

# THE RISK OF LOW VITAMIN D IN THE DEVELOPMENT OF PREECLAMPSIA



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## ABSTRACT

### *Background*

Preeclampsia is new-onset hypertension and proteinuria after 20 gestational weeks. A low vitamin D level is thought to associate with a higher risk of preeclampsia.

### *Objectives*

We aimed to find the association of serum vitamin D levels with preeclampsia in our population, in which vitamin D deficiency is common.

### *Patients and Methods*

A prospective cohort study was performed on 80 pregnant women who were admitted to Sulaimani Maternity Teaching Hospital, Sulaimani, Kurdistan, Iraq. The women were collected from October 1, 2019, to March 13, 2020. The women were randomly selected and enrolled into three groups according to their clinical features of preeclampsia; no features of preeclampsia, a mild degree of preeclampsia, and severe form of preeclampsia. The inclusion criterion was pregnant women, and exclusion criteria were women with a history of hypertension, history of proteinuria before pregnancy, and refusal to participate. Demographic features and detailed clinical examination were recorded. Also, the serum vitamin D (ng/dL) was measured by Cobas ® 6000 analyzer machine (F. Hoffmann-La Roche Ltd).

### *Results*

The mean  $\pm$  SD (standard deviation) of participants' age was  $31.33 \pm 6.05$  years, and there were no significant differences in demographic features among the three groups. Systolic and diastolic blood pressures among the three groups were significantly different. There was no significant association between pregnant women and serum vitamin D levels. However, all of the preeclamptic women had either deficient or insufficient serum vitamin D levels.

### *Conclusion*

There was no significant association between serum vitamin D levels in pregnant women and the occurrence of preeclampsia.

**Keywords:** *Preeclampsia; Vitamin D; Pregnancy; Sulaimani.*

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## INTRODUCTION

Preeclampsia is defined as new-onset hypertension and proteinuria after 20 weeks of gestation <sup>(1)</sup>. It is a multisystem disorder, and a significant worldwide cause of maternal and perinatal mortalities and morbidities <sup>(2)</sup>. About 2-8% of pregnant women are afflicted with preeclampsia <sup>(3)</sup>.

Preeclampsia can rapidly progress and lead to multiple organ failure, swelling, headaches, convulsions, and stroke <sup>(4)</sup>. The diagnosis of preeclampsia depends on two nonspecific signs, which are progressive proteinuria and hypertension <sup>(1,4)</sup>. The diagnostic value of these two classical signs is limited, especially when women have preexisting hypertension and proteinuria <sup>(1)</sup>.

Women who had preeclampsia have a higher risk of developing cardiovascular diseases many years postpartum, and preeclamptic pregnancy and premature birth itself predispose neonates to develop chronic diseases later in life <sup>(4)</sup>.

The exact mechanism and etiologies of preeclampsia are still unclear. Its heterogeneous nature is suggesting multiple mechanisms for its occurrence <sup>(5)</sup>. The placenta had been considered the organ that was essentially involved in preeclampsia's pathogenesis <sup>(2)</sup>. Further, the severity of preeclampsia is due to the maternal response to placental factors <sup>(2)</sup>.

The defect of the placenta in early pregnancy results in poor differentiation of trophoblast, and villous maturation, and villous trophoblast turnover impairments <sup>(2)</sup>. Moreover, cells on the cellular level develop the capability of maintaining their integrity in response to environmental stresses, in turn, activating the autophagy process <sup>(2)</sup>. If a cell failed to keep its integrity, it enters into the apoptosis process <sup>(2)</sup>. The main regulation of autophagy is made through nutrition <sup>(2)</sup>. One of the nutritional factors is vitamin D, 25-hydroxyvitamin D [25OHD], and its receptor, which is highly associated with the autophagy process and has central roles, through genomic and nongenomic actions, in cell processes like proliferation, differentiation, and immunometabolism <sup>(2)</sup>.

A low serum level of vitamin D in pregnancy is associated with a higher risk of developing preeclampsia <sup>(3)</sup>. However, no association was found between a high level of serum vitamin D and the development of preeclampsia in pregnant women. Vitamin D affects peripheral blood gene expression during pregnancy, and

therefore, it results in the development of preeclampsia due to underlying molecular mechanisms <sup>(3)</sup>.

The only effective treatment for preeclampsia is placental delivery, regardless of the gestational age <sup>(6)</sup>. Therefore, it is essential to find out the real cause of preeclampsia.

### Objectives

We aimed to find out the association of serum vitamin D levels with preeclampsia in our population, in which vitamin D deficiency is common.

## PATIENTS AND METHODS

This was a prospective cohort study that included 80 pregnant women who were admitted to the wards and labor room in Sulaimani Maternity Teaching Hospital, Sulaimani city, Kurdistan Region, Iraq. The women were collected during the period from October 1, 2019, to March 13, 2020. The women were randomly selected by using a simple random sampling method, and then, the women enrolled in three groups according to their clinical features of preeclampsia; a group with no features of preeclampsia (control), a group with mild preeclampsia (blood pressure  $\geq 140/90$  on two occasions of at least six hours apart but within one week), and a group with severe preeclampsia (blood pressure  $\geq 160/110$  on two occasions of at least six hours apart but within one week) <sup>(7)</sup>.

Research Ethical Committee of the Kurdistan Board of Medical Specialties (KBMS) approved the study proposal, and a formal acceptance letter was obtained from Sulaimani Maternity Teaching Hospital before starting the study. Also, written informed consent has been taken from the women for their recruitment in the study.

The inclusion criterion was pregnant women, and the exclusion criteria were women with a history of hypertension and or proteinuria and refusal to participate in the study.

The demographic features, including maternal age, smoking habits, and residencies, were taken. Clinical examination, including clinical features of preeclampsia and blood pressure, was assessed. Proteinuria was investigated by general urine examination (GUE) <sup>(8)</sup>. Also, the serum vitamin D (ng/dL) was measured by using Cobas ® 6000 analyzer machine (F. Hoffmann-La Roche Ltd) <sup>(9)</sup>.

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The “GPower 3.1” statistical program was used for the estimation of sample size, and the effect size of (0.5) and P-value of  $\leq 0.05$  were chosen. The estimation yielded 80 samples; thence, the sample size of 80 women for the study was chosen. By this, the power of the study became ( $>95\%$ )<sup>(10)</sup>.

The “IBM SPSS Statistics version 25” program was used for the analysis of the data, and both descriptive and inferential statistics were used. Further, means and standard deviation (SD) were used for continuous variables, and frequencies, as well as percentages, were used for categorical variables. Besides, a p-value of ( $\leq 0.05$ ) was considered statistically significant associations. Also, Pearson Chi-Square was used to find out the significance of the association between categorical independent and dependent variable pairs.

### RESULTS

The mean  $\pm$  SD (standard deviation) of the ages of all the participants was  $31.33 \pm 6.05$  years, and the obstetrical history of all the women is shown in Table 1. Also, there was no significant difference in demographic features among the three groups of participants, (Tables 1-3).

There was no statistically significant difference in ages among the three groups (Table 2).

Although most of the participants were from urban areas, there was no significant difference in participants’ residence (Table 3). Also, the smoking habit among the participants was statistically none significant, (Table 3).

The systolic and diastolic blood pressures among the three groups were significantly different (Table 4). However, serum vitamin D level was statistically none significant among the three groups, (Table 4). The results of the currents study showed no significant association between pregnant women who were afflicted with preeclampsia with serum vitamin D levels, although all of the preeclamptic women were afflicted with either deficient or insufficient levels of serum vitamin D (Table 5).

**Table 1. Demographic features of the participants**

<b>Variables</b>		<b>PE groups (%)</b>				<b>p value</b>
		<b>Mild PE</b>	<b>Severe PE</b>	<b>Control</b>	<b>Total (%)</b>	
<b>Age (year)</b>	Mean $\pm$ SD (range)	30.45 $\pm$ 6.35 (12-38)	32.4 $\pm$ 6.62 (18-43)	30.83 $\pm$ 5.1 (19-39)	31.33 $\pm$ 6.05 (12-43)	0.166
<b>Gravida</b>	Mean $\pm$ SD (range)	2.79 $\pm$ 1.12 (1-4)	3.88 $\pm$ 2.21 (1-10)	2.23 $\pm$ 0.92 (1-4)	3.03 $\pm$ 1.75 (1-10)	0.136
<b>Para</b>	Mean $\pm$ SD (range)	1.57 $\pm$ 1.09 (0-3)	2.36 $\pm$ 2.02 (0-9)	1.18 $\pm$ 0.91 (0-3)	1.75 $\pm$ 1.57 (0-9)	0.427
<b>Miscarriage</b>	Mean $\pm$ SD (range)	1 $\pm$ 0 (1-1)	1.33 $\pm$ 1.23 (0-4)	0.5 $\pm$ 0.71 (0-1)	1.14 $\pm$ 1.03 (0-4)	0.635
<b>Dead baby</b>	Mean $\pm$ SD (range)	1 $\pm$ 0 (1-1)	1 $\pm$ 0 (1-1)	0 $\pm$ 0 (0-0)	1 $\pm$ 0 (0-1)	0.500

PE = preeclampsia; SD = standard deviation

Table 2. Distribution of ages among the participants.

Age groups (year)	PE groups (%)			Total (%)	p-value
	Mild PE	Severe PE	Control		
12-19	1 (1.3)	1 (1.3)	1 (1.3)	3 (3.8)	0.166
20-29	6 (7.5)	9 (11.3)	10 (12.5)	25 (31.3)	
30-39	13 (16.3)	15 (18.8)	19 (23.8)	47 (58.8)	
40-43	0 (0)	5 (6.3)	0 (0)	5 (6.3)	
<b>Total</b>	20 (25)	30 (37.5)	30 (37.5)	80 (100)	

PE = preeclampsia

Table 3. Residence and smoking habit of the participants.

Variables		PE groups (%)				p values
		Mild PE	Severe PE	Control	Total (%)	
Residency	Urban	11 (13.8)	20 (25)	24 (30)	55 (68.8)	0.317
	Suburban	7 (8.8)	9 (11.3)	4 (5)	20 (25)	
	Rural	2 (2.5)	1 (1.3)	2 (2.5)	5 (6.3)	
Smoking	Yes	2 (2.5)	2 (2.5)	0 (0)	4 (5)	0.246
	No	18 (22.5)	28 (35)	30 (37.5)	76 (95)	

PE = preeclampsia

Table 4. Blood pressure and serum vitamin D level among the groups.

Variables		PE groups (%)				p values
		Mild PE	Severe PE	Control	Total (%)	
SBP (mmHg)	Mean±SD (range)	150±9.18 (130-160)	164.29±16.43 (130-220)	100±8.7 (90-125)	156 ± 19.06 (90-220)	<0.001
DBP (mmHg)	Mean±SD (range)	95.25±4.72 (90-100)	108.75±12.44 (90-140)	62.5±3.54 (60-95)	101.5 ± 14.22 (60-140)	<0.001
Vitamin D (ng/mL)	Mean±SD (range)	10.28±3.78 (4.77-16.8)	10.49±5.63 (3-23.58)	15.02±6.19 (7.5-33.08)	12.13 ± 5.85 (3-33.08)	0.335

DBP = Diastolic blood pressure; PE = preeclampsia; SBP = Systolic blood pressure; SD = standard deviation

**Table 5. Association of preeclampsia with serum vitamin D level.**

PE	Vitamin D groups (%)			Total (%)	p-value
	Deficient (≤20 ng/mL)	Insufficient (21-30 ng/mL)	Normal (30-50 ng/mL)		
Mild PE	20 (25)	0 (0)	0 (0)	20 (25)	0.335
Severe PE	27 (33.8)	3 (3.8)	0 (0)	30 (37.5)	
Control	25 (31.3)	4 (5)	1 (1.3)	30 (37.5)	
<b>Total</b>	72 (90)	7 (8.8)	1 (1.3)	80 (100)	

PE = preeclampsia

## DISCUSSION

Vitamin D is a fat-soluble vitamin that can be produced endogenously when the ultraviolet light of the sun exposes the skin <sup>(11-12)</sup>. Vitamin D is necessary for the homeostasis of phosphorus and calcium, regulation of proliferation, differentiation, and apoptosis of the body cells, hormonogenesis, and other body physiological mechanisms <sup>(11)</sup>. Besides, vitamin D deficiency during pregnancy had been shown to have associations with many maternal and fetal complications, such as early labor <sup>(13-17)</sup>. Further, despite adequate sunlight exposure, vitamin D deficiency is common in our Kurdish population like other populations <sup>(11, 13)</sup>. Moreover, the real cause(s) for preeclampsia is (are) still unclear despite suggesting multiple mechanisms for its occurrence <sup>(5)</sup>.

Furthermore, the only effective management for preeclampsia is delivery of placental despite the gestational age <sup>(6)</sup>. Thence, it is essential to find out the real cause of preeclampsia. Therefore, as vitamin D has a central role in many body processes <sup>(18)</sup>, we tried to find out the association of serum vitamin D levels with preeclampsia in the current study.

In the current study, we tried to compare three groups of participants; a group with mild preeclampsia, a group with a severe form of preeclampsia, and a group of healthy pregnant women. Also, we tried to eliminate as many confounders between the three groups of participants as possible. As they were shown in Tables 1-3, there were no significant statistical differences between the ages, obstetrical history, residency, and smoking habits of the participants. However, there were statistically significant differences between the participants' blood pressure components in the three groups (Table 4), and these were required.

Our results showed a statistically none significant association between serum vitamin D levels of

pregnant women with the occurrence of preeclampsia (Tables 4-5), although all of the preeclamptic women were afflicted with either deficient or insufficient levels of serum vitamin D (Table 5). A meta-analysis in Cochrane Library done by Palacios et al. <sup>(19)</sup> found that vitamin D supplementation would probably reduce preeclampsia risk. Also, the systematic review and updated meta-analysis of Akbari et al. <sup>(20)</sup> found that women with vitamin D deficiency at a cutoff of 20 ng/ml were more at risk of being afflicted with preeclampsia, and therefore, they suggested starting vitamin D supplementation before pregnancy. In contrast, our results showed an overall serum vitamin D level of <20 ng/mL (Table 4), and most of the participants (90%) in all the three groups were having a deficient level of serum vitamin D (Table 5). Despite all the participants, except one (1.3%) in the control group, were affected with either deficient (90%) or insufficient (8.8%) level of vitamin D, the association of serum vitamin D with the three groups was statistically none significant (Tables 4-5). Our results are compatible with the findings of the systematic review performed by Purswani et al. <sup>(21)</sup>, in which they found inconsistent evidence for supporting vitamin D as a cause for preeclampsia.

In conclusion, the results showed no significant association between serum vitamin D levels in pregnant women and the occurrence of preeclampsia. Also, almost all of our participants had either deficiency or insufficiency of serum vitamin D. Therefore, we suggest vitamin D supplementation, not only as prophylaxis of PE in pregnant women but for all who are deficient or insufficient.

### Conflict of interest

The authors declare no conflict of interest.

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