Childhood maltreatment and inflammation among pregnant women with gestational diabetes mellitus: A pilot study

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Abstract

Background: Women with childhood maltreatment histories are at increased risk for adverse birth outcomes. Mechanisms explaining this link are poorly understood. Past research is limited by sampling pregnant women at low risk for adverse maternal and neonatal outcomes.

Methods: This pilot study was a secondary data analysis of 24 women with gestational diabetes mellitus; 17% of the sample also reported a maltreatment history. Women provided a blood sample to measure inflammatory cytokines and insulin resistance, and saliva samples to measure diurnal cortisol. Birth outcomes for past and current pregnancies were recorded.

Results: Histories of maltreatment were associated with elevated interleukin-15 and a marginally greater incidence of preterm delivery in current and past pregnancies.

Conclusions: This pilot study was the first to demonstrate an association between childhood maltreatment history and inflammatory cytokine levels in pregnant women diagnosed with gestational diabetes mellitus.

Keywords

Maltreatment, inflammation, gestational diabetes, preterm birth

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Introduction

Childhood maltreatment is associated with morbidity and mortality in adulthood. Disorders associated with exposure to childhood maltreatment include psychiatric illness,¹ coronary heart disease, autoimmune disorders, and some cancers.^{2,3} Past research has identified numerous physiological mechanisms that may serve as pathways from maltreatment to later life health. These include altered hypothalamic-pituitary-adrenal (HPA) activity, increased production of pro-inflammatory cytokines (particularly interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β)),^{4–6} shortened telomere length,⁷ and changes in neural structure and function.^{8–10}

Emerging evidence suggests that the impact of childhood maltreatment on adult health reaches into pregnancy; women with histories of maltreatment are at an elevated risk for adverse maternal and neonatal outcomes including preterm birth,^{11–15} low birth weight,¹⁶ premature contractions, cervical insufficiency, and hospitalizations in pregnancy.¹³ Pregnant women with maltreatment histories are also at increased risk for gestational diabetes mellitus (GDM). In a recent review, Mason et al. reported a 68% higher risk for GDM among pregnant women with histories of physical and sexual abuse compared to women without abuse histories.¹⁷ The authors hypothesized that abuse may lead to chronic elevation of stress hormones and contribute to insulin resistance, resulting in GDM in pregnancy. Despite the increased risk for GDM and hypothesized biological pathways among women with maltreatment histories, no studies, to our knowledge, have examined associations among childhood maltreatment and insulin resistance or regulation of stress response systems (e.g. HPA activity and immune markers) in pregnancy.

A growing body of research has demonstrated that women who experienced childhood maltreatment may be vulnerable to dysregulated HPA activity in pregnancy, particularly within the context of ongoing psychosocial stress and family discord. Specifically, women with childhood sexual abuse histories display increasing cortisol awakening responses (CAR) over pregnancy,¹⁸ and this effect is exacerbated by elevated daily stress,¹⁹ and poorer perceived family

functioning.²⁰ However, these prior samples were selected to be at low risk for adverse maternal and neonatal outcomes, and it is currently unclear if maltreatment history predicts HPA dysregulation in higher risk pregnancies. Therefore, the relationship between childhood maltreatment and inflammation in high-risk pregnancies (such as women with GDM) is currently unknown.

In this study, we aimed to examine the associations among maternal childhood maltreatment history, immune and HPA regulation, and insulin resistance in an adult sample of pregnant women diagnosed with GDM. We hypothesized that women with histories of childhood maltreatment would exhibit greater pro-inflammatory cytokine levels (particularly IL-6, IL-1 β , and TNF- α), less cortisol production, and greater insulin resistance relative to women without maltreatment histories.

Methods

Setting and participants

Women diagnosed with gestational diabetes based on the 1- or 3-h glucose tolerance test were recruited at the time of a clinical visit to the nurse educator or the nutritionist at a large hospital based practice for an evaluation of the association of sleep disturbances with HPA

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axis function and insulin resistance. Women who met inclusion criteria were invited to participate and provided written informed consent. The study was approved by the Institutional Review Board.

Measures

Insulin resistance. Fasting blood was obtained and tested for glucose and C-peptide. The homeostatic model assessment for insulin resistance (HOMA-IR) was then calculated using the formula fasting insulin ($\mu\text{U/L}$) $\times$ fasting glucose (nmol/L)/22.5.

Diurnal cortisol. Salivary cortisol was collected using the passive drool method. Samples were collected at three time points; bedtime of the night of the sleep study, wake, and 45 min after wake. Participants were given written instructions regarding the collection process and dietary and lifestyle modifications required for this specific test. Participants also recorded the time of day at each sample collection. Saliva samples were stored at -80°C until analysis. Salivary cortisol levels were analyzed in duplicate by enzyme immunoassay and the average of the two measurements at each time point was then calculated.

Inflammatory markers. Fasting blood samples were collected using a peripheral venipuncture. Plasma was separated from the blood sample and stored at -80°C . Interleukin-15 (IL-15), TNF- α , IL-6, and IL-1 β cytokine levels were measured using an xMAP multiplexed bead array immunoassay. This approach allowed for simultaneous quantification of multiple cytokines in solution by capturing them onto antibody coated spectrally distinct fluorescent microspheres, and measuring fluorescence intensity using the Luminex-100 system (Luminex Corp., Austin, TX).

Childhood maltreatment. Childhood maltreatment history was measured using the Adverse Childhood Experiences (ACE) questionnaire.²¹ This is a 10-item self-report instrument that asks adults to indicate whether or not they experienced a number of adverse events prior to the age of 18 years old. Events include sexual and physical abuse, neglect, witnessing domestic violence, and living with a family member who abused drugs or alcohol, had a mental illness, or went to prison. Women who responded “yes” to the following items were included in the maltreatment group for the current study: “Did a parent or other adult living in the house often push, grab, slap, or throw something at you, or ever hit you so hard you had marks or were injured?” and/or “Did an adult or person at least 5 years older than you ever touch or fondle you or have you touch or fondle them in a sexual way, or try or actually have oral, anal, or vaginal sex with you?”

Depressive symptoms. To measure symptoms of depression, women completed the Patient Health Questionnaire-9 (PHQ-9), a nine-item self-report instrument in which women were asked to report how often over the past 2 weeks they experienced depressive symptoms. Response options range from 0 = not at all to 3 = nearly every day. The nine items of the PHQ-9 correspond to the nine symptoms of major depressive disorder within the DSM-IV. Scores of 10 or greater indicate clinically elevated symptoms of depression.²²

Perceived stress score. To measure symptoms of perceived stress, women completed the Perceived Stress Scale. Women are asked to respond to 10 items about how often they experienced certain feelings and thoughts over the past month. Response options range from 0 = never to 4 = very often with higher scores indicating greater perceived stress. Scores between 14 and 26 indicate “moderate” stress.²³

Birth outcomes. We collected preterm birth history by maternal interview and answers were verified by chart review. We collected infant gestational age at delivery, infant birth weight, and preterm birth status of the current pregnancy by medical chart review.

Statistical analyses

Analyses were performed using SPSS Version 20.0 (Armonk, NY: IBM Corp.). Participants were categorized into two groups, those who endorsed a history of childhood physical and/or sexual abuse, and those without a childhood physical or sexual abuse history (women in this group may have experienced other forms of childhood maltreatment). We tested for significant covariates using T-tests and Chi-square analyses. Cortisol and immune markers were significantly skewed and therefore were log transformed for analyses. Values that were ± 4 SD after log transformation were removed. We calculated the CAR by taking the difference between the two morning salivary cortisol values. We calculated the cortisol slope by taking the difference between the awakening and bedtime cortisol values. We used univariate analysis of variance (ANOVA) to examine if biological markers differed by maltreatment group. Chi-square analyses and t-tests were used to examine if maltreatment groups differed on birth outcomes: preterm birth history, infant gestational age, and infant birth weight. Logistic regression analyses were performed to determine if biomarkers mediated the association between maltreatment group and adverse birth outcomes.²⁴ Gestational age at saliva and plasma collection was included as a covariate in all analyses. Due to the small sample size and exploratory nature of the study, we did not apply a Bonferroni correction for multiple comparisons.

Results

Sample characteristics

A total of 31 patients consented to participate in the study; six signed a consent form but failed to attend the enrollment visit. Twenty-five patients were enrolled and completed the study. Twenty-four women completed the childhood maltreatment measure and were included in analyses for the current study. Among these women, 17% reported experiencing physical or sexual abuse in childhood. Median age was 30.6 (SD = 4.4) and average body mass index was 32.54 (SD = 7.5). Average gravida in this sample was 2 (SD = 1) and average parity was 1 (SD = 1). The cohort was mostly Caucasian (54%). Mean gestational age at enrollment was 30 weeks (SD = 3). Mean depression score was 4 (SD = 4) indicating mild depressive symptoms in the two weeks prior to the study session (three women reported depressive symptoms > 10). Mean perceived stress scores were 33 (SD = 8) indicating moderate-severe perceived stress in the past month. Four women (17%) reported a history of preterm delivery in a previous pregnancy. Four women (17%) had a preterm delivery in the current pregnancy. On average, women in this sample delivered at 38 weeks' gestation (SD = 2) and average birth weights were 3067 g (SD = 414) (6.76 lbs, SD = .91). See Table 1.

Covariate analysis

Correlation analyses revealed that neither maternal age nor BMI at diagnosis was significantly associated with immune markers (all p values > .08), cortisol values (p values > .23), or HOMA-IR (p = .29). Depression scores (measured using the PHQ9) were not significantly associated with immune markers (p values > .18), cortisol values (p values > .58), or HOMA-IR (p = .60). Perceived stress scores were also not significantly associated with immune markers (p values > .26), cortisol values (p values > .12), or HOMA-IR (p = .84). Race/ethnicity was not significantly associated with immune markers (p values > .25), cortisol values (p values > .34), or HOMA-IR (p = .40).

Table 1. Maternal and infant characteristics by childhood maltreatment group.

	Childhood maltreatment history	No childhood maltreatment history	
	Mean (SD)/%	Mean (SD)/%	<i>p</i>
Age	34.5 (1.29)	29.85 (4.45)	.05
Race/ethnicity (% White)	50%	55%	.86
Body mass index	28.91 (11.47)	33.15 (7.19)	.48
Gravida	3 (3)	2 (1)	.12
Parity	1 (2)	1 (1)	.39
Depression score ^a	6 (5)	4 (4)	.45
Perceived stress score	20 (6)	15 (7)	.21
Sexual abuse (% yes)	50%	0%	.001
Physical abuse (% yes)	50%	0%	.001
Emotional neglect (% yes)	25%	5%	.19
Domestic violence (% yes)	0%	0%	—
Past preterm birth (% yes)	50%	11%	.058
Current preterm birth (% yes)	50%	11%	.068
Gestational age at birth (weeks)	38 (3)	39 (1)	.32
Neonatal birth weight (g)	2930 (997)	3322 (485)	.24

^aDepression scores were measured using the PHQ-9.

Differences in biomarkers by maltreatment group. Maltreatment groups significantly differed on levels of IL-15 ($F = 8.69$, $p = .008$), such that women with histories of childhood maltreatment produced significantly higher amounts of IL-15 compared to women without maltreatment histories. Groups did not significantly differ on TNF- α ($F = .58$, $p = .46$), IL-6 ($F = 2.76$, $p = .11$), or IL-1 β ($F = .60$, $p = .45$). See Figure 1. Groups did not significantly differ on HOMA-IR ($F = 1.57$, $p = .23$). Groups did not show statistically significant differences on maternal cortisol (all p values $> .14$), however women with maltreatment histories displayed lower cortisol concentrations across the day. See Figure 2.

Maltreatment and birth outcomes. Results revealed that women with maltreatment histories were marginally more likely to have a history of preterm delivery ($\chi^2 = 3.58$, $p = .06$) and were marginally more likely to deliver preterm in the current pregnancy ($\chi^2 = 3.33$, $p = .07$). No significant maltreatment group differences were observed for infant birth weight ($t = 1.20$, $p = .24$).

Mediation maltreatment and preterm birth. We performed logistic regression analyses to test if IL-15 levels mediated the association between maltreatment group and PTB status in the current pregnancy. The association between maltreatment and PTB fell below significance ($p = .49$) when IL-15 was included in the model, indicating that IL-15 partially explained the association between maltreatment history and PTB.

Discussion

Results from this pilot study revealed that women with histories of maltreatment (childhood sexual and physical abuse) displayed elevated levels of the pro-inflammatory cytokine IL-15. We also found that women with maltreatment histories were marginally more likely to

Figure 1. IL-15 values differ by childhood maltreatment group. Note. Standardized values are presented in the figure due to the different metrics of immune markers. Log-transformed values were included in analyses. Statistical analyses controlled for gestational age at venipuncture. * $p < .05$.

deliver preterm in the current and past pregnancies. Levels of IL-15 mediated the association between maltreatment group and preterm delivery of the current pregnancy. These results were not better explained by covariates that may have been associated with inflammatory markers, including body mass index. Women with maltreatment histories displayed lower levels of diurnal cortisol, although this did not reach statistical significance. Results from this study are consistent with prior studies of pregnant and non-pregnant samples demonstrating increased inflammatory parameters among those with maltreatment histories.^{4–6} Findings are also in line with past studies demonstrating adverse neonatal outcomes among women with maltreatment histories.^{11–14,16}

Women with maltreatment histories did not show differences in HOMA-IR compared with women without maltreatment histories. We did not find that women with maltreatment histories displayed significantly greater levels of IL-6, IL-1 β , and TNF- α as we hypothesized, however, levels were elevated in the maltreatment group compared to women without maltreatment, and we may have lacked the statistical power to show group differences for these markers.

Only two prior studies, to our knowledge, have examined associations between childhood maltreatment and immune markers in pregnancy. Walsh et al.²⁵ reported that the severity of abuse history (emotional, physical, and/or sexual abuse) among healthy pregnant adolescents interacted with high depressive symptoms to predict higher IL-6 (but not TNF- α) levels in second trimester. They also reported that cortisol mediated the association between IL-6 and shortened gestational length. Conversely, Blackmore and colleagues²⁶ reported that a lifetime trauma history (not restricted to childhood) was associated with elevated TNF- α (but not IL-6) levels in healthy adult pregnancies. However, psychiatric symptoms were not associated with cytokine production, and cytokine levels were not associated with birth outcomes. Findings from the current study are consistent with past research and extend this work by examining associations among women with gestational diabetes.

Women with maltreatment histories are at increased risk for adverse neonatal outcomes. Pathways explaining elevated risk are poorly understood. Hypothesized pathways include dysregulation of stress hormones including cortisol and inflammatory markers. A small number of past studies support these hypothesized pathways by demonstrating elevated pro-inflammatory cytokines^{25,26} and altered patterns of cortisol production^{18–20} among pregnant women with trauma histories. However, findings from past studies are somewhat mixed and limited to samples of pregnant women at low risk for adverse neonatal outcomes. This is the first study, to our knowledge, to show a link between maltreatment history and inflammatory cytokines among women diagnosed with GDM. Stress hormones are dysregulated among pregnant women with GDM; pregnant women

Figure 2. Diurnal cortisol patterns in pregnant women with and without maltreatment histories. Note. Raw cortisol values are presented in the figure. Log transformed values were included in analyses.

diagnosed with GDM exhibit higher cortisol concentrations and a higher homeostatic model assessment insulin resistance (HOMA-IR) compared to women with normal glucose tolerance in pregnancy.²⁷ Pregnant women with GDM also display a loss of natural variations of C-reactive protein, suggesting altered modulation of inflammation.²⁸ Maternal GDM may also be associated with elevated levels of IL-6^{29–31} and TNF- α .^{32,33} Given evidence that women with GDM display elevated inflammation compared to pregnant women without GDM, findings from this study indicate that women with maltreatment histories and GDM show even greater production of pro-inflammatory cytokines. More research is needed to further understand these associations.

Results from this pilot study are exploratory and should be interpreted in light of a number of limitations. The sample was small and did not include a comparison group of women without GDM. Past studies have reported elevated cytokine production in individuals with maltreatment histories and current depression. We were unable to examine this interaction in the current study given the lack of depressive symptoms reported. We did not ask women to report on any current trauma and therefore do not know if elevated cytokine levels could be driven by adult maltreatment. Future studies are needed using larger samples in order to further understand mechanisms to PTB among women with maltreatment histories with and without GDM.

Despite these limitations, results from this pilot study contribute to a growing body of research demonstrating that pregnant women with histories of childhood maltreatment display differences in regulation of physiological systems that place women at increased risk for adverse neonatal outcomes, specifically preterm birth. In particular, women with childhood maltreatment histories may produce greater pro-inflammatory cytokines and display dysregulation of HPA activity, two systems involved in the timing of parturition. This study was the first, to our knowledge, to extend these findings to a sample of women with GDM. Prior studies have excluded women with high-risk pregnancies from participating, and by doing so only assessed women who may display resilience to consequences of adversity in childhood. These study findings may not generalize to the general population of women with childhood maltreatment. More studies are needed that examine physiological links among childhood maltreatment and adverse neonatal outcomes among women with high-risk pregnancies. Results from future studies of high-risk pregnancies may lead to improved understanding and clinical management of pregnant women with maltreatment histories.

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Ethical approval

This study was approved by the Lifespan Hospital and Women and Infants Hospital Internal Review Boards.

Guarantor

MB

Contributorship

All authors contributed to, reviewed, and edited the manuscript and approved the final version.

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