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ORIGINAL ARTICLE

Role of Vitamin D and IL-6 in Preeclampsia

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ABSTRACT
Background: Marked changes in vitamin D levels in the third trimester have been proven to be associated with severe preeclampsia; however, changes in interleukin-6 (IL-6) levels haven't been demonstrated enough in previous studies.
Aim: To find the relationship between the incidence of vitamin D deficiency and an increase in IL-6 level and severe late-onset preeclampsia in the third trimester.
Methods: This prospective cohort study was performed at Maternity Hospital and Outpatient Clinics of Obstetrics and Gynecology Department Zagazig University Hospitals during the period from March 2023 till September 2023 on primigravida pregnant with a single viable fetus. All participants were divided into two groups: the first group was the severe late-onset preeclamptic group, which was based on blood pressure and the presence of proteinuria; the second group was the healthy normotensive pregnant control group, who had an average blood pressure reading and no proteinuria. All individuals had their levels of vitamin D and IL-6 tested.
Results: There was a significant difference between both groups regarding vitamin D, which was lower in the preeclampsia group than in the control group, and IL-6, which was higher in the preeclampsia group than in the control group.
Conclusion: There was a substantial link between 25(OH) vitamin D insufficiency, IL-6, and the development of preeclampsia. Vitamin D insufficiency may be a risk factor for severe late-onset preeclampsia and may aid in the prediction of severity.
Keywords: vitamin D, interleukin-6, preeclampsia.

INTRODUCTION

One major source of vitamin D, a steroid hormone, is UVB radiation exposure, which triggers production in the skin. The liver hydroxylates vitamin D to create 25 hydroxy vitamin D, or 25(OH) vitamin D **[1].**

Vitamin D deficiency in mothers is a well-known issue. There are clear global rates of low vitamin D deficiency among expectant moms **[2].**

Serum 25(OH) D levels less than 20 nmol/l (10 ng/ml) are considered vitamin D deficient. Approximately one billion individuals worldwide are deemed to have inadequate health, with those residing in Europe, the Middle East, China, and Japan being especially vulnerable **[3].**

Numerous biological mechanisms are involved in the etiology of PE, and there are several theories regarding how vitamin D levels may impact these processes. **[4].**

The function of vitamin D in reducing oxidative stress and proinflammatory reactions in PE, stimulating angiogenesis via VEGF and gene regulation, and lowering blood pressure via the renin-angiotensin system (RAS) **[3].**

There are immunosuppressive effects of vitamin D. In normal women; there is a correlation between elevated proinflammatory cytokine secretion and vitamin D insufficiency. Research conducted in vitro has demonstrated that 1, 25(OH)2 D3 can regulate the expression of TNF-α and IL-6 via inhibiting NF-κB. **[5].**

Moreover, it has been discovered that vitamin D inhibits T cell activation and proliferation and increases the formation of T-regulatory cells and IL-10 release, all of which are essential for maternal immunological tolerance and healthy placenta implantation **[6].**

Maternal vitamin D levels and the pathophysiological development of preeclampsia are growing interest. It has been documented that women with preeclampsia had noticeably higher serum levels of inflammatory cytokines, including IL-6, TNF-α, and IL-10. **[7].**

Preeclampsia is five times more likely to occur in mothers who are vitamin D deficient than in normotensive controls. Vitamin D insufficiency has been linked to higher rates of cesarean sections, hyperemesis gravidarum, preeclampsia, and gestational diabetes in mothers. **[8].**

METHODS

This prospective cohort study was performed at Maternity Hospital and Outpatient Clinics of Obstetrics and Gynecology Department Zagazig University Hospitals during the period from March 2023 till September 2023 on primigravida pregnant with a single viable fetus. Informed written consent was obtained from all women. Approval was obtained from the Zagazig University Institutional Review Board (IRB). The study was conducted according to the Helsinki Declaration.

Primigravida pregnant women in the third trimester with a single viable fetus were included in the study. Pregnant females with malformed fetuses, pregnant women suffering from chronic illnesses (such as persistent hypertension, diabetes (pregestational or gestational DM), aberrant parathyroid hormone, chronic renal and hepatic disorders, pregnant women taking vitamin D supplements, and pregnant women with a BMI greater than 35 were excluded from the study.

All subjects were split into a sever late onset preeclamptic group and a pregnant healthy normotensive control group based on blood pressure and the presence of proteinuria (normal blood pressure reading, no proteinuria).

Each patient was subjected to the following personal history taking: current pregnancy history, abdominal Examination, ultrasound, and laboratory investigations, including CBC, coagulation profile, liver and kidney function tests, random blood sugar, urine analysis, vitamin D, and IL-6 Levels. Serum levels of IL-6 were assessed using the ELISA technique (Sunrise, China). Vitamin D was measured using the enzyme immunoassay technique (Sunrise, China).

Care in Preeclampsia with Severe Features

Delivery is typically suitable when a diagnosis of severe symptoms of preeclampsia is made after 34 weeks of gestation. The disease severity and the probability of a successful induction determine the delivery route. However, whenever possible, attempts at vaginal delivery should be made, and routine obstetric indications should only warrant a cesarean section **[9].**

Regardless of gestational age, women with severe signs of preeclampsia who had nonreassuring fetal conditions, ruptured membranes, labor, or maternal distress were delivered. A woman diagnosed with severe signs of preeclampsia who was 32 weeks' gestation or older and had taken steroids was also delivered. Patients with hypertension and/or proteinuria who presented with severe, continuous headache, visual impairment, and right upper quadrant pain were handled very cautiously **[10].**

Expectant management of preeclampsia with severe features

Expectant therapy was considered if a patient fits the strict criteria outlined by **Sibai and Barton. [11]** Moreover, it comes with severe preeclampsia before 34 weeks of gestation but looks to be stable, and the fetal status is reassuring. Only in a tertiary center was this kind of management taken into consideration. Furthermore, regardless of gestational age, some authorities view delivery as the only acceptable course of action because it is always best for the mother. However, for a premature fetus, birth might not be the best option. Thus, expectant management may benefit the fetus in a properly selected population without significantly sacrificing maternal health **[12].** Before any decisions on the expectant management of these patients could be made, they were all assessed for twenty-four hours in a labor and delivery unit. Maternal and fetal evaluations during this time must demonstrate that there is no significant growth restriction or fetal distress. Maternal urine output also needs to be sufficient. Except for slightly raised liver function test results that are less than twice the usual value and manageable hypertension, the woman's laboratory findings must be essentially normal **[13].**

Every day, non-stress testing and ultrasounds should be done as part of fetal monitoring to check for the onset of oligohydramnios and decreased fetal movement. To confirm proper fetal growth, measurements were also made at 2-week intervals. Urine was collected for protein again throughout a 24-hour

period. Before 34 weeks, corticosteroids were given to the fetus in order to promote lung maturity. A daily blood test was conducted for LDH, uric acid, CBC counts, and liver function tests (LFTs). Patients were told to report any headache, altered vision, pain in the epigastrium, or reduced fetal movement **[9].**

Regardless of the length of each woman's pregnancy, all pregnant women and their unborn children were monitored beginning with the first day of each woman's pregnancy and continuing until the day she gave birth. There was documentation prepared that details the result of the newborn, including information such as the Apgar score, fetal growth, death, and weight, as well as admission to the NICU.

Patients and their neonates were followed up. Fetal outcomes included GA at delivery (weeks and days), birth weight (g), and Apgar score at 1 minute and 5 minutes. Maternal outcomes included serum Vit-D Level, serum IL-6 Level, and the occurrence of Preeclampsia and related complications.

STATISTICAL ANALYSIS

The collected data were computerized and statistically analyzed using the SPSS program (Statistical Package for Social Science) version 25.0. Means and standard deviations (SD) were calculated for continuous variables, and percentages were calculated for categorical variables. The Independent Samples t-test was used to compare the means of continuous variables between the two groups, and the Chi-square test was used to compare the proportions of categorical variables between the two groups. The p-value was calculated for each test to determine the statistical significance. A p-value of less than 0.05 was considered statistically significant.

RESULTS

There was no significant difference between the two groups in terms of maternal age, gestational age at blood collection, gestational age at delivery, or smoking status (Table 1). There was high significant difference between both groups as regard SBP and DBP (Table 2). There was high significant difference between both groups as regard Vitamin D and IL-6 (Table 3). There was a high significant difference between both groups as regard APGAR score (Table 4). 2 with Placental abruption, 1 with Acute renal failure, 1 with DIC, 4 with HELLP (Table 5). Twenty-two neonates need oxygen after delivery, and 20 with NICU admission (Table 6). Maternal hospital stay was 7±4 days, and ICU stay was 3±1 (Table 7).

Table 1: Demographic data of studied cases.

Mean	**1st Group (n=38)**	**2nd Group (n=38)**	**P**
Maternal age (year)	25.5±2.4	25.6±2.3	0.79
Gestational age at blood collection (wk)	26.1±2.2	26.0±2.5	0.82
Gestational age at delivery (wk)	35.5±1.4	36.9±1.8	0.80
Smoking status			
Yes	10	11	0.44
No	28	27	

Table 2: Vital signs and mode of delivery of studied cases.

	1st Group (n=38)	**2nd Group (n=38)**	**P**
SBP (mmHg)	155.3±14.81	115.00±5.4	**<0.0001***
DBP (mmHg)	97.50±8.88	75.00±7.8	**<0.0001***
BMI (kg/m2)	29.12±1.5	29.22±1.1	0.45
Mode of delivery CS Vaginal delivery	 25 13	 22 16	0.47

Table 3: Vitamin D and IL-6 of studied cases.

	1st Group (n=38)	**2nd Group (n=38)**	**P**
Vitamin D(ng/ml)	16.9±3.8	27.9±5.8	**<0.0001***
IL-6 (pg/ml)	4.5±1.52	2.5±0.50	**<0.0001***

Table 4: Neonatal outcome of studied cases.

	1st Group (n=38)	2nd Group (n=38)	P
Live birth	30 (78.9%)	33 (86.4%)	0.36
IUGR	4 (10.5%)	1 (2.6%)	0.16
APGAR score	7.1±1.5	8.5±0.5	**<0.0001***

Table 5: Complications among PE cases.

	N (%)
Placental abruption	2 (5.3%)
Acute renal failure	1 (2.6%)
DIC	1 (2.6%)
HELLP	4 (10.5%)
Pulmonary edema	0 (0%)
Maternal mortality	0 (0%)

Table 6: Neonatal complication among PE cases

	N (%)
Neonatal need for oxygen after delivery	22 (57.9%)
NICU admission	20 (52.6%)

Table 7: Duration of Maternal hospital stay

	N (%)
Hospital stay/days	7±4
ICU stay (Duration/days)	3± 1

DISCUSSION

The main way that vitamin D is obtained is through the hormone that the skin produces in reaction to UVB ray exposure. One such steroid hormone is vitamin D. It undergoes hydroxylation in the liver, which results in the formation of 25-hydroxyvitamin D (also written as 25(OH) vitamin D) **[14].**

Lack of vitamin D in mothers is a condition that is well-known to exist. There is evidence that a significant percentage of pregnant women around the world do not get enough vitamin D **[2].**

There are various hypotheses that explain how the levels of vitamin D may alter the biological processes involved in the pathogenesis of PE **[15].**

Vitamin D is responsible for regulating proinflammatory responses and lowering blood pressure through the renin-angiotensin system (RAS), reducing oxidative stress in PE, boosting angiogenesis through gene regulation and vascular endothelial growth factor (VEGF), and reducing oxidative stress in PE **[16].**

There is evidence that vitamin D can depress the immune system. In women who are otherwise healthy, a lack of vitamin D has been linked to an increased production of cytokines that contribute to inflammation. Studies conducted in vitro have demonstrated that 1, 25(OH)2 D3 has the ability to decrease NF-B, hence modulating the expression of IL-6 and TNF **[14].**

There has been a recent uptick in research into the role that a mother's vitamin D level plays in the pathophysiological processes that lead to preeclampsia. Serum concentrations of inflammatory cytokines, such as TNF-, IL-10, and IL-6, have been shown to be obviously higher in preeclamptic women, according to research that has been conducted **[15].**

Regarding our results, the study showed that the two groups did not differ much in terms of maternal age, gestational age at the time of blood collection, Gestational age at delivery, or Smoking status.

Mohammed et al. [17] aimed to evaluate the relationship between the third trimester of pregnancy preeclampsia and vitamin D insufficiency. In a prospective case-control study, 90 pregnant women between the ages of 27 and 40 weeks participated and were selected from the university hospital's outpatient clinic, and their 25(OH) vitamin D levels were estimated along with transabdominal ultrasounds. Preeclampsia cases were monitored till birth in order to evaluate the fetal outcome. The cases were split into two groups: preeclampsia (n = 60) and control (n = 30). The preeclampsia cases were split into two categories according to severity: mild preeclampsia (n = 40) and severe preeclampsia (n = 20). In terms of maternal age, gestational age (GA), and BMI, the two groups were matched.

This study shows a significant difference between the controls and the PE group, with a mean serum level of 25 (OH) in PE cases of 12.3 ±25.6, which coincides with our results.

Xu et al. [18] postulated that a shortage in vitamin D leads to raised levels of interleukin-6 (IL-6) and increased inflammation, which in turn accelerates the development of preeclampsia. The study found no statistically significant distinctions in maternal age, BMI, gestational age at the time of blood collection, ethnicity, or smoking history between preeclamptic and normotensive controls.

Regarding blood pressure, our study demonstrated a high significant difference between both groups as regard SBP and DBP. This was in agreement with **Mohammed et al. [17],** who reported that the blood pressure differences between the two groups were extremely significant. This may be due to the classification of the study groups into two groups regarding the occurrence of preeclampsia.

Regarding the measuring of Vit -D and IL-6 in both groups, this study shows that there were high significant variation in vitamin D levels between the two groups and IL-6. This was in agreement with **Mohammed et al. [17],** who reported that serum 25(OH) vitamin D levels in moderate, severe, and controlled preeclampsia patients differed significantly. Serum 25(OH) vitamin D levels were considerably lower in severe preeclampsia cases compared to control groups and mild preeclampsia, where the mean serum level was 7.3 ± 25.6.

Mohammed et al. [17] found that just 6% of the preeclamptic individuals had normal vitamin D concentrations, whereas 62% had vitamin D insufficiency and 32% had severe vitamin D deficiency. Women with preeclampsia had plasma 25(OH)D concentrations that were 19% lower than those of controls (p = 0.01). A favorable correlation was found (p = 0.02) between a vitamin D deficiency and an elevated risk of preeclampsia.

Wetta et al. [18], who conducted a case-control study and evaluated serum 25(OH) vitamin D levels, concluded that there was no significant difference in mean serum 25(OH) vitamin D levels between women with preeclampsia and controls (p.value = 0.46). Our results were inconsistent with their findings. This difference was because **Wetta et al. [18]** performed their study on patients with different demographic data and age groups.

Singla et al. [20] measured the serum 25(OH) vitamin D level in both normotensive and preeclamptic cases. Researchers found that preeclamptic subjects had a mean serum 25(OH) vitamin D level that was considerably lower (mean±SD 9.7± 4.95 ng/ml) than normotensive controls (14.8 ± 6.68 ng/ml), with a p-value of 0.0001. The findings of **Singla et al. [20]** were consistent with our research.

Preeclampsia affected 74 pregnant women, of whom 28 had severe preeclampsia, 46 had mild preeclampsia, and 75 healthy pregnant women participated in a case-control study conducted by **Hashemipour et al. [21].** They discovered that in the normal, the mean serum 25(OH) vitamin D level for the mild preeclampsia, severe preeclampsia, and 22.9±15.9 groups was 27.7±15.3, 22.9±15.9, and 27.6±16.6; hence, there was no difference in 25(OH) vitamin D deficiency across the groups (P >0.05). The study found no correlation between the severity of preeclampsia and 25 (OH) vitamin D insufficiency. So **Hashemipour et al. [21]** were different than ours, this may be due to the fact that not all the pregnant women were in the third trimester, and some of them were not primigravida.

The current study found that the preeclamptic group's mean maternal vitamin D concentrations and the normal pregnancy group were as follows: among the 38 controls, the mean concentration of 25(OH)D was 27.9±5.8 nmol/L. Thirty-eight participants had 25(OH)D values < 25 nmol/L, indicating severe vitamin D insufficiency.

Xu et al. [18] revealed that the preeclamptic group's and the normal pregnancy group's mean vitamin D levels in mothers. The 100 controls had a mean 25(OH)D concentration of 49.4 ± 22.6 nmol/L. Vitamin D deficiency was severe in thirty patients (25(OH)D concentrations < 37.5 nmol/L); vitamin D insufficiency was present in fifty-four

patients (25(OH)D concentrations < 37.5 nmol/L); and normal vitamin D concentrations were present in sixteen subjects (above 75 nmol/L). The mean 25(OH)D concentration in the preeclampsia group was 42.3 ± 17.3 nmol/L. Vitamin D concentrations (40.1 ± 14.6 nmol/L) were found to be lower in patients who fulfilled at least one HELLP criterion. Just 5% of the 100 preeclamptic individuals had normal vitamin D concentrations, while 41% and 54% of them had insufficient levels and significant vitamin D deficiency. Plasma 25(OH)D concentrations were 14% lower in preeclamptic women than in control subjects (p = 0.01). They found a correlation (p=0.03) between a vitamin D deficit and a higher risk of preeclampsia.

Xu et al. [18] revealed that the preeclampsia and control groups had median (Q1, Q3) IL-6 concentrations of 4.4 (2.2, 10.0) pg/ml and 2.0 (1.3, 3.4) pg/ml, respectively (p < 0.01). Using the higher quartile of preeclamptic women as the threshold, 7% of the non-preeclamptic women were assigned to the increased IL-6 group (p < 0.01).

This study cleared that 5.3% of cases with placental abruption, 2.6% with acute renal failure, 2.6% with DIC, and 10.5% with HELLP.

Mostafa et al. [22] revealed that the percentage of IUGR was 13%. Furthermore, neonatal outcomes showed that 67% and 62% of newborns required oxygen after birth and were admitted to the NICU, respectively. 69% of live births occurred at an earlier birth time. Furthermore, 47% of newborns had an APGAR score of less than 7.

This study reported that 22 Neonates needed oxygen after delivery, 20 with NICU admission, Hospital stay/days were 7±4, and ICU stay (Duration/days) were 3±1.

Mostafa et al. [22] revealed that the average length of hospital and intensive care unit stays were 7±4 and 3±1 days, respectively. The only significant factor that affected the incidence of NICU hospitalization and low APGAR score was gestational age.

PE showed a strong, statistically significant correlation with both vitamin D and IL-6.

Xu et al. [18] demonstrated that Vitamin D concentrations, IL-6, and the risk of preeclampsia were examined using logistic regression analysis. Elevated IL-6 was associated with four times increased chances of preeclampsia (odd ratio = 4.43, 95% CI (1.82, 10.80), p = 0.001). Vitamin D deficiency resulted in a quadrupling of the odds of preeclampsia (odd ratio = 4.23, 95% CI (1.40, 12.81), p = 0.038), whereas vitamin D insufficiency caused the odds to triple (odd ratio = 3.26, 95% CI (1.12 9.54), p = 0.038).

Xu et al. [18] tested the theory that high levels of IL-6 would accompany low vitamin D levels in preeclamptic women. First, women with and without vitamin D deficiency did not significantly vary in the prevalence of IL-6 rise (27.1% vs. 22.0%, p = 0.56). Next, they determined the Spearman correlation coefficient (ρ = 0.22, p = 0.03) between the ranking concentrations of IL-6 and vitamin D. In preeclamptic women, there was no evidence of a negative connection, indicating that low IL6 and high vitamin D are unrelated. In addition, a linear regression model was utilized to evaluate the correlation between Vitamin D and log transformed IL-6, confirming that there was no significant relationship between low Vitamin D concentrations and high IL-6 concentrations. Similarly, they included all 200 participants for these analyses, 100 control people and women with or without preeclampsia, and found no evidence of a link between elevated IL-6 and insufficient vitamin D.

CONCLUSIONS

We concluded that there was a link between 25(OH) vitamin D insufficiency, IL-6, and the occurrence of preeclampsia. Vitamin D insufficiency may be a risk factor for severe preeclampsia and may aid in predicting its severity.

Conflict of interest: None
Financial Disclosure: None

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