{DEN}$=253) F	P	AA (n=160) χ²	P	OE (df$_{DEN}$=112) F	P	ER (df$_{DEN}$=112) F	P	MQ (df$_{DEN}$=245) F	P	BRS (df$_{DEN}$=232) F	P
Exposure (2)	1.91	.1508	2.77	.0646	1.33	.5131	0.76	.4679	0.03	.9711	2.30	.1026	0.72	.4857
Age (1)	7.89	.0054	0.84	.3597			0.44	.5087	3.65	.0587	0.61	.4359	0.34	.5626
Exposure×age (2)	0.24	.7886	1.41	.2449			0.64	.5315	0.12	.8831	2.56	.0791	0.50	.6072
Age² (1)	9.91	.0018	0.80	.3707			0.89	.3470	2.96	.0879	0.09	.7694	0.45	.5012
Exposure×age² (2)	0.15	.8635	1.15	.3181			0.44	.6448	0.33	.7189	3.16	.0441	0.55	.5792

Model II, adjusted for MRS and SIGH-ADS$_{29}$

Measure (df$_{NUM}$)	MDI (df$_{DEN}$=234) F	P	PDI (df$_{DEN}$=234) F	P	AA (n=156) χ²	P	OE (df$_{DEN}$=98) F	P	ER (df$_{DEN}$=98) F	P	MQ (df$_{DEN}$=226) F	P	BRS (df$_{DEN}$=214) F	P
Exposure (2)	1.95	.1443	2.20	.1131	1.75	.4178	0.55	.5808	0.05	.9559	2.14	.1198	0.69	.5012
Age (1)	7.32	.0073	0.49	.4835			1.23	.2702	2.77	.0993	0.40	.5298	0.78	.3783
Exposure×age (2)	0.15	.8648	1.02	.3624			0.38	.6832	0.10	.9010	2.36	.0963	0.61	.5419
Age² (1)	9.47	.0023	0.51	.4778			1.71	.1937	2.38	.1263	0.02	.8827	0.83	.3639
Exposure×age² (2)	0.07	.9353	0.83	.4362			0.23	.7922	0.30	.7442	2.98	.0529	0.74	.4763
MRS (1)	0.42	.5176	0.00	.9775	4.18	.0410	1.21	.2739	1.92	.1689	0.44	.5084	0.06	.8004
SIGH-ADS$_{29}$ (1)	0.90	.3432	0.15	.7019	1.09	.2961	0.38	.5386	1.75	.1886	1.19	.2759	0.42	.5166

Model III, adjusted for MRS, SIGH-ADS$_{29}$, mother's age, college degree, and marital status (where necessary)

Measure (df$_{NUM}$)	MDI (df$_{DEN}$=233) F	P	OE (df$_{DEN}$=98) F	P	BRS (df$_{DEN}$=213) F	P
Exposure (2)	1.02	.3607	0.77	.4648	0.69	.5022
Age (1)	6.62	.0107	0.47	.4950	0.74	.3901
Exposure×age (2)	0.06	.9464	0.62	.5396	0.58	.5594
Age² (1)	8.54	.0038	0.72	.3996	0.78	.3772
Exposure×age² (2)	0.01	.9860	0.45	.6421	0.71	.4926
MRS (1)	0.41	.5228	1.67	.1996	0.07	.7879
SIGH-ADS$_{29}$ (1)	1.47	.2264	0.22	.6437	0.37	.5420
Mother's age (1)	1.99	.1596	9.67	.0024	0.30	.5844
College degree (1)	3.70	.0555				
Married (1)	0.94	.3341				

Abbreviations: AA=Attention Arousal (BRS subscale), BRS=Behavioral Rating Scale, BSID-II=Bayley Scales of Infant Development, Second Edition, df$_{DEN}$=denominator degrees of freedom, df$_{NUM}$=numerator degrees of freedom, ER=Emotional Regulation (BRS subscale), MDI=Mental Development Index, MQ=Motor Quality (BRS subscale), MRS=Mania Rating Scale, OE=Orientation/Engagement (BRS subscale), PDI=Psychomotor Development Index, SIGH-ADS=Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement.

were also more likely to belong to a minority group than nonexposed women.

As expected, the SIGH-ADS and MRS scores of mothers in both the BD+ (SIGH-ADS 18.5±8.82, MRS 1.98±3.68) and BD− (SIGH-ADS 18.8±7.09, MRS 1.77±4.19) groups were significantly higher than mothers in the nonexposure group (SIGH-ADS 7.33±4.15, MRS 0.18±0.66) (P values < .0001 and .0016) (Table 1). While not statistically significant at the α < .05 level, bipolar subtype was related to psychotropic exposure, with women in the BD+ more likely to be diagnosed as bipolar I or NOS and women in the BD− as bipolar II (P = .0576).

The characteristics of infants are shown in Table 1. BSID-II examinations were administered at 12 weeks (mean = 15.7 ± 3.4 weeks), 26 weeks (mean = 31.3 ± 4.5 weeks), and 52 weeks (mean = 56.2 ± 6.1 weeks). Infants of BD− mothers were more likely to have significantly smaller head circumference than BD+ (P = .030) and nonexposed infants (P < .001).

Missing Data

At each of the postpartum assessments, missed assessments of mother-infant pairs varied by exposure group (52% and 74% [BD+/BD−] vs 83% [nonexposed] retention at the 52-week assessment); therefore, we examined whether baseline characteristics were predictive of study completion. Women who were older (mean = 30.4 years vs mean = 27.2 years, P < .001), were employed (65.1% vs 35.9%, P = .0022), completed a university education (72,5% vs 27.5%, P < .001), were currently married/cohabitating (62.8% vs 37.2%, P = .0045), did not smoke tobacco (58.4% vs 41.6%, P = .0475), had no lifetime diagnosis of bipolar disorder (70.7% vs 29.3%, P < .001), and had no psychiatric hospitalizations (56.0% vs 44.0%, P = .0401) were more likely to have completed all 3 infant assessment time points in the study.

Models

Our models tested the main effects of and the interaction between exposure during pregnancy and weeks postpartum on BSID-II measures (Table 2). Model I (unadjusted) tested the main effects of infant age and exposure (BD+, BD−, nonexposed) on BSID-II measures at each of the 3 assessment time points (12, 26, and 52 weeks) and age-by-exposure interaction. A quadratic term (age²) was added to each model since there is a curvilinear relationship between BSID-II scores and time. There was a significant effect of

Table 3. Mean BSID-II Mental Development Index (MDI) and Psychomotor Development Index (PDI) Scores

	No Exposure (n = 116)						BD+ (n = 54)						BD− (n = 27)					
	12 wk (n = 99)		26 wk (n = 106)		52 wk (n = 96)		12 wk (n = 44)		26 wk (n = 31)		52 wk (n = 28)		12 wk (n = 17)		26 wk (n = 16)		52 wk (n = 20)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
MDI	104.7	8.2	107.8	6.4	104.4	12.6	97.2	7.9	103.3	7.1	99.7	11.8	102.9	6.0	104.1	6.1	100.1	12.2
PDI	100.5	9.4	100.9	4.1	101.7	16.4	93.8	10.7	100.3	12.5	98.1	18.9	99.8	8.4	99.3	8.6	96.5	15.5

Abbreviations: BD− = maternal bipolar disorder not treated with pharmacotherapy, BD+ = maternal bipolar disorder treated with pharmacotherapy, BSID-II = Bayley Scales of Infant Development, Second Edition.

Table 4. Proportion of Infants With a Percentile Score of 75 or Higher (total score, Orientation/ Engagement, Emotional Regulation, Motor Quality) and Mean Score (Attention/Arousal) on Components of the BSID-II Behavioral Rating Scale by Exposure During Pregnancy and Weeks Postpartum

	No Exposure (n = 116)				BD+ (n = 54)				BD− (n = 27)			
	26 wk (n = 105)		52 wk (n = 91)		26 wk (n = 30)		52 wk (n = 26)		26 wk (n = 16)		52 wk (n = 19)	
BRS Component	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Total score	89.0	3.1	90.8	3.1	93.3	4.6	76.0	8.7	86.7	9.1	78.9	9.6
OE	87.6	3.2	89.0	3.3	90.0	5.6	80.8	7.9	86.7	9.1	78.9	9.6
ER	91.4	2.7	85.7	3.7	93.3	4.6	65.4	9.5	86.7	9.1	77.9	9.6
MQ	47.6	4.9	48.4	5.3	40.0	9.1	11.5	6.4	25.0	11.2	40.0	11.2

	None (n = 116) 12 wk (n = 99)		BD+ (n = 55) 12 wk (n = 44)		BD− (n = 26) 12 wk (n = 17)	
	Mean	SE	Mean	SE	Mean	SE
AA	83.7	37.2	86.4	34.7	94.1	24.3

Abbreviations: AA = Attention/Arousal, BD− = maternal bipolar disorder not treated with pharmacotherapy, BD+ = maternal bipolar disorder treated with pharmacotherapy, BRS = Behavioral Rating Scale Total Score, BSID-II = Bayley Scales of Infant Development, Second Edition, ER = Emotional Regulation, MQ = Motor Quality, OE = Orientation/Engagement, SE = standard error.

age and age^2 on MDI scores, with MDI scores showing an increase in early infancy across groups (P = .0103) and a subsequent slight decrease in MDI scores across the exposure groups (P = .0056) (Table 3). There were no significant effects of exposure, age, age^2, or interactions on PDI, BRS, or BRS subscales (Attention Arousal, Orientation/Engagement, Emotional Regulation, or Motor Quality) except for an exposure-by-age^2 effect on the Motor Quality (MQ). Infants of BD+ mothers were less likely to be at or above the 75th percentile than infants of nonexposed mothers on the MQ subscale (P = .0441) (Table 4). Distributions of MDI and PDI scores by week are shown in Figure 2.

Model II added SIGH-ADS and MRS scores to the initial model to control for the effects of baseline symptomatology on Bayley scores. While the age and age^2 effects remained significant on MDI scores (P = .0073 and .0023, respectively), the significant exposure-by-age^2 interaction on the MQ became nonsignificant (P = .0529).

Model III (Table 2) tested significant confounders in addition to Model II where applicable. Model III was adjusted for maternal age and for postbirth SIGH-ADS and MRS scores to assess the impact of maternal mood on MDI, BRS total score, and Orientation/Engagement. Completion of university education and married/cohabiting status were added as predictors in the model for MDI only. The significant curvilinear relationship between infant age at assessment and MDI score (P values = .0107 and .0038, respectively) persisted with the added predictors. Maternal

age made no difference in either model for BRS total score or Orientation/ Engagement.

DISCUSSION

In our investigation, infants whose mothers maintained their psychotropic bipolar disorder medication during pregnancy had poorer Motor Quality on the BSID-II. Contrary to our hypothesis, maternal mood disorder itself did not impact infant functioning as measured by the BSID-II in the domains of neuromotor, cognitive, and behavioral development.
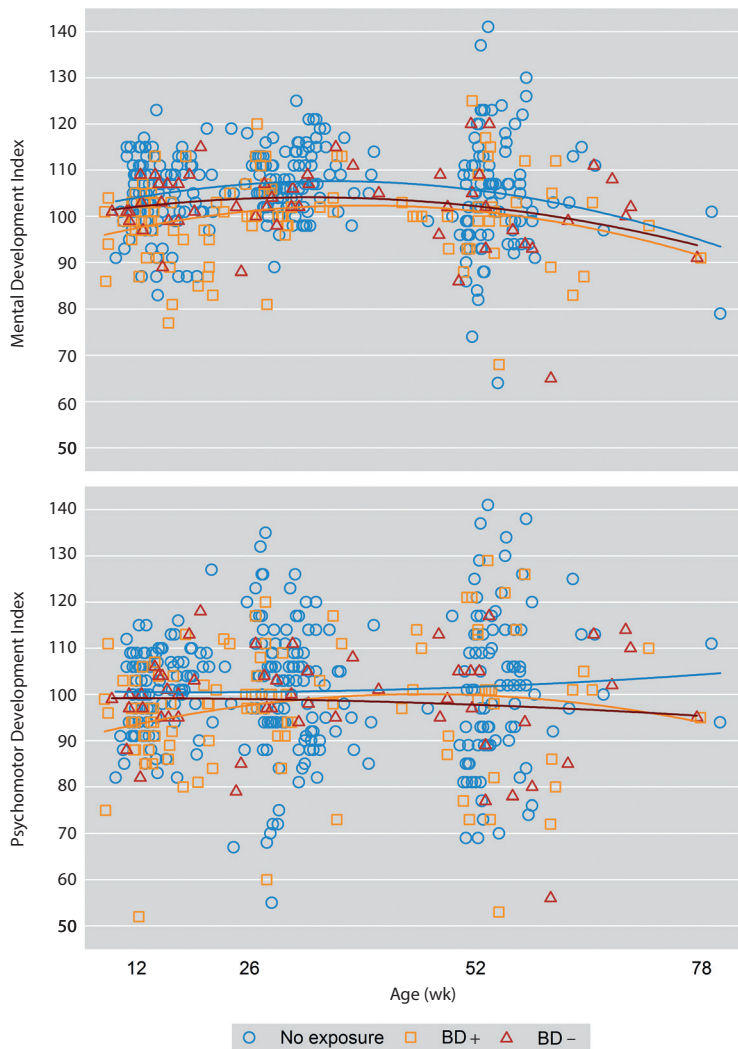
The Motor Quality subscale is an examiner-rated evaluation of infant gross and fine motor movement required by tasks, overall control of movement, hypo/hypertonicity, tremulousness, slowed and delayed movement, and frenetic movement.[24] Infants of BD+ mothers in our sample were more likely to be below the 75th percentile on this subscale, particularly at the 52-week developmental assessment (11.5% above the 75th percentile vs 40.0% in the BD− group and 48.4% in the nonexposed group). Our findings are consistent with those of Johnson et al,[12] who found that infants with a history of intrauterine antipsychotic exposure (the majority were treated with multiple medications, as in our sample) had significantly lower scores on a standardized neuromotor examination. Another study found hypertonicity and other motor issues in newborn infants exposed to antipsychotics.[27] Given the affinity of antipsychotic medications for the dopamine D_2 receptor and, in some cases, the serotonin 5-HT$_{1A}$ receptor,[28] early deficits in infant motor performance are biologically plausible since both neurotransmitters play a critical role in the development of motor skills and reinforcement of motor pathways.

We did not find an effect of maternal mood disorder on infant developmental outcomes as measured by the BSID-II; however, the BSID-II may not be sufficiently sensitive to early developmental consequences of prenatal or postnatal exposure to maternal mood disorders, or the most salient effects may manifest only in older children. Previous studies have shown that children and adolescents of women with bipolar disorder have higher rates of attentional and memory problems,[29] impaired social functioning, and mood and

Figure 2. Distribution of BSID-II Mental Development Index and Psychomotor Development Index Across Assessment Time Points (12, 26, and 52 Weeks)

Abbreviations: BD+ = maternal bipolar disorder treated with pharmacotherapy, BD− = maternal bipolar disorder not treated with pharmacotherapy, BSID-II = Bayley Scales of Infant Development, Second Edition.

assessment. Neither postbirth maternal SIGH-ADS nor MRS scores significantly affected the BSID-II outcome scales.

A limitation of our sample was that we were unable to examine the effects of specific agents on infant outcomes due to the heterogeneity of treatment in the BD+ group. However, polypharmacy is a common treatment for bipolar disorder,[34] and our sample reflects this, with two-thirds of the BD+ women treated with multiple medications. Although treatment heterogeneity and diagnostic variability (bipolar I, bipolar II, bipolar NOS) represent significant limitations to the study design, these sample characteristics can also be regarded as a strength as our sample represents a community sample of women treated for bipolar disorder.

A final limitation is the measure used to assess infant outcomes. Although a strength of the BSID-II is sensitivity to delayed development in a broad range of areas of functioning, a disadvantage is that this instrument cannot tell us the specificity of the delays.[35] Although the infants in the BD+ maternal group appeared to have some minor deficits in motor quality (gross and fine motor movement required by tasks, overall control of movement, hypo/hypertonicity, tremulousness, slowed and delayed movement, and frenetic movement), it is difficult to determine what this might mean for everyday functioning and future mastery of specific motor skills. Future studies might compare exposed and nonexposed infants on fine and gross motor tasks requiring differing levels of attentional control.

CONCLUSIONS

Since many women with psychiatric illness require pharmacotherapy during pregnancy, our study provides an important contribution that informs patient and their physicians regarding the risks of treatment for bipolar disorder during pregnancy compared with the risks of untreated illness. Future studies that longitudinally follow mother-infant pairs well into childhood are needed to define developmental trajectories. Such studies must also evaluate the overall environmental stability in which the child develops in addition to the maternal-child relationship quality. It is noteworthy that women in our study without bipolar disorder were more likely to be in a committed relationship, to have present employment, and to have completed university-level education. Identification of supportive relationships and removal of barriers to care may have the best consequences for maternal and child outcomes in these vulnerable dyads.

behavioral dysfunction and may themselves go on to develop psychiatric disorders.[30] An emerging body of literature has suggested that children of parents with bipolar disorder are more likely to show early deficits in executive functioning, higher cognitive functions that are essential for the control of information processing, planning, decision-making, and problem resolution, emerging from critical pathways within the prefrontal cortical regions.[31,32] Infant and toddler assessments that target the developing prefrontal pathways, such as the A-not-B task,[33] may be more sensitive to early differences in executive functioning.

Inclusion of a sample of both BD+ and BD− women allowed us to model the potential developmental outcomes related to maternal bipolar disorder during the prenatal period with and without exposure to pharmacotherapy, as well as multiple timepoints of both maternal and infant

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