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Pregnant women with bipolar disorder who have a history of childhood maltreatment: Intergenerational effects of trauma on fetal neurodevelopment and birth outcomes

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Abstract

Objectives: Intergenerational transmission of trauma occurs when the effects of childhood maltreatment (CM) influence the next generation's development and health; prenatal programming via maternal mood symptoms is a potential pathway. CM is a risk factor for bipolar disorder which is present in 1.8% of pregnant women. Mood symptoms are likely to increase during pregnancy, particularly for those with a history of CM. We examined whether there was evidence for intergenerational transmission of trauma in utero in this population, and whether maternal mood was a transmission pathway.

Methods: CM and maternal mood were self-reported by $N = 82$ pregnant women in treatment for bipolar disorder. Fetal heart rate variability (FHRV) was measured at 24, 30, and 36 weeks' gestation. Gestational age at birth and birth weight were obtained from medical charts.

Results: A cluster analysis yielded two groups, Symptom+ (18.29%) and Euthymic (81.71%), who differed on severe mood symptoms ($p < 0.001$) but not on medication use. The Symptom+ group had more CM exposures ($p < 0.001$), a trend of lower FHRV ($p = 0.077$), and greater birth complications (33.3% vs. 6.07% born preterm $p < 0.01$). Maternal prenatal mood mediated the association between maternal CM and birth weight in both sexes and at trend level for gestational age at birth in females.

Conclusions: This is the first study to identify intergenerational effects of maternal CM prior to postnatal influences in a sample of pregnant women with bipolar disorder. These findings underscore the potential enduring impact of CM for women with severe psychiatric illness and their children.

KEYWORDS
bipolar disorder, birth weight, childhood maltreatment, childhood trauma, fetal heart rate, gestational age at birth, intergenerational transmission of trauma, pregnancy, pregnancy complications, preterm birth

1 | INTRODUCTION

Intergenerational trauma is identified when parents' exposure to childhood maltreatment (CM) influences the development and health of their children. These effects can occur independently of shared genes or children's direct exposure to significant life stressors.[1] Prenatal programming—the process whereby qualities of pregnant women's lives fundamentally shape fetal development and susceptibility to disease—presents the opportunity to study mechanisms of intergenerational transmission prior to birth.[2,3] There is emerging evidence to support an association between maternal history of CM and characteristics of pregnancy including increased psychiatric symptoms and alterations in maternal-placental gestational biology, which influence fetal brain-behavior development.[4,5] In the present study, we sought to investigate whether a history of CM in women with bipolar disorder would be associated with increased symptoms during pregnancy, with implications for fetal neurodevelopment and birth outcomes, suggesting intergenerational trauma transmission.

Bipolar disorder is a rare affective disorder characterized by lifelong recurrent episodes of depression and elevated mood (i.e., mania or hypomania).[6] With a typical onset between 18 and 30 years of age, bipolar disorder coincides with common childbearing years and is present in 1.8% of pregnant women.[7,8] In recent meta-analyses, a history of CM in individuals with bipolar disorder has been demonstrated to predict a more severe presentation and course of illness, including earlier age of onset, greater symptom severity, more rapid cycling, increased frequency and severity of depressive and manic episodes, greater comorbidity with post-traumatic stress and substance use disorders, and increased risk for suicide.[9,10] During pregnancy, a history of CM has been associated with increased symptoms of depression, anxiety, and post-traumatic stress,[11] and is likely to be associated with increased symptoms of bipolar disorder during this same period. A possible explanation is that role transition to motherhood during pregnancy might activate thoughts and emotions, and related biological responses, of early traumatic memories and other childhood experiences from being parented, including experiences of abuse and neglect.[11] Particularly with sexual trauma, physical sensations during pregnancy and delivery might especially activate memories of abuse.[12] Possible biological explanations include lasting alterations of the hypothalamic pituitary adrenal stress axis, epigenetic changes, and shortened telomere length.[13] Specifically in individuals with bipolar disorder as compared to those without psychiatric disorders, a history of CM has been associated with increased amygdala and hippocampus volumes, which may contribute to greater abnormalities in response to stress and in emotion processing.[14] With CM as a risk factor for bipolar disorder, and likely associated with increased symptoms during pregnancy, there is an opportunity to identify evidence for intergenerational transmission of trauma in utero, and determine whether it is mediated by maternal mood in this specific population of women.

Assessment of fetal development allows for the identification of potential effects of transgenerational transmission of trauma prior to postnatal influences. Fetal heart rate variability (FHRV) is an index of fetal neurodevelopment that reflects the development of the autonomic nervous system and the maturation of the parasympathetic innervation of the heart, and is a physiological substrate of emotion regulation associated with future child neurodevelopment and mental health.[15,16] In children and adults, greater heart rate variability is associated with increased emotion regulation, and lower heart rate variability with increased risk for psychopathology.[16] FHRV typically increases throughout gestation, and lower FHRV has been associated with a more reactive temperament (i.e., greater irritability),[17] which, in turn, is a risk factor for childhood and adolescent neuropsychiatric disorders including depression, anxiety, attention-deficit hyperactivity disorder, and behavioral problems.[18–21] We and others have shown that increased maternal prenatal distress is associated with lower FHRV.[15,22] However, some have found evidence to suggest accelerated development where maternal distress was associated with increased FHRV, and others found no association.[16] In another study from our group, maternal report of childhood emotional abuse was associated with lower FHRV, mediated by maternal sleep disturbance across pregnancy.[16] FHRV has the potential to inform our understanding of the consequences of maternal CM prior to postnatal exposures, including whether maternal history of CM may be mediated by prenatal mood symptoms.

Bipolar disorder is associated with compromised birth outcomes including earlier gestational age at birth and lower birth weight,[7,8] which in turn are associated with risk for infant mortality, child physical and mental morbidity, and neurodevelopmental impairments[23] such as attention problems, lower academic achievement, mood and behavior dysregulation, and difficulties with executive functioning.[24] These findings account for, and are in addition to, the potential effects of psychotropic medication use.[25] Maternal depression, anxiety, and stress also are associated with pregnancy complications,[23] as is a history of CM.[26,27] In offspring of women with bipolar disorder, compromised birth outcomes may have their earliest origins in maternal history of CM.

We hypothesized that pregnant women in treatment for bipolar disorder who were exposed to CM, as compared to those unexposed or with lower exposure, would have comparatively elevated mood symptoms, which overall would have implications for fetal neurodevelopment and birth outcomes, and suggest intergenerational effects of trauma. Specifically, we aimed to demonstrate that (1) certain pregnant women with bipolar disorder would continue to have clinically significant mood symptoms even in the context of psychiatric treatment, (2) clinically symptomatic women would report greater exposure to CM, and (3) associations between exposure to CM with offspring outcomes including lower FHRV, earlier gestational age at birth, and lower birth weight, would be mediated by elevated maternal mood symptoms during pregnancy.

2 | METHODS

2.1 | Participants

Pregnant women 18 to 45 years of age were recruited from the Women's Mental Health Program at Emory University School of Medicine to participate in a longitudinal study of prenatal mood and child neurodevelopment. Of the 275 women enrolled before

16 weeks' gestation with fetal assessments, $N = 82$ were selected based on a primary diagnosis of bipolar disorder. Information on maternal age, parity, gravidity, self-reported race and ethnicity, marital status, and whether the pregnancy was planned or desired, was obtained at study enrollment. Fetal assessments were conducted at 24, 30, and 36 weeks' gestation. Participants were predominantly White and non-Hispanic, and from socioeconomically advantaged backgrounds. Diagnosis of bipolar disorder I or II (see Table 1) was

TABLE 1 Demographic characteristics for $N = 82$ pregnant women with bipolar disorder and group differences between euthymic ($n = 67$) versus symptom+ ($n = 15$)

	Overall sample	Euthymic	Symptom+	Group difference[a]
	n (%)	*n* (%)	*n* (%)	*p*-value
Self-reported race*				0.011
Black	8 (9.76)	5 (7.46)	3 (20.00)	
White	66 (80.49)	58 (86.57)	8 (53.33)	
Other	8 (9.76)	4 (5.97)	4 (26.67)	
Self-reported ethnicity				1
Hispanic	2 (2.44)	2 (2.99)	0 (0.00)	
Married—Yes	60 (73.17)	51 (76.12)	9 (60.00)	0.213
Planned pregnancy—Yes*	54 (66.67)	48 (72.73)	6 (40.00)	0.031
Desired pregnancy**				0.002
Yes	60 (75.00)	54 (83.08)	6 (40.00)	
No	2 (2.50)	1 (1.54)	1 (6.67)	
Ambivalent	18 (22.50)	10 (15.38)	8 (53.33)	
Tobacco use—Yes*	12 (14.63)	7 (10.45)	5 (33.33)	0.038
Preterm birth**	9 (11.11)	4 (6.06)	5 (33.33)	0.009
Biological sex—Female	36 (43.90)	29 (43.28)	7 (46.67)	1
Medication				0.235
None	7 (9.86)	7 (12.07)	0 (0.00)	
SSRI only	5 (7.04)	4 (6.90)	1 (7.69)	
Bupropion only	1 (1.41)	0 (0.00)	1 (7.69)	
Lamotrigine only	7 (9.86)	7 (12.07)	0 (0.00)	
Atypical only	8 (11.27)	6 (10.34)	2 (15.38)	
Cardio only	2 (2.82)	2 (3.45)	0 (0.00)	
Two or more without SSRI	18 (25.35)	15 (25.86)	3 (23.08)	
Two or more + SSRI	23 (32.39)	17 (29.31)	6 (46.16)	
Primary diagnosis				0.06
Bipolar I	61 (74.39)	48 (71.64)	13 (86.67)	
Bipolar II	17 (20.73)	16 (23.88)	1 (6.67)	
Bipolar other	3 (3.66)	3 (4.48)	0 (0.00)	
PTSD and Bipolar	1 (1.22)	0 (0.00)	1 (6.67)	
	M (SD)	*M* (SD)	*M* (SD)	*p*-value
Mother's age	32.44 (4.70)	32.58 (4.61)	31.81 (5.24)	0.640
Mother's years of education	15.44 (2.18)	15.66 (2.18)	14.47 (1.96)	0.059
Gravidity	2.67 (1.63)	2.52 (1.49)	3.33 (2.09)	0.194
Parity	0.79 (1.09)	0.78 (1.14)	0.87 (0.83)	0.374
Gestational age at birth	38.9 (1.4)	39.1 (1.3)	38.3 (1.6)	0.062
Birth weight*	3348.52 (402.95)	3398.94 (372.35)	3126.67 (468.38)	0.049
Adjusted birth weight	0.02 (0.37)	0.06 (0.36)	−0.12 (0.39)	0.231

Abbreviations: PTSD, post-traumatic stress disorder;SSRI, selective serotonin reuptake inhibitors.

[a]Group differences were assessed with Wilcoxon signed rank test, Chi-square test and Fisher's Exact test.

*$p < 0.05$; **$p < 0.01$.

established using the Structured Clinical Interview for DMS-IV Axis I Disorders (*SCID*).[28] All women were in outpatient treatment consisting of medication management and support from a psychiatrist; 90.14% continued with pharmacotherapy throughout pregnancy ($n = 7$ were not on medication). More detailed study information has previously been published.[29]

2.2 | Measures

2.2.1 | Maternal mood symptoms

Six symptom measures were administered three times throughout pregnancy at 24, 30, 36 weeks' gestation. Two measures were self-report questionnaires of depressive symptoms, that is, the Beck Depression Inventory (*BDI*)[30] and the Edinburgh Postnatal Depression Scale (*EPDS*).[31] Four measures were interview-based, that is, the 17-item Hamilton Depression Rating Scale (*HRSD*-17),[32] the Hamilton Anxiety Rating Scale (*HRSA*),[33] the Clinical Global Impressions Scale (*CGI*),[34] and the Mania Rating Scale (*MRS*).[35] At each time point, total scores for each measure were computed as the sum of all items, and log transformed to remove skewness. Symptom scales were analyzed as continuous, and predetermined clinical cut points were used for descriptive purposes. The predetermined clinical cut points were ≥10 for the *BDI*,[36] ≥ 11 for the *EPDS*,[37] ≥ 15 for the *HRSD*-17,[38] ≥15 for the *HRSA*,[39] ≥3 for the *CGI*,[34] and ≥1 for the *MRS*.[40]

2.2.2 | Maternal childhood maltreatment

Participants completed the Childhood Trauma Questionnaire (*CTQ*) at study enrollment. The *CTQ* is a 28-item retrospective self-report measure with five subscales, including emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.[41] Retrospective report on the *CTQ* is reliable for use in both clinical and non-clinical populations, including bipolar disorder (intraclass correlations $r = 0.05$ to $r = 0.96$; Cohen's kappas 0.44 to 0.76).[42] Subscale scores and total scores were computed as the sum of the respective items, and log-transformed to remove skewness. Exposure to CM was determined by having at least one subscale of CM that met a predetermined cut point as compared to having low or no exposure to CM. The predetermined cut points were ≥13 for emotional abuse, ≥10 for physical abuse, ≥8 for sexual abuse, ≥15 for emotional neglect, and ≥10 for physical neglect.[43]

2.2.3 | Fetal neurodevelopment and birth outcomes

Fetal assessment took place three times throughout pregnancy at 24, 30, 36 weeks' gestation; more detailed descriptions of the fetal monitoring procedures have previously been published.[15,29] Briefly, women were in a semi-recumbent position for 5 min as resting-state fetal heart rate was measured using a Toitu MT 325 fetal actocardiograph (Toitu Co., Ltd.). The Toitu detects fetal heart rate via a single transabdominal Doppler transducer and processes this signal through a series of filters. Fetal data were collected from the Toitu's output port digitized at 50 Hz using a 16-bit A/D card (National Instruments 16XE50), and analyzed offline using custom MATLAB programs (http://www.math-works.com/) developed for this project. Resting-state FHRV was calculated as previously described, using the standard deviation of fetal heart rate from the 5-min measurement period.[15] Birth outcomes were obtained through medical chart abstraction, including gestational age at birth and birth weight.

2.2.4 | Covariates

Potential confounding factors were obtained at study enrollment and from medical charts. They included maternal age, self-reported race and ethnicity, marital status, education, psychotropic medication use, tobacco use, whether the pregnancy was planned, whether the pregnancy was desired, gravidity, parity, and gestational age at birth (not including when gestational age at birth was the outcome). Covariates were included in final models only if they were significantly associated with the outcome of interest, or if they differed significantly by group (i.e., groups yielded from a cluster analysis as described in the Statistical Analysis and Results sections).

2.3 | Statistical analysis

Nonparametric K-means cluster analysis for joint longitudinal data (KmL)[44] was conducted to identify groups based on trajectories of maternal prenatal mood symptom severity across 24, 30 and 36 weeks' gestation. Optimal number of clusters was determined using the maximum votes between Calinksi and Harabasz criterion, Ray and Turi criterion, and Davies and Bouldin criterion.[44] The six mood measures included were the *BDI*, *EPDS*, *HRSD*-17, *HRSA*, *CGI*, and *MRS*. Fisher's Exact test and Chi-square test for categorical measures and Wilcoxon signed rank test for continuous measures were used to assess for potential group differences (i.e., groups yielded from a cluster analysis) on demographics, mood symptoms, history of CM, psychotropic medication use, and birth outcomes. Mixed effect models were performed to assess for potential group difference in FHRV at each study visit (three levels: 24, 30, and 36 weeks' gestation), by group (two levels, i.e., two groups yielded from a cluster analysis), including visit-by-group interactions, adding covariates as fixed effects and random intercept to account for within-subject correlation due to repeated measurement. When the visit-by-group interaction was not significant at the 5% significance level, we refit the mixed effect model after removing the visit-by-group interaction terms to access main effects of visit

and group. Linear regressions were used to compare differences in gestational age at birth and adjusted birth weight by maternal symptom group. A mediation analysis was used to test potential associations between exposure to CM with FHRV and birth outcomes (i.e., gestational age at birth and adjusted birth weight) mediated by maternal mood (i.e., symptoms of depression from the *HRSD*-17 and symptoms of anxiety from the *HRSA*). Because maternal mood was assessed at multiple time points, the random intercept and random slope of the maternal mood variables from the latent growth model were used as the mediators (see Figure S1). Similarly, the random intercept and slopes of the fetal variables were used as the outcome (see Figure S1).[45,46] In sum, there was a total of six mediation tests, and statistical significance of the indirect effect was tested using a bootstrapping procedure.[47] As exploratory analyses, we stratified the regression and mediation models by biological sex. Additionally, we ran a post hoc mediation analysis to confirm our findings when removing the minority of participants who were not on psychotropic medication. The cluster analysis and mediation models were conducted in R 4.0.0 and all other tests in SAS 9.4. With a sample size of $N = 82$ women with bipolar disorder, the minimum detectable effect sizes were Cohen's $d = 0.81$ and correlation coefficient $r = 0.31$ to have 80% power at 5% significance level.

2.3.1 | Post hoc analysis

We conducted post hoc mediation analyses to explore associations between select subscales of maternal CM on the *CTQ* with FHRV and birth outcomes (i.e., gestational age at birth and adjusted birth weight), mediated by maternal mood (i.e., symptoms of depression from the *HRSD*-17 and symptoms of anxiety from the *HRSA*). The selection of subscales was based on whether there were group differences (i.e., groups yielded from a cluster analysis) on (1) the predetermined cut point or (2) a significantly higher frequency of exposure.

3 | RESULTS

3.1 | Demographic statistics and group differences

Demographic, clinical, and birth outcome descriptive statistics are summarized in Table 1. The cluster analysis yielded two groups whereby 18.29% ($n = 15$) of women were symptomatic, designated as the *Symptom+* group, and 81.71% ($n = 67$) were *Euthymic* (see Figure 1). At 24, 30, and 36 weeks' gestation, women in the Symptom+ group had significantly greater symptom scores than

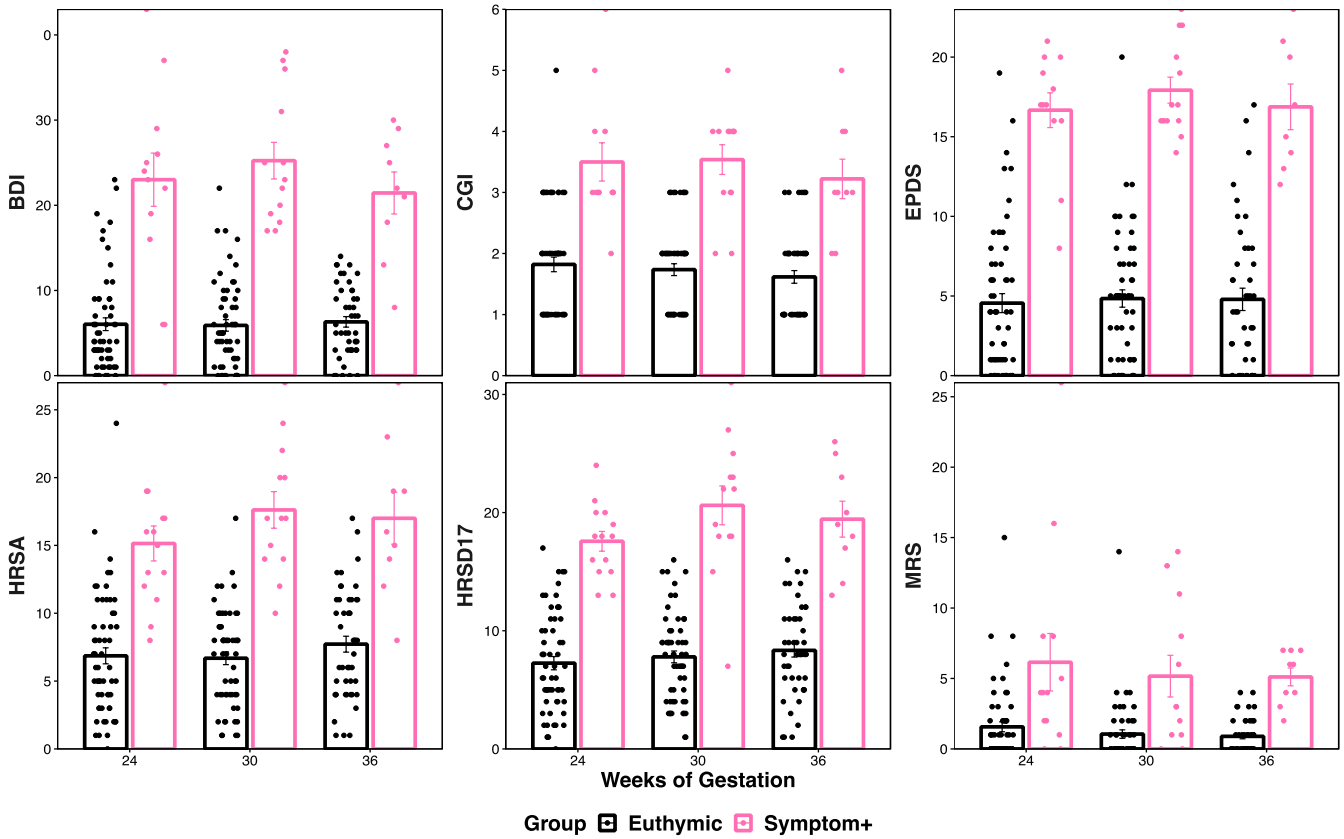

FIGURE 1 Maternal prenatal symptoms at 24, 30, and 36 weeks' of gestation: euthymic versus symptom+ group differences. BDI, Beck Depression Inventory; CGI, Clinical Global Impressions Scale; EPDS, Edinburgh Postnatal Depression Scale; HRSA, Hamilton Anxiety Rating Scale; HRSD-17, Hamilton Depression Rating Scale; MRS, Mania Rating Scale

women in the Euthymic group on both self- and clinician-rated measures ($p < 0.001$ for each comparison; see Figure 1 and Table S1). Symptom+ women's average scores on each symptom measure at each time point were at a level of clinical significance, whereas Euthymic women's average scores were at a level of clinical significance only at 24 and 30 weeks' gestation on the mania scale only (see Table S1). Additionally, the Symptom+ group were more likely to be African American, endorse Tobacco use, or report unplanned or undesired pregnancies (see Table 1). There were no group differences for medication use (see Table 1).

As compared to women in the Euthymic group, women in the Symptom+ group reported significantly greater scores on four of the five subscales of CM, significantly greater sum scores of CM, and had a significantly greater number of CM subscales that reached the predetermined cut point (see Table 2). Specifically, women in the Symptom+ group reported scores above the predetermined cut point for sexual abuse and emotional abuse, whereas those in the Euthymic group reported scores below the predetermined cut point on all categories of CM (see Table 2). The Symptom+ group also reported a higher frequency of emotional neglect compared to the Euthymic group (see Table 2). In the Symptom+ group, 46% of women reported emotional neglect and 86.67% reported at least one CM subscale that met the predetermined cut point, as compared to 16.4% and 41.79%, respectively, in the Euthymic group (see Table 2).

3.2 | Mixed effect models

3.2.1 | Fetal neurodevelopment

When comparing the Symptom+ and Euthymic groups, infants from the Symptoms+ group had significantly lower FHRV throughout gestation (F [1, 111] = 4.05, p = 0.047), which became a trend when adjusting for covariates (F [1, 109] = 3.19, p = 0.077) (see Figure 2). When the analysis was stratified by biological sex, males in the Symptom+ group had significantly lower FHRV throughout gestation (F (1, 56) = 4.79, p = 0.033), which became a trend when adjusting for covariates (F (1, 55) = 2.53, p = 0.117) (see Figure 2). The covariates included in the FHRV mixed effect models were self-reported race, tobacco use, and whether the pregnancy was planned or desired.

3.2.2 | Birth outcomes

Overall, infants in the Symptom+ versus Euthymic groups did not differ in gestational age at birth. However, 33.3% (n = 5) of infants in the Symptom+ group were born preterm (i.e., before 37 weeks' gestation) as compared to only 6.06% (n = 4) in the Euthymic group (p = 0.009). When stratifying the analysis by biological sex, males in the Symptom+ group were born at a significantly earlier gestational

TABLE 2 Scores and frequencies on the childhood trauma questionnaire for N = 82 pregnant women with bipolar disorder and group difference between euthymic (n = 67) versus symptom+ (n = 15)

	Overall sample	Euthymic	Symptom+	Group difference[a]
	M (SD)	*M* (SD)	*M* (SD)	*p*-value
Subscale score				
Emotional abuse**	10.71 (4.82)	10.13 (4.83)	13.27[b] (4.01)	0.009
Physical abuse**	7.23 (3.43)	6.78 (2.94)	9.27 (4.68)	0.006
Physical neglect**	6.99 (2.99)	6.63 (2.54)	8.6 (4.24)	0.003
Sexual abuse*	6.88 (4.04)	6.28 (3.03)	9.53[b] (6.46)	0.015
Emotional neglect	10.73 (4.91)	10.22 (4.71)	13 (5.3)	0.066
Sum score***	42.54 (15.11)	40.04 (13.77)	53.67 (16.29)	<0.001
Number of subscales to reach predetermined cut point**	1.04 (1.32)	0.87 (1.29)	1.8 (1.21)	0.003
	Frequency (%)	Frequency (%)	Frequency (%)	*p*-value
Emotional abuse	25 (30.50)	18 (26.9)	7 (46.70)	0.213
Physical abuse	13 (15.9)	9 (13.40)	4 (26.70)	0.243
Sexual abuse	18 (22.00)	12 (17.90)	6 (40.00)	0.085
Emotional neglect**	18 (22.00)	11 (16.40)	7 (46.70)	0.017
Physical neglect	11 (13.4)	8 (11.90)	3 (20.00)	0.414
At least one exposure**	41 (50.00)	28 (41.79)	13 (86.67)	0.003

Note: The predetermined cut points were as follows: emotional abuse ≥13, physical abuse ≥10, sexual abuse ≥8, emotional neglect ≥15, and physical neglect ≥10.

[a]Group differences were assessed with Wilcoxon signed rank test and Chi-square test.

[b]Mean score is clinically significant.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

FIGURE 2 Fetal heart rate variability at 24, 30, and 36 weeks' of gestation: euthymic versus symptom+ group comparisons. FHRV, fetal heart rate variability

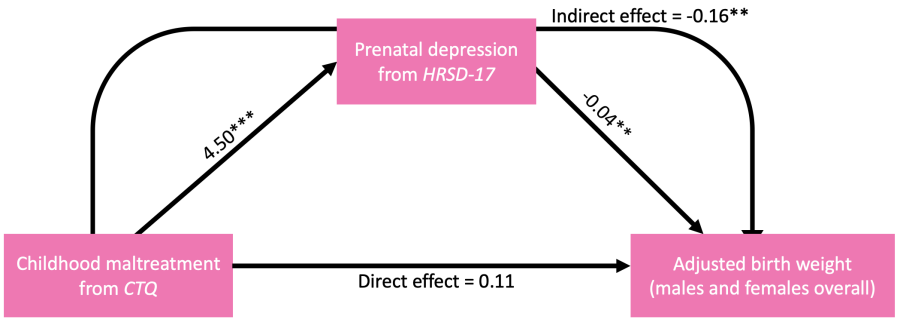

FIGURE 3 The association between maternal history of childhood maltreatment and adjusted birth weight mediated by maternal prenatal symptoms of depression. Maternal history of childhood maltreatment was measured on the *Childhood Trauma Questionnaire* (*CTQ*). Maternal symptoms of prenatal depression were measured on the *Hamilton Depression Rating Scale* (*HRSD*-17). The final model was adjusted with covariates as follows: parity, marital status, whether pregnancy was planned, whether pregnancy was desired, self-reported race, and tabaco use. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

age as compared to males in the Euthymic group ($\beta = 1.45$, $t = 2.05$, $p = 0.043$), adjusting for self-reported race, tobacco use, and whether the pregnancy was planned or desired. There were no group differences in gestational age at birth for females, and no group differences in adjusted birth weight for males or females.

3.3 | Mediation analyses

The mediation analyses predicting FHRV and gestational age at birth were not significant. Associations between maternal history of CM and infant adjusted birth weight were mediated by maternal symptoms of depression ($\beta = -0.16$, $p = 0.008$; see Figure 3) and anxiety ($\beta = -0.14$, $p = 0.048$), adjusting for self-reported race, marital status, tobacco use, whether the pregnancy was planned or desired, and parity (see Table 3).

In exploratory analyses stratifying by biological sex, the mediation models predicting FHRV were not significant. The association between a history of maternal CM and gestational age at birth was mediated by maternal symptoms of depression for female infants (indirect effect: $\beta = -1.01$, $p = 0.039$); this association became a trend when adjusting for self-reported race, tobacco use, and whether the pregnancy was planned or desired (indirect trend: $\beta = -0.68$, $p = 0.061$). An association between history of maternal CM and adjusted birth weight was mediated by maternal symptoms of depression for female infants only, adjusting for self-reported race, marital status, tobacco use, whether the pregnancy was planned or desired, and parity (indirect effect: $\beta = -0.16$, $p = 0.008$).

TABLE 3 The association between maternal history of childhood maltreatment and adjusted birth weight: mediation by maternal prenatal symptoms of depression and anxiety

Mediator	Effect	β	*p*-value
Depression	Path A (Childhood maltreatment to depression)***	4.50	<0.001
	Path B (Depression to adjusted birth weight)**	−0.04	0.002
	Path C (Childhood maltreatment to adjusted birth weight)	0.11	0.279
	Mediation—Indirect effect on adjusted birth weight**	−0.16	0.008
	Total effect	−0.04	0.616
Anxiety	Path A (Childhood maltreatment to anxiety)***	4.29	<0.001
	Path B (Anxiety to adjusted birth weight)*	−0.03	0.019
	Path C (Childhood maltreatment to adjusted birth weight)	0.10	0.395
	Mediation—Indirect effect on adjusted birth weight*	−0.14	0.048
	Total effect	−0.04	0.616

Note: Maternal history of childhood maltreatment was measured on the *Childhood Trauma Questionnaire* (*CTQ*). Maternal symptoms of prenatal depression were measured on the *Hamilton Depression Rating Scale* (*HRSD*-17) and symptoms of prenatal anxiety on the *Hamilton Anxiety Rating Scale* (*HRSA*). Mediation models were adjusted with covariates as follows: self-reported race, marital status, tobacco use, whether the pregnancy was planned or desired, and parity.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

3.4 | Post hoc analyses

In post hoc mediation analyses, we confirmed a similar pattern of results to our primary mediation analyses. Specifically, the mediation analyses testing associations between emotional abuse, sexual abuse, and emotional neglect with FHRV and gestational age at birth mediated by maternal symptoms of depression and anxiety were not significant. The association between emotional neglect and adjusted birth weight was mediated by maternal symptoms of depression (indirect effect: $\beta = -0.19$, $p = 0.015$) and anxiety (indirect effect: $\beta = -0.12$, $p = 0.016$), adjusting for self-reported race, marital status, tobacco use, whether the pregnancy was planned or desired, and parity. Further, the association between emotional abuse and adjusted birth weight was marginally mediated by maternal depression (marginal indirect effect: $\beta = -0.09$, $p = 0.069$), and significantly mediated by maternal anxiety (indirect effect: $\beta = -0.10$, $p = 0.033$), adjusting for self-reported race, marital status, tobacco use, whether the pregnancy was planned or desired, and parity. However, the analyses testing associations between sexual abuse and adjusted birth weight mediated by maternal depression and anxiety were not significant.

4 | DISCUSSION

Our study is one of the first to identify intergenerational effects of maternal childhood trauma prior to postnatal influences, and the first in a sample of offspring of pregnant women with bipolar disorder. We also are the first to provide evidence for the hypothesis[48] that a history of maternal CM is associated with increased mood symptoms during pregnancy in women with bipolar disorder. Even in the context of ongoing psychiatric treatment, compared to those who remained euthymic, certain women remained clinically symptomatic throughout pregnancy, and those who were symptomatic were more likely to report histories of CM, characterized by increased severity and significant levels of CM exposures. Offspring of women in the symptomatic group were more likely to have lower FHRV especially if they were male, earlier gestational age at birth specifically if they were male, and higher rates of preterm birth. The associations between maternal history of CM with adverse birth outcomes were mediated by maternal mood symptoms of depression and anxiety. Specifically, the adverse birth outcomes were earlier gestational age at birth in females and lower birth weight in both sexes, key risk factors in the development of childhood psychopathology.[24,49] Some of these findings were at trend level once covariates were included in the models. Our findings support the intergenerational transmission of trauma through prenatal programming—CM associated with worse prenatal mood symptoms putting the future generation at risk for neuropsychiatric illness before substantive postnatal influences.

Despite being in treatment for bipolar disorder, nearly 20% of the women in our sample continued to experience elevated mood symptoms throughout pregnancy, were more likely to have mood symptoms that reached the clinical cut point, and to have a history of CM. In contrast, women with bipolar disorder with low or no exposure to CM were more likely to be euthymic throughout gestation. Specifically, in the symptomatic group, 46% of women reported emotional neglect and 87% reached the predetermined cut point on

at least one CM category compared to 16% and 42%, respectively, in the euthymic group. Additionally, the majority of women in the symptomatic group reported a history of emotional abuse or sexual abuse that reached the predefined level of significant exposure. There were no group differences in psychotropic medication use. Although the likelihood had previously been suggested,[48] we are the first to provide evidence that pregnancy is a period of increased risk for elevated mood symptoms among women with bipolar disorder who have a history of CM. Our findings are consistent with those from studies on non-pregnancy samples that found an association between a history of CM and reduced treatment response in individuals with chronic depression[50] and bipolar disorder.[51] CM-related variation in treatment effectiveness might contribute to intergenerational trauma effects.

Our findings support the prenatal programming of fetal neurodevelopment with suggestive origins in maternal CM-related mood symptoms that coincide with the timing of that programming. Specifically, offspring of women in the symptomatic group with greater exposure to maternal CM had lower FHRV, especially males. This result is consistent with previous studies, including in our own work, providing evidence for an association between increased maternal prenatal distress and lower FHRV.[15,22] As previously discussed, lower FHRV is associated with a more reactive temperament in infancy, and can indicate less adept emotion regulation as well as biological sensitivity and susceptibility to stress and stress-related psychopathology.[52]

With respect to group differences in birth outcomes, women in the symptomatic versus euthymic group were more likely to give birth preterm. Otherwise, there were no differences between groups for gestational age at birth or birth weight when taking into account offspring from both sexes. As previously described, birth outcomes such as earlier gestational age at birth and lower birth weight are indicators of altered fetal growth and development[16] associated with various neurodevelopmental impairments.[23,24]

Overall, our findings yielded interesting biological sex differences. First, the association between greater maternal mood symptoms and lower FHRV was stronger in males. Second, greater maternal mood symptoms were associated with earlier gestational age at birth only in males. Lower FHRV and earlier gestational age at birth in males is consistent with previous evidence that males exposed to prenatal stress are at increased risk for preterm birth[53] and neurodevelopmental disorders, especially ones identified early in development.[54]

Evidence for intergenerational transmission of maternal CM via prenatal programming was specific to birth outcomes only. Maternal mood symptoms mediated the associations between history of CM and earlier gestational age at birth in females and lower birth weight in both sexes. These findings provide support for effects of intergenerational trauma on birth outcomes mediated by, and not independent of or distinct from, maternal mood symptoms in pregnant women with bipolar disorder. Sex differences were also present in certain outcomes, whereby the association between maternal history of CM and earlier gestational age at birth mediated by mood symptoms was specific to females, and the association between maternal history of CM and lower birth weight seemed to be stronger among females. Given that males are at greater risk for preterm birth,[55] it is possible that we were less likely to detect intergenerational effects of maternal CM mediated by mood symptoms in male birth outcomes as there likely were other contributing factors on age at birth.

We did not find evidence for mediation of CM effects on FHRV by maternal mood symptoms. In the only other study investigating associations between maternal CM and FHRV in a sample of healthy pregnant adolescents, we found that the association was mediated by maternal sleep disturbance.[7] Disrupted sleep is strongly associated with mood symptoms and abuse histories, however, depressive symptoms were not associated with FHRV in the current study. More studies are needed to determine the behavioral pathways for this association, as well as the underlying biology.

A possible biological mechanism for the intergenerational transmission of maternal CM—with or without mood symptoms—is maternal-placental-fetal gestational biology, which encompasses stress-sensitive cascades of bidirectional interactions with the environment and shapes fetal growth and brain development.[4] Maternal exposure to CM is associated with endocrine and immune physiology (e.g., greater hypothalamic–pituitary–adrenal axis reactivity) that affects responsivity to subsequent stress. Because the developing feto-placental unit senses and responds to biological signals from the mother, maternal CM-related alterations in physiology can shape fetal brain structure and function, programming offspring susceptibility to stress and compromised mental health. From this perspective, effects of maternal history of CM are biologically transmitted in utero, and perpetuate integenerational cycles of risk for developing neurobehavioral and psychiatric disorders.[4]

In post hoc sensitivity analyses, we found that associations between emotional neglect and emotional abuse, but not sexual abuse, with lower birth weight were mediated by elevated maternal mood symptoms. We focused on these three subscales of the CTQ for further analysis as they were the most prominent forms of CM reported by the women in the symptomatic group. Emotional abuse previously has been associated with FHRV, mediated by maternal prenatal sleep.[16] Emotional neglect is putatively the most potent form of CM,[16,56] and the emotional neglect subscale has been suggested to have the most subjective items of the CTQ.[56] There is research to support that subjective reports of CM are (1) separable from concurrent psychiatric illness, and (2) more strongly associated with future psychiatric symptoms compared to objective measures.[56] These results strengthen and confirm our primary findings that the association between maternal CM and lower birth weight is mediated by maternal mood symptoms in pregnant women with bipolar disorder, and add that emotional neglect and abuse are possibly the forms of abuse that have the most enduring consequences for these women and future generations.

Our findings are to be considered within the context of certain limitations. Our sample size ($N = 82$) and data-driven approach to identify and characterize groups based on mood symptoms during

pregnancy (i.e., Symptom+ and Euthymic) may have hindered the statistical power to find more subtle effects, and points to the need for replication. Nevertheless, this was a convenience sample gathered from a hospital setting that allowed us to enroll pregnant women with bipolar disorder during pregnancy, a rare population (1%–2% prevalence)[7,8] who may be less likely to engage in research studies that involve intensive data collection. Unfortunately, our sample is relatively homogenous in terms of self-reported race and ethnicity, which limits the generalizability of our findings, especially given that these sample characteristics are associated with different types and intensities of maltreatment and differences in stress response.[56] We want to highlight the importance that future studies in the developmental neurosciences consider increasing sample diversity to better represent Black, Hispanic, and low socioeconomic populations, as they are disproportionately exposed to and affected by trauma,.[56] Another factor to be considered—most of the women in our sample were on psychotropic medication. A challenge when studying effects of fetal programming in relation to bipolar disorder is determining possible impacts of symptoms separate from medication effects; in the few published studies that compared women with bipolar disorder who were and were not medicated during pregnancy, birth outcomes appeared to be similar across groups,[25] including earlier gestational age at birth and lower birth weight.[7,8,57] Given that psychotropic medication is the mainstay of bipolar treatment, there are relatively few published studies that compare women who are and are not prescribed medication.[25] Furthermore, we did not take into account that women exposed to CM are at greater risk for maltreatment in adulthood, including intimate partner violence in pregnancy,[58] which could affect them and their developing child. And finally, we did not assess maternal physiological markers of distress (e.g., cortisol, cytokines). We are aware of one study that found that maternal depression was associated to lower cortisol to total corticosteroids ratio (i.e., the ratio of cortisol to cortisol plus cortisone that can be used to represent active cortisol in the fetoplacental unit), whereby the lower cortisol ratios were then associated with lower FHRV.[56] In past studies, we have found no differences in maternal physiology (i.e., heart rate, blood pressure, respiration) based on psychiatric diagnosis or mood symptoms, and no association between maternal autonomic nervous system activity and fetal indices of neurodevelopment.[59,60]

In contrast to animal studies, research with humans that provides evidence for pathways of intergenerational transmission of trauma prior to birth or related to birth outcomes are in their early beginnings.[2] In this report, findings indicate that maternal history of CM in women with bipolar disorder can be passed down to the next generation through prenatal programming, as identified in early markers of risk for psychopathology (i.e., pregnancy complications), and the modifiable maternal mood symptoms including depression and anxiety as the programming pathway. We are the first to identify these effects in a sample of pregnant women with bipolar disorder. We also demonstrate that women with bipolar disorder who have a history of CM are at increased risk for exacerbated symptoms during pregnancy. Our study extends decades of prenatal programming research, and does so in a specific psychiatric population of women with bipolar disorder, demonstrating that mothers' childhood experiences of trauma can affect the next generation prior to postnatal influences.

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CONFLICTS OF INTEREST

Dr. Newport has received research support from Eli Lilly, Glaxo SmithKline (GSK), Janssen, Sage Therapeutics, Takeda Pharmaceuticals, the Texas Health & Human Services Commission, and Wyeth. He has served on speakers' bureaus and/or received honoraria from Astra-Zeneca, Eli Lilly, GSK, Pfizer, and Wyeth. He has served on advisory boards for GSK, Janssen, and Sage Therapeutics. He has never served as a consultant to any biomedical or pharmaceutical corporations. Neither he nor his family members have ever held equity positions in biomedical or pharmaceutical corporations. Dr. Stowe has received research support from GSK, Janssen, Sage Therapeutics, Wyeth, and Pfizer; he has served on speaker or advisory boards for Eli Lilly, GSK, Sage Therapeutics, Pfizer, Wyeth, and BMS and has received honoraria from Eli Lilly, GSK, Pfizer, and Wyeth. Dr. Monk has a research grant from Johnson & Johnson. Ms. Knight has received research support from Janssen, Sage Therapeutics, and Boehringer Ingelheim; and has a son employed by GlaxoSmithKline who has stock options in the company.

All other authors report no financial relationships with commercial interests.

DATA AVAILABILITY STATEMENT

The corresponding author has access to all data from the study, and had complete freedom to direct the analysis and its reporting without influence from commercial interests.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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