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ORIGINAL ARTICLE

Lower prenatal vitamin D status and postpartum depressive symptomatology in African American women: Preliminary evidence for moderation by inflammatory cytokines

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Abstract Vitamin D deficiency and elevated pro-inflammatory cytokines have each been associated individually with postpartum depression (PPD). African American women are at increased risk for prenatal vitamin D deficiency, inflammation, and prenatal and postpartum depressive symptoms, but biological risk factors for PPD in this population have rarely been tested. This prospective study tested whether low prenatal vitamin D status (serum 25-hydroxyvitamin D, 25[OH]D) predicted PPD symptomatology in pregnant African American women and whether high levels of prenatal inflammatory cytokines interacted with low 25(OH)D in effects on PPD symptoms. Vitamin D status was measured in the first trimester in a sample of 91 African American pregnant women who had a second trimester blood sample assayed for inflammatory markers. Depressive symptoms were assessed at a postpartum visit. An inverse association between prenatal log 25(OH)D and PPD symptomatology approached significance ($\beta=-0.209$, $p=0.058$), and interleukin-6 and IL-6/IL-10 ratio significantly moderated the effect. Among women with higher levels of inflammatory markers, lower prenatal log 25(OH)D was associated with significantly higher PPD symptoms ($p<0.05$). These preliminary results are intriguing because, if replicable, easy translational opportunities, such as increasing vitamin D status in pregnant women with elevated pro-inflammatory cytokines, may reduce PPD symptoms.

Keywords Pregnancy · Vitamin D · 25(OH)D · Cytokines · Inflammation · Postpartum depression

Introduction

Postpartum depression is a serious mental health condition occurring after childbirth characterized by emotional disturbance and behavioral changes. It is estimated that 10 to 20 % of American women experience symptoms of magnitude and duration to meet criteria for PPD (Centers for Disease Control and Prevention 2008). A recent meta-analysis (Molyneaux et al. 2014) estimated rates of diagnosed PPD to be higher in overweight and obese pregnant women (13 vs. 10 % of normal-weight women). Depression after childbirth portends maternal suffering, more likelihood of parenting ineffectiveness, and possible difficulties for the entire family (Grace et al. 2003; Paulson et al. 2006; Zelkowitz and Milet 1996). Therefore, it is advantageous to increase our understanding of the risk factors, etiology, and mechanisms of depression in women following birth. Independent risk factors include prenatal depression, high life stress, low social support, low education, and African American race (Beck 2001; Bennett et al. 2004). A comprehensive systematic review on postpartum depressive symptoms and diagnosis highlighted that most biological factors have been studied in isolation (Yim et al. 2015). We investigated vitamin D status, inflammatory cytokines, and PPD symptoms together in a sample of African American pregnant women, many of whom were overweight or obese.

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Vitamin D is a unique neurosteroid hormone required for normal brain homeostasis and development. Vitamin D_3 is produced in the skin when exposed to the sun's ultraviolet rays and is also absorbed from various food sources, such as oily fish (Zhang and Naughton 2010).[1] Low levels of vitamin D have also been associated with several mental disorders including depression (McCann and Ames 2008). According to a recent meta-analysis of 31,424 males and females, vitamin D was inversely associated with depression (Anglin et al. 2013); however, none of the included studies were on pregnancy or the postpartum. In a prospective study of 796 women, a negative association was found between prenatal vitamin D levels at 18 weeks gestation and PPD symptoms (Robinson et al. 2014; see also Murphy et al. 2010). Another recent prospective study reported that lower maternal 25(OH)D3 levels in the second trimester of pregnancy were associated with higher levels of PPD symptoms at 1 week, 6 weeks, and 6 months postpartum (Gur et al. 2014). Cross-sectional studies have also been published in support of these prospective ones (Brandenbarg et al. 2012; Cassidy-Bushrow et al. 2012a). Thus, the larger literature on low vitamin D levels and depression has been extended into pregnancy and postpartum. To our knowledge, no studies have investigated the combined effects of prenatal vitamin D status and inflammatory markers on PPD symptoms in any ethnic group.

A complex and incompletely understood relationship between vitamin D and the immune system has been described (Arora and Hobel 2010; Liu et al. 2006; McCann and Ames 2008). Expression of the vitamin D receptor has been detected on a variety of immune cells including monocytes, T lymphocytes, dendritic cells, and macrophages (Veldman et al. 2000). Vitamin D is beneficial, acting as an influential immune moderator of both the adaptive and innate immune systems through its ability to alter cytokine secretion (Adams and Hewison 2008; Van Etten and Mathieu 2005), and acts as a regulator of cell signaling pathways via its effect on toll-like receptor expression and function (Liu et al. 2006; Thota et al. 2012; Van Etten and Mathieu 2005; Zhang et al. 2012). In pregnancy, vitamin D regulates placental development and function and promotes tolerance of the fetus (Arora and Hobel 2010) and vitamin D deficiency has been associated with neonatal and birth outcomes (Aghajafari et al. 2011, 2013; Wei et al. 2013; Theodoratou et al. 2014). Further, early pregnancy vitamin D is inversely associated with inflammatory cytokines in mid-pregnancy (Bobbitt et al. 2014). High vitamin D status might also be a protective factor in the link between pro-inflammatory cytokines and depression. Numerous research studies have demonstrated a strong

positive association between inflammation and depression (e.g., Dantzer et al. 2008; Howren et al. 2009; Miller et al. 2009), as well as an emerging body of research on the role of stress, inflammation, and depression in perinatal health (Christian 2012; Coussons-Read 2012). The role of vitamin D status in this set of processes is unknown.

Inflammation is of interest in pregnancy because of the physiological changes that occur during normal gestation. At the uterine level, early pregnancy (implantation) and late pregnancy when approaching delivery are pro-inflammatory states, whereas mid-pregnancy is an anti-inflammatory state (Mor et al. 2011). Recent studies have longitudinally profiled inflammatory markers throughout the perinatal period. Interleukin-6 (IL-6), for example, increased slightly over gestation in a racially diverse sample of 57 healthy pregnant women with a significant postpartum increase (Christian and Porter 2014). Blackmore and colleagues (2014) studied women at 4 time points in pregnancy and postpartum. They reported elevations in serum pro-inflammatory markers in African American compared to non-African American women, but when controlling for BMI, the effect of race on IL-6 levels was no longer significant. Furthermore, neither IL-6 nor TNF-α were associated with depression (Blackmore et al. 2014).

Significant associations between perinatal depression and inflammation have been reported in several studies. For example, depression was associated with inflammation during pregnancy in three studies (Cassidy-Bushrow et al. 2012b; Christian et al. 2009; Coussons-Read et al. 2007), and inflammation in the postpartum period was associated with PPD in three more studies (e.g., Boufidou et al. 2009; Corwin and Pajer 2008; Maes et al. 2000), although not in two other studies (Okun et al. 2011; Skalkidou et al. 2009). Moreover, prenatal depression consistently predicts PPD (Bennett et al. 2004). Nonetheless, some experts feel firm conclusions cannot be made about the role of inflammatory processes in perinatal depression as yet (Osborne and Monk 2013). Firm conclusions are complicated by use of a broad range of tools for mood assessment, different cutoff points, measurement of different cytokines, and racially and socioeconomically homogenous samples.

African American women appear to have among the highest rates of prenatal and postpartum depression compared to other racial groups in the USA (Howell et al. 2006; Orr et al. 2006; Segre et al. 2006). They are also at increased risk for vitamin D deficiency (Nassar et al. 2011) because darker skin limits synthesis of vitamin D and due to lower intake of supplemental vitamin D (Bodnar and Simhan 2010). Furthermore, higher levels of inflammatory markers have been documented in African American men and women (Deverts et al. 2010) and in both non-pregnant and pregnant African American women in a stress reactivity study (Christian et al. 2013). Thus, data on African American

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[1] Approximately 0.5 MED of UVB radiation would be absorbed after an average of 5 to 10 min of exposure of the arms and legs to direct sunlight depending on the time of day, season, latitude, and skin sensitivity (Zhang and Naughton 2010).

women in pregnancy and postpartum is well suited to our research questions.

The purpose of this study was to examine associations prospectively between prenatal vitamin D status and postpartum depressive symptomatology in a sample of African American women. We hypothesized that in pregnant women with higher prenatal inflammatory markers there would be a stronger negative association of prenatal 25(OH)D, and postpartum depressive symptoms as compared to those with lower inflammation, and this association would remain after controlling for BMI.

Methods

Participants and procedures

We analyzed prospective data obtained during pregnancy and the postpartum from a previous study to test our study hypotheses (see Cassidy-Bushrow et al. 2012a, b for methodological details). The study population consisted of pregnant women who were patients in the Henry Ford Health System (HFHS), in Detroit MI. Potential participants were identified by accessing patient appointment lists in the electronic medical record (EMR) of nine HFHS obstetrics and gynecology (OB/GYN) clinics. Clinics were chosen based on the likelihood that they would have a large number of African American patients of varying socioeconomic status. African American women, aged 18–44 years, in the second trimester of pregnancy (13–28 weeks gestation based on self-reported last menstrual period [LMP] or expected delivery date [EDD] defined by ultrasound) were identified as potential participants. Trained interviewers arranged to meet women at an upcoming clinic appointment. Recruitment spanned February 2009 to June 2010. A total of 203 women completed the prenatal study visit. Eleven women were unable to complete the entire prenatal study visit in person. In addition, three women with very morbid obesity (BMI>60 kg/m^2) were excluded.

For the current study on postpartum depression, we excluded two women with ≥1 inflammatory biomarkers exceeding ±3 standard deviations from the mean for comparability with a prior study (Christian et al. 2009). Following written consent, eligible women provided self-reported demographic information, and a 10-ml blood sample was obtained during the second trimester research visit (13–28 weeks gestation). The final analytic sample consisted of 91 women with a first trimester 25(OH)D measurement, second trimester measure of inflammatory markers, and who had a postpartum visit during which the depression screening was completed (N=98 did not return for postpartum visit). The study protocol was approved by the Institutional Review Boards at the respective institutions.

Vitamin D status

Serum 25-OHD is considered the best measure of overall vitamin D nutrition status and the most useful clinically. As part of routine obstetrical care, vitamin D status (serum 25-OHD) was measured during the first prenatal care visit (M=9.7± 3.7 weeks gestation). Serum samples were assayed using a competitive chemiluminescence immunoassay platform (Rao 1999), similar to other reported methods (Ersfeld et al. 2004; Hollis 2008). Serum 25-OHD level was used as a continuous variable in all regression analyses.

Inflammatory biomarkers

All assays were performed in serum collected from women during the second trimester research visit (stored at −80 °C), which was scheduled around a pre-existing obstetrics visit (M=21.3±3.8 weeks gestation). Time of day for the blood draw therefore varied, and women did not fast beforehand. High-sensitivity C-reactive protein (hs-CRP) was measured by enzyme immunoassay as per the manufacturer's instructions (BioCheck, Inc., Foster City, CA, USA) and concentrations (mg/l) calculated from a standard curve. The limit of detection (LOD) is 0.1 mg/l. Interleukins, IL-1β, IL-6, IL-10, and TNF-α concentrations (pg/ml) were assayed on a Bio-Plex 200 System using Bio-Plex Pro Cytokine Assay custom 4-plex kits (Bio-Rad, Hercules, CA, USA). LOD for these cytokines are 0.6, 2.6, 0.3, and 6.0 pg/ml. Results are reported only for inflammatory markers with <20 % of the sample outside of the LOD (J. Carroll personal communication; Breen et al. 2011). Therefore, results for IL-6, IL-10, and hs-CRP are reported and those for TNF-α (54 % sample below LOD) and IL-1β (42 % sample below LOD) are not.

The link between depression and inflammatory disorders may be partially explained by a disruption of the immune-regulatory balance between pro- and anti-inflammatory cytokines (e.g., IL-6 and IL-10, respectively). In addition to their absolute concentrations, the relative concentrations of pro- to anti-inflammatory cytokines may provide a useful index of the net inflammatory milieu and of immune dysregulation (Dhabhar et al. 2009). After confirming that IL-6 and IL-10 were not significantly associated (r=0.1; p=0.174), we calculated the IL-6/IL-10 ratio and hypothesized that this ratio as well as IL-6 (but not IL-10 alone) would moderate the association between prenatal 25(OH)D and PPD symptomatology.

Postpartum depressive symptoms

The Edinburgh Postnatal Depression Scale (EPDS; (Cox et al. 1987)) is a 10-item scale that assesses the cognitive and affective components of depressive symptomatology, while excluding somatic symptoms specific to postpartum. The EPDS has been validated for use in pregnant and postpartum

women and the sensitivity and specificity was 86 and 78 %, respectively (Cox et al. 1987). The EPDS was administered to assess depressive symptoms during routine postpartum visits, which are typically scheduled 4–6 weeks post-delivery ($M=4.5\pm1.8$ weeks). EPDS scores were available electronically from medical records with participant consent. The EPDS score was used as a continuous variable in all regression analyses.

Covariates

Participants reported date of birth, marital status, education, employment status, and cigarette smoking at the second trimester research visit. Pre-pregnancy height and weight were self-reported, and pre-pregnancy body mass index (BMI) calculated as weight (kg)/height (m^2). They also reported prenatal depressive symptoms using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; (Radloff 1977)). The prenatal CES-D score was used as a continuous variable in all regression analyses. A history of self-reported prior depressive illness (prior to pregnancy) was abstracted from the OB intake form within the electronic medical record. Additional medical variables (Table 1) for descriptive purposes were abstracted from the electronic medical record.

Statistical analysis

We used standard statistical software programs (SPSS 20.0 & STATA 14) to conduct all analyses, statistical significance was defined as $p<0.05$, and marginal effects were interpreted at $0.05<p<0.10$. Descriptive statistics were calculated to characterize participants. Linear regression models were fitted to estimate associations between prenatal 25(OH)D (ng/ml), inflammatory markers, and postpartum depressive symptoms. Models were adjusted for demographic and medical variables (see tables for details). To reduce non-normality in vitamin D status, values were log transformed and are referred to as log (25-OHD) or log vitamin D status. To examine moderation by inflammatory markers, interaction terms were created combining log vitamin D status with hs-CRP, inflammatory markers IL-6 and IL-10 (log transformed to reduce non-normality), as well as the calculated IL-6/IL-10 ratio.

Results

Demographic characteristics

Women in the current study ($N=91$, Table 1) were on average 26 years old (SD=5.9). The majority of women were unmarried (75 %), currently employed (63 %), and approximately half had a high school diploma (58 %). Few had a history of

Table 1 Descriptive characteristics for sample

	Total sample ($N=91$)
Demographic variables	
Maternal age (years)	26 ± 6
Married	23 (25 %)
≥High school diploma	53 (58 %)
Currently employed	57 (63 %)
Annual income ($)[a]	$36,623\pm34,609
Medical variables	
History of chronic hypertension	4 (4 %)
History of preterm birth	8 (9 %)
Preterm birth in this pregnancy[b]	6 (7 %)
Low birth weight in this pregnancy[b]	7 (8 %)
Nulliparous[c]	43 (47 %)
Smoking in this pregnancy	2 (2 %)
Pre-pregnancy BMI (kg/m^2)	29 ± 8
Psychological variables	
Prenatal CES-D	16.1 ± 11
History of depression	6 (7 %)
EPDS	5.20 ± 4.95
Vitamin D variables	
Vitamin D season:	
April–December	55 (60 %)
January–March	36 (40 %)
Vitamin D status ng/ml	13.2 ± 9.4
Vitamin D≤20 ng/ml[d]	77 (85 %)
Inflammatory cytokines	
IL-6 (pg/ml)[e]	4.0 ± 2.1
IL-10 (pg/ml)	2.0 ± 0.5
IL-6/IL-10	2.1 ± 1.1
hs-CRP (pg/ml)	4.6 ± 3.0

Data are N (%) or mean±standard deviation

EPDS Edinburgh Postnatal Depression Scale, *CES-D* Center for Epidemiologic Studies Depression Scale

[a] Income data for 79 women

[b] Birth outcomes for 90 women

[c] Defined as no previous pregnancy lasting at least 6 months

[d] Inadequate or deficient vitamin D (Institute of Medicine 2011)

[e] 18 women with inflammatory biomarker IL-6<LOD (19.8 % were set to the mid-point between 0 and LOD (Alper et al. 2010)

depression (7 %), history of hypertension (9 %), or history of preterm birth (9 %). A total of 6 of the 91 women delivered babies before 37 weeks of gestation (7 % preterm birth). Many women were overweight ($N=24$, BMI 25–30) or obese ($N=34$, BMI>30); average BMI was 29.2 (SD=8.2). The majority did not smoke during this pregnancy (98 %).

We compared the 91 women in the analytic sample to the 85 women with 2nd trimester vitamin D and inflammation data but no postpartum EPDS score. There were no significant differences in any of the key variables: maternal age, 2nd

trimester CESD score, rate of preterm birth or levels of 25-OHD, hs-CRP, IL-6, or IL-10 (all $p>0.05$).

Sample characteristics on vitamin D status

Sixty percent had their vitamin D status measured during April–December whereas 40 % had vitamin D levels measured during January–March. The average level of 25(OH)D in the sample was 13.2 ng/ml (SD=9.4), and 85 % (N=77) met criteria for vitamin D inadequacy or deficiency (vitamin D≤20 ng/ml) by the standard cutoff (Ross et al. 2011). Furthermore, 97 % (N=88) did not meet the level suggested for pregnant or lactating women (vitamin D≥30 ng/ml) by the Endocrine Society's Clinical Practice Guideline (Holick et al. 2011). An authoritative source on recommended serum levels of vitamin D for African Americans, or specifically pregnant African Americans, does not exist. Therefore, we examined two additional vitamin D cutoffs (risks for cardiovascular disease and all-cause mortality) to be conservative.[2]

Vitamin D status and PPD symptoms

The mean EPDS score was 5.20 (SD=4.95). Twelve percent of this sample had EPDS scores ≥12 indicating probable PPD, a rate comparable to rates in other reports (Centers for Disease Control and Prevention 2008), and EPDS scores were significantly higher in overweight and obese women (mean=5.98, SD=5.17) as compared to normal-weight women (mean= 3.82, SD=4.28, $p<0.05$), as reported in a recent meta-analysis (Molyneaux et al. 2014), although rates were still in the low range of the EPDS in both groups. The entire depressed subgroup (11 of 11) was below the most lenient cutoff for low vitamin D status (≤30 ng/ml), although the rate was not statistically significant from the non-depressed subsample in which 96 % (77 of 80) were vitamin D deficient.

Sample characteristics on inflammatory markers

Levels of prenatal inflammatory biomarkers (Table 1) were higher than those reported in other studies (Coussons-Read et al. 2007; Madan et al. 2009; Vassiliadis et al. 1998), potentially due to differing assay modalities or racial composition of the samples.[3]

Associations of 25(OH)D and inflammatory markers with PPD symptoms

We first examined the association between demographic and medical variables with postpartum depressive symptoms to determine whether these should be included in the model as potential confounders. The significant associations between history of depression[4], BMI, and low education with postpartum depressive symptoms were the basis for inclusion of these three variables in analyses. Additional theoretically derived confounding variables included maternal age, marital status, prenatal depressive symptoms (CES-D), and season of vitamin D measurement. Regression analyses were then conducted to examine whether vitamin D status and inflammatory marker levels were associated with depressive symptoms.

Tables 2 and 3 display results from regression analyses. Table 2 shows that log 25(OH)D was not significantly associated with postpartum depressive symptomatology in unadjusted regression analyses (β=−0.145, p=0.172). When adjusted for covariates, the effect was marginally significant (β=−0.209, p=0.058); higher log 25(OH)D was associated marginally with lower EPDS symptoms. None of the individual inflammatory markers were significantly associated with EPDS scores; however, as shown in Table 3, IL-6 and the IL-6/1 L-10 ratio both significantly moderated the association between prenatal 25(OH)D levels and PPD symptoms. Figures 1 and 2 depict moderation results. The unstandardized simple slope for women 1 SD above the mean of IL-6 was significant, such that in women with higher levels of IL-6, lower prenatal 25(OH)D levels were associated with higher levels of postpartum depressive symptoms. The unstandardized simple slope for women 1 SD above the mean of the IL-6/IL-10 ratio was also significant, such that in women with greater levels of IL-6/IL-10 ratio, lower prenatal vitamin D levels were associated with higher levels of PPD symptoms. A test of moderation by IL-10 alone was marginally significant (p=0.09), and there was no evidence that hs-CRP moderated the association (p=0.12). Finally, these findings persisted when controlling for prenatal depressive symptoms, using a standardized though different screener measured in second trimester (CES-D, Radloff 1977) and when controlling for preterm birth (results not shown).

Discussion

Findings from this study suggest that higher levels of 25(OH)D in early pregnancy in African American women

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[2] The other vitamin cutoffs we considered were vitamin D≤15 ng/ml for risk of cardiovascular disease (Wang et al. 2008) and vitamin D≤10 ng/ml used for risk for all-cause mortality (Dobnig et al. 2008). Analyses showed that 69 % of our sample (63 women) met the cardiovascular risk cutoff, and 48 % (44 women) were at risk of all-cause mortality.

[3] A table displaying the Spearman correlation coefficients among the main study variables, including vitamin D status and each inflammatory marker can be provided by the authors.

[4] History of depression was abstracted from the electronic medical record. We do not know if any women sought out psychological or complementary treatments for depression nor how long ago a previous episode occurred. One woman in our study reported taking antidepressants (Zoloft) during her postpartum visit, and removing her from analyses did not change our results.

Table 2 Linear regression model testing the main effects of log-transformed vitamin D status and cytokines on EPDS

Variable	Unadjusted		Adjusted	
	β	p	β	p
Log 25(OH)D	−0.145	0.172	−0.209	0.058
Log IL-6	0.084	0.430	0.142	0.180
Log IL-10	−0.004	0.971	0.094	0.349
Log IL-6/IL-10 ratio	0.089	0.401	0.100	0.354
Log hs-CRP	0.174	0.099	0.147	0.209

Dependent variable: Edinburgh Postnatal Depression Scale (EPDS) score, $N=91$. Each independent variable in the "Unadjusted" column was run separately. Each variable in the "Adjusted" column was run separately with the following covariates: maternal age, education (high school diploma), marital status, history of depression, season of vitamin D measurement, and pre-pregnancy BMI. Results pertaining to covariates were obtained but were omitted from this table. Only two covariates were consistently statistically significantly associated with EPDS; "education" was negatively associated, and "history of depression" was positively associated with EPDS in each analysis. Also, "being married" was positively associated with EPDS in the Log Vitamin D analysis

may contribute to lower postpartum depressive symptoms, though the association of vitamin D status and EPDS scores was only marginally significant ($p=0.058$). Moreover, when pregnant African American women were lower in 25(OH)D and higher in pro-inflammatory cytokine levels (specifically IL-6, IL-6/IL-10 ratio) in adjusted models, they reported more

Table 3 Linear regression models testing the interactive effects of log-transformed vitamin D and cytokines on EPDS

| Variable	β	p
a. Log 25(OH)D	−0.123	0.271
Log IL-6	0.062	0.559
Log 25(OH)D X Log IL-6	−0.232	*0.025*
b. Log 25(OH)D	−0.208	0.057
Log IL-10	0.061	0.535
Log 25(OH)D X Log IL-10	−0.166	0.093
c. Log 25(OH)D	0.257	0.233
Log IL-6/IL-10 Ratio	−0.065	0.580
Log 25(OH)D X Log IL-6/IL-10 ratio	−0.531	*0.016*
d. Log 25(OH)D	−0.182	0.097
Log hs-CRP	0.155	0.178
Log 25(OH)D X Log hs-CRP	−0.152	0.118

Statistically significant p values are shown in italics

Models "a–d" were adjusted for maternal age, education (high school diploma), marital status, history of depression, season of vitamin D measurement, and pre-pregnancy BMI. Results pertaining to covariates were obtained but were omitted from this table. Only two covariates were consistently statistically associated with EPDS in all above models; "education" was negatively associated, and "history of depression" was positively associated with EPDS. In models a, c, and d, "being married" was also positively associated with EPDS
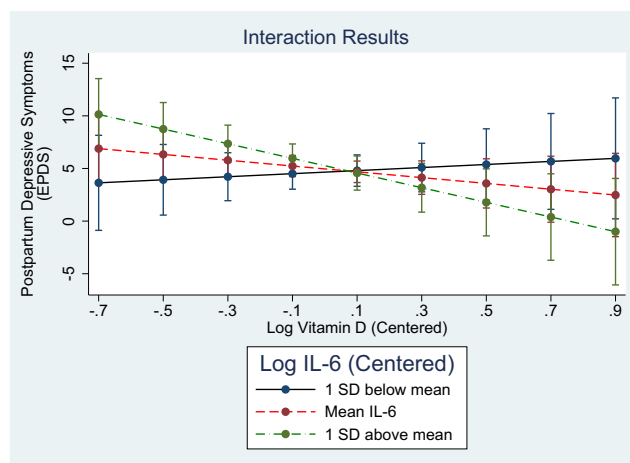
Fig. 1 Interleukin-6 (IL-6) significantly moderates the relationship between log 25(OH)D and EPDS

postpartum depressive symptoms. Although two recent investigations reported an association between prenatal vitamin D status and PPD symptoms similar to ours, neither study assessed prenatal depression; thus, depression symptoms may have predated the measurement of 25(OH)D (Gur et al. 2014; Robinson et al. 2014). In contrast, our study found evidence for a possible inverse association between 25(OH)D and PPD symptoms controlling for prenatal depressive symptoms and also for history of depression.

Previous research has shown that vitamin D appears to downregulate the Th1 or cellular immunity pathway and stimulate the Th2 or humoral immunity pathway (McCann and Ames 2008). Vitamin D also regulates placental development and function and promotes tolerance of the fetus, likely by enhancing anti-bacterial and anti-inflammatory responses in both the maternal and fetal components of the placenta (Arora and Hobel 2010). These regulatory shifts are accomplished in part by decreasing the production of pro-inflammatory cytokines and by increasing the production of anti-inflammatory cytokines (McCann and Ames 2008).
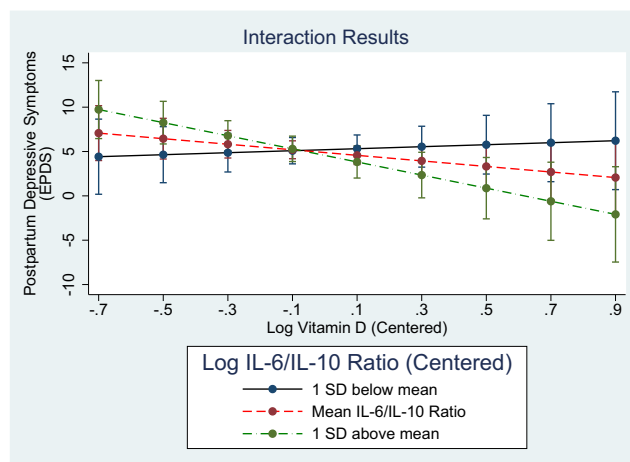
Fig. 2 The ratio of interleukin-6 (IL-6) to interleukin-10 (IL-10) significantly moderates the relationship between log 25(OH)D and EPDS

Additionally, cytokine signals from the periphery can be transmitted to the brain via the circumventricular organs, unique areas of the brain outside the blood-brain barrier (BBB), or vagal afferents (Buller 2001; Maier 2003), potentially leading to changes in maternal neurotransmission and later depressive symptomatology. Since inflammatory markers were collected in the second trimester and may be mechanisms linking first trimester vitamin D status to PPD symptomatology, we ran an exploratory analysis on possible mediation by each inflammatory marker of the association between 25(OH)D and PPD symptoms. None of these analyses were statistically significant. We recommend testing this in future studies with larger samples. We also did not find strong evidence for direct effects of inflammatory markers on postpartum depressive symptoms although we note that reviews of this literature show mixed results (Osborne and Monk 2013). It is possible that higher levels of cytokines and lower levels of 25(OH)D increase risk for later depressive symptoms in pregnant women only when acting synergistically. Whether this is unique to African American women, we do not know. We also did not find evidence of significant moderation by hs-CRP, a marker of low-grade inflammation. Consistent with our results, a recent study in a non-pregnant sample found an association between depression and CRP in Caucasian but not African American women (Amyre et al. 2011).

Levels of prenatal inflammatory markers were higher here than those reported in other studies (Coussons-Read et al. 2007; Madan et al. 2009; Vassiliadis et al. 1998), perhaps because the sample was all African American women. Differences in assay modality (differing LOD) may also have led to some differences between our study and others. Our findings, however, were similar to those of Christian et al. (2009) whose sample was 57 % African American (Christian et al. 2009). Two recent studies focused on levels of cytokines across pregnancy in racially diverse samples, and one attributed differences in levels of cytokines to high BMI, not race (Blackmore et al. 2014; Christian and Porter 2014). Notably, our findings remained significant even after controlling for BMI.

We suspect that null results in past studies of vitamin D status and depression in non-pregnant (e.g., Bertone-Johnson 2009) and pregnant (Nielsen et al. 2013) samples may be due to low levels of inflammatory markers. Our preliminary findings suggest that the effects of low 25(OH)D on PPD symptoms may be potentiated only in the presence of inflammation. Whether inflammation moderates the relationship between low 25(OH)D and depression in non-pregnant samples is therefore worth testing.

Strengths, limitations, and future directions

Compared to prior research, this prospective study utilized a relatively large sample which permitted us to test interactions of study variables. In addition, women in our sample were studied both in pregnancy and postpartum, and having medical and psychosocial data enabled us to control for many relevant confounders. The sample was also solely African Americans who are at higher risk of inflammation and low vitamin D status. Finally, vitamin D measures that were obtained as part of HFHS clinical care were assayed with a competitive chemiluminescence immunoassay platform, consistent with other large clinical laboratories. Importantly, HFHS participates in the Vitamin D External Quality Assessment Scheme, as recommended by experts in the field (e.g., Hollis 2008).

Limitations of this secondary data analysis include some missing data on depressive symptoms 6 weeks postpartum because a portion of women either did not return for their routine postpartum visits or their clinician did not record the EPDS result. Future research would benefit from assessing depressive symptoms repeatedly rather than only once in the first 6 weeks at their obstetrics postpartum follow-up visit, e.g., at 12 weeks. Additionally, the percentage of women with elevated postpartum depression scores in our sample is consistent with other reports of low income African American women (Dolbier et al. 2013). Further, participants dropped from analyses due to lack of EPDS scores were of similar age and 25(OH)D levels and had comparable prenatal CES-D scores to those included. Thus, underestimates of depressive symptoms due to attrition seem less probable.

Finally, 74 % of women in this sample reported use of a vitamin D supplement (50,000 IU/week of vitamin D_2) which might have raised mean levels in the sample and also may have favorably affected levels of inflammatory markers. However, serum levels of 25(OH)D were measured between 9 and 13 weeks gestation with supplementation prescribed thereafter in only a portion of women.[5] Inflammatory markers were measured later between 13–28 weeks of gestation, and they are normally lower at this point during pregnancy and higher in early and late pregnancy. However, if a short-term benefit of vitamin D supplementation occurred, it would most likely have attenuated the association we detected with inflammatory markers and PPD symptoms. In a small subset of women in the sample ($n=38$ of 203), we measured the same inflammatory cytokines again in the 3rd trimester. There were high paired sample correlations among the cytokines from the 2nd to 3rd trimester: IL-6 ($r=0.57$; $p<0.001$), IL-10 ($r=0.53$; $p=0.001$). This suggests that our results were not necessarily influenced by large trimester-specific changes in these cytokines.

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[5] IU refers to international units, which equal 25 ng. Vitamin D supplements were prescribed to 87 % of the women with 74 % reporting use of the supplement at a prenatal care visit. Most vitamin D supplements prescribed were 50,000 IU, taken once weekly.

In addition to obtaining concurrent measures of 25(OH)D, inflammatory markers, and depressive symptoms throughout pregnancy and postpartum, it would be ideal to track adherence of vitamin D use and determine whether levels of 25(OH)D influence the trajectory of depression during pregnancy and from pregnancy to postpartum. Future research would also benefit from collecting dietary intake data and sun exposure information from participants. We studied four inflammatory markers/marker combinations, thus our findings may be subject to multiple testing issues. Because exploratory studies such as this rarely correct for multiple comparisons and Bonferroni correction is considered conservative (Gelman et al. 2012), it is not necessarily appropriate to hold the findings to that standard; nonetheless, our significant moderation results were very close to significance when tested by Bonferroni criteria.[6] While these results are preliminary and do not establish causation, they are novel and particularly important given the prevalence of low 25(OH)D in this population of African American women. We hope that they may spark interest in further research on this topic including randomized controlled studies. Furthermore, this study does not involve confirmed cases of PPD and future research can include diagnostic interviews.

An important clinical implication is to determine if increased prenatal vitamin D supplementation can reduce PPD symptoms using a randomized controlled trial. Supplementation is particularly relevant for overweight and obese pregnant women, as they are more likely to have insufficient 25(OH)D levels (Bodnar et al. 2007) and higher rates of PPD (Molyneaux et al. 2014). Arguably, supplementation might also be recommended only for those women with high levels of inflammatory cytokines in pregnancy and those with clinically significant depression. Indeed, two recent systematic reviews of vitamin D supplementation on depressive symptoms in the non-pregnant state suggested no overall effect on depressive symptoms. In one review, the evidence suggested that supplementation might be effective in reducing depressive symptoms in individuals with clinically significant pre-existing depression (Shaffer et al. 2014). The other, a meta-analysis, separated randomized control trials into those with and without methodological flaws and concluded that studies without flaws demonstrated a statistically significant improvement in depression with vitamin D supplements (Spedding 2014). Vitamin D supplementation is a cost-effective and safe intervention during pregnancy (Hollis et al. 2011) that may reduce prenatal and postpartum symptoms of depression and benefit the mother's health and that of the developing fetus (Kalra et al. 2012; Morales et al. 2012). A recent randomized, double-blind, placebo-controlled clinical trial of vitamin D supplementation in 48 pregnant women resulted in significant decreases in serum hs-CRP, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure compared with placebo (Asemi et al. 2013). However, depressive symptoms were not measured in this study. Randomized controlled trials of prenatal vitamin D supplementation to reduce postpartum depression, especially in overweight women with high levels of prenatal inflammation, may be merited.

Conclusion

These findings provide the first evidence that low prenatal 25(OH)D and high prenatal inflammation together might predict future postpartum depressive symptomatology in African American women. We know of no other studies that investigated inflammatory moderation of the relationship between 25(OH)D levels and later depressive symptomatology in non-pregnant women or men. These results may therefore elucidate inflammatory moderators linking vitamin D status to depressive symptoms, not only in pregnant African American women, but potentially in other subgroups of the population. Future research on the synergistic relationship of 25(OH)D and inflammation on depression is worthwhile. Understanding how vitamin D alters the immune system may shed new light on the emerging links between inflammation and depression.

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[6] Bonferroni critical p of 0.0125 (IL-6 $p=0.025$; IL-6/IL-10 $p=0.016$).

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