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Original Article

Comparison of Vitamin D levels in cases with preeclampsia, eclampsia and healthy pregnant women

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Abstract: The aim of this study is to assess vitamin D levels in eclampsia, preeclampsia and healthy pregnant women and the role of vitamin D deficiency in the etiology of preeclampsia (PE). Forty healthy pregnant women, 83 preeclamptic and 32 eclamptic pregnant women were included. Maternal and infant medical records were reviewed. Blood samples were obtained from all groups. Demographics and serum vitamin D levels were compared between the groups. No statistical differences were observed in age, gravidity, parity, weight, height and BMI between the three groups. Week of pregnancy and weight at birth in eclamptic and preeclamptic patients were lower compared to the healthy patients (P<0.001 and P<0.001, respectively). Systolic and diastolic blood pressures were higher in eclamptic (P<0.001) and preeclamptic patients (P<0.001) compared to the healthy pregnant group. The rate of cesarean section was found to be higher in preeclamptic and eclamptic patients (P<0.001). Vitamin D levels were lower in both preeclamptic and eclamptic patients compared to healthy normotensive pregnant women (P<0.001). Preeclamptic and eclamptic women were similar in terms of the data compared. Vitamin D supplementation is considered to decrease the risk of both preeclampsia and eclampsia in the patient population at risk for vitamin D deficiency.

Keywords: Vitamin D, preeclampsia, eclampsia, hypertension, 25-hydroxy vitamin D

Introduction

Preeclampsia (PE) is a disease specific to pregnancy, affecting many bodily systems, characterized by high blood pressure and proteinuria after the 20th week of pregnancy, complicating 2-8% of pregnancies and increasing maternal and fetal mortality and morbidity [1-3]. Multiple factors, such as maternal constitutional factors, angiogenetic factors, endothelial dysfunction, syncytiotrophoblastic microparticles (STMP), and inflammatory activation, play a role in the development and progression of preeclampsia [4]. The maternal diet is among the factors related to the etiology of preeclampsia; an insufficient diet, especially in terms of calcium, magnesium, selenium and vitamin A and C, is a contributing factor to preeclampsia [5, 6].

Recent epidemiological studies have emphasized the role of vitamin D deficiency in the development of preeclampsia [7]. Recent in vitro studies have demonstrated the improvement of angiogenesis and inhibition of release of adhesion molecules from endothelial cells by vitamin D [8, 9]. The role of vitamin D deficiency in immunomodulation and placental development has been emphasized in various studies and thus, they put the emphasis on vitamin D deficiency, regarding its possible role in the pathophysiology of preeclampsia [10-12].

The recommendation of calcium supplementation for individuals with decreased calcium intake to prevent and treat PE by the World Health Organization (WHO) has increased the popularity of calcium and vitamin D trials in particular [13]. Our study also aimed to investigate the serum vitamin D levels in eclampsia, preeclampsia and healthy pregnant women and to assess its role in the etiology of PE and eclampsia.

Materials and methods

This study was conducted at the Clinic of Obstetrics and Gynecology at the Hospital of Kahramanmaras Sutcu Imam University. A total of one hundred and fifty-five volunteers (Thirty-two eclamptic pregnant women, forty healthy pregnant women and eighty-three preeclamptic pregnant women) were included in the study. The diagnosis of preeclampsia was confirmed using the "Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy" criteria. Based on these criteria, patients with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (measured after a period of rest of four hours, twice daily) and proteinuria (≥300 mg protein/24 h) were diagnosed as preeclampsia [14].

The diagnosis of eclampsia was based on the presence of tonic-clonic seizures in patients that were followed up with the diagnosis of preeclampsia with no systemic disease that may cause seizures [15].

The acceptance criteria for preeclamptic women for the study was if they had normal blood pressure during the first 20 weeks of gestation, no previous history of metabolic disorders, twin pregnancy, recurrent miscarriage, fetal growth retardation, placenta abruption, thrombophilia, renal disease, chronic hypertension or diabetes mellitus as well as no history of antioxidant intake and no medication for hypertension. Gestational age was defined as the interval between the first day of the mother's last menstrual period and date of delivery.

None of these patients were on any medication at the time of collection of blood samples. All subjects signed an informed written consent form. Demographic and clinical data were collected during routine obstetric visits. Healthy pregnant women did not suffer from medical conditions, such as diabetes or obesity and none of them had a history of small for gestational age (SGA) or hypertensive disorders in any previous pregnancy. Maternal and infant medical records were reviewed to collect detailed information concerning antepartum labor, delivery characteristics and condition of the newborn, including birth weight and gestational age at delivery.

Ten- to twelve-hour fasting venous blood specimens were drawn from the antecubital vein and collected in vacutainers (blood-collecting tubes) with no additives (Becton-Dickinson, Franklin Lakes, NJ) in accordance to standard hospital guidelines for venipuncture and sample collection. The serum separator tube specimens were allowed to clot and then centrifuged for 10 minutes at 3,000 g to separate the serum and stored at -70°C until analyzed.

Approval for the study was granted by the Local Research Ethics Committee of Kahramanmaras Sutcu Imam University School of Medicine.

Total vitamin D assays were analyzed with the fully automatic Advia Centaur XP immunoassay systems (Siemens, USA). Results were automatically calculated to the standard deviation.

The SPSS 22.0 program (IBM statistics for Windows version 22, IBM Corporation, Armonk, New York, United States) was used to analyze the data. Normal distribution was tested using the Shapiro-Wilk test and variability coefficients. The data with normal distribution and non-normal distribution were analyzed using parametric methods and non-parametric methods, respectively. Two independent groups were compared using the Mann-Whitney U test, while multiple groups were compared using the One-Way Anova (Robust Test: Brown-Forsythe) and the Kruskal-Wallis H Test.LSD and Games-Howell tests for post hoc analyzes [Non-parametric post-hoc test (Miller, 1966)]. Categorical variables were compared using the Pearson Chi-Square test using Monte Carlo simulation technique. Quantitative data was expressed as a mean ± SD (standard deviation), median and range (Maximum-Minimum) values. Categorical values were expressed as numbers (n) and percentages (%). Data was analyzed with a 95% confidence interval and a p value less than 0.05 was accepted as significant.

Results

In this study, 40 healthy normotensive pregnant women, 83 preeclamptic and 32 eclamptic pregnant women were included. No statistically significant differences were found in age, gravidity, parity, weight, height and body mass index (BMI) among the demographic data between the groups. Week of pregnancy and birth weight were significantly lower in the eclamptic and preeclamptic patient groups compared to the healthy pregnant women

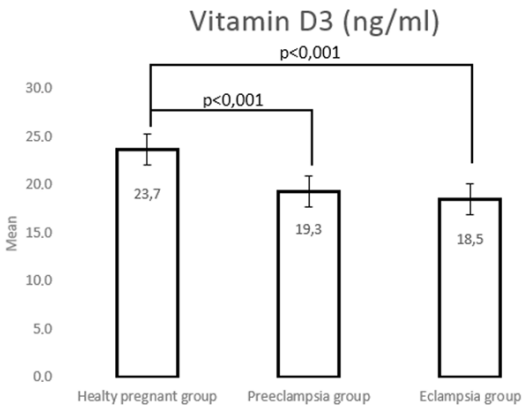

Figure 1. Comparison of vitamin D levels within the selected groups.

(P<0.001 and P<0.001, respectively). Systolic and diastolic blood pressures were significantly higher in the eclamptic and preeclamptic patient groups compared to the healthy pregnant women (P<0.001 and P<0.001, respectively). Among the types of birth delivery choices, choosing a cesarean section was statistically significantly higher in the eclamptic and preeclamptic patient groups compared to healthy pregnant women (P<0.001). When the vitamin D levels were compared among the three groups, vitamin D level was found to be 23.7 ± 5.93, 18.5 ± 5.47 and 19.3 ± 4.31 ng/ml in healthy pregnant women, eclamptic women and preeclamptic women, respectively (**Figure 1**). Vitamin D levels were found to be significantly lower in the eclamptic and preeclamptic groups compared to healthy pregnant women (P<0.001). Among all the variables analyzed, no statistically significant differences were found between the eclamptic and preeclamptic patient groups (**Table 1**).

Discussion

Factors that play a role in the pathogenesis of preeclampsia and eclampsia have not yet been fully determined. Many hypotheses have been suggested through clinical testings [4]. Pathogenesis of preeclampsia is complex and a vitamin D deficiency is one of the factors in the etiology of preeclampsia. Vitamin D is considered as having a major role in the synthesis and regulation of genes that are effective in the early developmental phase of the placenta [10, 11]. Placental abnormalities associated with preeclampsia occur before the remodeling in the vascular structures providing the placental nutrition is completed. Deep trophoblast invasion and remodeling of the vascular structures in the placental bed both play a role in the development of PE [16]. Vitamin D deficiency has been suggested to be a predisposing factor in the peripheral vascular phase modulation, which will result in inadequate placental development and the development of preeclampsia during the early weeks of pregnancy [15].

Production of vitamin D in the decidua, placenta and the maternal kidneys increases during pregnancy [17]. Since vitamin D level is dependent on the exposure of sunlight, vitamin D support and dietary factors, there will be little or no change in the level of vitamin D during pregnancy [18]. In recent studies carried out in the USA, Australia, the Middle East and South Asia, vitamin D deficiency was detected in 26-98% of pregnant women. Vitamin D deficiency is around 66-100% in women with a dark skin color [19-21]. When defining the level of vitamin D in the serum, though not standard, the cut-off level for vitamin D deficiency is acceptable at 20 ng/ml in the latest studies, although previously it was accepted at 15 ng/ml [22, 23].

Based on the literature, establishing the relationship between preeclampsia and vitamin D is complicated [24-26]. There are various studies on the role of vitamin D on the development and pathophysiology of preeclampsia and eclampsia. A low vitamin D level in the second trimester has been emphasized in previous studies to be an indicator of preeclampsia [25, 27].

Many studies have supported the hypothesis of the role of vitamin D in the etiology of preeclampsia and eclampsia. Studies have pointed out different ways vitamin D plays a role in the etiology of preeclampsia.

Vitamin D has been thought to play a potent endocrine suppressor role in renin biosynthesis for the regulation of the renin-angiotensin system (RAS). In addition, hypertension is suggested to be tied to preeclampsia and eclampsia [15].

In addition, in other studies on the role of vitamin D in the development of preeclampsia, vitamin D has been emphasized to play an immunomodulatory and anti-inflammatory role in many systems [28]. Vitamin D also has been suggested to play a role in major signal and gene regulations in the development of placental trophoblasts in the placental growth phase

Table 1. Comparison of the demographics, clinical features and vitamin D levels in all cases

	Healthy pregnant (n: 40)	Preeclampsia (n: 83)	Eclampsia (n: 32)	*P* Value
Age (Years)*	28.9 ± 5.80	29.2 ± 8.40	29.1 ± 8.47	NS
Gravida**	2 (7-1)	2 (9-1)□	2 (9-1)□	NS
Parity**	1 (4-0)	1 (4-0)	1 (4-0)	NS
Weight (Kg)*	78.6 ± 9.17	75.9 ± 10.89	74.8 ± 10.97	NS
Height (Cm)*	160.4 ± 5.04	161.0 ± 6.47	159.8 ± 6.36	NS
BMI (Kg/m^2)*	30.6 ± 3.72	29.3 ± 4.75	29.4 ± 4.74	NS
Gestation (Weeks)*	38.5 ± 1.43	35.3 ± 2.94□	34.1 ± 3.87□	<0.001
Systolic blood pressure (mmHg)**	114.5 (140-90)	156 (179-146)□	162.5 (205-149)□	<0.001
Diastolic blood pressure (mmHg)**	68.9 ± 8.77	105.7 ± 6.62□	106.8 ± 8.13□	<0.001
Type of Birth (CS/NVB)†	16 (40)/24 (60)	65 (78.3)/18 (21.7)	35 (83.3)/7 (16.7)	<0.001
Fetal birth weight (g)*	3.248.8 ± 548.68	2.434.1 ± 854.29□	2.169.5 ± 809.55□	<0.001
Vitamin D (ng/ml)*	23.7 ± 5.93	19.3 ± 4.31□	18.5 ± 5.47□	<0.001

One-way ANOVA Test (Brown-Forsythe) Post Hoc Test: LSD-Games Howell; Kruskal Wallis Test Post Hoc Test: nonparametric post-hoc test (Miller, 1966); Pearson Chi Square Test (Monte Carlo)-Mann-Whitney U Test. †n (%); *Mean ± SD (standard deviation); **Median Range (Maximum-Minimum); □P<0.001 Significant based on Healthy Pregnant Group.

[10-12]. In addition, a decrease in the level of vitamin D has been suggested to cause excess activity in Th-1 type cytokines and to decrease immunological tolerance for implantation and to trigger preeclampsia. Immunomodulatory properties of 1.25(OH)2D have been reported to play a key role in the development of immunological tolerance in pregnancy and the presence of a sufficient level of vitamin D has been emphasized to have a role in the management and prevention of PE [29]. Insufficient vitamin D levels has been associated with increased IL-6 concentrations through stress induced kinase, p38 inactivation, and inhibition of inflammatory cytokines of TNF (Tumor Necrosis Factor) alpha as an origin in coronary endothelial cells [30]. Studies conducted on this subject point out the role of deficient vitamin D levels in preeclampsia through increasing inflammation and all such studies are compatible with the anti-inflammatory role of vitamin D [31].

In addition, vitamin D is reported to develop angiogenetic properties in endothelial progenitor cells and to play a major mediating role in the endothelial cell function and dysfunction in cell culture models [8, 32]. The placental growth factor (PlGF) was detected to be significantly decreased and intercellular adhesion molecule-1 (ICAM-1) was found statistically to have significantly increased in cases where plasma 25(OH)D level is less than 50 nmol/L in pregnant women. These results may confirm that vitamin D is a biomarker that can play a role in the pathophysiology of preeclampsia disease [26].

Women with preeclampsia have lower levels of vitamin D compared to healthy pregnant women and this also supports the hypothesis of its role in the pathogenesis of preeclampsia [25]. There are other studies with similar results [28, 33]. In a meta-analysis of this issue, Tabesh et al. established the association of low 25(OH)D level and preeclampsia [34]. Also, in a prospective cohort study, maternal vitamin D concentration during the 24-26th week of pregnancy was found to be 14% lower in the patient group with preeclampsia compared to the group of healthy pregnant women (48.9 nmol/L-57.0 nmol/L) [7].

Another issue that points to the role of vitamin D in the development of preeclampsia is that vitamin D is used in the prevention of preeclampsia. An increase of 25 nmol/L in 25(OH) D level provided a 63% decrease in the incidence of severe PE with early onset. In a relatively large prospective study performed in Norway by Haugen et al., the risk of PE was found to be decreased by 27% in patients who received vitamin D in a dose of 400-600 IU/daily through supplemental treatment [35]. In addition, vitamin D support in the early weeks of pregnancy was shown to decrease the risk of encountering preeclampsia during the advanced phases of pregnancy [27]. Although maternal 25(OH)D level is increased with vitamin D supplementation during pregnancy, there has been no randomized controlled trail (RCT) performed on the dose of vitamin D that decreases the risk of PE and research data is limited on this subject [36, 37].

However, some studies have not supported the association between vitamin D and preeclampsia and eclampsia. In one study, vitamin D levels were found to be similar in patients with and without development of preeclampsia during the first and second trimester [24]. Also Wetta et al., in their case control study, demonstrated that serum 25(OH)D levels measured at the 15th and 21st week of pregnancy were statistically similar in their two groups that comprised of 89 cases with diagnosed preeclampsia at the 37th week of pregnancy and 177 controls [38]. In a RCT conducted by Marya et al., no significant difference was found in the incidence of preeclampsia between cases with or without vitamin D (1,200 IU/daily) and calcium (375 mg/daily) support during the 20th and 24th week of pregnancy in 400 patients [39].

Following the demonstration of the role of vitamin D in the etiology of preeclampsia; studies began on the role of vitamin D on the severity of preeclampsia and its association with eclampsia. No significant difference was found in the vitamin D levels in cases with intermediate and severe preeclampsia in a study and the severity of preeclampsia was found to be unrelated with vitamin D concentration in the same study. Vitamin D levels were reported to be around 20 ng/ml in cases with sudden development of eclampsia and in patients with eclampsia; however, they reported that their results were inconclusive. The comparison of the mean serum levels in patients with and without development of eclampsia revealed no significant results. As a result of these findings, vitamin D was found to play a role in the prevention of the development of preeclampsia; however, it was found to have no role on the severity of the condition [23].

In another compatible study, the risk of preeclampsia in mothers with vitamin D deficiency was found to be increased by three- to five-fold, with a similar increase in the risk of eclampsia. A dose-response association was demonstrated in this study with serum 25(OH)D3 concentration and the risk of development of preeclampsia and eclampsia. An important feature of this study is that it establishes the association of eclampsia and 25(OH)D3 deficiency. In this study, the corrected risk for eclampsia was found to be five-fold when the 25(OH)D3 level was <30 ng/ml and the 25(OH)D3 level was found to be quite low in eclamptic women (mean serum 25(OH)D3 21.56 ng/ml). Vitamin D supplementation has been shown to decrease the risks of both preeclampsia and eclampsia in the patient population at risk for vitamin D deficiency [15]. Our study also revealed that the vitamin D levels were significantly lower in patients with PE and eclampsia compared to the healthy pregnant women. In addition, our study revealed that vitamin D levels were similar in the PE and eclamptic groups.

In conclusion, although several studies have reported to the contrary, our study demonstrates that vitamin D plays a role in the etiology and pathophysiology of preeclampsia. In populations in the risk group of vitamin D deficiency, the risk of hypertensive pregnancy diseases may be decreased through vitamin D support. Our study also suggests that vitamin D support in patients with a history of preeclampsia in previous pregnancies may decrease the risk of preeclampsia and eclampsia during the current pregnancy.

Disclosure of conflict of interest

None.

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References

[1] Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010; 376: 631-44.

[2] Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005; 365: 785-99.

[3] James JL, Whitley GS, Cartwright JE. Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. J Pathol 2010; 221: 363-78.

[4] Roberts JM, Hubel CA. The two-stage model of preeclampsia: variations on the theme. Placenta 2009; 30 Suppl A: S32-7.

[5] Homfmyer GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of preeclampsia and related problems: a systematic review and commentary. BJOG 2007; 114: 933-943.

[6] Wallis AB, Saftlas AF. A gram of prevention: a modest increase in fiber consumption may reduce risk of preeclampsia. Am J Hypertens 2008; 21: 849-50.

[7] Wei S, Audibert F, Hidiroglou N, Sarafin K, Julien P, Wu Y, Luo ZC, Fraser WD. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. BJOG 2012; 119: 832-9.
[8] Grundmann M, Haidar M, Placzko S, Niendorf R, Darashchonak N, Hubel CA, von Versen-Höynck F. Vitamin D improves the angiogenic properties of endothelial progenitor cells. Am J Physiol Cell Physiol 2012; 303: C954-62.
[9] Kudo K, Hasegawa S, Suzuki Y, Hirano R, Wakiguchi H, Kittaka S, Ichiyama T. 1α,25-Dihydroxyvitamin D(3) inhibits vascular cellular adhesion molecule-1 expression and interleukin-8 production in human coronary arterial endothelial cells. J Steroid Biochem Mol Biol 2012; 132: 290-4.
[10] Fischer D, Schroer A, Ludders D, Cordes T, Bücker B, Reichrath J, Friedrich M. Metabolism of vitamin D3 in the placental tissue of normal and preeclampsia complicated pregnancies and premature births. Clin Exp Obstet Gynecol 2007; 34: 80-4.
[11] Novakovic B, Sibson M, Ng HK, Manuelpillai U, Rakyan V, Down T, Beck S, Fournier T, Evain-Brion D, Dimitriadis E, Craig JM, Morley R, Saffery R. Placenta-specific methylation of the vitamin D 24-hydroxylase gene: implications for feedback autoregulation of active vitamin D levels at the fetomaternal interface. J Biol Chem 2009; 284: 14838-48.
[12] Diaz L, Noyola-Martinez N, Barrera D, Hernández G, Avila E, Halhali A, Larrea F. Calcitriol inhibits TNF-alpha-induced inflammatory cytokines in human trophoblasts. J Reprod Immunol 2009; 81: 17-24.
[13] World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: World Health Organization; 2011.
[14] Snydal S. Major Changes in Diagnosis and Management of Preeclampsia. J Midwifery Womens Health 2014; 59: 596-605.
[15] Ullah MI, Koch CA, Tamanna S, Rouf S, Shamsuddin L. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. Horm Metab Res 2013; 45: 682-7.
[16] Huppertz B. Placental origins of preeclampsia challenging the current hypothesis. Hypertension 2008; 51: 970-975.
[17] Pérez-López FR. Vitamin D: the secosteroid hormone and human reproduction. Gynecological Endocrinology 2007; 23: 13-24.
[18] Fernández-Alonso AM, Dionis-Sánchez EC, Chedraui P, González-Salmerón MD, Pérez-López FR; Spanish Vitamin D and Women's Health Research Group. First-trimester maternal serum 25-hydroxyvitamin D_3 status and pregnancy outcome. Int J Gynaecol Obstet 2012; 116: 6-9.
[19] Asemi Z, Taghizadeh M, Sarahroodi S, Jazayeri S, Tabasi Z, Seyyedi F. Assessment of the relationship of vitamin D with serum antioxidant vitamins E and A and their deficiencies in Iranian pregnant women. Saudi Med J 2010; 31: 1119-1123.
[20] Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, Hollis BW. Vitamin D deficiency and insufficiency is common during pregnancy. Am J Perinatol 2011; 28: 7-12.
[21] Teale GR, Cunningham CE. Vitamin D deficiency is common among pregnant women in rural Victoria. Aust N Z J Obstet Gynaecol 2010; 50: 259-261.
[22] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930.
[23] Singla R, Gurung P, Aggarwal N, Dutta U, Kochhar R. Relationship between preeclampsia and vitamin D deficiency: a case control study. Arch Gynecol Obstet 2015; 291: 1247-51.
[24] Powe CE, Seely EW, Rana S, Bhan I, Ecker J, Karumanchi SA, Thadhani R. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. Hypertension 2010; 56: 758-763.
[25] Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 2007; 92: 3517-3522.
[26] Wei SQ, Audibert F, Luo ZC, Nuyt AM, Masse B, Julien P, Fraser WD; MIROS Study Group. Maternal plasma 25-hydroxyvitamin D levels, angiogenic factors, and preeclampsia. Am J Obstet Gynecol 2013; 208: 390, e1-6.
[27] Haugen M, Brantsaeter AL, Trogstad L, Alexander J, Roth C, Magnus P, Meltzer HM. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology 2009; 20: 720-6.
[28] Xu L, Lee M, Jeyabalan A, Roberts JM. The relationship of hypovitaminosis D and IL-6 in preeclampsia. Am J Obstet Gynecol 2014; 210: 149, e1-7.
[29] Wamberg L, Cullberg KB, Rejnmark L, Richelsen B, Pedersen SB. Investigations of the Anti-infl ammatory Eff ects of Vitamin D in Adipose Tissue: Results from an In Vitro Study and a Randomized Controlled Trial. Horm Metab Res 2013; 45: 456-62.
[30] Nonn L, Peng L, Feldman D, Peehl DM. Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D. Cancer Res 2006; 66: 4516-24.

[31] Bednarek-Skublewska A, Smolen A, Jaroszynski A, Załuska W, Ksiazek A. Effects of vitamin D3 on selected biochemical parameters of nutritional status, inflammation, and cardiovascular disease in patients undergoing long-term hemodialysis. Pol Arch Med Wewn 2010; 120: 167-74.

[32] Ertek S, Akgül E, Cicero AF, Kütük U, Demirtaş S, Cehreli S, Erdoğan G. 25-Hydroxy vitamin D levels and endothelial vasodilator function in normotensive women. Arch Med Sci 2012; 8: 47-52.

[33] Baker AM, Haeri S, Camargo CA, Espinola JA, Stuebe AM. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. J Clin Endocrinol Metab 2010; 95: 5105-5109.

[34] Tabesh M, Salehi-Abargouei A, Tabesh M, Esmaillzadeh A. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. J Clin Endocrinol Metab 2013; 98: 3165-73.

[35] Robinson CJ, AlanisMC, Wagner CL, Hollis BW, Johnson DD. Plasma 25-hydroxy vitamin D levels in early-onset severe preeclampsia. Am J Obstet Gynecol 2010; 203: e361-e366.

[36] De-Regil LM, Palacios C, Ansary A, Kulier R, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev 2012; 2: CD008873.

[37] Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2012; 26 Suppl 1: 75-90.

[38] Wetta LA, Biggio JR, Cliver S, Abramovici A, Barnes S, Tita AT. Is Midtrimester Vitamin D Status Associated with Spontaneous Preterm Birth and Preeclampsia? Am J Perinatol 2014; 31: 541-6.

[39] Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Gynecol Obstet Invest 1987; 24: 38-4.