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Relationship between inflammatory biomarkers, vitamin D levels, and depressive symptoms in late pregnancy and during the postpartum period: a prospective, observational study

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Abstract

Background: Perinatal depression impacts maternal and fetal health, and exhibits a high rate of continuity postpartum. Not only does it impair the maternal quality of life, it also increases the risk of adverse birth and developmental problems in offspring. Vitamin D deficiency and excessive inflammation have been associated with perinatal depression. There is a scarcity of evidence regarding the biological causes of maternal depression in Iraq, therefore, the present study aims to assess perinatal depressive symptoms associations with inflammatory markers and vitamin D levels, and to investigate the interaction between vitamin D and the inflammatory markers. A prospective, observational study design was utilized to recruit healthy pregnant women from private obstetrics clinic in Baghdad, Iraq, from April to September 2021. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure depressive symptoms during the third trimester and at 6 months postpartum. Serum levels of interleukin (IL)-6, C-reactive protein (CRP), and 25-hydroxy vitamin D (25-OH-D) were quantified, using a fully automated chemiluminescence immunoassay analyzer.

Results: Eighty patients were eligible for inclusion. The antenatal EPDS scores demonstrated a significant association with square root IL-6 ($B = -0.025$, $p = 0.040$) and no association with CRP or vitamin D levels. The severity of postpartum depressive symptoms tended towards a positive association, with larger increases of CRP concentration ($p = 0.065$). In contrast, the association between marital relationship quality and CRP was statistically significant ($p = 0.001$). There was a statistically significant association between CRP and vitamin D concentration ($p = 0.041$). Antepartum EPDS significantly predicted the postpartum EPDS score ($p = 0.000$, $B = 0.180$, R^2 for the model = 0.976, CI (0.17–0.19)).

Conclusions: The study findings show a significant association between third trimester depressive symptoms and IL-6 concentration. CRP and vitamin D levels do not correlate with perinatal depressive symptoms and a poor marital relationship significantly elevates the CRP level. In addition, vitamin D level was associated with CRP level and antepartum depressive symptoms predict postpartum EPDS score. Future studies involving a larger population and including women with pregnancy complications would provide a further insight into the role of inflammation and vitamin D deficiency in the etiology of perinatal depression.

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Keywords: Pregnancy depressive symptoms, Postpartum depressive symptoms, Inflammatory markers, Poor marital relationship, Inflammation, Vitamin D level, Interleukin-6, C-reactive protein

Background

Maternal depression, including major depressive disorder, dysthymia and depressive symptoms, is a public health concern that affects 7–20% of pregnant women [1, 2]. Antenatal depression can negatively impact maternal and fetal health and shows a high rate of continuity postpartum [1, 2]. Not only does it impair the maternal quality of life, it also increases the risk of low birth weight, future neurodevelopmental problems and mood disorders among offspring [1, 3]. In addition, maternal depression often co-occurs with other pregnancy comorbidities, such as preeclampsia, gestational diabetes, and preterm labor [1].

Maternal depression is correlated with many psychological and obstetric factors [1–3]. However, the biological underpinnings of how these factors impact depression outcomes remain largely vague. Genetic vulnerability, sensitivity to changes in estrogen, progesterone, and cortisol levels are among the cited theories [4]. Recently, the inflammatory immune response has received special attention as an etiological mechanism for maternal depression [2–4]. Several cross-sectional and prospective studies have examined the correlation between various inflammatory markers and depression [2–7]. Other studies explore differences in vitamin D levels during pregnancy [8]. There is only one study that has examined the association between vitamin D, proinflammatory marker levels, and postpartum depressive symptoms in African women [9]. Similar studies involving pregnant women in Middle Eastern countries, including Iraq, are scarce.

Dramatic immune changes during pregnancy suggest a role for the inflammatory response in perinatal depression [10]. The first trimester is proinflammatory, allowing implantation and placentation [10]. The second trimester is anti-inflammatory to allow for rapid foetal growth and the third trimester is proinflammatory to prepare for delivery and parturition [10]. This corresponds to the epidemiological prevalence of antenatal depression being highest in the third trimester and lowest in the second trimester, further supporting the association between depression and inflammation [11]. Perinatal depression is associated with an increase in the level of centrally and peripherally produced proinflammatory cytokines [12]. In addition, poor marital relationships are associated with excessive inflammation in several studies [7, 13].

Cytokines are small protein messengers, secreted by immune cells that exert actions on all body tissues including the brain [12]. Studies indicate that circulating cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-a and C-reactive protein (CRP) are the most reliable biomarkers of inflammation in depressed patients [14]. Proinflammatory cytokines in the brain induce damage to neuronal cells and inhibit neuronal cell growth in the hippocampus, anterior cingulate and prefrontal cortex [15]. Cytokines such as IL-6 downregulate 5-hydroxytryptamine $_{1A}$ (5-HT_{1A}) receptors in the region essential for the regulation of emotion and psychomotor function [12]. These cytokines can also stimulate general markers of inflammation, such as CRP [12]. Studies in pregnant women provided mixed results; some studies reported a positive association (IL-6, CRP) [2, 6] and other studies reported a negative association (IL-6) [13] or no association [7].

The role of vitamin D in depression stems from the abundance of vitamin D receptors in regions of the brain implicated in depression pathophysiology, and the presence of the alpha-1 hydroxylase enzyme that converts vitamin D to the physiologically active form [16]. In addition, vitamin D has neuroprotective effects by upregulating glutathione and antioxidant enzyme production, thus reducing oxidative damage to neuronal cells and enhancing neurotrophin production and release [16]. Furthermore, vitamin D modulates the transcriptions of genes required for the synthesis of Gamma-aminobutyric acid (GABA), dopamine, and serotonin [16, 17]. Moreover, a vitamin D deficiency impairs serotonin and dopamine neurotransmission in animal studies [17].

The role of vitamin D as an immunomodulator is supported by the presence of vitamin D receptors on most immune cells, including lymphocytes, monocytes and macrophages [16]. In addition, immune cells can locally activate vitamin D by converting 25-hydroxy vitamin D (25-OH-D) to 1,25 dihydroxy vitamin D [16]. Vitamin D as an immunoregulator can suppress the production of proinflammatory cytokines [18] and therefore, may mitigate depressive symptoms in pregnant women by virtue of its anti-inflammatory and immunomodulation properties [9].

A systematic review and meta-analysis of 31,424 non-pregnant women show a statistically significant association between vitamin D deficiency and a clinical diagnosis of depression [19]. Studies relating to the association between vitamin D levels and depressive symptoms during pregnancy are inconclusive [20]. A recent study of 4236 pregnant women, recruited to assess the impact of vitamin D levels on antenatal depression,

indicates that those with lower levels of vitamin D had higher depression scores compared to those with a higher level [21]. Another study shows a negative association between vitamin D concentration during the early stages of pregnancy and antenatal depression [22]. However, other studies failed to find an association with antenatal depressive symptoms [20, 23].

Despite the high prevalence of depression during the perinatal period and the negative impact of perinatal depression on maternal and fetal outcomes [2], there is a scarcity of evidence regarding inflammatory markers and vitamin D levels in pregnant women with depressive symptoms in Iraq. We sought to (1) examine association between inflammatory markers, vitamin D and antenatal depressive symptoms and determine whether third trimester inflammatory biomarkers and vitamin D concentrations can predict postpartum depressive symptoms; (2) examine association between inflammatory markers and vitamin D; (3) assess the impact of poor marital relationship on biomarkers, given its association with depression and inflammation [7], as well as other factors such as age, parity, and BMI; and (4) investigate changes in depressive symptoms from pregnancy to postpartum and determine whether antepartum depressive symptoms can predict postpartum depression score. We did this by using the Edinburgh Postnatal Depression Scale (EPDS) as a measurement of depressive symptoms and focusing on two biomarkers (CRP, IL-6), most reliably associated with depression in clinical literature [14]. Clinical evidence consistently indicates that postnatal depression affect 10% of women between 3 and 6 months following childbirth with a higher rate in the early postpartum phase [24]. Accordingly, EPDS was administered at 6 months postpartum to determine the changes in the depressive symptoms postpartum.

Methods

Study design and setting

A prospective, observational study design was utilized to recruit healthy pregnant women from private obstetrics clinic in Baghdad, Iraq, from April to September 2021. Due to economic constraints, and the exploratory nature of the study, a sample size of 80 was deemed appropriate; women were recruited via convenience sampling methodology.

Ethical approval

The study was approved by Mustansiriyah University and the ethical committee of the Ministry of Health (reference no.: 16531; date 16 March 2021). Patients were verbally invited to participate, the study goals and procedures were explained to patients, and they were asked to provide written consent confirming their agreement to participate in the study.

Participant selection

Women were recruited from private obstetrics and the gynecological clinic in Baghdad, Iraq, from April to September 2021. Demographic, clinical and obstetric characteristics, psychological assessment questionnaires, and contact details were obtained during the interview, using a data collection form. Gestational age was determined by the last menstrual period and ultrasound, and body mass index (BMI) was measured upon enrolment. To screen for marital relationship quality, patients were asked to describe the relationship with their husbands as good, average, or poor.

The inclusion criteria for participants included pregnant women in the third trimester (28–39 weeks) with singleton gestation; they were aged between 18 and 39 years and had been assessed by an obstetrician as having a healthy pregnancy. Exclusion criteria applied to inflammatory and autoimmune conditions that might confound the study results, given their association with depression, including a history of depression, chronic or gestational hypertension, preeclampsia, chronic or gestational diabetes, asthma, rheumatoid arthritis, hepatitis, thyroid disorders, fetal anomalies and infection, as well as fever and use of anti-inflammatory medications, such as aspirin, non-steroidal anti-inflammatory drugs, steroids, or anti-depressants.

Psychological assessment

The EPDS was used to measure depressive symptoms. It comprises 10 multiple choice questions and each question has a (0–3) Likert scale, accounting for sum points estimates of 0–30, with a value of $\geq$ 13 indicating probable depression [25]. It is a reliable tool that measures psychological signs of depression and demonstrates high specificity and sensitivity in the current literature [25]. The Arabic version of EPDS was used and in a study by Ghubash et al., it demonstrated sensitivity and specificity of 91% and 84%, respectively [26]. Screening for depression was carried out at the baseline interview and again at 6 months postpartum through phone call.

Blood collection

Upon completion of the interview questionnaires, patients were asked to provide a 5-ml blood sample in the laboratory under aseptic conditions. Blood was transferred into a vacutainer, centrifuged to obtain serum, aliquoted into Eppendorf tubes, barcoded, and stored at – 20 °C until analyzed. The samples were collected during office hours between 1:30 pm and 5 pm. Due to diurnal

variation with the IL-6 test, the sampling time for each patient was recorded.

Analyses of biological markers

As recommended by the current literature, vitamin D status was assessed using the 25-OH-D level, as this is the most reliable marker for determining vitamin D status [27]. The 25-OH-D level was measured using a fully automated analyzer cobas e 411 (Roche Diagnostics, Mannheim, Germany) which employs patented ElectroChemiLuminescence (ECL). The minimum limit of detection is 3 ng/ml. In line with the Institute of Medicine, we defined vitamin D deficiency as serum 25-OH-D less than 20 ng/ml, insufficiency as 21–29 ng/ml and a sufficient level as ≥ 30 ng/ml [27].

The level of CRP was assessed using a fully automated analyzer cobas c 111 (Roche Diagnostics). IL-6 was measured using a fully automated analyzer Maglumi 800 (Snibe, Shenzhen, China). The assay employs the principle of sandwich chemiluminescence immunoassay and the limit of detection is 0.5–5000 pg/ml. All samples were tested anonymously.

Statistical analysis

Descriptive statistics were used to describe the sociodemographic and obstetric characteristics of the study population. Bivariate correlation was used to test the association between EPDS used as a continuous variable and the biological markers. Simple linear regression was used to estimate the association between depressive symptoms and biomarkers, if related to EPDS scores with a p value ≤ 0.20. One-way ANOVA was used to compare the mean of EPDS and biomarkers for three categories of marital relationship quality. Statistical analysis was performed using SPSS V.22.0, Chicago, IL, USA, and the differences were deemed to be significant if $p < 0.05$.

Results

Cohort characteristics

One hundred and thirty-two patients were interviewed and 52 were excluded. The reasons for exclusion included gestational DM ($n = 14$), gestational hypertension ($n = 10$), febrile illness ($n = 8$), taking aspirin ($n = 5$), urinary tract infection ($n = 4$), twin pregnancy ($n = 2$), history of depression ($n = 2$), under 18 years ($n = 2$), and hypothyroidism ($n = 2$). Other reasons included severe oligohydramnios, blood disorders and a hepatitis B virus infection ($n = 5$). Therefore, 80 patients were eligible for inclusion. The baseline characteristics are summarized in Table 1. The mean age of participants was 27.0 years (SD = 5.6 years, range 18–39 years) and all women were married and were non-smokers. One third of patients had a university education and the majority of participants (92.5%) were unemployed. Only 20% were primigravida and in terms of parity, 72.5% were multiparous; nearly one third of the women had a history of abortion. The majority (83.7%) reported a good relationship with their husbands. Thirty-one (38.7%) patients had an EPDS score of ≥ 13. The mean antenatal EPDS scores were 8.3, 13.6, and 13 for good, average, and poor marital relationships, respectively ($p = 0.023$). The mean of the postpartum EPDS scores was 6.1, 9.9, and 16.5 for good, average, and poor marital relationships, respectively ($p = 0.006$). Women expecting a female baby had a 3.08 higher antenatal EPDS score compared to those having a male baby (10.4 vs 7.3, $p = 0.037$). Table 2 illustrates the summary statistics of EPDS, CRP, IL-6, and 25-OH-D.

Table 1 Sociodemographic and obstetric characteristics of the study population

Variables	Total (80 patients) *N* (%) or mean (S.D)
Age (years)	27.0 (5.6)
Education	
Illiterate	1 (1.2)
Primary	32 (40)
Middle	14 (17.5)
Secondary	9 (11.2)
University	24 (30)
Employment	
Employed	6 (7.5)
Unemployed	74 (92.5)
BMI	30.1 (4.5)
Gestational age upon enrollment	33.0 (3.3)
Gravida	
Primigravida	17 (21.2)
Multigravida	63 (78.7)
Parity	
Nulliparous	22 (27.5)
Multiparous	58 (72.5)
History of abortion	
Yes	23 (28.7)
No	57 (71.2)
Marital relatonship	
Good	67 (83.7)
Average	10 (12.5)
Poor	3 (3.7)
Fetal gender [a]	
Female	48 (62.3)
Male	29 (37.6)

BMI Body mass index

[a] Available for 77 women

Table 2 Descriptive statistics of EPDS and biomarkers

Variable	Range	Mean	SE	SD	Median
Antepartum EPDS	21.00	9.10	0.71	6.35	9.50
Postpartum EPDS	23.00	7.04	0.72	5.37	6.00
CRP (mg/l)	20.10	5.54	0.46	4.06	5.00
IL-6 (pg/ml)	10.36	4.05	0.31	2.54	3.40
25-OH-D (ng/ml)	26.90	10.00	0.69	6.21	8.00

EPDS Edinburgh Postpartum Depression Scale, *CRP* C-reactive protein, *IL-6* interleukin-6, *25-OH-D* 25-hydroxy vitamin D, *SE* Standard error, *SD* Standard deviation

Table 3 Biomarkers association with antepartum and postpartum EPDS score

Variables	Antepartum EPDS score		Postpartum EPDS score	
	Spearman's rho	*P* value	Spearman's rho	*P* value
CRP	0.16	0.153	0.25	0.065
IL-6	− 0.24	0.049	− 0.18	0.224
25-OH-D	− 0.05	0.648	0.10	0.460

EPDS Edinburgh Postpartum Depression Scale, *CRP* C-reactive protein, *IL-6* interleukin-6, *25-OH-D* 25-Hydroxy vitamin D

The values of biomarkers and postpartum EPDS scores were square root transformed to decrease non-normality, in order to meet the assumptions of the linear regression test (Table 4).

The mean level of vitamin D in the study population was 10.0 ng/ml, with 45% of participants having vitamin D levels of 5–10 ng/ml; ninety-two percent had vitamin D levels below 20 ng/ml (Fig. 1). There was a statistically significant relationship between vitamin D levels and CRP levels ($p = 0.023$); however, no statistically significant association was observed between vitamin D and IL-6 levels (Table 5).

Marital relationship and biomarkers

The correlation between CRP and marital agreement was investigated with a one-way ANOVA test, using the CRP level as the dependent variable. There was a statistically significant difference in CRP levels between at least two groups ($F(2,76) = [8.32]$, $P = 0.001$). Turkey's HSD test for multiple comparisons found that the mean value of CRP was significantly different between good and poor marital relationship groups ($p = 0.001$, 95% CI = [− 13.41, − 2.89]). There was no statistically significant difference in CRP levels between good and average relationship groups ($p = 0.123$) or between average and poor relationship categories ($p = 0.062$). In contrast, for vitamin D and IL-6, the model was not significant. Figure 2 illustrates the difference in the mean of CRP among the three categories of marital relationship quality.

Table 4 Linear regression analysis examining association between biomarkers and EPDS scores

Variables	Antepartum EPDS score				Sqrt Postpartum EPDS score			
Estimate		*P* value	95% CI	R^2	Estimate	*P* value	95% CI	R^2
Sqrt CRP	1.21	0.140	− 0.41, 2.83	0.03	0.58	0.061	− 0.02,0.77	0.06
Sqrt IL-6	− 2.54	0.040	− 4.96, − 0.12	0.06	− 0.42	0.160	− 1.03,0.17	0.04

Sqrt Square root, *CRP* C-reactive protein, *IL-6* interleukin-6, *EPDS* Edinburgh Postpartum Depression Scale

Antenatal depression symptomatology and biological markers

The values of CRP, IL-6, and 25-OH-D were skewed, as demonstrated by the Shapiro-Wilk normality test. Therefore, non-parametric tests of association were used to investigate the relationship between biomarkers and depression measures. Four values of vitamin D and 11 values of IL-6 were below the limit of detection; one value of CRP and two values of IL-6 were outliers and thus, were coded into SPSS as missing values. There was no correlation between IL-6 and the time of sampling, BMI or parity (Supplementary Table A1). However, there was a statistically significant association between CRP and BMI.

There was no statistically significant relationship between the antenatal EPDS score and CRP or vitamin D. In contrast, there was a statistically significant association between IL-6 and the EPDS score ($p = 0.049$) (Table 3).

Table 5 Bivariate correlation between biological variables

Variable 1	Variable 2	Spearman's rho	*p* value
25-OH-D	CRP	0.24	0.041
IL-6	CRP	0.18	0.151
25-OH-D	IL-6	-0.11	0.380

25-OH-D 25-Hydroxy vitamin D, *CRP* C-reactive protein, *IL-6* interleukin-6

Postpartum depression symptomatology

Of the 80 participants, 56 (70%) were able to provide a 6 months postpartum depression screen. Only 12/56

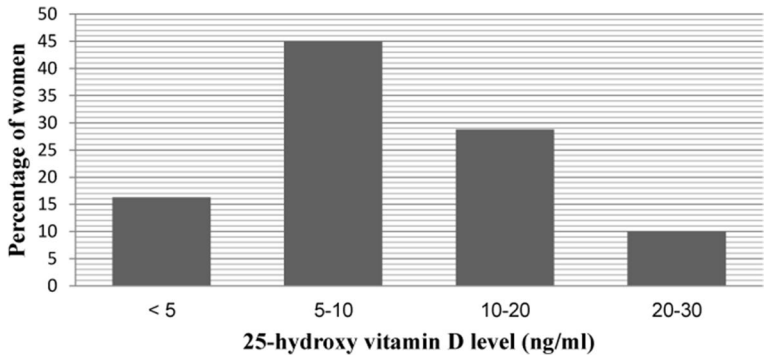

Fig. 1 Vitamin D level of the study population

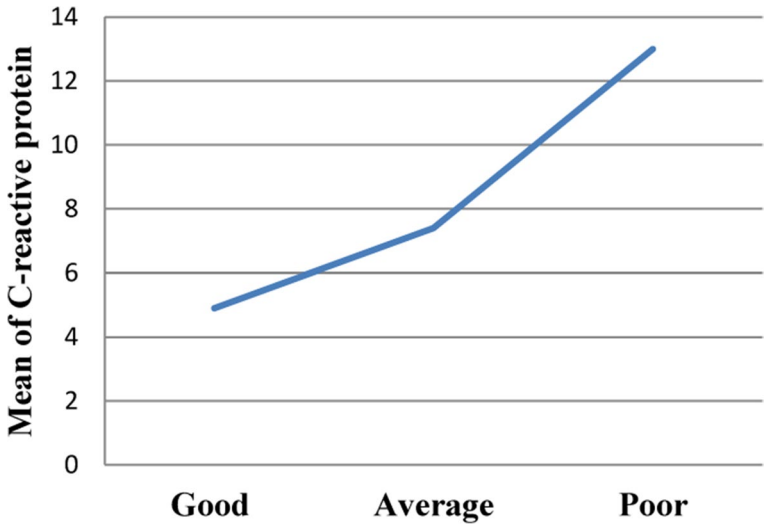

Fig. 2 Mean of CRP for the three categories of marital relationship quality

(21.4) had EPDS of ≥ 13. The antepartum EPDS score was strongly associated with the postpartum EPDS score (Rho = 0.624, $p = 0.000$) and antepartum depressive symptoms were a significant predictor of the postpartum EPDS score ($p = 0.000$, $B = 0.180$, R^2 for the model = 0.976, CI (0.17–0.19)). The severity of postpartum depressive symptoms tended towards a positive association, with greater increases in CRP concentration during pregnancy ($p = 0.065$) (Table 3). In contrast, there was no statistically significant association between vitamin D, IL-6, and postpartum depressive symptoms.

Discussion

The present study aimed to assess depressive symptoms in association with inflammatory markers and vitamin D levels and to investigate the interaction between vitamin D and inflammatory markers among pregnant women in the third trimester. Contrary to our hypothesis, pregnancy depressive symptoms, measured by EPDS, were not associated with CRP or vitamin D levels. Antenatal EPDS scores were negatively associated with IL-6 and although not statistically significant, the severity of postpartum depressive symptoms tended towards a positive association, with greater increases in CRP concentration ($p = 0.065$). Nearly 92% of the study population met the criteria for vitamin D deficiency. As predicted, there was a statistically significant association between CRP and vitamin D concentration, and poor marital relationship significantly elevates CRP levels. Antepartum depressive symptoms were significant predictor of the postpartum EPDS score.

Our results are in line with earlier studies that found a negative association with IL-6 [13, 28] and no association between antepartum EPDS scores and CRP [3, 5]. The negative association between IL-6 and EPDS scores in our study may be due to an exaggerated immune response, as depressive symptoms activate

hypothalamic-pituitary-adrenal (HPA) axis, which promotes immune quiescence, leading to a lower IL-6 level [13]. A study carried out by Blackmore et al. did not find a link between depressive symptoms and proinflammatory cytokines during the second and third trimesters [7]. However, several other studies found an association between inflammatory markers and depressive symptoms during the first and second trimesters [6, 29]. While the relationship between inflammatory markers and depression in the general population shows consistency in many studies, a demonstration of this relationship in pregnant women remains inconsistent [7]. This may be due to pregnancy-induced immunomodulation, which may disguise the link with depressive symptoms [10, 12]. Inconsistent findings among studies may also be due to differences in instruments used to measure depressive symptoms, different cut-offs, the trimester in which the blood samples were collected and the methods used to measure the concentration of serum inflammatory markers. In addition, by excluding women with inflammatory conditions, perhaps we selected a subgroup of depressed pregnant women with a non-inflammatory phenotype.

Another issue is that most studies rely on serum or plasma inflammatory markers to correlate with depression scores. Only one study measured inflammatory cytokines in CSF in pregnant women, prior to having a caesarean section [15]. Although there was no relationship between antenatal depression and plasma inflammatory cytokines, depression scores and CSF inflammatory cytokines were positively correlated. Thus, depression may be reflected by central neuroinflammation in the absence of peripheral inflammation.

While the CRP level was not significantly elevated in women with postpartum depressive symptoms, the association was marginally significant. In addition, there was a statistically significant association between marital relationship quality and CRP levels. Stressors activate immune cells centrally and peripherally, to induce the release of inflammatory markers that lead to neurotransmission changes and altered behavior [29, 30]. Exposure to stressors, such as poor marital relationships is associated with inflammation through sympathetic, parasympathetic pathways, and HPA axis dysfunction [7, 31]. Thus, the crosstalk between the immune system and HPA may be disturbed, leading to excessive production of proinflammatory markers [7]. A high level of CRP has been associated with depression and cardiovascular mortality among the general population [2]. Excessive inflammation induces the tryptophan metabolizing enzyme, Indole Amine Pyrrole 2,3 dioxygenase, causing decreased production of serotonin in the synaptic cleft and at the same time increasing the production of neurotoxic substances through the kynurenine pathway [28]. A recent study proposes a model utilizing inflammatory cytokines and kynurenine metabolites that has > 99% probability of predicting depression in the third trimester [4].

We observed a relationship between vitamin D and CRP. Depression is speculated to alter the T helper1/T helper2 (Th1/Th2) balance of a normal pregnancy, favoring Th1 dominance and contributing to abortion or unfavorable pregnancy outcomes [12]. Vitamin D decreases Th1 activity and enhances Th2 activity, thereby enhancing pregnancy outcomes [32]. Vitamin D down-regulates the expression of proinflammatory cytokines and stimulates anti-inflammatory cytokines production, promoting placental function and development, while enhancing the placental tolerance of the fetus [9, 32]. An inverse relationship between CRP and vitamin D is also demonstrated among the general population in a large study in the UK [33]. The statistically significant association between BMI and CRP is due to low-grade inflammation induced by obesity. Even a modest increase in weight can raise CRP levels [34].

The lack of association between vitamin D and EPDS may be due to the high frequency of vitamin D deficiency in our sample. Vitamin D deficiency is common in many countries, such that it is reported to be affecting 33%, 67%, and 90% of the pregnant population in the USA, Iran, and Turkey, respectively [35]. A similar study in Iran reported an 87.6% prevalence of vitamin D deficiency [23]. Dermal sun exposure is the primary source of vitamin D [18, 35]; additional sources include fatty fish, fortified food and supplements [18, 35]. Low sun exposure, due to the religious costume, can contribute to the vitamin D deficiency in our sample.

To the best of our knowledge, this is the first study to assess the concentration of vitamin D and inflammatory markers in relation to the severity of depressive symptoms during pregnancy in the Middle East, including Iraq. Depression was assessed twice during the third trimester and at 6 months postpartum, using the well-validated tool EPDS [36].

Measurements of vitamin D, CRP, and IL-6 using a fully automated reliable analyzer were taken in large clinical laboratories. We focused on two proinflammatory biomarkers (CRP, IL-6) most reliably associated with depression [2, 14, 28]. CRP is a long-half life that detects low-grade chronic inflammation, which is the most commonly used inflammatory marker in psychiatric literature [2, 14]. Increased activity of CRP and IL-6 during pregnancy renders them suitable biomarkers for antenatal depression [2] and the inclusion of potential confounders of inflammatory biomarkers is another strength point.

Serum levels of IL-6 display circadian rhythm variation [37]. Samples were collected during clinic hours between 1:30 pm and 5:30 pm and the sampling time was

recorded for each patient. Studies indicate that there is a minimal variation in the serum level of IL-6 measured in the morning versus the afternoon, with a higher level at night and a low, stable level during the day [37]. In addition, statistical analysis showed no relationship between the collection time and the IL-6 serum level. Our study is moderate in size, however, most published studies are of a similar sample size [3, 5, 7, 9]. Our findings can be considered valid and reliable, given the consistency with previous studies conducted in this field.

Our sample included healthy pregnant women, thus, our findings may not be generalizable to a more diverse, obstetric population, including those with pregnancy-related complications such as gestational hypertension, diabetes, and other inflammatory conditions. Depression was assessed using a depression-screening tool, whereas assessment using a structured, clinical interview to confirm cases of depression could have bolstered our results.

Vitamin D deficiency is associated with adverse maternal and fetal outcomes, such as preterm labor, preeclampsia, and gestational diabetes [20]. Supplementation has been shown to decrease CRP and optimize blood pressure and blood glucose control [38]. Vitamin D supplementation is a cost-effective approach of meeting the increased requirement during pregnancy and enhancing maternal and fetal health and may be especially beneficial for those with clinically significant depressive symptoms [9]. This has led the Royal College of Obstetrics and Gynaecology in the UK to recommend daily vitamin D supplements to all pregnant women [39].

Although IL-6 is among the best-studied cytokines in depression, it cannot be used as the only predictor for diagnosis and treatment response evaluation. However, using a group of cytokines would provide more insight. An example is the cytokine scoring system developed by Xu et al., which uses the values of four cytokines to predict mortality in pediatric patients with septic shock [40]. A recent study has proposed a model that uses cytokines and kynurenine metabolites to predict third trimester depression [4].

Conclusions

The study findings show a significant association between third trimester depressive symptoms and IL-6 concentration, however, CRP and vitamin D levels do not correlate with perinatal depressive symptoms. We found that a poor marital relationship significantly elevates CRP levels. In addition, vitamin D level was associated with CRP level and antepartum depressive symptoms are significant predictor of the postpartum EPDS score. Future studies among a larger population with diverse socioeconomic characteristics and including women with pregnancy complications would provide a further insight into the role of inflammation in the etiology of perinatal depression. We also recommend a longitudinal assessment of inflammatory markers and depressive symptoms across three trimesters to track changes in symptoms and biomarkers levels, which will aid in understanding the mechanisms of neuroinflammation in perinatal depression.

Abbreviations

EPDS: Edinburgh Postnatal Depression Scale; IL-6: Interleukin-6; 25-OH-D: 25-hydroxy vitamin D; CRP: C-reactive protein; TNF-a: Tumor necrosis factor-a; 5-HT_{1A} receptor: 5-hydroxytryptamine $_{1A}$ receptor or serotonin 1A receptor; GABA: Gamma-aminobutyric acid; BMI: Body mass index; ECL: ElectroChemi-Luminescence; HPA axis: Hypothalamic-pituitary-adrenal axis; (Th1/Th2) balance: (T helper 1/T helper 2) balance.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43045-022-00241-w.

Additional file 1: Supplementary Table A1. Relationship between biomarkers and several confounders.

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Authors' contributions

All authors contribute to conception and design, analysis and interpretation of data, writing and revising the manuscript for important intellectual content. The authors read and approved the final manuscript.

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Availability of data and materials

Data is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by Mustansiriyah University and the ethical committee of the Ministry of Health (reference no.: 16531; date 16-3-2021). Patients were verbally invited to participate, the study goals and procedures were explained to patients, and they were asked to provide written consent confirming their agreement to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests to disclose.

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