

Comparison of Serum level of Vitamin D in Pregnant Women with Preeclampsia and a Control Group in Ayatollah Mousavi Hospital in Zanjan

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ABSTRACT

Background & Objective: Conflicting results have been reported about the association between vitamin D and preeclampsia. The aim of the current study is to compare the serum levels of vitamin D in preeclamptic, and non-preeclamptic pregnant women admitted to the Ayatollah Mousavi Hospital in Zanjan.

Materials & Methods: In this case-control study, 120 pregnant women were selected using convenience sampling in Zanjan in 2018-2019. Then they were divided into two groups, preeclampsia and non- preeclampsia. Both groups were matched one by one. The data were collected using a demographic information questionnaire and a researcher-made checklist. After obtaining consent from participants, blood samples were collected using the peripheral venous catheter. Then the ELISA test was used to measure vitamin D in participants. Data were analyzed by SPSS version 16 using, independent t-test, and Chi-square test ($P \leq 0.05$).

Results: Of the participants, 64 (53.4 %) were between 20-35 years old, 48 (40%) were older than 35 years, and 8 (6%) were younger than 20 years. Most of the participants' gestational age was between 34 and 39 weeks (89.1%). The Mean (SD) of serum level of vitamin D was significantly higher in healthy pregnant women (19.06 (7.48)) than women with preeclampsia (16.60 (5.87)) ($P < 0.01$). Among those with preeclampsia, the highest vitamin D level (17.17) was observed at 37-39 weeks of gestation. The lowest level (10.8) was for those with less than 34 weeks gestational age.

Conclusion: This study demonstrated that vitamin D could be a protective factor for preeclampsia in pregnant women. However, further studies are recommended.

Keywords: Preeclampsia, Pregnancy, Outcomes, Vitamin D



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Introduction

Vitamin D deficiency in pregnant women is a worldwide public health problem (1). Vitamin D is a steroid hormone that has an important role in the innate immune system as well as several cellular activities (2). Vitamin D deficiency during pregnancy is associated with many short- and long-term problems for fetuses and infants, including developmental delay, skeletal problems, type 1 diabetes, asthma, and schizophrenia (3, 4).

There are two main reasons for the epidemic of vitamin D deficiency in pregnant women: insufficient sun exposure and low vitamin D intake from diet, so

even taking 400 IU/day of a multivitamin during pregnancy won't prevent vitamin D deficiency (1, 5, 6).

Vitamin D stimulates the immune response in the decidua tissue of the placenta, which results in its healthier activity (7). Some studies mentioned the imbalance of placental biomarkers and vitamin D deficiency as risk factors for preeclampsia (8, 9). Preeclampsia is a multifactorial pregnancy complication that develops after 20 weeks of gestation (10, 11).

The higher prevalence and more severe cases of preeclampsia in black women strengthen the association between vitamin D and preeclampsia (12,

13). Some studies reported a seasonal pattern of preeclampsia in such a way that the lowest incidence is in summer when the serum concentration of 25(OH)D is at its highest, and its peak is in winter when the serum concentration of 25(OH)D is at its lowest (14, 15).

Bodnar *et al.* suggested vitamin D deficiency in pregnant women under 22 weeks gestation as an independent and strong risk factor for preeclampsia. This study also reported an association between reduced maternal vitamin D levels and the incidence of preeclampsia. They also reported a deficiency in neonatal serum vitamin D as a result of maternal vitamin D deficiency (16).

Many hypotheses have been suggested to justify the pathogenesis of preeclampsia. In this regard, vitamin D deficiency has been emphasized as a stimulating agent of vascular and systemic inflammation that causes insufficient placental growth (17, 18). However, due to the complex nature of preeclampsia, there is no clear association between vitamin D deficiency and the incidence of preeclampsia.

A systematic review of clinical trials investigating the impact of vitamin D supplementation has reported a positive effect on reducing the risk of preeclampsia (19, 20). On the other hand, some studies reported the role of vitamin D in improving endothelial function during placenta replacement. However, in vitro studies have reported the negative impact of vitamin D on the renin-angiotensin system. These studies showed a significant relationship between vitamin D and blood pressure, although the main mechanism and its exact role in hypertension have not been determined yet (21, 22). The current study aims to compare serum levels of vitamin D in pregnant women with preeclampsia admitted to the Ayatollah Mousavi Hospital in Zanjan, Iran, with a control group.

Methods

TSampling Method

In this case-control study, 240 pregnant women admitted from October 2018 to October 2019 were divided into two groups of preeclampsia (case) and non-preeclampsia (control) (each with 120 subjects). Participants were selected using the convenience sampling technique. Participants of both groups were matched one by one. Inclusion criteria were pregnant women aged 14-45 years from the beginning of 21 weeks of gestational to the end of 40 weeks (based on nuchal translucency scan, or 12-scan, and LMP criteria for patients without ultrasound), living in the Zanjan province, preeclampsia for those in the case group, and pregnancy without preeclampsia for those in the control group. The exclusion criteria included unwillingness to participate and having kidney disease, malabsorption syndromes, Vitamin D toxicity,

metastatic cancers, hypo and hyper thyroids, lupus, rheumatoid arthritis, and natural pregnancy (no IVF).

Data were collected using a demographic information questionnaire and a researcher-made checklist, which included gestational age, number of pregnancies, history of chronic diseases, history of preeclampsia, and history of preeclampsia in the family members. The validity of the checklist was assessed by ten faculty members of the obstetrics and gynecology department of the Zanjan University of Medical Sciences.

The goals of the study were explained to all participants, and then we obtained written consent from them. To avoid additional interventions, blood samples were collected using the patient's peripheral venous catheter. The collected samples were stored in the refrigerator and transferred to the laboratory within 20 minutes. Then, samples were placed inside the incubator at 25-28°C. Finally, serum levels of vitamin D were measured by the ELISA test. The measured values were classified into three groups: severe deficiency (less than 10 ng/L), mild deficiency (10 to 24 ng/L), and appropriate (24.1 to 80 ng/L). All participants were selected from one province to control the confounding variable of sunlight exposure.

Data Analysis

Data were analyzed using descriptive statistics, independent t-test, and Chi-square in SPSS version 16 (SPSS Inc., Chicago, Ill., USA). To test the normal distribution of data, the Kolmogorov-Smirnov test was applied. The significant level in this study was considered below 0.05 ($P < 0.05$).

Results

The youngest and oldest participants were 14 and 45 years old, respectively. The mean serum level of vitamin D was not significantly associated with age, gestational week, and history of preeclampsia in previous pregnancies (Table 1).

In general comparison, the mean vitamin D level of those in the case group (16.60 ± 5.87 ng/mL) was lower than the control group (19.06 ± 7.48 ng/mL), which was statistically significant ($P < 0.05$).

According to the findings, out of 240 participants, 23 (9.58%) had a severe deficiency, 174 (72.5%) mild deficiency, and 43 (35.84%) had an appropriate vitamin D level. A significant difference between the two groups in terms of serum level of vitamin D was observed. Those in the preeclampsia group had a significantly lower serum level of vitamin D ($P = 0.01$). The majority of participants in the case (80.84%) and control (64.16%) groups had mild vitamin D deficiency (Table 2).

Table 1. Mean serum level of vitamin D of participants separated by gestational age (less than 37 weeks and above 37 weeks)

Variable		Frequency	Mean vitamin D (ng/ml)	Standard deviation
Gestational week	Less than 34	1	10/8	-
	34 to 37	54	16/73	5/32
	37 weeks and 1 day Up to 39 weeks	53	17/17	6/10
	39 weeks and 1 day up to 41 weeks	12	15/59	7/36
Mother age	Younger than 20 years	8	12/42	3/43
	20 to 35 years	64	18/28	5/61
	Older than 35 years	48	15/06	5/83
History of preeclampsia	Yes	99	16/77	6/13
	No	21	15/78	4/44

Table 2. Comparison of vitamin D levels in case and control groups based on independent t-test

Group	Vitamin D (ng/mL)	Frequency	Percentage	t	P-value*
Case	Severe deficiency (< 10 ng/L)	11	9/16	2/83	0/001
	Mild deficiency (10 to 24 10 ng/L)	97	80/84		
	Appropriate (1/24 to 10 ng/L 80)	12	10/0		
Control	Severe deficiency (< 10 ng/L)	12	10/00	2/83	0/001
	Mild deficiency (10 to 24 10 ng/L)	77	64/16		
	Appropriate (1/24 to 10 ng/L 80)	31	25/84		

*t-test

Discussion

According to the results, the level of vitamin D in pregnant women serum with preeclampsia was significantly lower than non-preeclampsia pregnant women. It was not significantly associated with age, gestational week, and history of preeclampsia.

According to the Hamedanian *et al.* study conducted in Karaj, Iran, the serum level of vitamin D in pregnant women with preeclampsia was lower than in healthy pregnant women. They found no correlation between vitamin D deficiency and predicting factors of preeclampsia (23). A cohort study conducted in Pennsylvania, with a sample size of 2327 subjects, reported that increased serum level of vitamin D up to 50 ng/L was associated with decreased risk of preeclampsia, and in amounts above 50 ng, this risk remained constant (test of nonlinearity $P < 0.05$) (24). Achkar *et al.*, in a study conducted in Canada, also reported that preeclampsia was significantly higher in

pregnant women with serum levels less than 30 nmol/L compared with those with at least 50 nmol/L of vitamin D (25). There are other studies that reported an association between low serum levels of vitamin D and preeclampsia (26, 27).

A systematic review of clinical trials on the association of vitamin D supplementation on preeclamptic women reported that vitamin D supplementation could reduce the risk of preeclampsia by up to 53% compared to placebo (28). In a case-control study, Bodnar *et al.* have compared two groups of preeclampsia and control. They have investigated the serum level of D(OH)22 during pregnancy and before the onset of preeclampsia and women with preeclampsia. They reported that, in women with preeclampsia, at the initial weeks of pregnancy, the serum level of D(OH)22 was lower than the control group. These authors reported that when vitamin D levels reduced to 22

ng/L, the risk of preeclampsia increased by two folds. According to their report, maternal vitamin D deficiency could be an independent risk factor of preeclampsia (1).

However, Burris *et al.*, in a study performed in the United States, found no statistically significant association between preeclampsia and vitamin D levels. Also, in contrast to the hypothesis of this study, increasing maternal vitamin D levels were associated with an increased chance of developing preeclampsia. At the end of their paper, Burris *et al.* mentioned that this finding is most likely due to chance and does not indicate a causal association between vitamin D and preeclampsia. They recommended performing clinical trials to investigate this issue (29) further.

It seems that vitamin D can prevent preeclampsia. Three justifications for this issue are as follows: adequate intake of vitamin D can stabilize calcium homeostasis and consequently reduce blood pressure (30) or directly suppress the smooth muscles of the vessels (31). Second, vitamin D can act as an endocrine inhibitor of the renin-angiotensin system, which has a major role in regulating blood pressure. Third, as a balancer of T helper cell activity, it plays a role in strengthening the immune system (32).

In the present study, there was no significant association between gestational age and serum level of vitamin D. However, according to a study that has compared the risk of preeclampsia in 12-18 and 24-26 weeks of pregnancy, in cases with vitamin D deficiency, low levels of D(OH)25 in the late second trimester was associated with an increased risk of preeclampsia. So that there was a remarkable dose-response relationship between serum levels of D(OH)25 of maternal plasma during 24-26 weeks of gestation with the risk of preeclampsia ($P=0.03$).

Although this association was not significant at the gestational age of 12-18 weeks ($P=0.16$)

Wei *et al.* reported that in pregnant women, serum levels of D(OH) lower than 50 nmol/L at 24-26 weeks are associated with a 3.2-fold increase in the risk of preeclampsia (OR=24.3; CI 95% 1.37-7.69). This association was not significant at gestational weeks of 12-18 (OR=24.1; CI 95% 0.58-2.67). Also, there are other case-control studies that reported no significant association between the serum levels of mothers and the risk of developing preeclampsia during the first trimester of pregnancy (33-36).

Conclusion

According to the results of the present study and other research, there is a significant association between the serum level of vitamin D during pregnancy and preeclampsia. Considering the importance of this issue and the ease of treatment and prevention of vitamin deficiency in pregnant women, it is recommended to perform clinical trials with special emphasis on gestational age and other confounding variables.

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Conflict of Interest

The authors declared no conflict of interest.

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