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Comparison of vitamin D, calcium and phosphorus values of essential hypertensive, preeclamptic and normotensive pregnant women

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ABSTRACT

Objective: The aim of this study to examine the levels of 25 hydroxy vitamin D (25-OH D), calcium (Ca) and phosphorus (P) in preeclamptic, essential hypertensive and normotensive pregnant groups.

Material and methods: A total of 120 pregnant women who came to our clinic for delivery between 35 and 40 weeks of gestation between April 2017 and November 2017 were included in the study. The study group consisted of 40 preeclamptic (n = 40) and 40 essential hypertensives (n = 40), and the control group consisted of 40 normotensive pregnant women (n = 40). The demographic, obstetric and laboratory results of the three groups were compared in terms of 25-OH D levels, calcium and phosphorus levels.

Results: Maternal age, BMI and proteinuria were significantly lower in the preeclamptic and essential hypertensive group compared to the control group ($p < 0.05$). Week of gestation was observed to be earlier in the preeclamptic group compared to the other two groups ($p < 0.05$). The mean systolic and diastolic blood pressure of the preeclamptic and essential hypertensive groups were found to be statistically significantly higher than the control group ($p < 0.05$). No statistically significant difference was found between the groups in terms of transaminase. It was found that creatinine in the control group was statistically lower than the average creatinine level in the other two groups ($p < 0.001$). The Blood Urea Nitrogen (BUN) average of the control group was statistically significantly lower than the average of the other two groups ($p = 0.001$). Phosphorus levels were significantly higher in preeclamptic and essential hypertensive pregnant women compared to normotensive pregnant women ($p<0.05$). However, no statistically significant difference was found between calcium and 25-OH D levels in all three groups.

Conclusion: Low phosphorus level is likely to play a role in the etiology of essential hypertension and preeclampsia. The effects of maternal vitamin D and calcium level on the development of preeclampsia are uncertain, but more extensive research is required on potential positive effects.

Keywords: essential Hypertension; phosphorus; pre-eclampsia; pregnancy; vitamin D

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Introduction

Preeclampsia is one of the leading causes of maternal and fetal mortality and morbidity despite advances in obstetrics. Although the true cause of preeclampsia is unknown, it complicates 5-8% of nullipars and 2-3% of all pregnancies [1]. Hypertension in pregnancy; It may present as gestational hypertension, preeclampsia and eclampsia. Many markers that could be significant in predicting preeclampsia have been investigated, and the changes in maternal calcium, phosphorus and 25-hydroxyvitamin D levels during pregnancy trimesters have been evaluated in many studies [2]. Changes occur in most vitamin and mineral levels during pregnancy and lactation. The deficiency of some of these minerals and vitamins is thought to be responsible for many diseases ranging from maternal bone mineral loss density to preeclampsia [3].

Calcium is the most abundant inorganic element in the human body. Calcium metabolism is regulated by hormones such as vitamin D, parathyroid hormone and calcitonin. Oral calcium is absorbed from the intestines by the effect of 1,25 dihydroxycholecalciferol, the parathyroid hormone increases the synthesis of 1,25-dihydroxycholecalciferol in the kidneys, increasing both the intestinal absorption of calcium and the mobilization of bone calcium.

Some adaptations develop in order to provide sufficient calcium and phosphorus to the fetus developing during pregnancy. In normal pregnancy, the total serum calcium concentration decreases, but the ionized serum calcium level does not change. Although circulating 25-hydroxyvitamin D, phosphate, parathyroid hormone and ionized calcium levels are normal in preeclamptic patients, 1,25 dihydroxycholecalciferol levels are low. Ionized calcium excretion from the kidney is increased due to the increase in glomerular filtration in normal pregnancy. On the other hand, urinary calcium release in preeclampsia and superimposed preeclampsia with chronic hypertension; significantly decreased (less than 50 mg / day) compared to normal pregnant women. It has been reported that this hypocalciuria can be used to distinguish preeclampsia from other hypertension types during pregnancy [4]. Recently, there are publications showing that calcium determination in urine has a value in predicting preeclampsia [5]. The cause of this hypocalciuria in preeclamptic patients is an increase in calcium tubular reabsorption and a decrease in renal fractionated calcium excretion.

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In some studies, serum ionized calcium and phosphorus levels did not change in patients with preeclampsia compared to normal pregnancy [6].
Significant differences are seen in vascular and cellular calcium in normal and preeclamptic pregnancies. In normal pregnancy, erythrocyte and platelet and endothelial intracellular calcium increase. This increase enables the production of vasodilator substances such as nitric oxide and prostacyclin. It is thought that decreased vasodilation, increased vasoconstriction and vascular resistance may develop as a result of deterioration of the balance between plasma and vascular cell calcium in preeclampsia. Increasing dietary calcium intake in the prevention of preeclampsia has been studied for many years, and many randomized controlled studies indicate that calcium supplementation reduces the incidence of the disease. It has been shown that hypertensive diseases during pregnancy increase creatinine metabolism and uric acid levels and decrease serum calcium levels due to metabolic changes [6].
Vitamin D prevents calcium malabsorption and reduces bone loss. When clinical studies on Vitamin D and pregnancy outcomes are examined; It has been stated that vitamin D deficiency may be related to the increased risk of preeclampsia, gestational diabetes, low birth weight, preterm birth, cesarean delivery and infectious diseases, but more randomized controlled studies are needed to confirm these effects. A relationship between vitamin D and hypertension has been shown in recent studies. The important role of the renin-angiotensin system in the regulation of blood pressure is known. It has been found that vitamin D deficiency directly affects the renin angotensin system and thus increases the risk of hypertension [7]. 25-OH D has implantation and placentation, angiogenic and anti-inflammatory roles. Some studies have shown that high 25-OH D levels are protective for preeclampsia. Therefore, it has been suggested that severe 25-OH D deficiency below 10 ng / ml may increase the risk of preeclampsia and eclampsia during pregnancy [8].
Ideal recommendations for mineral and vitamin supplements in pregnant women are still controversial. The aim of the study is to examine the relationship between 25-OH D, calcium and phosphorus levels in preeclamptic, essential hypertensive and normotensive pregnant women.

Material and methods

This study is a prospective, cross-sectional and case-controlled study. A total of 120 pregnant women who came to our clinic for delivery between 35 and 40 weeks of gestation between April 2017 and November 2017 were included in the study. The study group consisted of 40 preeclamptic (n = 40) and 40 essential hypertensive (n = 40), and the control group consisted of 40 normotensive pregnant women (n = 40). The demographic, obstetric and laboratory results of the three groups were compared in terms of 25-OH D levels, calcium and phosphorus levels.

The diagnosis of preeclampsia was made according to the criteria in the hypertension during pregnancy guideline of the American Society of Gynecology and Obstetrics (ACOG-2013). Preeclampsia criteria; It was defined as systolic 140 mmHg and / or diastolic 90 mmHg and more in two measurements at 4-hour intervals, proteinuria 300 mg / dl or more in the 24-hour urine test after the 20th week of pregnancy, or dipsthetic 1+ or more [9]. As normotensive pregnant group; Pregnant women whose blood pressure was normal (systolic / diastolic <120/80 mmHg) before pregnancy were included in this group. Pregnant women with high blood pressure (systolic> 140 and diastolic> 90 mmHg) before pregnancy were included in the essential hypertensive group.

Pregnant women between the ages of 18 and 40 who applied to our clinic at 35-40 weeks of gestation were included in the study group. Metabolic disease, thyroid diseases, uterine anomalies, multiple pregnancies, pregnancies obtained through assisted reproductive techniques, pregnant women with known genetic and structural anomalies, intrauterine growth retardation, pregestational and gestational diabetes, membrane rupture, chorioamnionitis, fetal tachycardia or unknown cause patients with fever were excluded from the study. The control group consisted of healthy pregnant women who gave birth between 35-40 weeks of gestation without any medical condition or poor obstetric characteristics (history of diabetes, hypertension, obesity or thyroid disease). Clinical parameters include age, body mass index, gestational week, gravida, abortion, neonatal weight, and 1–5. minute Apgar scores have been included.

Laboratory analysis: Blood samples were collected in the delivery room. Blood samples were taken from the volunteers after at least 8 hours of fasting into gel and clot activator tubes (BD Vacutainer SST II Advance, 5 mL, 13x100 mm, catalog number 367955, Becton Dickinson, NJ, USA). After waiting for 30 minutes, the blood samples taken into the tubes were centrifuged at room temperature for 10 minutes and their serums were separated. Hemolytic, icteric or lipaemic samples were excluded from the study. Calcium and phosphorus measurement in serum samples was carried out in the biochemistry laboratory using the spectrophotometric method on the Beckman Coulter AU-5800 autoanalyzer. 25 (OH) D measurements were performed on the Advia Centaur XP analyzer (Siemens Healthineers, Erlangen, Germany) using the chemiluminescence immunoassay method.

Ethics committee approval was received for this study on 12/01/2017. The decision number is 2017 / 01-22. Each patient participating in the study was informed and they were included in the study after the participation form was approved by the patient.

Statistical analysis

Data were analyzed using Statistical Package Soci-al Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are expressed as standard deviations and means for numerical variables. Kolmogorov-Smirnov test was used for regular distribution of variables, and Mann-Whitney U test was used for sub-group comparisons. Pearson Chi-Square test was used for categorical variables. A p value of <0.05 was considered significant. For multi-group comparisons, one-way ANOVA (Strength test: Brown-Forsythe) and Kruskal-Wallis H test post hoc analysis and non-parametric post hoc tests (Miller, 1996) were used.

Results

The comparisons of the sociodemographic, clinical and laboratory data of the groups are presented in Table 1. There was no statistically significant difference between the three groups in terms of BMI, number of miscarriages and socioeconomic status ($p> 0.05$). Maternal age, gravida, parity, gestational week, birth weight and Apgar scores were significantly lower in the preeclamptic group compared to the control group ($p <0.05$).

In terms of age distribution, the average age of the individuals in the control group was found to be statistically significantly lower than the other two groups ($p=0.006$). It was observed that the individuals in the preeclamptic group were in the earlier gestational week compared to the other two groups, and there was a statistically significant difference between both groups ($p<0.001$). The mean blood pressure of the preeclamptic group was found to be statistically significantly higher than the other two groups. In addition, the mean systolic blood pressure of individuals with essential hypertension was found to be statistically significantly higher than the control group ($p<0.001$).

In terms of mean diastolic blood pressure, the blood pressure mean of the individuals in the preeclamptic group was found to be statistically significantly higher than the average diastolic blood pressure of the individuals in the

other group (essential hypertension and control). In addition, the average diastolic blood pressure of individuals with essential hypertension was found to be statistically significantly higher than those in the control group (p<0.001).

Table 1. Comparison of demographic, clinical and laboratory data of preeclamptic, essential hypertensive and normotensive pregnant women

Parameters	Normotansive n=40	Essential hypertensive n=40	Preeclamptic n=40	P value
Age (year)	25.85 ± 4.74	30.32 ± 7.01	30.02 ± 8.22	0.006
BMI, kg/m^2	28.92 ± 3.48	32.75 ± 5.29	33.06 ± 4.84	<0.001
SBP, mmHg	115.25±5.98	129.50±1.18	141.12±12.7	<0.001
DBP, mmHg	74.00 ± 6.32	84.50 ± 9.04	89.17 ± 9.00	<0.001
Gestational week	38.33 ± 0.94	38.05 ± 1.19	37.08 ± 1.30	<0.001
BUN, mg/Dl	15.52 ± 4.26	17.77 ± 6.58	20.15 ± 8.17	0.001
Creatinine, mg/dL	0.61 ± 0.08	0.72 ± 0.11	0.78 ± 0.22	<0.001
ALT, IU/L	13.00 ± 5.63	14.20 ± 6.61	14.05 ± 8.37	0.704
AST, IU/L	19.72 ± 6.20	26.12±16.87	25.95±18.36	0.094
Ca	8.79 ± 0.97	8.70 ± 0.48	8.55 ± 0.57	0.315
P	4.01 ± 0.94	3.60 ± 0.51	3.74 ± 0.54	0.032
Vitamin D	14.17 ± 8.42	13.77 ± 6.70	12.10 ± 6.26	0.397
Proteinuria	0 (0-1)	1 (0-3)	2 (0-4)	<0.001
Apgar skor 1. min 5. min	 7 (7-8) 8 (7-9)	 7 (4-8) 8 (6-9)	 7 (3-8) 8 (7-8)	 0.183 0.097

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BUN: Blood Urea Nitrogen, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Ca: Calcium, P: Phosphorus

There was a statistically significant difference in BMI between the three groups. In the post-hoc analysis, it was understood that this difference originated from the individuals in the control group. It was determined that the BMI of the individuals in the control group was statistically lower than the BMI average of the individuals in the other two groups. There was no statistically significant difference in BMI between the essential hypertensive group and the preeclamptic group.

A statistically significant difference was found between the three groups in terms of creatinine (p<0.001). In the post-hoc analysis, it was understood that this difference originated from the individuals in the control group. It was determined that the creatinine in the control group was statistically lower than the creatinine average of the individuals in the other two groups. There was no statistically significant difference in creatinine between the essential hypertensive group and the preeclamptic group. When the groups were compared in terms of transaminases (ALT, AST), no statistically significant difference was found between the groups.

When the groups were compared according to their BUN values, a statistically significant difference was found between the three groups (p=0.001). In the post-hoc analysis, it was seen that this difference originated between the individuals in the control group and the preeclamptic group. The mean BUN of the individuals in the control group was found to be statistically significantly lower than the average of the preeclamptic group. A statistically significant difference was found between the three groups in terms of phosphorus (p=0.032). In the post-hoc analysis, it was seen that this difference was caused by the control group and the group with essential hypertension. Phosphorus level was found to be statistically significantly higher in individuals in the control group than in essential hypertensive individuals. When the groups were compared in terms of Ca and vitamin D, no statistically significant difference was found between the groups. A statistically significant difference was found between the groups in terms of proteinuria (p<0.001). In the post-hoc analysis, it was understood that this difference was caused by the preeclamptic and essential hypertensive groups. Proteinuria was found to be significantly higher in individuals in the preeclamptic group than in the other two groups. Proteinuria in the essential hypertensive group was statistically higher than the control group.

Discussion

Preeclampsia is still one of the leading causes of maternal fetal morbidity and mortality, despite advances in obstetrics. Many studies are carried out in order to detect the disease early, based on many events thought to be involved in the pathophysiology of preeclampsia. These include measurements of serum calcium, phosphorus and 25-hydroxyvitamin D levels. 25-OH D deficiency, calcium and phosphorus deficiency during pregnancy are important in terms of fetal and maternal outcomes. In a study on the relationship between 25-OH D deficiency and placentation, they found that vitamin D plays a critical role in the formation of vascular pathologies [10]. In the study conducted by Linnea Bärebring et al in 2016 in which the relationship between preeclampsia and blood pressure changes and vitamin D in pregnancy was investigated in 1834 pregnant women, 80 of the women who were followed-up blood pressure in every 3 trimesters developed preeclampsia. In this study, 25- (OH) D values of pregnant women in the first trimester were not associated with preeclampsia. However, there was a negative correlation between preeclampsia and 25- (OH) D concentration in the third trimester. Therefore, it was concluded that vitamin D values in early pregnancy may not play an important role in placental development and therefore in the development of preeclampsia, but an increase of at least 30 nmol / L in 25-(OH) D value during pregnancy may prevent the development of preeclampsia [11]. Haugen et al. Based on the low levels of vitamin D in preeclamptic nulliparous pregnant women in recent years, they concluded that the development of preeclampsia was 27% less in pregnant women with dietary vitamin D levels of 15-20 microg / day compared to those who received lower doses of vitamin D [12]. In a study conducted on animals, it was determined that short-term vitamin D deficiency in mice damaged target organs and exacerbated hypertension, and vitamin D deficiency showed this effect on the severity of hypertension by directly affecting the renin angotensin system [13]. In a study conducted by Vimaleswaran et al., It was stated that the increased plasma concentration of 25 (OH) D reduces the risk of hypertension [14]. It is stated that the risk of preeclampsia may increase due to placental dysfunction or insufficiency, abnormal angiogenesis, systemic inflammation, and hypertension, which are among the biological and molecular pathways in which vitamin D takes place [15]. In a study conducted with 55 pregnant women with preeclampsia and 219 pregnant women without preeclampsia, 25 (0H) vitamin D levels were found to be lower in the case of preeclampsia.

Therefore, it has been stated that vitamin D supplementation in the early period of pregnancy can help prevent the risk of preeclampsia [16]. Baker et al. (2010) showed that there was a relationship between 25-hydroxyvitamin D levels measured in the midgestational period and the severity of preeclampsia, and showed that as the 25-hydroxyvitamin D level decreased, the severity of preeclampsia increased [2]. In a different study, 697 pregnant women were evaluated and 25-hydroxyvitamin It has been determined that the risk of preeclampsia increases in patients with a vitamin D level of 50 nmol / l [17]. It was observed that parathyroid hormone, calcitonin and 1-25 dihydroxy vitamin D3 levels did not change significantly in preeclamptic patients compared to normal pregnancy [18]. In another study, no significant relationship was found between preeclampsia and maternal serum calcium and 25 (OH) vitamin D levels in the first trimester of pregnancy [19]. Bodnar et al. (2007) stated that serum 25-hydroxyvitamin D levels of preeclamptic pregnant women in the early period were lower than the control group, and a decrease of 5 nmol / lt increased the risk of preeclampsia twice [16]. In the study conducted by Hamedanyan et al. In 2019, 60 pregnant women with preeclampsia and 60 normal pregnant women were compared in terms of vitamin d, calcium, parathyroid hormone and phosphorus. Only vitamin d level was found to be significantly lower in the pregnant group with preeclampsia, but no relationship was observed between vitamin d status and the risk of developing preeclampsia [20] In our study, no significant relationship was found between normotensive pregnant women and 25-hydroxyvitamin D levels and the development of preeclampsia.

Many studies have been conducted on maternal serum calcium in the early diagnosis and prevention of preeclampsia. Reminding the role of calcium in the development of hypertension, Alain et al. (2010) focused on circulating and vascular bioactive factors that are effective in gestational hypertension, and drew attention to the role of mediators released from the endothelium, vascular smooth muscle and extracellular matrix during pregnancy. Among them, they emphasized the importance of intracellular free calcium concentration that controls vascular smooth muscle contraction and the following activation chain [21]. In a study conducted in Nigeria in 2012, Ikechukwu et al. Investigated blood lead (BPb) and its relationship with calcium and phosphorus in the development of preeclampsia. Blood samples were collected from 59 preeclamptic, 150 normal pregnant and 122 non-pregnant women. At the end of this study, it was concluded that the increase in blood lead parallel to the decrease in serum calcium and phosphorus may be related to the development and progression of preeclampsia in this environment [22].

In a study conducted by Salari et al. In 2014, 100 pregnant women between the ages of 20-30 with a gestational week of 28-40 weeks were studied. Patients were divided into two groups, 50 female case group (preeclampsia) and 50 female control group (normal pregnancy). Serum albumin, total protein and phosphorus levels were measured in both groups. There was no significant difference between the two groups in terms of mean albumin, total protein and phosphorus levels [23]. In a study conducted by Owusu Darkwa et al. In 2017, they concluded that there was no significant difference between serum magnesium and total calcium levels between 30 preeclamptic pregnant women over 30 weeks of gestation and 30 normal pregnancies [24]. Sukonpan et al. (2005) were normal. and compared maternal serum calcium and magnesium levels in preeclamptic pregnant women and found that both cations were significantly low in preeclamptic pregnant women [25]. In 2020, Abbasalizadeh et al.'s study comparing vitamin d, calcium and phosphorus in pregnant women with normotensive and preeclampsia found no significant difference between the two groups, but they argued that hypocalcemia could increase the risk of preeclampsia up to 8.5 times [26].

On the other hand, Levine et al. (1997), who investigated the effect of calcium supplementation on the incidence of preeclampsia, stated that preeclampsia and pregnancy-related hypertension could not be prevented in pregnant women who were given 2 g calcium supplements between 13 and 21 weeks of gestation [27]. In our study, no significant change was found in calcium level in all three trimesters.

Limitations of our study include the inhomogeneous distribution of the groups in terms of age and BMI and the small number of patients.

In our study, we investigated how calcium, phosphorus and vitamin D values changed in essential hypertensive, preeclamptic and normotensive groups, which are the control groups. In the statistical analysis, we concluded that there was no significant difference between groups in terms of calcium and vitamin D. When the groups were compared in terms of phosphorus values, it was seen that there was a statistically significant difference between the three groups. Phosphorus level was found to be statistically significantly higher in individuals in the control group than in individuals with essential hypertension. In most of the studies conducted for early diagnosis and prevention of preeclampsia, it has been stated that low levels of calcium and vitamin D in pregnancy can be significant in predicting the disease. However, in our study, an increase in 25-hydroxyvitamin level was not detected in the last trimester and a significant relationship was not established between the development of preeclampsia. As a result, we concluded that there were no significant changes in calcium and vitamin D metabolism in preeclamptic and essential hypertensive pregnant women due to high blood pressure compared to the control group. However, studies with larger series are needed.

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Disclosure

Authors have no potential conflicts of interest to disclose.

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