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Relationship between Vitamin D and Preeclampsia in Pregnant Women: A Comparative Descriptive Study

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ABSTRACT

Aims Pregnancy poisoning or preeclampsia is a serious and specific disorder of pregnancy that affects 8% of the pregnant women. Similar studies conducted in this regard showed disagreement about the relationship between vitamin D deficiency and preeclampsia. Hence, the present study was conducted to evaluate the serum level of vitamin D in preeclampsia patients hospitalized in the maternity ward compared to healthy pregnant women.

Instruments & Methods This descriptive comparative study was conducted on 180 pregnant women with a severe preeclampsia below the gestational age of 33 weeks and 200 non-preeclampsia pregnant women in Yasuj City from 2017 to 2019. Blood samples were taken from all subjects to measure vitamin D levels. The levels of 25-hydroxy vitamin D were measured in the laboratory using the ELISA method. Data were analyzed using SPSS 20 software.

Findings There was no significant difference between the preeclampsia group and healthy pregnant women in terms of mean levels of vitamin D (p=0.49). Preeclamptic women with normal level of vitamin D and vitamin D deficiency showed no significant differences in the mean of uric acid, systolic blood pressure, diastolic blood pressure, and the number of previous pregnancies (p>0.05).

Conclusion There is no relationship between serum vitamin D3 levels and hypertensive conditions of pregnancy such as preeclampsia in pregnant women. Also, vitamin D3 levels are insufficient in both groups.

Keywords Preeclampsia; Vitamin D; Proteinuria; Uric Acid

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Introduction

Pregnancy poisoning or preeclampsia is a serious and specific disorder of pregnancy that is clinically characterized by new hypertension during pregnancy and proteinuria and affects 8% of the pregnant women [1]. Proteinuria does not occur in some patients, and other criteria such as thrombocytopenia, renal dysfunction, and elevated liver enzymes occur in these patients [2].

The World Health Organization (WHO) reported that of the 9,735 maternal deaths in 2006, 16.7% occurred in developing countries, 9.1% in Africa, and 25.7% in Latin America due to hypertensive disorders [3]. In a study conducted in Iran, the results showed that 14% of maternal deaths were caused by preeclampsia [3]. Statistics showed that preeclampsia is the cause of approximately 60,000 deaths in pregnant women annually worldwide [4].

In addition, the maternal and neonatal complications caused by preeclampsia are high. Intra-cerebral hemorrhage, intravascular coagulopathy, renal failure, pulmonary edema, liver rupture, and low birth weight are considered as some of these maternal complications [5].

The etiology of preeclampsia has not been well recognized. Inadequate nutrients, especially protein, calcium, magnesium, selenium, vitamins A and C may predict the preeclampsia [6]. Vitamin D plays an important role during pregnancy. Because low maternal vitamin D reserves may lead to problems and increase the risk of maternal-related diseases [7]. Some studies have indicated that the vitamin D deficiency may be a risk factor for preeclampsia, preterm labor, low birth weight, intrauterine growth retardation, and gestational diabetes [8]. The pathogenesis of preeclampsia includes some biological processes that may be directly or indirectly affected by vitamin D. They include immunodeficiency, placental implantation, abnormal angiogenesis, hyperinflation, and hypertension.

As vitamin D deficiency is common in people with hypertension, it is assumed that vitamin D deficiency can affect the risk of the preeclampsia. However, many of these mechanisms, which refer to the association between the vitamin D levels and paraclinical onset of the preeclampsia, have not been proven [9, 10].

Similar studies conducted in this regard have shown that there is no agreement on the relationship between vitamin D deficiency and the preeclampsia. In some studies, there was a correlation between the serum levels of 25-hydroxy vitamin D and the preeclampsia [11]. However, in the study conducted by Shand *et al*., there was no significant relationship between the preeclampsia, gestational hypertension, and preterm labor and 25-hydroxy vitamin D levels [12].

There is a limited number of studies conducted in this field and about high prevalence of this vitamin deficiency in Iranian pregnant women [13]. Therefore, this study was conducted to evaluate the levels of vitamin D in preeclampsia patients hospitalized in the maternity ward of Imam Sajjad Hospital in Yasuj, Iran.

Instruments and Methods

This descriptive-comparative study was conducted on pregnant women aged 15 to 45 years below the gestational age of 33 weeks with preeclampsia and healthy pregnant women (without preeclampsia, hypertension and proteinuria) in Yasuj City from 2017 to 2019.

Based on the studies conducted by Robinson *et al*. [14], in which preeclampsia rate was seen in the case group (women with the preeclampsia and vitamin D deficiency) in 54% and in the control (women without hypertension and with vitamin D deficiency) group in 27%, the sample size was determined at least 92 people considering the confidence coefficient of 92% and the test power of 90% according formula.

A total of 380 patients were studied by convenience sampling method. Out of this number, 180 pregnant women had preeclampsia (case group) and 200 were healthy pregnant women (control group). The case group consisted of patients with preeclampsia admitted to Imam Sajjad Hospital and the control group included patients without preeclampsia referred to the gynecology clinic in Yasuj, Iran. Pregnant women with multiple pregnancy, known chronic hypertension, overt diabetes, liver failure, use of drugs affecting vitamin D levels (such as anticonvulsants and calcium and phosphorus), hyperparathyroidism and hypothyroidism, malabsorption of vitamin D, use of glucocorticoids, and kidney failure were excluded from the study. The control group included pregnant women without preeclampsia, hypertension and proteinuria.

Demographic and clinical data were recorded in the form. The serum level of the vitamin D was checked in the mothers who referred to the hospital due to hypertension, headache, heartburn, convulsion, and blurred vision. At 20 to 28 weeks of pregnancy, about 3 to 5 cc of blood were taken from the antecubital vein of mothers to measure vitamin D3 levels using ELISA kits. Pregnant women whose serum vitamin D3 level was below 30 ng/L were considered as pregnant women with vitamin D3 deficiency.

Blood pressure of both groups was also checked. The systolic blood pressure above 140 mmHg and the diastolic blood pressure above 90 mmHg at two different times (a 6-hour interval) were considered a high blood pressure. The proteinuria more than 300 mg in 24 hours or proteinuria +1 in dipstick twice at 4-hour interval or proteinuria +2 once was considered a mild proteinuria and the proteinuria

above 5 g was considered a severe proteinuria. Data were recorded in both groups in the demographic form of part 2.

The normality of the data was first examined using the one-sample Kolmogorov-Smirnov test. If the data were normal, appropriate parametric methods such as Student's t-test were used, and otherwise, the Mann-Whitney test was used. Pearson Chi-Square test was used to analyze the data in the nominal scale and Fisher's exact test was used in cases where more than 20% of the expected frequencies were less than 5 (Cochran). SPSS 20 software was also used.

Findings

There was no significant difference in mean age between the preeclampsia group and healthy pregnant women (p=0.08). Also, these two groups were not significantly different in terms of mean levels of vitamin D, uric acid and number of previous pregnancies (p>0.05). But as expected, the two groups showed statistically significant differences in mean systolic blood pressure and diastolic blood pressure (p<0.05), so that these variables were higher in the preeclampsia group than the control group (Table 1).

Table1) Comparison of mean variables between preeclampsia group and healthy women group

Variable	Case group (preeclampsia)	Control group (healthy)	P-value
Maternal age (year)	31.22±6.95	32.32±9.10	0.08
Vitamin D (ng/ml)	18.95±14.12	18.78±9.79	0.49
Uric acid (mg/dl)	5.10±3.50	4.82±1.32	0.82
Systolic blood pressure (mmHg)	152.42±12.95	116.52±9.61	0.0001
Diastolic blood pressure (mmHg)	96.83±6.84	77.06±7.71	0.0001
Number of the previous pregnancy	1.78±0.91	1.75±0.84	0.93

All pregnant women with serum vitamin D levels less than 32 ng/ml were considered as vitamin D deficient women and other pregnant women who had serum vitamin D levels greater than or equal to 1 ng/ml were considered as pregnant women with normal vitamin D levels.

There was no significant difference between pregnant women with vitamin D deficiency and pregnant women with normal levels of vitamin D in mean age, uric acid level, systolic blood pressure, diastolic blood pressure and number of previous pregnancies (Table 2).

Table 2) Comparison of mean variables between women with vitamin D deficiency and women with normal vitamin D levels

Variable	Vitamin D deficiency	Normal vitamin D level	P-value
Maternal age (year)	31.27±6.89	30.9±7.48	0.81
Uric acid (mg/dl)	5.11±3.70	5.08±1.42	0.97
Systolic blood pressure (mmHg)	152.04±12.56	155.13±15.56	0.29
Diastolic blood pressure (mmHg)	96.93±6.83	96.18±7.01	0.63
Number of the previous pregnancy	1.79±0.90	1.68±0.94	0.57

Discussion

The present study was conducted to evaluate the serum level of vitamin D in pregnant women with preeclampsia and non-preeclampsia pregnant women.

The results of the present study showed that there is no statistically significant difference between the serum levels of vitamin D in women with preeclampsia and healthy pregnant women. The results of the present study were consistent with the results of other studies. In a cohort study conducted by Burris *et al*., no associations was found between the level of the 25-hydroxy vitamin D at 27.9 weeks after the labor and the risk of preeclampsia [15]. In another similar study conducted by Yu *et al*., the results showed no significant differences between the women with early and late preeclampsia and the control group women in terms of the mean levels of 25-hydroxy vitamin D [16]. However, some studies have shown that low levels of 25-hydroxy vitamin D are associated with the potential for pregnancy injuries [17]. Recently, a randomized clinical trial evaluated the use of vitamin D supplements during the pregnancy and showed that the use of these supplements did not affect the adverse complications of the pregnancy, such as preeclampsia, and fetal growth [18].

Studies that have investigated 25-hydroxy vitamin D in the late stages of pregnancy, especially in the third trimester, may be too late for intervention and testing its level may not yield benefits [19]. In addition, some studies have shown that genetic differences in the vitamin D receptor affect vitamin D metabolism in individuals, which may influence disease susceptibility and weight loss in mothers with vitamin D deficiency [20]. Thus, future studies classified by the genetic diversity may be necessary.

The results of some studies were in contrast to the results of the present study. In a similar study conducted by Bodnar *et al*., it was reported that the women with preeclampsia experienced vitamin D deficiency in early pregnancy about 2.5 times more than other women [11]. Also, Ghomian *et al*. [21], Zhao, *et al*. [22] Mohammadian *et al*. [23], and Karpa *et al*. [24] indicated in their studies that vitamin D was lower in women with preeclampsia than in the control group and this difference was significant. In a systematic review, Purswani *et al*. [25] showed that in

several case-controls and correlational studies between vitamin D and preeclampsia, correlation was observed, but in several clinical trial studies, the effect of vitamin D in the prevention of preeclampsia was not observed. Moreover, the results of Akbari *et al*.'s study [26] showed that pregnant women with vitamin D levels less than 20 ng/ml are at a higher risk for preeclampsia. This correlation can be up to 90% at a specific cutoff of 10.60 ng/ml. These differences with the present study can be due to the difference in vitamin D dose, time and duration of vitamin D intake.

In the study conducted by Haugen *et al*., women who used higher levels of vitamin D (15-20 µg per day), showed a lower rate of preeclampsia than those who used less than 5 µg per day [27]. In the study conducted by Bodnar *et al*. in 2007 at the Petersburg University on 55 patients whose gestational age was less than 22 weeks, preeclampsia rate in patients with serum levels less than 37 nmol/lit was 5 times more compared to the group with serum levels of above 50 nmol/lit [11]. This difference in the results of the present study and other studies may be due to the assessment of serum 25-OHD levels in different weeks of pregnancy [28, 29]. It can be stated that the assessment of the serum level of 25-OHD in the first trimester of pregnancy is a better predictor of the risk of preeclampsia than in the second and third trimesters. In addition, other factors might justify the differences in the results of studies conducted in this regard, including prevention of using the vitamin D supplements [27], different eating habits, ethnicity, smoking [12], and seasonal changes [30]. Hence, a more comprehensive assessment of the role of vitamin D in the prevention and treatment of the hypertensive disorders is needed.

It is biologically accepted that low levels of 25-OHD are the cause of unfavorable pregnancy and neonate. However, the nature of the examined data suggests that it cannot be certainly stated that low pre-pregnancy 25-OHD levels predict post-pregnancy complications. In addition, 25-OHD levels at different stages of pregnancy may be associated with different clinical outcomes, and further research is needed to identify such "critical windows" in the relationship between 25-OHD deficiency and pregnancy outcomes [31].

The results of the current study also showed that there is no significant relationship between vitamin D levels and proteinuria, uric acid, and systolic and diastolic blood pressure. The data showed that there is no convincing evidence for a strong relationship between low levels of 25-OHD and adverse maternal outcomes, and the results of various studies failed to show a dose-response relationship, so more research is needed in this regard [32]. However, some pregnancy outcomes may be associated with low serum levels of 25-OH vitamin D, and further studies such as clinical trials are needed to evaluate the effect of supplementation and screening on maternal and neonatal outcomes.

The significant result of the current study was the low levels of vitamin D3 in both the case and control groups, which may be due to insufficient exposure to sunlight in the studied women or the nutritional habits of the studied population. As there was no significant difference between pregnant women with preeclampsia and healthy pregnant women in terms of serum vitamin D3 levels, further studies are needed to confirm the relationship between serum vitamin D3 levels and the prevalence of preeclampsia.

The lack of information about the sources of vitamin D and calcium intake in two groups was one of the limitations of the study.

Conclusion

There is no relationship between serum vitamin D3 levels and hypertensive conditions of pregnancy such as preeclampsia in pregnant women. Also, vitamin D3 levels are insufficient in both groups.

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Ethical Considerations: Ethical approval was obtained from the Ethics Committee of Yasuj University of Medical Sciences (IR.YUMS.REC.1399.097). Informed written consent forms were taken from all participants before participation.

Conflicts of interest: The authors declare that there is no conflict of interest.

Author's contribution: Masnavi E. (First author), Original researcher/ Methodologist/ Introduction author/ Discussion author (25%); Hoseini M. (Second author), Original researcher/ Methodologist/ Introduction author/ Discussion author (30%); Aramesh Sh.T. (Third author), Assistant researcher/ Introduction author/ Discussion author (20%); Hasanzadeh S. (Forth author), Original researcher/ Discussion author/ Statistical analyst (25%)

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