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Psychosocial and behavioral factors affecting inflammation among pregnant African American women☆

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ABSTRACT

African American women are reported to have greater inflammation compared with women from other racial groups. Higher inflammation during pregnancy has been associated with increased risk of adverse perinatal outcomes. We hypothesized that maternal inflammation is related to depressive symptoms and social and behavioral risk factors among pregnant African American women. Pregnant African American women (n = 187) were recruited at prenatal clinics in the Midwest. Women completed questionnaires and had blood drawn at a prenatal visit. Plasma levels of cytokines (interferon gamma [IFN]-γ, interleukin [IL]-6, IL-8, IL-10, tumor necrosis factor [TNF]-α) and C-reactive protein (CRP) were measured by multiplex assays. Women had a mean age of 26.58±5.42 years and a mean gestational age at data collection of 16.35±5.95 weeks. Twenty-six percent of women had Center for Epidemiological Studies-Depression (CES-D) scores ≥23 (scores that have been correlated with clinical diagnosis of depression), 15.5% smoked cigarettes, 16.6% used marijuana, and 5.3% reported experiencing intimate partner violence (IPV). Higher CES-D scores were correlated with higher plasma CRP levels ($r = 0.16$, $p = 0.046$). Women who reported any experiences of IPV during pregnancy had higher levels of IL-8 ($p = 0.018$) and lower levels of IFN-γ ($p = 0.012$) compared with women who did not report IPV. Cigarette smoking during pregnancy was associated with lower levels of the anti-inflammatory cytokine IL-10 ($p = 0.003$). These findings suggest that depressive symptoms, IPV, and cigarette smoking during pregnancy relate to select inflammatory markers in pregnant African American women. The relationships of inflammation with these factors should be further investigated to better understand the mechanisms which influence maternal and fetal health outcomes.

1. Introduction

Inflammation is a natural immunological response to infection and injury which can be acute or chronic depending on the stimulus (Chen et al., 2018). Chronic low-grade systemic inflammation is reported to be associated with cardiovascular disease, hypertension, diabetes, chronic kidney diseases, and other chronic diseases (Chen et al., 2018; Furman et al., 2019). Studies have shown one's social environment and lifestyle can lead to the development of systemic low-grade chronic inflammation (Furman et al., 2019) which, in turn, is a risk factor for poor cardiovascular health and mortality (Mattina et al., 2019). Social and environmental stressors can activate the stress response, where production of cortisol is increased by activation of the hypothalamic-pituitary-adrenal (HPA) axis; this activation often results in plasma elevation of proinflammatory cytokines that include interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α). In turn, IL-6 signals for the release of the acute phase protein C-reactive protein (CRP) from the liver (Black and Garbutt, 2002; Sproston and Ashworth, 2018). Interleukin-10 (IL-10) contributes to the downregulation of this inflammatory response (Black and Garbutt, 2002). Elevated systemic

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inflammation during pregnancy can be harmful not only for the mother but also for the fetus, and has been associated with the development of immune system dysfunction in the offspring (Goldstein et al., 2020; Han et al., 2021). The maladaptive response of the maternal immune system has been associated with pre-eclampsia and preterm birth (<37 completed weeks gestation) (Sawyer, 2021). Social and environmental stressors and maternal inflammation are linked to the developmental programming of the offspring which may lead to neurodevelopmental disorders later in life (Han et al., 2021). In a recent Danish study, higher CRP levels in mothers at 24 weeks gestation were correlated with higher CRP levels in babies at 6 months of age (Fink et al., 2019).

The regulation of cytokines during pregnancy is a critical and complex mechanism (Chatterjee et al., 2014). A mother's immune system plays an important role during embryo implantation, placental and fetal development, and during birth. An innate immune response in the first trimester of pregnancy is followed by a period of relatively lower inflammation during the second trimester. Later in pregnancy, inflammation is involved in the onset of labor (Shynlova et al., 2013). The duration of gestation can be influenced by both the social environment and stressors during pregnancy (Schminkey and Groer, 2014). Studies have shown a relationship between higher stress and depressive symptoms, preterm birth, pregnancy complications, and low birth weight infants (<2500 g) (Hobel et al., 2008; Lalani et al., 2021; Sanchez et al., 2013).

Approximately 12% of women experience depressive symptoms during pregnancy (Centers for Disease Control and Prevention, 2020a). Studies have shown that pregnant African American (AA) women report higher levels of depressive symptoms compared to other ethnicities/races (Mukherjee et al., 2016). Importantly, predictors of depression among pregnant AA women may differ compared to pregnant White women (Mukherjee et al., 2016). In a systematic review, parity, perceived stress and low self-esteem significantly predicted antenatal depression among AA women, while less satisfaction with social support predicted depression among White women (Mukherjee et al., 2016). Evidence supporting the link between depression and peripheral proinflammatory mediators is growing (Benedetti et al., 2020; Majd et al., 2020), including the bi-directional relationship between negative moods and inflammation (Leonard and Maes, 2012; Messay et al., 2012). Researchers have reported depressive symptoms are associated with increased systemic inflammation among pregnant AA women (Cassidy-Bushrow et al., 2012). Pregnant AA women are more likely to have greater systemic inflammation compared with non-Hispanic White women (Blackmore et al., 2014). The occurrence of both depressive symptoms and systemic inflammation together are similarly reported to be associated with adverse birth outcomes (e.g., preterm birth, low birth weight) (Giurgescu et al., 2015; Nazzari et al., 2019).

Intimate partner violence (IPV) is one of the social environment risk factors affecting maternal physical and mental health. IPV is defined as abuse, threatened or attempted, or aggression that occurs in a romantic relationship. IPV includes stalking, physical violence, sexual violence, psychological violence by a current or former intimate partner (Breiding et al., 2015). IPV can result in physical injury and mental health problems such as depression (Centers for Disease Control and Prevention, 2020b). AA women are at a significantly higher risk for being exposed to IPV (Holliday et al., 2017) and maternal IPV has been associated with increased risk of preterm birth (Donovan et al., 2016). Individuals who reported experiencing IPV during their lifetime were more likely to also report adverse health conditions and health risk behaviors (Black, 2011; Stockman et al., 2015). For example, women who reported IPV were more likely to report cardiovascular disease, asthma, smoking, and heavy alcohol use (Stockman et al., 2015). Pregnant women who experience IPV often report increased use of smoking or substance use compared with women who do not experience IPV (Alhusen et al., 2013). Holden and colleagues (Holden et al., 2012) found a positive relationship between depressive symptoms, self-reported violence, and history of alcohol and/or drug use during pregnancy among an ethnically diverse cohort. Pregnancy may represent a period of heightened vulnerability to IPV which could negatively impact maternal and fetal health (Alhusen et al., 2013). Pregnant women who experience IPV often report increased use of smoking or substance use compared with women who do not experience IPV (Alhusen et al., 2013). The factors related to IPV and its consequences may place women at higher risk for altered immune and inflammatory processes (Heath et al., 2013) which in turn may increase the risk for preterm birth.

Better understanding the relationship between inflammation and individual risk factors including depressive symptoms, IPV, and behavioral risk factors (e.g., cigarette smoking or substance use) for poor birth outcomes (e.g. preterm birth, low birthweight, infant mortality) may lead to effective approaches that improve outcomes for women and their infants. In recent reports, the association of IPV before pregnancy with substance use during pregnancy was found to be mediated through perceived stress in AA women (Zhang et al., 2021) and maternal stress was reported to increase peripheral inflammatory markers during pregnancy (Coussons-Read et al., 2007; Hantsoo et al., 2019). The relationship between individual social and behavioral risk factors and inflammation during pregnancy needs further investigation to better understand the mechanisms by which maternal and fetal health could be impacted. Here, we investigated plasma C-reactive protein (CRP) as a marker of systemic inflammation and other inflammatory markers (pro-inflammatory cytokines interferon [IFN]-γ, tumor necrosis factor [TNF]-α, IL-6, IL-8, and the anti-inflammatory cytokine IL-10) to study the association of these factors with inflammation during pregnancy. We hypothesized that the depressive symptoms, IPV and substance use during pregnancy are related to higher levels of inflammation during pregnancy among AA women (see Fig. 1).

2. Methods

Design and sample. The data reported here were collected as part of the Biosocial Impact on Black Births (BIBB) study. BIBB is a prospective cohort study that examines the role of maternal factors on birth outcomes among AA women. Pregnant AA women (n = 187) were recruited at prenatal clinics in the Midwest (Detroit, Michigan and Columbus, Ohio). Pregnant women were eligible for the study if they met the following criteria: (a) self-identify as African American or Black: (b) were at least 18 years of age; (c) had a singleton pregnancy; (d) were of any parity; and (e) were English speaking. Women were excluded if they had a multiple gestation pregnancy (e.g., twins) or were <18 years of age (due to psychological issues related to teenage pregnancy). Women >45 years of age were excluded due to the lower fertility rates, higher risk for miscarriages and fetal abnormalities that occur with this age group.

Procedures. The study was approved by the Institutional Review Boards (IRB) at the participating universities and clinical sites. Women were approached by the research staff before or after the regular prenatal visits during normal clinic office hours. Women who agreed to participate in the study completed an informed consent process. The participants completed a survey on a tablet including questionnaires about depressive symptoms, IPV, and smoking and substance use during pregnancy.

Blood sample collection and processing. Participant's venous blood (unfasted) was drawn into a sterile 6 mL EDTA tube through antecubital venipuncture (within 30 s) by a certified medical assistant from the participating clinical sites according to the approved protocol. The blood samples were kept on ice or in a refrigerator until processing and were centrifuged (1600 g × 15 min at 4 °C) within 2 h of collection. Plasma aliquots were collected (~0.5 cc/aliquot) from supernatant and stored at −20 °C at the prenatal clinic. At the end of each day, samples were transferred to −80 °C alarm temperature monitored freezers where they were stored until analysis. The women were reimbursed $30 for their participation.

2.1. Measures

Inflammatory markers. Pro- (IL-6, IL-8, TNF-α, IFN-γ) and anti- (IL-

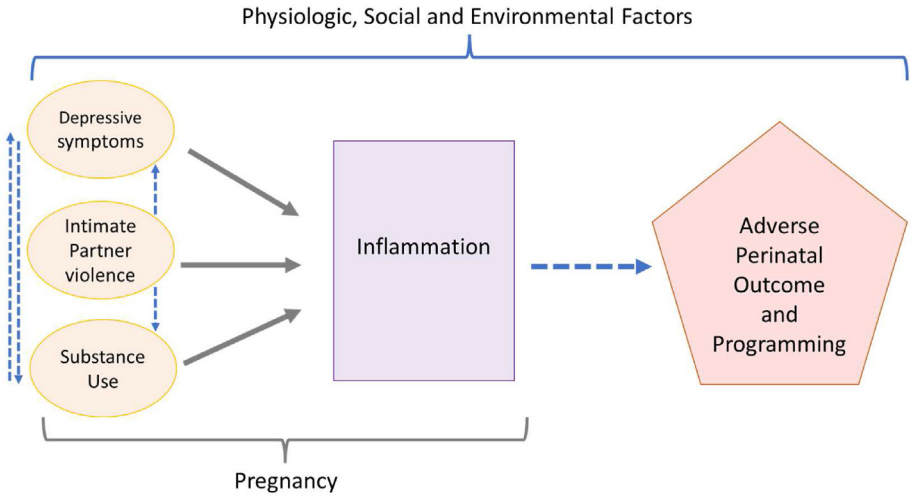

Fig. 1. Association of depressive symptoms, IPV, and substance use with inflammation during pregnancy. Blue lines represent relationships not investigated in this study but reported elsewhere.

10) inflammatory cytokines were measured using V-plex multiplex assays (Meso Diagnostics, Rockville MD). Multiplex assays provide simultaneous quantitative analysis of these cytokines and reduces the amount of sample which is needed. CRP was assessed in a separate assay from cytokines. The minimum detection limit for these assays was ≤0.06 pg/mL for each cytokine and 1.33 ng/mL for CRP. All samples were run in duplicate. Sample pairs with coefficients of variation (CVs) greater than 15% were rerun. For cytokines, the intra-assay and inter-assay coefficient ranges were 2.7–5.0% and 5.0–10.1%, respectively. For CRP, the intra-assay and inter-assay coefficient ranges were 2.3–4.1%, and 6.7–9.9%, respectively. Values below the minimum detection limit were treated as missing data.

Depressive symptoms. The Center for Epidemiological Studies-Depression Scale (CES-D) is a 20-items scale that assesses depressive symptoms experienced within the past seven days (Radloff, 1977). The details of this measure have previously been reported (Dove-Medows et al., 2020). The score ranges from 0 to 60 with higher scores indicating a greater number and/or severity of symptoms. CES-D scores ≥23 have been correlated with major clinical depression diagnosis (Orr et al., 2002).

Smoking and substance use during pregnancy. Participants were asked in the survey if they smoked cigarettes, used alcohol, used tobacco and/or marijuana, or used any other drugs not prescribed by a doctor during pregnancy. If participants answered yes to these behaviors these responses were coded as "1", otherwise responses were coded as "0".

Intimate partner violence (IPV). IPV was assessed using one question: "While you are pregnant this time, has your husband or partner hit, pushed, slapped, kicked, choked, or threatened your safety in any other way?". IPV is a binary variable that was coded as yes = "1" and no = "0".

Sociodemographic characteristics. Socio-demographic characteristics (age, education, employment status and household annual income) were measured by self-report.

Statistical analysis. Statistical analyses were performed on IBM SPSS Statistics for Windows (Version 26.0. Armonk, NY: IBM Corp). The inflammatory markers data (pg/ml) were log-10 transformed; a log(x+1) formula was used for easier interpretation as many values were below one. A test for normal distribution of each of the six cytokines was performed. Outliers were identified and removed based on the standardized value (Z-score) and Kolmogorov-Smirnova significance ($p < 0.05$) of test of normality (Ghasemi and Zahediasl, 2012). Descriptive statistical analyses were conducted. The differences of mean values (of six cytokines with log(x+1) transformation) between the categories of predicting variables were examined using *t*-test/ANOVA (Table 1). Values of inflammatory markers below the minimum detection limit were treated as missing data; these values were not used in analysis. An average of 9% of outliers were removed: IFN- γ (9%), IL-6 (8%), IL-8 (1%), IL-10 (29%), TNF-α (1%), CRP (8%). Missing data of demographic factors including gestational age (1.6%), education (2.7%), income (4.3%), and employment status (2.1%) in our sample were under 5% on average. Listwise deletion techniques were used to handle these missing data. Pearson correlation analyses were conducted to relate CES-D scores with each cytokine level (Table 2) as all were continuous variables. Multiple linear regression analysis models were performed (Supplementary data) to examine the associations with depressive symptoms, experience of IPV during pregnancy, substance use, and levels of inflammatory markers. If a variable listed in Table 1 or Table 2 showing a statistically significant association with any of the six inflammatory markers in the bivariate analysis, it was included in multiple regression models; predictors were CES-D, IPV, and cigarette smoking and marijuana; covariates were age, education, and household income. A p-value < 0.05 was set as significance; 95% confidence intervals for the differences in the means were calculated.

3. Results

Women had a mean age of 26.58 ± 5.42 years and a mean gestational age at data collection of 16.35 ± 5.95 weeks. More than half of the 102 women (55.7%) were employed, 62 women (34.1%) had higher than high school education and 76 women (42.5%) reported an annual household income < $10,000. Forty-seven women (26.3%) had CES-D scores ≥23 indicating major depression (Orr et al., 2006). During pregnancy, 10 women (5.3%) reported IPV, 29 women (15.5%) reported smoking cigarettes, 5 women (2.7%) used alcohol, 31 women (16.6%) used marijuana, and 5 women (2.7%) used any other drugs (e.g., cocaine) that were not prescribed by a physician (see Table 1).

3.1. Depressive symptoms during pregnancy related to higher CRP

Higher CES-D scores were correlated with higher plasma CRP levels ($r = 0.16$, $p = 0.046$) (see Table 2). Multiple linear regression analysis indicated that CES-D scores were significantly positively associated with CRP levels (B = 0.01, 95% CI = 0.00–0.02, $p = 0.006$) after controlling for IPV, maternal age, education, household annual income, and cigarette smoking and marijuana use (see Model 1 in Table 3).

This is consistent with the trend observed in Table 1 where higher CRP levels were related to higher CES-D scores [≥23 related to major depression diagnosis (Orr et al., 2006)] compared to those who reported lower CES-D scores (<23 $p = 0.12$, Table 1).

Table 1
Maternal factors and their associations with inflammatory markers.

Maternal factors	N (%)	Mean and standard deviation of inflammatory markers (log10 (x+1) transformation) ‡					
		IFN-γ (n = 169)	IL-6 (n = 172)	IL-8 (n = 185)	IL-10 (n = 132)	TNF-α (n = 186)	CRP (n = 168)
		pg/ml (log10 x+1)	pg/ml (log10 x+1)	pg/ml (log10 x+1)	pg/ml (log10 x+1)	pg/ml (log10 x+1)	mg/L (log10 x+1)
Total	187	2.04 (0.46 ± 0.15)	0.67 (0.21 ± 0.08)	1.62 (0.38 ± 0.17)	0.17 (0.07 ± 0.02)	1.15 (0.33 ± 0.07)	0.0120 (6.92 ± 0.40)
Gestational age at data collection (week), mean ± SD	16.35 ± 5.95						
8–12 weeks	67 (36.4)	2.12 (0.47 ± 0.14)	0.70 (0.23 ± 0.06)	1.84 (0.39 ± 0.16)	0.17 (0.07 ± 0.02)	1.15 (0.33 ± 0.07)	0.0140 (6.97 ± 0.41)
13–29 weeks	117 (63.6)	2.00 (0.45 ± 0.15)	0.65 (0.21 ± 0.09)	1.78 (0.38 ± 0.17)	0.18 (0.07 ± 0.02)	1.15 (0.33 ± 0.06)	0.0111 (6.90 ± 0.39)
p-value		0.345	0.131	0.817	0.344	0.783	0.241
95% CI for the difference in the means		−0.02, 0.07	−0.01, 0.04	−0.04, 0.06	−0.01, 0.00	−0.02, 0.02	−0.05, 0.20
Age (years), mean ± SD	26.58 ± 5.42						
18-24 years	74 (39.6)	1.94 (0.44 ± 0.14)	0.65 (0.21 ± 0.09)	1.37 (0.35 ± 0.14)	0.18 (0.07 ± 0.02)	1.17 (0.33 ± 0.06)	0.0106 (6.85 ± 0.41)
≥ 25 years	113 (60.4)	2.11 (0.47 ± 0.15)	0.67 (0.22 ± 0.08)	1.79 (0.40 ± 0.18)	0.17 (0.07 ± 0.02)	1.13 (0.32 ± 0.07)	0.0129 (6.96 ± 0.39)
p-value		0.360	0.0561	**0.021**	0.332	0.419	0.083
95% CI for the difference in the means		−0.07, 0.02	−0.03, −0.02	**−0.10, −0.01**	0.00, 0.01	−0.01, 0.03	−0.23, 0.01
Education†							
< High school	26 (14.3)	1.65 (0.41 ± 0.12)	0.57 (0.19 ± 0.08)	1.53 (0.33 ± 0.20)	0.14 (0.06 ± 0.02)	1.07 (0.31 ± 0.05)	0.0101 (6.83 ± 0.41)
High school/GED	94 (51.6)	2.03 (0.46 ± 0.13)	0.65 (0.21 ± 0.07)	1.60 (0.39 ± 0.15)	0.18 (0.07 ± 0.02)	1.14 (0.33 ± 0.06)	0.0120 (6.92 ± 0.39)
> High school	62 (34.1)	2.30 (0.48 ± 0.18)	0.74 (0.23 ± 0.09)	1.74 (0.40 ± 0.18)	0.18 (0.07 ± 0.02)	1.20 (0.34 ± 0.08)	0.0136 (6.98 ± 0.40)
p-value		0.119	0.063	0.241	**0.030**	0.362	0.299
95% CI for the difference in the means£		−0.16, 0.01	−0.09, 0.00	−0.16, 0.03	**0.00, 0.03**	−0.06, 0.02	−0.39, 0.09
Employment status							
Not working	81 (44.3)	2.05 (0.46 ± 0.13)	0.70 (0.22 ± 0.08)	1.67 (0.38 ± 0.17)	0.17 (0.07 ± 0.02)	1.13 (0.32 ± 0.06)	0.0135 (6.96 ± 0.42)
Working	102 (55.7)	2.08 (0.46 ± 0.16)	0.65 (0.21 ± 0.08)	1.60 (0.38 ± 0.16)	0.17 (0.07 ± 0.02)	1.16 (0.33 ± 0.07)	0.0112 (6.90 ± 0.38)
p-value		0.807	0.245	0.871	0.836	0.567	0.367
95% CI for the difference in the means		−0.04, 0.05	−0.01, 0.04	−0.05, 0.05	−0.01, 0.01	−0.03, 0.01	−0.07, 0.18
Household annual income†							
< $10,000	76 (42.5)	2.01 (0.46 ± 0.14)	0.67 (0.22 ± 0.08)	1.72 (0.39 ± 0.17)	0.17 (0.07 ± 0.02)	1.20 (0.34 ± 0.07)	0.0129 (6.96 ± 0.38)
$10,000-$19,999	32 (17.9)	2.10 (0.47 ± 0.13)	0.64 (0.21 ± 0.08)	1.42 (0.36 ± 0.15)	0.18 (0.07 ± 0.02)	0.98 (0.29 ± 0.06)	0.0095 (6.81 ± 0.42)
$20,000-$29,999	32 (17.9)	2.02 (0.45 ± 0.16)	0.73 (0.23 ± 0.09)	1.82 (0.42 ± 0.17)	0.15 (0.06 ± 0.02)	1.18 (0.33 ± 0.07)	0.0152 (7.06 ± 0.38)
$30,000-$39,000	22 (12.3)	1.93 (0.44 ± 0.15)	0.67 (0.22 ± 0.08)	1.58 (0.37 ± 0.19)	0.19 (0.08 ± 0.02)	1.15 (0.33 ± 0.06)	0.0114 (6.91 ± 0.39)
≥ $40,000	17 (9.5)	2.39 (0.48 ± 0.20)	0.64 (0.21 ± 0.08)	1.42 (0.35 ± 0.16)	0.18 (0.07 ± 0.02)	1.16 (0.33 ± 0.07)	0.0094 (6.82 ± 0.36)
p-value		0.886	0.883	0.581	0.424	**0.030**	0.122
95% CI for the difference in the means§		−0.11, 0.08	−0.04, 0.06	−0.07, 0.14	−0.02, 0.01	**0.01, 0.08**	−0.09, 0.40
Depressive symptoms							
CES-D score <23	132 (73.7)	2.09 (0.46 ± 0.15)	0.67 (0.21 ± 0.08)	1.55 (0.37 ± 0.16)	0.18 (0.07 ± 0.02)	1.14 (0.32 ± 0.07)	0.0115 (6.90 ± 0.41)
CES-D score ≥23	47 (26.3)	2.02 (0.45 ± 0.15)	0.69 (0.22 ± 0.09)	1.82 (0.40 ± 0.19)	0.16 (0.07 ± 0.02)	1.18 (0.33 ± 0.06)	0.0139 (7.01 ± 0.37)
p-value		0.631	0.767	0.424	0.417	0.376	0.121
95% CI for the difference in the means		−0.04, 0.07	−0.03, 0.02	−0.08, 0.03	−0.01, 0.01	−0.03, 0.01	−0.25, 0.03
Cigarette smoking							
Yes	29 (15.5)	1.88 (0.43 ± 0.17)	0.58 (0.19 ± 0.09)	1.86 (0.39 ± 0.20)	0.14 (0.06 ± 0.02)	1.15 (0.32 ± 0.05)	0.0095 (6.87 ± 0.33)
No	158 (84.5)	2.07 (0.46 ± 0.14)	0.68 (0.22 ± 0.08)	1.58 (0.38 ± 0.16)	0.18 (0.07 ± 0.02)	1.12 (0.33 ± 0.07)	0.0125 (6.93 ± 0.41)
p-value		0.229	0.096	0.701	**0.003**	0.811	0.491
95% CI for the difference in the means		−0.02, 0.10	−0.01, 0.06	−0.08, 0.05	**0.01, 0.02**	−0.02, 0.03	−0.11, 0.22
Alcohol use							
Yes	5 (2.7)	2.50 (0.47 ± 0.27)	0.47 (0.17 ± 0.04)	1.69 (0.39 ± 0.21)	0.17 (0.07 ± 0.02)	1.15 (0.35 ± 0.09)	0.0073 (6.83 ± 0.18)
No	182 (97.3)	2.03 (0.46 ± 0.15)	0.67 (0.22 ± 0.08)	1.62 (0.38 ± 0.17)	0.17 (0.07 ± 0.02)	1.27 (0.33 ± 0.07)	0.0122 (6.92 ± 0.40)
p-value		0.179	0.918	0.965	0.490	0.614	0.806
95% CI for the difference in the means		−0.02, 0.12	−0.16, 0.14	−0.02, 0.02	−0.08, 0.04	−0.27, 0.45	−0.17, 0.13
Marijuana use							
Yes	31 (16.6)	1.96 (0.44 ± 0.17)	0.58 (0.19 ± 0.09)	1.71 (0.37 ± 0.19)	0.14 (0.06 ± 0.02)	1.15 (0.32 ± 0.08)	0.0106 (6.88 ± 0.37)
No	156 (83.4)	2.06 (0.46 ± 0.14)	0.68 (0.22 ± 0.08)	1.60 (0.38 ± 0.16)	0.18 (0.07 ± 0.02)	1.14 (0.33 ± 0.06)	0.0123 (6.93 ± 0.40)
p-value		0.412	0.057	0.795	**0.008**	0.770	0.570
95% CI for the difference in the means		−0.04, 0.08	0.00, 0.06	−0.06, 0.07	**0.00, 0.02**	−0.02, 0.03	−0.12, 0.22
Other drugs (e.g., cocaine) use							
Yes	5 (2.7)	1.46 (0.36 ± 0.19)	0.65 (0.20 ± 0.13)	3.42 (0.46 ± 0.39)	0.16 (0.06 ± 0.01)	1.15 (0.34 ± 0.04)	0.0068 (6.80 ± 0.20)
No	182 (97.3)	2.06 (0.46 ± 0.15)	0.67 (0.21 ± 0.08)	1.57 (0.38 ± 0.16)	0.17 (0.07 ± 0.02)	1.19 (0.33 ± 0.07)	0.0122 (6.92 ± 0.40)
p-value		0.138	0.703	0.275	0.719	0.686	0.535
95% CI for the difference in the means		−0.03, 0.23	−0.06, 0.09	−0.23, 0.07	−0.02, 0.02	−0.07, 0.05	−0.27, 0.52
Experienced intimate partner violence							
Yes	10 (5.3)	1.25 (0.33 ± 0.16)	0.67 (0.21 ± 0.09)	2.43 (0.50 ± 0.18)	0.19 (0.07 ± 0.02)	1.14 (0.35 ± 0.06)	0.0122 (6.94 ± 0.39)

(*continued on next page*)

Table 1 (*continued*)

Maternal factors	N (%)	Mean and standard deviation of inflammatory markers (log10 (x+1) transformation) ‡					
		IFN-γ (n = 169)	IL-6 (n = 172)	IL-8 (n = 185)	IL-10 (n = 132)	TNF-α (n = 186)	CRP (n = 168)
		pg/ml (log10 x+1)	pg/ml (log10 x+1)	pg/ml (log10 x+1)	pg/ml (log10 x+1)	pg/ml (log10 x+1)	mg/L (log10 x+1)
No	177 (94.7)	2.08 (0.46 ± 0.15)	0.67 (0.21 ± 0.08)	1.57 (0.37 ± 0.16)	0.17 (0.07 ± 0.02)	1.26 (0.33 ± 0.07)	0.0120 (6.92 ± 0.40)
p-value		**0.012**	0.979	**0.018**	0.447	0.272	0.872
95% CI for the difference in the means		**0.03, 0.24**	−0.05, 0.05	**−0.23, -0.02**	−0.02, 0.01	−0.07, 0.02	−0.28, 0.24

Note: P-value and 95%CI are bolded if the associations showing the statistical significance. SD = standard deviation. CI = confidence interval. ‡The means of the original values and log10(x+1) transformation values ± SD for six inflammatory markers are provided. The numbers in parentheses are mean ± SD of log10(x+1) transformation data). The Independent Sample *t*-test was performed using log10(x+1) transformation data. †ANOVA. £Post Hoc Bonferroni comparison between <High school and >High school (other categories for post hoc group comparison did not show significance). §Post Hoc Bonferroni comparison between <$10,000 and $10,000-$19,999 (other categories for post hoc group comparison did not show significance). The age variable was dichotomized based on WHO definition for youth (15–24 years)-https://www.un.org/esa/socdev/documents/youth/fact-sheets/youth-definition.pdf.

Table 2
Correlation analysis for depressive symptoms and inflammatory markers.

	1.CES-D	2. IFN-γ	3. IL-6	4. IL-8	5. IL-10	6. TNF-α	7.CRP
1. CES-D	1						
2. IFN-γ	−0.07 (.385)	1					
3. IL-6	0.03 (.752)	0.27 (.001)	1				
4. IL-8	0.05 (.475)	0.01 (.859)	0.25 (.001)	1			
5. IL-10	−0.16 (.072)	0.23 (.010)	0.18 (.044)	0.08 (.395)	1		
6. TNF-α	0.07 (.361)	0.23 (.002)	0.15 (.050)	0.20 (.007)	0.24 (.006)	1	
7. CRP	**0.16 (.046)**	0.10 (.245)	0.56 (.000)	0.20 (.011)	0.14 (.130)	0.25 (.001)	1

Note: Numbers in parentheses are p-values.
Log10(x+1) transformation values were used for these models.
CES-D score = a composite score of 20 summed items of depressive symptoms.

Table 3
Adjusted regression analysis models of inflammatory markers.

Model	Predictor	Inflammation marker	Unstandardized regression coefficient	(95% confidence interval)	*p*
Model 1δ	CES-D score	CRP	0.01	(0.00, 0.02)	0.006
Model 2∞	IPV	IL-8	0.12	(0.01, 0.24)	0.030
Model 3φ	IPV	IFN-γ	−0.13	(-0.25, −0.02)	0.019
Model 4ϖ	Cigarette smoking	IL-10	−0.01	(-0.02, −0.00)	0.092

Note: log(x+1) scores were used for these models. IPV=intimate partner violence.
δ Covariates were maternal age, education, household income, IPV, cigarette smoking, marijuana.
∞ Covariates were maternal age, education, household income, CES-D, cigarette smoking, marijuana.
φ Covariates were maternal age, education, household income, CES-D, cigarette smoking, marijuana.
ϖ Covariates were maternal age, education, household income, CES-D, IPV, marijuana.

3.2. Intimate partner violence during pregnancy related to higher IL-8 and lower IFN-γ

Women who reported IPV during pregnancy had higher levels of IL-8 ($p = 0.018$) and lower levels of IFN-γ ($p = 0.012$) compared with women who did not report IPV (see Table 1). Multiple regression showed that IPV during pregnancy was positively associated with IL-8 (B = 0.12, 95% CI = 0.01–0.24, $p = 0.030$) and negatively associated with IFN-γ (B = −0.13, 95% CI = −0.25 - −0.02, $p = 0.019$) after controlling for maternal age, education, household income, CES-D, cigarette smoking, and marijuana (see Model 2 and Model 3 in Table 3).

3.3. Smoking during pregnancy related to lower IL-10

Women who reported cigarette smoking and marijuana use had lower levels of plasma IL-10 compared with women who did not report cigarette smoking ($p = 0.003$) or marijuana use ($p = 0.008$) (see Table 1). Multiple regression analysis showed that after controlling for maternal age, education, household income, CES-D scores, and IPV only cigarette smoking showed a negative trend with IL-10 (B = −0.01, 95% CI = −0.02 to −0.00, $p = 0.092$) (see Model 4 in Table 3).

The associations of education and household income with inflammatory markers were confounded by other psychosocial factors. Women who had lower than high school education had lower levels of IL-10 compared to women who had higher than high school education ($p = 0.030$, Table 1). In a multiple linear regression model that included covariates of maternal age, income, CES-D, IPV, cigarette smoking and marijuana, significance was not observed for education (Supplementary Table 4). Household income <$10,000 was found to be related to higher levels of TNF-α compared to the group with income between $10,000 and $19,000 ($p = 0.030$, Table 1). However, in the multiple linear regression model that included covariates of maternal age, education, CES-D, IPV, cigarette smoking and marijuana, no significance was observed (Supplementary Table 5).

4. Discussion

This study examined the association of depressive symptoms, intimate partner violence, and substance use with markers of inflammation among pregnant AA women. Approximately 26% of women in our cohort reported CES-D scores ≥23, a cut-off that has been related to major clinical depression (Orr et al., 2006). This proportion of CES-D scores ≥23 was similar to that found in other studies with pregnant AA women (20% and 27%, respectively) (Giurgescu et al., 2017; Wilusz et al., 2014). In this study, higher levels of depressive symptoms were associated to higher levels of plasma CRP, a marker of systemic inflammation (Karadag et al., 2008; Luan and Yao, 2018). Other researchers have reported depressive symptoms related to maternal systemic inflammation among

AA women (Cassidy-Bushrow et al., 2012), in that study CES-D was not found to be related to CRP (Cassidy-Bushrow et al., 2012): however other researchers have reported an association of depressive symptoms with inflammatory markers including CRP in early and mid-gestation among pregnant women from diverse racial/ethnic groups (Azar and Mercer, 2013; Elovainio et al., 2006; Mwendwa et al., 2013). Further investigation into the relationship between depressive symptoms and CRP are needed to gain mechanistic insight of the effects of depressive symptoms on pregnancy and perinatal outcomes among AA women.

It is clear based on the literature that a healthy immune system is important to maintain a healthy pregnancy and there is an important role of the innate immune system in controlling complex immunomodulation that occurs in pregnancy (Leff-Gelman et al., 2016). Neuroinflammation is a well-accepted possible etiology of major depression that may contribute to the development of perinatal depression (Leff-Gelman et al., 2016). The increased number of natural immune cells increases the expression of cytokines that protect the pregnancy, at least initially (Leff-Gelman et al., 2016), and the genes related to inflammation can also be upregulated by maternal psychosocial stressors (Christian, 2020), such as exposure to IPV. It is unclear whether inflammation occurs first and causes depression which, in turn, increases the risk for preterm birth but multiple studies have shown these associations (Christian, 2020). More insight is needed into the biological pathway(s) that link(s) depression and inflammation with adverse pregnancy outcomes such as preterm birth. A critical factor in AA pregnant women is their exposure to structural racism and how that may contribute to depressive symptoms (Shenassa et al., 2021). Depression during pregnancy can lead to adverse perinatal outcomes and has been related to pregnancy complications, increased substance use, inadequate weight gain, and preterm birth (Giurgescu et al., 2015; Marcus, 2009; Vlenterie et al., 2021). Lower birth weight, reduced Apgar scores, and smaller head circumference have also been reported in babies exposed to maternal depression during pregnancy (Giurgescu et al., 2015; Marcus, 2009). Therefore, adequately screening and treating AA pregnant women for depression throughout pregnancy may be a critical intervention for preventing adverse birth outcomes. With the advancement of screening and assessment tools, women can be identified and diagnosed for depression early in prenatal care. However, screening tools alone are insufficient to substantially increase the overall proportion of women who receive treatment for depression (Marcus, 2009). Moreover, Black women have been reported to be less likely to initiate mental health care postpartum, or to receive follow-up treatment or continued care when they do initiate care, compared to white women (Kozhimannil et al., 2011). Black women experience systemic oppression and unequal treatment contributing to healthcare access disparities (Chinn et al., 2021). Exposure to chronic stressors including racism increases the risk for mental health problems and negatively affects reproductive health (Chinn et al., 2021). Healthcare providers should screen and encourage pregnant women to participate in programs and treatment options for depressive symptoms during pregnancy. Women who are encouraged during pregnancy to seek treatment by their health providers are more likely to take advantage of available treatment options (Marcus, 2009).

An important social risk factor associated with inflammation examined in our study was IPV in pregnancy. We previously reported that 7.6% of the women in our pregnant AA women cohort reported IPV in the 12 months *before* pregnancy (Zhang et al., 2021). Here, we found that a slightly lower proportion (5.3%) of women in our study reported IPV *during* pregnancy. Despite its low prevalence, we found that IPV was significantly associated with inflammatory markers suggesting the effects of IPV exposure were strong. Specifically, IPV during pregnancy was related to higher levels of plasma IL-8 and lower levels of plasma IFN-γ. IL-8 is involved in tissue repair and infection as a chemokine by attracting and activating neutrophils, basophils, and T-cells to the site of inflammation; studies have shown heightened IL-8 in diseases like rheumatoid arthritis, cancer, inflammatory bowel disease and psoriasis (Grimm et al., 1996; Schroder et al., 1992; Seitz et al., 1991; Skov et al., 2008). This chemokine is released in response to inflammation by a variety of cell types in the kidney, intestine, and placenta. Importantly, elevated levels of IL-8 have been associated with an increased risk of preterm birth in a recent study (Sullivan et al., 2020). In a cohort of pregnant women in the second trimester, higher levels of IL-8 mediated the relationship between poor sleep quality and lower gestational age at birth in AA women only (Blair et al., 2015). The authors concluded that elevated IL-8 was associated with an increased risk of preterm birth specifically in AA women (Blair et al., 2015). In addition, elevated maternal serum levels of IL-8, TNF-α, and IL-6 have been related to preeclampsia (Tosun et al., 2010), and elevated IL-8 and TNF-α have been related to the severity of preeclampsia and intrauterine growth restriction (Tosun et al., 2010).

We also observed that IPV during pregnancy was associated with lower levels of IFN-γ, which plays a critical role in maintaining healthy pregnancy (Murphy et al., 2009). Due to the complex relationship of IFN-γ with the pregnancy timeline, it is very important to maintain appropriate levels of IFN-γ during pregnancy (Murphy et al., 2009; Reyes-Lagos et al., 2017). A similar negative association of IFN-γ was recently reported in a study of post-traumatic stress disorder (PTSD) (Michopoulos et al., 2020), with lower levels of IFN-γ evident in the PTSD group. IPV is a traumatic stress factor and can be associated with a higher risk of developing PTSD; lower levels of IFN-γ may relate to a compensatory response to the experience of IPV (Michopoulos et al., 2020). IPV during pregnancy has been related to many pregnancy complications (e.g., anemia, infection, lower weight gain during pregnancy, placental abruption) and adverse perinatal outcomes (e.g., low birth weight infants, fetal injury, preterm birth, stillbirth) (Berhanie et al., 2019; Donovan et al., 2016; McFARLANE & WUST, 1996; Parker et al., 1994). In data from 118,579 participants from 26 US states (2000–2003, Pregnancy Risk Assessment Monitoring System), IPV before and during pregnancy was related to multiple pregnancy complications (high blood pressure/edema, vaginal bleeding, nausea vomiting or dehydration, kidney/urinary tract infections for the mother; preterm birth, low birth weight, and the requirement of intensive care unit for the infant) (Silverman et al., 2006). The present results suggest that IPV may be contributing to a heightened and altered inflammatory environment as evidenced in higher levels of plasma IL-8 and lower levels of IFN-γ levels; as discussed above, these associations may increase the risk for adverse pregnancy outcomes.

In our cohort, 15.5% of women smoked cigarettes. Smoking during pregnancy is related to increased risk of pregnancy complications including miscarriage, low birth weight infants, and preterm birth (CDC, the Surgeon General's report "Highlights: Overview of Findings Regarding Reproductive Health"). In the present study, cigarette smoking during pregnancy was associated with lower levels of plasma IL-10, and less than high school education was also found to be associated with lower levels of IL 10. This can be partially explained by the reports of the high prevalence of smoking in pregnant women with high school and less than high school education compared to women with more than high school education (Azagba et al., 2020; Tong et al., 2013). IL-10 is an anti-inflammatory cytokine and regulates the balance of immune response to antigens; this is especially important during pregnancy in building tolerance to fetal antigens (Mobini et al., 2016). IL-10 plays an important role in normal pregnancy and its dysregulation can result in pregnancy complications including preterm labor (Mobini et al., 2016). IL-10 levels increase early during pregnancy and remain elevated until the third trimester before the onset of labor (Thaxton and Sharma, 2010), suppressing the production and function of pro-inflammatory cytokines (Hakimi et al., 2014; Mobini et al., 2016; Tabary et al., 2003). The present results suggest that the important anti-inflammatory effects of IL-10 may be reduced during pregnancy in women who smoke cigarettes.

Importantly, IPV has been related to tobacco use and smoking during pregnancy (Cheng et al., 2015; Zhang et al., 2021). It was reported recently that IPV before pregnancy is related to higher perceived stress, smoking, and marijuana use among pregnant AA women (Zhang et al., 2021). In the present study, it is interesting to note that IPV during

pregnancy was related to higher levels of IL-8 which can be regulated by IL-10. Hence, IPV possibly has both direct effects on inflammation (via IL-8) and indirect effects (via pathways involving factors such as smoking and IL-10) through which it might increase the risk for poor pregnancy outcomes. Further investigation is required of these associations pertaining to IPV, both before and during pregnancy.

4.1. Strength and limitations

African American women have higher systemic inflammation (Blackmore et al., 2014) and report higher levels of depressive symptoms during pregnancy compared to other racial groups (Mukherjee et al., 2016). We are reporting significant associations of depressive symptoms and behavioral risk factors (Intimate partner violence and smoking) with specific inflammation markers in a cohort of AA women. Strengths include the prospective study design which allowed us to collect samples during pregnancy. Another strength of the study is the use of a panel of inflammatory markers which included pro-inflammatory and anti-inflammatory cytokines and CRP. There are limitations to these findings since this was a cross-sectional analysis and involved self-reported measures of depression, IPV, and smoking. There are validated measures for substance use and these will be incorporated in future follow-up studies including 4 P's Plus (Chasnoff et al., 2007) or the SURP-P (Substance Use Risk Profile-Pregnancy) scale (Yonkers et al., 2010). Because body mass index, prior history of clinical depression, and autoimmune disease were not assessed in the questionnaire, these factors were not controlled in analyses. Future work is needed to investigate these associations and understand the mechanisms involved with assessment at multiple time points during pregnancy.

5. Conclusions

Depressive symptoms were found to be positively associated with plasma CRP levels, whereas IPV during pregnancy was related to higher levels of IL-8. Smoking during pregnancy showed a negative association with plasma IL10 levels. More research is needed to clarify the pathophysiological link between individual risk factors (i.e., depressive symptoms, IPV, smoking) and inflammation. While we cannot state that these findings are specific to AA women, some research reports have demonstrated that AA women experience IPV more frequently than White women. Given the associations between IPV and inflammation (and smoking), further study of IPV and its relationship to birth outcomes in all races is merited.

The possible bi-directional association of systemic inflammation with depressive symptoms should be explored in future research in the context of pregnancy. Detailed investigation of depressive symptoms and IPV with positive and negative coping behaviors, and their effects on health and inflammatory status, is needed to understand the relationship of these factors. The role of inflammation during pregnancy is very complex and dysregulation can result in adverse perinatal outcomes including miscarriage, preterm birth, and immune system dysregulation in the infant. There is a strong need for the development of new guidelines for healthcare providers to screen for social and behavioral risk factors and systemic inflammation, especially among high-risk population groups. Pregnant women should be screened for depressive symptoms by healthcare providers and encouraged to participate in programs to manage and treat depressive symptoms during pregnancy.

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Declaration of competing interest

Authors have no competing interests to declare.

Appendix A. Supplementary data

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