Associations Among Child Abuse, Depression, and Interleukin-6 in Pregnant Adolescents: Paradoxical Findings

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ABSTRACT

Objective: Limited data exist on child abuse–related immune variation during pregnancy, despite implications for maternal and infant health and extensive data showing that abuse history and depression are related to increased inflammation in other populations. This study examined associations among child abuse, depression, circulating levels of inflammatory markers, and perinatal health in pregnant adolescents, a group at high risk for childhood abuse and poor birth outcomes.

Methods: Pregnant teenagers ($n = 133$; 14–19 years; 89.5% Latina) reported on abuse and depression and had two blood draws (24–27 and 34–37 gestational weeks, second and third trimesters, respectively) for interleukin-6 (IL-6) and C-reactive protein; birth outcomes were collected.

Results: Abuse and depression interacted to predict higher IL-6 at second trimester ($B = 0.006$, $p = .011$) such that severely abused adolescents with high depression had higher IL-6 relative to severely abused adolescents with low depression; depression did not differentiate IL-6 levels for those with low abuse severity. Abuse and IL-6 also interacted to predict gestational age at birth ($B = 0.004$, $p = .040$) such that those with low abuse and high IL-6 and those with high abuse and low IL-6 had infants with earlier gestational age at birth. Cortisol at the second trimester mediated the association between IL-6 and gestational age at birth (indirect effect estimate=−0.143, $p < .039$).

Conclusions: Depression severity distinguished IL-6 levels among more severely abused pregnant Latina adolescents, but it was unrelated to IL-6 among less severely abused adolescents. Cortisol explained the relationship between IL-6 and earlier gestational age at birth. Multiple adversities and inflammation may influence birth outcomes and potentially affect intergenerational health.

Key words: interleukin-6, cortisol, pregnancy, adolescents, abuse, depression.

INTRODUCTION

Although the teen pregnancy rate is declining in the United States, it remains one of the highest among developed countries (1) and, hence, presents a significant public health issue. Pregnant adolescents have elevated rates of childhood abuse (2,3), abuse-related depression (4), and poor birth outcomes (e.g., younger gestational age at birth, low birth weight, and neonatal and infant mortality) (5–7). More specifically, pregnant adolescents with histories of childhood abuse have higher levels of depression during pregnancy and give birth to smaller, less mature infants (8). However, biological mechanisms that may explain the associations among abuse, depression, and poor birth outcomes are not well understood.

Inflammation has been identified as an important potential explanatory variable in the pathway from abuse to depression and poor health. Indeed, systemic inflammation, evidenced by elevated levels of Interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor α (TNF-α), has been observed among adults (9–11) and

AUC = area under the curve, **BMI** = body mass index, **CRP** = C-reactive protein, **CUMC** = Columbia University Medical Center, **HPA** = hypothalamic-pituitary-adrenal, **IL-6** = interleukin-6, **T2** = trimester 2, **T3** = trimester 3, **TNF-α** =tumor necrosis factor α

adolescents (12–15) exposed to early adversity. Depression, a common sequela of childhood abuse (16–18), also has been associated with higher levels of cytokines such as IL-6 (19), and the association between depression and inflammation has been observed consistently among those exposed to childhood adversity (14,20). Furthermore, abuse and depression each have been related to glucocorticoid resistance (21), which may contribute to excessive inflammation (22). Despite the potential influence of abuse and depression on prenatal immune activity (23); however, only one study has considered the impact of trauma history and psychiatric symptoms in relation to circulating levels of inflammatory markers during pregnancy (23). Specifically, lifetime trauma exposure, but not current mood symptoms, was associated with higher levels of TNF-α, but not IL-6, in a sample of pregnant adults (23). Similarly, higher levels of CRP (an acute-phase reactant that is produced in response to IL-6 and other proinflammatory signals) have been associated with increased risk for preeclampsia and low birth weight (24) as well as preterm birth (25). These associations have yet to be studied among pregnant adolescents, a population with heightened risk for childhood abuse and perinatal depression.

Healthy immune function is critical during pregnancy. The immune system strives to balance the proinflammatory responses needed to protect mothers from infectious disease with the immunosuppression necessary to prevent fetal rejection (26–28). The cytokine IL-6, which has both proinflammatory and anti-inflammatory properties, has multiple functions in fertility and pregnancy maintenance, including implantation, trophoblast invasion, and regulation of endometrial function (29). Consequently, dysregulation of IL-6, up or down, can jeopardize a pregnancy (29–31). Indeed, studies have shown that higher levels of IL-6 in peripheral blood are associated with increased risks for miscarriage (32), preterm birth (25), and gestational diabetes mellitus (33), as well as preeclampsia and low birth weight (24). In addition, IL-6 in local tissue has been associated with recurrent miscarriage (30,31) and preterm birth (34). However, this link between immune dysregulation and poor birth outcomes has not been studied in pregnant adolescents.

Proinflammatory cytokines also have been shown to activate the hypothalamic-pituitary-adrenal (HPA) axis and contribute to heightened cortisol secretion (35), particularly in response to stressors. Heightened levels of cortisol have been linked with increased risk for poor birth outcomes, including preterm birth (36). Extended activation of glucocorticoid receptors has been shown to attenuate the production of proinflammatory cytokines. Among those exposed to chronic stress, however, the development of glucocorticoid resistance can lead to cytokine dysregulation, whereby the negative association between cortisol and immune activation is no longer observed (37). To date, this phenomenon has yet to be studied in pregnant adolescents and it is unclear whether associations among trauma, neuroendocrine function, and inflammation vary by trimester.

The current study examined how child abuse severity and depression are related to circulating levels of immune markers (as assessed through IL-6 and CRP), cortisol, and birth outcomes in adolescent pregnancy. This study was unique for several reasons. First, it focused on associations among abuse severity, depression, and circulating levels of immune markers in pregnant Latina adolescents, an understudied population. Second, the study offered opportunities to examine associations between neuroendocrine function and circulating levels of immune markers separately by trimester. We hypothesized that a) adolescents' abuse severity and depressive symptoms would be positively and independently associated with IL-6 and CRP; b) abuse severity would interact with depression severity to predict higher levels of IL-6 and CRP compared with low abuse and depression severity; and c) immune dysregulation would interact with abuse and depression to predict pregnancy complications (i.e., hypertension/preeclampsia, vascular complications, and gestational diabetes mellitus), younger gestational age at birth, and lower birth weight. Because abuse, depression, and circulating levels of immune markers have been associated with increased glucocorticoid resistance in prior studies (21,22), we also conducted post hoc analyses to examine whether cortisol mediates associations among abuse severity, depression, associated immune markers, and poor birth outcomes.

METHODS

Study Design

Pregnant adolescents were recruited through the Departments of Obstetrics and Gynecology at Columbia University Medical Center (CUMC) and Weill Medical College of Cornell University between July 2009 and August 2011. Recruitment flyers also were posted in the CUMC neighborhood. This study included a subset ($n = 133$) of a larger sample of 205 nulliparous pregnant adolescents, between 14 and 19 years of age. See Figure 1 for sample determination. Psychosocial and salivary cortisol assessments took place at 13–16, 24–27, and 34–37 gestational weeks (±1 week). Blood was collected at the latter two assessments. Birth outcome and pregnancy complication information was obtained from participants' medical charts. Study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute/CUMC and all participants younger than 18 years provided assent with parental written informed consent, whereas those 18 years and older provided written informed consent.

Participants

All adolescents had a healthy pregnancy at the time of recruitment. Exclusion criteria included a lack of fluency in English, multiparity, or frequent use of any of the following: nitrates, steroids, β-blockers, triptans, and psychiatric medications. Participants also were excluded for cigarette smoking or use of recreational drugs as assessed through self-report and one random urine toxicology screen for the use of cannabinoids, amphetamines, benzodiazepines, opioids, and cotinine. The sample was predominantly Latina (89.5%). Participants included in our study did not differ from those who were excluded with respect to age (Wilcoxon test, $p = .30$) and ethnicity
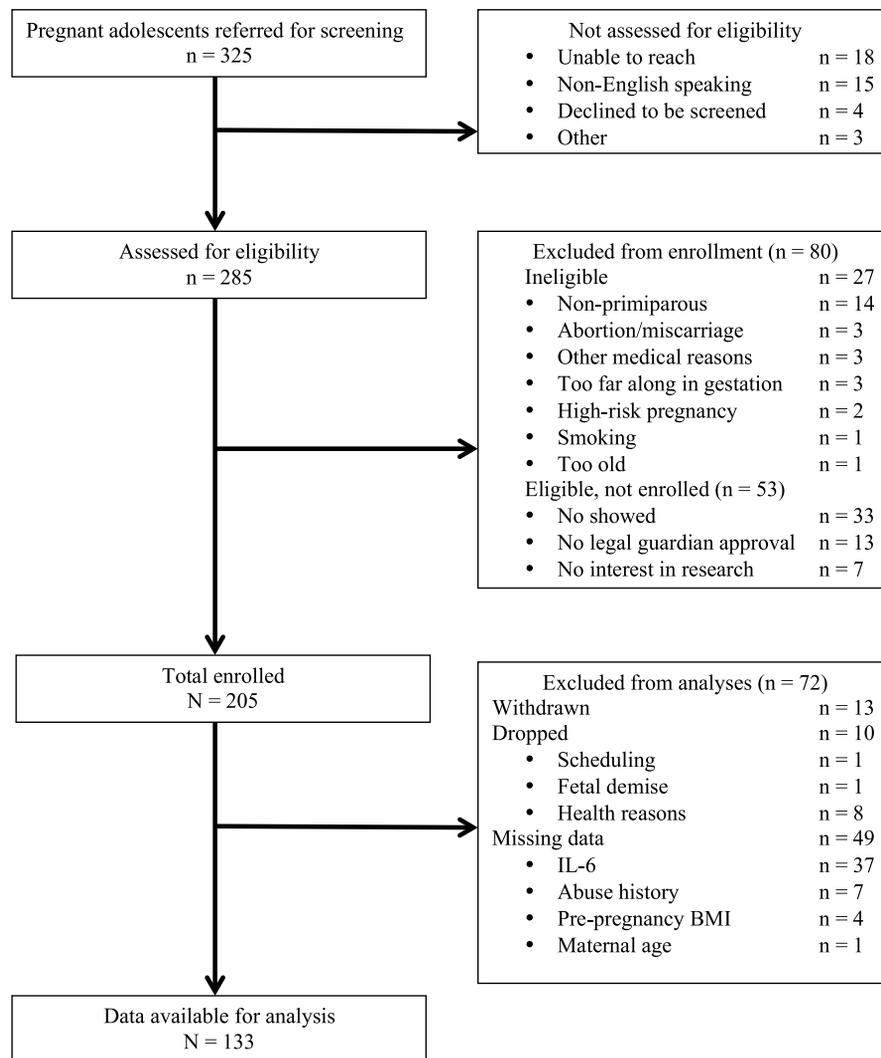
FIGURE 1. Flowchart showing participant enrollment and sample size determination. IL-6 = interleukin-6; BMI = body mass index.

(χ^2 test, $p = .079$). Among participants with complete data for abuse history and depression symptoms, abuse history and depression symptoms did not differ between participants with and without IL-6 samples (Wilcoxon test, not significant).

Measures

Demographic data were self-reported. Prepregnancy body mass index (BMI; kg/m^2) was calculated using self-reported prepregnancy weight and height from medical records. Pregnancy weight gain was collected at each trimester, and complications, including infection, were coded from medical charts. Birth weight (corrected for gestational age (38)) was determined from the medical record. Gestational age at birth was determined through the medical record reporting of dating based on ultrasound examinations and last reported menstrual cycle.

Abuse was assessed through the Childhood Trauma Questionnaire (39), a widely used self-report measure (40) composed of 28 items that assesses lifetime exposure to five types of childhood maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Respondents indicate whether they experienced each type of childhood maltreatment based on a series of statements that are scored on a Likert-type scale from 1 (never true) to 5 (very often true). Response scores

are summed to reflect the severity of each type of abuse or neglect. Following Ref. (41), we used a summary score reflecting the severity of emotional, physical, and sexual abuse.

Depressive symptoms were assessed using the depression subscale of the Symptom Checklist-90 (SCL-90-R), (42), which consists of 9 Likert-type items about dysphoric mood and affect, anhedonia, hopelessness, suicidal ideation, and other cognitive and somatic symptoms of depression. Items are rated from 0 (not at all) to 4 (extremely). The SCL-90 has good psychometric properties and acceptable concurrent validity with interview-based measures of depression (43). The SCL-90 has been normed in an adolescent sample; therefore, in the current study, the adolescent-normed t score for the depression subscale was used to reflect the severity of depression symptoms.

Consistent with previous studies assessing IL-6 through a single blood draw (37,44,45), 10 ml blood samples were collected in EDTA tubes. Samples were placed on ice, spun down, and frozen at −80°C within 60 minutes of collection. IL-6 and CRP were assayed using high-sensitivity commercial enzyme-linked immunosorbent assay kits (HS-IL-6: R&D Systems, Minneapolis, MN; Zymutest HS-CRP: Diapharma, West Chester, OH). IL-6 values increased slightly from the second to third trimesters (T2 and T3, respectively; $t(99) = −2.17$, $p = .033$). Consistent with prior research suggesting that CRP is stable across the last two trimesters of pregnancy

(46), there were no significant differences in average CRP values between study visits ($t(99) = 1.63$, $p = .105$). As described in Ref. 47, all samples were run in duplicate. Extraction efficiency was 70%. The detection limit was 20 pg/ml and intra-assay coefficient of variation was less than 10%. The interassay coefficients of variation were 4% to 11%.

Diurnal salivary cortisol was collected for 48 hours beginning at the time of the study session visit. Subsequent samples were collected on the following schedule: at waking; 45 minutes, 2.5 hours, 3.5 hours, and 8 hours after waking; and at 10 PM or before going to bed. Participants continued the collection schedule at the next collection point relative to their study visit. Salivette tubes (Sarstedt, Newton, NC) were used for cortisol collection. Cotton used for each sample was kept in a bottle with a Medication Event Monitoring System cap (Aardex, Union City, CA) to record the time of opening. Once used, the cotton was placed in a Salivette tube. After return to the laboratory, samples were kept frozen until assayed using a commercial enzyme-linked immunosorbent assay kit (Salimetrics, State College, PA). Cortisol area under the curve (AUC) was calculated using samples from the second collection day only, as this provided the most uniform collection schedule. At least two cortisol samples were required: one needed to be the waking sample and at least one other needed to be collected 8 hours or more after the waking sample. Cortisol AUC was calculated from waking until the eighth hour (47). Cortisol AUC increased from T2 to T3 ($t(65) = -2.07$, $p = .043$).

Data Preparation

Before testing primary hypotheses, we examined possible covariates for inclusion in our models. Consistent with findings in the literature, in our sample, maternal prepregnancy BMI and age were positively correlated with IL-6 and CRP and were included as covariates in all analyses. Fifty-four participants (40.60%) reported having a minor infection (either a urinary tract or yeast infection) at some point during pregnancy; however, this was unrelated to abuse severity, depression symptoms, IL-6, and CRP levels and thus was excluded from analyses. We also examined sleep quality (using the Pittsburgh Sleep Quality Index (48)) and pregnancy-specific distress (Revised Pregnancy Distress Questionnaire (49)) as potential covariates, but these variables were not correlated with IL-6 or CRP and thus were not included in analyses. Finally, among the birth outcomes, gestational age was positively skewed, and hence, a variable created by subtracting gestational age at birth from 42 weeks (based on maximum gestational age at birth in our sample) was used.

Data Analytic Plan

Analyses were conducted in PASW Statistics Version 21.0. To test the independent and interactive effects of abuse history and depression severity on IL-6 and CRP, linear regression analyses were conducted separately for each time point and each outcome controlling for age and BMI; additionally, at T3, we also controlled for T2 inflammatory markers. Abuse and depression were centered and entered on the first step along with covariates, and an interaction term reflecting the product of these centered variables was entered on the second step. To examine whether abuse or depression interacted with circulating levels of inflammatory markers to predict poor birth outcomes, separate linear regressions were conducted for gestational age at birth and birth weight and logistic regression was used for any birth complications. Separate models were estimated for the interactions between abuse and inflammatory markers and the interactions between depression and the inflammatory markers. For all birth outcomes, mode of delivery (0 = spontaneous vaginal delivery, 1 = vaginal delivery with induction/augmentation, or 2 = cesarean section) was included as an additional categorical covariate. Finally, to examine whether cortisol at each time point mediated associations between inflammatory markers at that trimester and poor birth outcome, we tested indirect effects models with bootstrapped standard errors specifying that inflammatory markers predicted cortisol at the same occasion, which in turn predicted poor birth outcomes.

RESULTS

Descriptives

Table 1 includes descriptive and sample size information of the key variables in the study. Most complications were related to labor and delivery (e.g., arrest of dilation) followed by infection (e.g., chorioamnionitis), and preeclampsia/hypertension; complications were unrelated to child abuse ($F = 0.23$, $p = .63$) or depression ($F = 0.76$, $p = .39$) severity. Of the sample, 10 (7.5%) participants had a baby born before 37 weeks, and 6 (4.5%) gave birth to a baby weighing less than 2500 grams (5 lb, 8 oz).

Correlations

Table 2 shows the correlations among the predictor, outcome, and covariate variables. IL-6 at T2 and T3 was not correlated with the Childhood Trauma Questionnaire abuse severity score, depression severity, or cortisol AUC at T3; however, IL-6 at T2 was positively associated with cortisol AUC at T2. Abuse was positively associated with depression symptoms, and depression at both trimesters was positively associated with age. IL-6 at both trimesters was positively associated with BMI. CRP at T2 and T3 was positively associated with IL-6 at T2 and T3 as well as with BMI, and CRP at T2 was positively associated with maternal age. Cortisol AUC at T2 was negatively associated with gestational age and birth weight.

Abuse and Circulating Levels of Inflammatory Markers Across Pregnancy

To test whether abuse history was associated with IL-6 or CRP after controlling for age and prepregnancy BMI, we regressed IL-6 and CRP at T2 and T3 on the abuse severity score controlling for significant demographic variables. Abuse was not significantly associated with IL-6 at T2 ($B = -0.01$, $p = .56$) T3 ($B = -0.05$, $p = .074$) or with CRP at T2 ($B = 0.005$, $p = .39$) or T3 ($B = -0.003$, $p = .57$).

Depression and Circulating Levels of Inflammatory Markers Across Pregnancy

To test whether depression was associated with IL-6 and CRP after controlling for age and prepregnancy BMI, we regressed IL-6 and CRP at T2 and T3 on the depression score at the same trimester. Depression at T2 was not associated with IL-6 ($B = 0.01$, $p = .68$) or CRP ($B = 0.005$, $p = .37$) at T2, and depression at T3 was not associated with IL-6 ($B = -0.02$, $p = .40$) or CRP ($B = 0.002$, $p = .77$) at T3.

Interaction Between Abuse and Depression on Circulating Levels of Inflammatory Markers During Pregnancy

Consistent with other literature (10,14,20), we regressed IL-6 on the centered abuse and depression variables and their interaction controlling for age and prepregnancy

TABLE 1. Descriptive Data

Variable	n	Min	Max	Mean	SD
Ethnicity	133				
Hispanic	119				
Non-Hispanic	14				
Income	133				
$0–$15,000	47				
$16,000–$25,000	44				
$26,000–$50,000	22				
$51,000–$100,000	4				
$101,000–$250,000	1				
>$250,000	0				
Unknown	15				
CTQ Abuse score	133	15	55	21.12	7.56
SCL-90 Depression t score at T2	102	29	81	53.30	9.18
SCL-90 Depression t score at T3	101	34	82	53.40	9.22
Interleukin-6* at T2, pg/ml	124	0.28	12.79	1.86	1.73
Interluekin-6 * at T3, pg/ml	109	0.57	18.22	2.20	1.96
C-reactive protein at T2	124	0.25	49.56	8.32	9.44
C-reactive protein at T3	109	0.01	29.06	7.31	6.13
AUC cortisol at T2, μg/dl	98	0.74	5.64	2.26	0.77
AUC cortisol at T3, μg/dl	89	1.20	5.33	2.56	0.84
Gestational age at birth, wk	119	27	42	39.01	2.27
Corrected birth weight, grams	119	947	4525	3209.19	560.26
Mode of delivery	120				
Vaginal	37				
Vaginal (induction/augmentation)	54				
Cesarean delivery	29				
Pregnancy complications	122				
Yes	61				
Infection (e.g., chorioamnionitis)	15				
Preeclampsia/hypertension	14				
Vascular complications	1				
Other (e.g., arrest of dilation)	31				
No	61				
Maternal age, y	133	14	20	17.80	1.22
Prepregnancy body mass index, kg/m^2	133	17	48	25.67	6.10

SD = standard deviation; CTQ Abuse score = Childhood Trauma Questionnaire score for physical, sexual, and emotional abuse; SCL-90 = Symptom Checklist-90; T2 = trimester 2; T3 = trimester 3; AUC = area under the curve.

BMI. As shown in Table 3, abuse and depression significantly interacted to predict IL-6 at T2 ($B = 0.006$, $p = .011$), but not T3 ($B = 0.002$, $p = .63$). Specifically, at T2, adolescents with high abuse and high depression had higher IL-6 compared with adolescents with high abuse and low depression ($p = .043$). Depression did not differentially relate to IL-6 for adolescents with low abuse severity ($p = .27$; see Fig. 2). Furthermore, post hoc tests comparing those above and below the mean on both abuse severity and depression revealed that IL-6 levels did not differ between those high on abuse and depression compared with those low on both ($F = 0.36$, $p = .56$). Finally, adolescents with a higher prepregnancy BMI also had higher IL-6 at T2 after controlling for abuse, depression, their interaction, and maternal age. Also shown in Table 3, abuse and depression did not interact to predict CRP at T2 or T3; however, prepregnancy BMI was significantly associated with CRP at both time points.

TABLE 2. Correlations Among Study Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. CTQ Abuse	—													
2. T2 Depression	0.30**	—												
3. T3 Depression	0.31**	0.80***	—											
4. T2 IL-6	0.01	0.07	0.10	—										
5. T3 IL-6	−0.15	−0.02	−0.02	0.44***	—									
6. T2 CRP	0.11	0.14	0.18	0.39***	0.36***	—								
7. T3 CRP	−0.01	0.09	0.05	0.27**	0.29**	0.83***	—							
8. Age	0.07	0.33***	0.36***	0.06	0.26**	0.23*	0.09	—						
9. Prepregnancy BMI	0.10	0.04	0.01	0.31***	0.28**	0.44***	0.38***	0.14	—					
10. Gestational age	0.05	0.03	−0.08	−0.16	−0.10	−0.07	−0.13	−0.04	0.10	—				
11. Birth weight	0.05	0.13	0.09	−0.02	−0.09	−0.05	−0.11	−0.01	0.15	0.76***	—			
12. Complications	−0.04	0.18	0.15	0.07	0.01	−0.03	−0.06	0.06	0.04	−0.14	−0.09	—		
13. Cortisol AUC at T2	−0.13	−0.03	−0.13	0.21*	0.02	−0.05	0.05	−0.13	−0.18	−0.35***	−0.34***	0.17	—	
14. Cortisol AUC at T3	−0.001	−0.06	0.05	−0.03	−0.03	−0.003	−0.14	0.01	−0.19	−0.13	−0.19	0.05	0.21	—

CTQ = Childhood Trauma Questionnaire; T2 = trimester 2; T3 = trimester 3; IL-6 = interleukin-6; CRP = C-reactive protein; BMI = body mass index; AUC = area under the curve.

$* p < .05$, $** p < .01$, $*** p < .001$.

Birth Outcomes

Child abuse severity, depression, IL-6, and CRP levels at T2 and T3 were not independently associated with gestational age at birth, birth weight, or pregnancy complications. In addition, depression symptoms did not interact with IL-6 to predict birth outcomes. However, IL-6 at T2 and abuse severity interacted to predict gestational age at birth ($B = 0.004$, $p < .040$) after controlling for age, prepregnancy BMI, and mode of delivery. Specifically, adolescents with lower abuse severity and higher IL-6 at T2 had babies born at an earlier gestational age than did adolescents with lower abuse severity and lower IL-6 ($p = .050$). However, among adolescents with higher abuse, having lower levels of IL-6 at T2 actually predicted younger gestational age compared with adolescents with higher abuse and higher IL-6 ($p = .046$). Prepregnancy BMI was a positively associated with gestational age after accounting for cortisol and IL-6 at T2. Neither abuse nor depression interacted with CRP at either trimester to predict poor birth outcomes.

Post Hoc Analyses for HPA Axis

Because glucocorticoid resistance has been linked with both maltreatment and inflammation (9,22), we conducted post hoc analyses to assess whether HPA axis activation, measured by cortisol AUC, might mediate associations between IL-6 and poor birth outcomes. Cortisol and IL-6 were positively associated at T2 ($r = 0.21$, $p < .041$), although this association did not hold at T3 ($r = −0.03$, $p = .76$). As shown in Table 4, an indirect effects model with bootstrapped standard errors revealed that higher IL-6 levels at T2 were related to younger gestational age at birth through heightened cortisol AUC at T2 (indirect effect estimate = −0.143, standard error = 0.07, $p < .039$). This model accounted for 13% of the variance in gestational age at birth. BMI also contributed significantly to cortisol at T2 such that girls with a higher prepregnancy BMI had lower T2 cortisol AUC. Significant effects were not observed for IL-6 and cortisol AUC at T3.

DISCUSSION

To our knowledge, this is the first study to examine abuse-related immune variation in a sample of pregnant adolescents. Unlike other health research linking past trauma to elevated immune activity and poor health outcomes, in this sample, neither abuse nor depression was associated independently with IL-6 or CRP levels in the second (24–27 weeks) or third trimesters (34–37 weeks) in pregnancy. However, abuse and depression interacted to predict IL-6 such that adolescents with more severe abuse and depression had higher IL-6 at the second trimester compared with adolescents with high abuse and low depression. Paradoxically, adolescents with low abuse

TABLE 3. Interaction Between Abuse Severity and Depression on IL-6 and CRP

Variable	Interleukin-6 at 2nd Trimester, $F(5,124) = 5.58$, $p < .001$			Interleukin-6 at 3rd Trimester, $F(5,85) = 1.17$, $p = .34$		
	Estimate B	SE	p	Estimate B	SE	p
Maternal age	0.01	0.12	.92	0.27	0.18	.15
Body mass index	0.08	0.02	**<.01**	0.04	0.03	.11
Abuse	−0.03	0.02	.11	−0.04	0.03	.22
Depression	0.01	0.02	.54	−0.02	0.03	.35
Abuse by depression	0.006	0.002	**.01**	0.002	0.003	.65
	CRP at Trimester 2, $F(5,94) = 5.00$, $p < .001$			CRP and Trimester 3, $F(5,90) = 3.21$, $p = .011$		
	B	SE	p	B	SE	p
Maternal age	0.06	0.04	.13	0.02	0.04	.70
Body mass index	0.03	0.01	**<.001**	0.03	0.01	**<.001**
Abuse	0.01	0.1	.50	−0.01	0.01	.44
Depression	0.003	0.006	.58	0.002	0.006	.75
Abuse by depression	0.001	0.001	.58	0.0001	0.001	.98

IL-6 = interleukin-6; CRP = C-reactive protein; SE = standard error.
Bold indicates significant effects.

and low depression had comparable levels of IL-6 relative to adolescents with high abuse and depression. That is, although two adversities— higher scores on childhood abuse and depression—compared with just one were associated with higher IL-6, the relative increase was not significantly different from those with the healthiest profiles, low scores on abuse and depression. Finally, through its association with higher cortisol, higher IL-6 predicted a poor birth outcome and earlier gestational age at birth.

Given that numerous adult studies have related psychosocial adversities such as abuse and depression to higher levels of inflammation, it is curious that this sample of pregnant adolescents did not evidence the expected pattern of associations between abuse, depression, IL-6, and CRP. Although speculative, one explanation for these unexpected findings centers on developmental and ethnic differences in inflammation-promoting IL-6 gene expression. Specifically, the inflammation-related function of a polymorphism
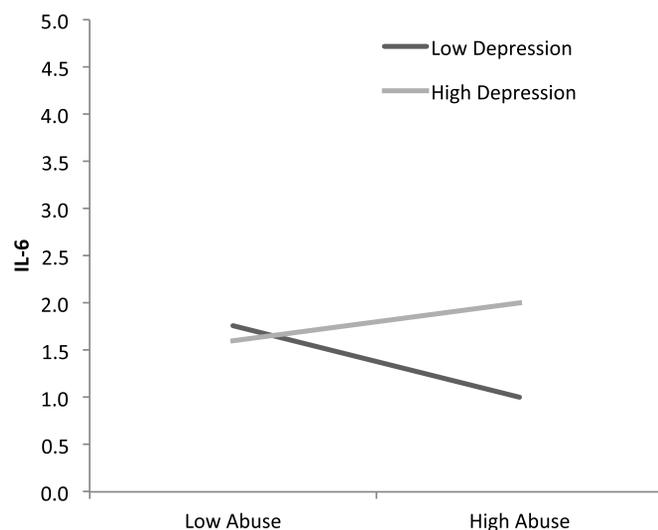

FIGURE 2. Interaction between abuse severity and depression on IL-6 at second trimester. Continuous predictor variables are graphically depicted here; however, follow-up analyses using dichotomous predictors revealed that only three adolescents with severe abuse histories did not have clinically significant depression; therefore, this interaction should be interpreted cautiously. IL-6 = interleukin-6; BMI = body mass index.

TABLE 4. Cortisol AUC as an Indirect Path from IL-6 to Gestational Age

Variable	2nd Trimester Predictors			3rd Trimester Predictors		
	Estimate *B*	Standard Error	*p*	Estimate *B*	Standard Error	*p*
Gestational age on:						
Maternal age	−0.21	0.18	.25	−0.15	0.13	.22
Body mass index	0.03	0.04	.46	0.04	0.02	.06
Cortisol	−1.02	0.32	**<.001**	−0.21	0.18	.24
IL-6	−0.06	0.15	.69	−0.09	0.12	.47
Cortisol on:						
Maternal age	−0.09	0.06	.14	0.001	0.07	.99
Body mass index	−0.03	0.01	**.03**	−0.03	0.01	.07
IL-6	0.14	0.04	**<.001**	−0.01	0.04	.87
Indirect effect	0.14	0.07	**.037**	0.001	0.009	.87

AUC = area under the curve; IL-6 = interleukin-6.

Bold indicates significant effects. Indirect effects were calculated using bootstrapped standard errors.

in the human *IL-6* promoter (rs1800795; *IL-6*—174 G/C) may be moderated by developmental stage and exposure to stress such that older adult carriers of the G allele evidence chronic inflammation in the context of interpersonal stress (50), whereas adolescents with the G allele show resilience toward inflammation (12). Notably, the distribution of the IL-6 genotypes differs significantly as a function of ethnicity, such that Latino populations are more likely to carry the G allele (12). Because our sample was composed primarily of pregnant Hispanic adolescents, genetic and/or developmental factors may help explain the results: participants with high abuse and low depression showed resilience in inflammation relative to those with high abuse and high depression. However, in contrast to other studies using older, ethnically diverse samples, IL-6 was not significantly higher in the high abuse–high depression adolescents compared with low abuse–low depression adolescents (9,10,23).

Another explanation for the lack of a significant difference on IL-6 in the third trimester between the high abuse–high depression and the low abuse–low depression adolescents may lie in the general good health of our sample. The severity scores for both abuse and depression were fairly low level. Based on the larger study aims, we only included adolescents with healthy pregnancies and deliveries, and we excluded those who were taking psychiatric medications. Thus, null findings may be a function of recruiting a relatively healthier sample where the abuse and depression were not severe enough to affect IL-6 levels in expected ways. As support for this notion, although IL-6 values in the current sample fell within the range of those reported in other studies with pregnant women, and we observed an increase in IL-6 from T2 to T3, which is consistent with prior work noting renewed inflammation in the third trimester to stimulate labor and facilitate delivery (51), the means for our sample (means = 1.86 and 2.20)

were slightly lower than the means observed in healthy adult pregnant women (e.g., mean = 3; range, 0.4–7.6) (52), which may reflect the relative youth and health of the current sample. Alternatively, the overall lower IL-6 values compared with studies with adult pregnant women and the lack of different levels between high- and low-risk participants may reflect an element of risk in this adolescent sample given that lower IL-6 levels are associated with poor birth outcomes.

Third, pregnancy-related factors also could explain the unexpected results. For instance, some studies show that the balance between T_H1 and T_H2 cytokines may provide a more comprehensive picture of immune functioning during pregnancy than an examination of IL-6 alone (53,54). An examination of interferon-γ and the T_H1/T_H2 (interferon-γ/IL-10) ratio (55) may provide a more nuanced understanding of maltreatment-related immune findings in pregnant adolescents, as well as pregnant women. In addition, a previous study with pregnant adults found that trauma exposure was associated with higher levels of TNF-α but not IL-6; thus, future studies should consider including multiple indicators of inflammatory markers.

Cortisol AUC at T2 was positively associated with IL-6 at T2 and cortisol at T2 mediated the inverse association between IL-6 at T2 and younger gestational age at birth. At least one other study did not observe the typical inverse association between cortisol and IL-6 among low-income, minority pregnant women (37). Because cortisol and other glucocorticoids are down-regulators of IL-6 gene expression, the positive association between cortisol and IL-6 evidenced at T2 may result from cortisol's relation to other stress-related mediators such as catecholamine signaling, which is associated with a stimulatory effect on IL-6 gene expression (50). In addition, abuse can lead to glucocorticoid receptor desensitization, resulting in complex alterations in

typical regulatory dynamics (56). In our sample, the positive associations between cortisol and IL-6 did not persist to T3, which is consistent with other studies showing that biomarkers in the second trimester are associated with risk for younger gestational age. Specifically, elevated IL-6 and corticotropin releasing hormone levels detected in amniotic fluid during the second trimester have been associated with risk for preterm birth (57,58). Further exploration of associations between neuroendocrine dysregulation and inflammation in the second trimester and poor birth outcomes is warranted.

Abuse severity and IL-6 also interacted to predict gestational age at birth such that adolescents with high abuse and low IL-6 as well as adolescents with low abuse and high IL-6 had babies with lower gestational ages at birth. These findings fit with work showing that inflammation is implicated in preterm birth (25,59), which can have negative downstream effects on later cognitive (60,61) and health (62) outcomes. Findings are consistent with recent work suggesting that pregnancy is a carefully regulated inflammatory state where both high and low inflammation may be detrimental to a pregnancy (63), and contextual factors like abuse severity may increase the likelihood of dysregulation. It is important to note that our findings were specific to gestational age at birth, and we did not note associations with birth weight or pregnancy-related complications. These differential associations with various birth outcomes suggest that it will be important to extend this work with more thorough examinations of abuse and circulating levels of inflammatory markers in pregnancy.

Consistent with other studies emphasizing the importance of prepregnancy BMI in inflammation and pregnancy complications (64), adolescents with a higher prepregnancy BMI also had higher IL-6 at T2 and T3, and this relationship remained significant in the multivariate model for IL-6 at T2. Prepregnancy BMI also was a significant predictor of lower gestational age after accounting for cortisol and IL-6 at T2. This risk factor for inflammation is partially modifiable through diet and exercise; thus, it may be important to target these behaviors in high-risk adolescents to reduce risk for inflammation and associated poor birth outcomes.

Our findings should be considered within the context of limitations. First, consistent with other studies (37), we collected blood at a single time-point either in the late morning or early afternoon in T2 and T3 for IL-6 analysis and thus could not account for diurnal variation in IL-6. Because we were collecting multiple markers in addition to cytokines, we used EDTA tubes and thus could not rule out the possibility that the tubes interfered with cytokine production by removing calcium. Second, we did not collect markers of inflammation during the first trimester and thus were unable to examine how inflammation across all three trimesters was related to abuse, depression, cortisol, and

poor birth outcomes. Third, although participants reported a low severity of abuse on average, we did not assess abuse characteristics such as the frequency or duration of the abuse or the relationship to the perpetrator, and we have no data on whether the abuse was currently ongoing, which could have skewed results. We also lack data on other stressors or traumatic events that could be present and accounting for some of the similarities between adolescents with low and high abuse severity. Fourth, our assessment of depression was based on the SCL-90, a widely used measure of clinical depression that has adolescent norms; however, measures like the Edinburgh Depression Scale are commonly used to assess symptoms of perinatal depression and may be useful for drawing comparisons to other studies of pregnant girls and women. Fifth, we had relatively low power to detect interaction effects so findings should be replicated in larger samples with greater variability in abuse and depression severity.

In summary, for adolescents with more severe abuse, more severe depression was associated with higher levels of IL-6 compared with those with high abuse and low depression. Unexpectedly, adolescents with high abuse and high depression had statistically similar levels of IL-6 compared with adolescents with low abuse and low depression suggesting paradoxical physiological adaptation to adversity in this sample of young, pregnant, Latina women. Furthermore, higher IL-6 levels were associated with younger gestational age at birth, and cortisol explained the relationship between IL-6 and younger gestational age at birth, suggesting that immune and HPA axis markers are important to examine in relation to pregnancy outcomes. The current report indicates that biomarkers at the second trimester (Weeks 24–27) were especially important to consider in risk for poor birth outcomes. The results suggest a pathway by which maternal factors such as abuse history and depression influence not only immune profiles during pregnancy but also the health of the next generation.

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