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ORIGINAL ARTICLE

Severe 25-OH vitamin D deficiency as a reason for adverse pregnancy outcomes

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ABSTRACT

Objective: There is a growing concern about the unfavorable effects of vitamin D deficiency in general population, including pregnant women, worldwide. The aim of this study is to evaluate the effect of severe maternal serum 25-OH vitamin D levels on adverse pregnancy outcomes in first trimester.

Material and methods: Serum samples of 86 pregnant women in first trimester were collected prospectively from May 2017 to June 2017. Serum 25-OH vitamin D levels were analyzed by enzyme immunoassay method. Patients were classified according to maternal serum 25-OH vitamin D levels as group 1 ($n = 34$) <10 ng/ml and group 2 ($n = 52$) >10 ng/ml. The two groups were compared in terms of adverse pregnancy outcomes.

Results: The mean 25-OH vitamin D levels of the total 86 pregnant women were 13.83 (6–48) ng/ml. 40% of the pregnant women had low level of 25-OH vitamin D levels (<10 ng/ml). The adverse pregnancy outcomes were significantly increased in group 1 ($p < .018$).

Conclusions: Maternal serum 25-OH vitamin D levels <10 ng/ml is a risk factor for adverse pregnancy outcomes. 25-OH vitamin D levels should be screened in high-risk pregnant women and treated in case of deficiency.

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KEYWORDS
25-OH vitamin; adverse outcomes; first trimester; pregnancy

Introduction

Maternal vitamin D deficiency is a major health problem all over the world (Bodnar LM). Its prevalence in pregnant women ranges from 20 to 85% [1]. Vitamin D deficiency or insufficiency affects the health of both pregnant women and infants. During pregnancy, vitamin D requirements should meet for the placenta, the fetus, and the health of the mother. There is no consensus on vitamin D metabolism and serum vitamin D concentrations in pregnancy [2] despite the fact that vitamin D deficiency is a prevalent problem (Bener, Bowyer). The major causes of vitamin D deficiency are insufficient sunlight, light skin pigmentation and inadequate vitamin D intake (Pittas). Lifestyle, nutritional and environmental factors are responsible for the high prevalence of vitamin D deficiency in Turkey [3]. Low serum 25-OH vitamin D levels have been found as related to adverse obstetric outcomes like preterm birth, low birth weight, cesarean section, gestational diabetes and hypertension [4–6].

The aim of our study is to investigate the effect of vitamin D levels on perinatal outcomes in the first trimester.

Material and methods

This is a prospective cohort study conducted in a university-affiliated hospital between May 2017 and June 2017. Informed consent was taken from all participants. Ethics committee approval was obtained with decision number of 23.05.2017/77. Women who admitted to obstetrics outpatient clinic at 11–13 weeks of pregnancy were involved in the study. The participants are selected from 18 to 40-year-old pregnant women who accepted the aneuploidy screening and agreed on the informed consent. Multiple gestations, current vitamin D intake, existence of chronic metabolic diseases (e.g. heart, liver, hypertension, renal diseases, type 1 or 2 diabetes mellitus) were defined as exclusion criteria. The demographic characteristics, gestational age at the sampling time, gravity and parity were recorded at first visit. Type of delivery and all of the complications related to the gestation or delivery were recorded. Delivery before 37th week of gestation was defined as preterm delivery [7]. Rupture of membranes before the onset of labor was defined as PROM (premature rupture of membranes) [8].

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TABLE 1. Demographic characteristics of pregnant women in both groups

Variables	≤ or <10-ng/ml Vitamin D (Group1) ($n = 34$)	> 10-ng/ml Vitamin D (Group 2) ($n = 52$)	p values .026
Adverse Outcomes	19	15	.018*
Age (years)	27.46 ± 5.6	28.75 ± 5.93	.315
BMI (kg/m^2) [Median (min–max)]	26.78 ± 3.31	26.49 ± 2.83	.667
Parity [Median (min–max)]	1 (0–2)	1 (0–3)	.466
Birth-weight (grams) [Mean ± sd]	3386 ± 418	3394 ± 383	.927
Apgar1	8 (6–9)	8 (6–9)	.304
Apgar2	10 (8–10)	10 (8–10)	.008
Sigara	2	5	.695
Cesarean-section [n (%)]	15	24	.826
Gestational age at delivery (weeks) [Median (min–max)]	39 (32–41)	39 (39–42)	.19
Hemoglobin levels	12.82 ± 0.81	12.85 ± 0.75	.884

Gestational diabetes mellitus was diagnosed according to results of 100 g oral glucose tolerance test which were evaluated through Carpenter's and Coustan's reference values [9]. Women who had ≥140 mm Hg systolic blood pressure or ≥90 mm Hg diastolic blood pressure with ≥300 mg proteinuria in a 24-h collected urine sample were diagnosed as preeclampsia [10]. Total of the sum of purely amniotic fluid containing four vertical pouches ≤50 mm was defined as oligohydramnios [11]. Estimated fetal weight for gestational age ≤10 percentile was recognized as fetal growth restriction [12]. The clinical outcomes and necessity of neonatal intensive care unit were recorded for each fetus. Maternal peripheral venous blood serum samples were centrifuged at 3000 rpm for 8 min and stored at −80 °C until analyzed in order to keep 25(OH)D3 vitamin stable. 25(OH)D3 levels were measured chromatographically, using the HPLC (High-Pressure Liquid Chromatography) system.

Women were classified into two groups according to the serum vitamin D levels. Due to the low levels of vitamin D in our population, severe 25(OH)D3 vitamin was defined as serum concentrations ≤ veya <10 ng/ml.

Statistical analysis

Statistical analyses were performed by IBM SPSS for Windows version 22.0 statistical package. Continuous variables presented as mean ± standard deviation or median [minimum–maximum]. Categorical variables summarized as frequencies and percentages. Normality of the continuous variables was evaluated by Kolmogorov Smirnov test. Differences between the two groups according to continuous variables were determined with independent samples t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared by chi-square or Fisher's exact test. Univariate associations between variables were estimated by Pearson's coefficient correlation. p values less than .05 was considered as statistically significant.

Results

A total of 86 women with a singleton pregnancy fulfilling the inclusion criteria were included in this study. The mean vitamin D level of all participants was detected as 13.59 ± 6.57 ng/ml (MIN6-max 48). Among all participants, 34 women with severe vitamin D deficiency (vitamin D level <10 ng/ml) were included in group 1 and 52 women with vitamin D level >10 ng/ml were included in group 2 (Table 1, $p<.026$). The demographic characteristics of women were given in Table 1. No statistically significant difference was found between the two groups in terms of mean age, parity, body mass indexes, type of the delivery, gestational week at the delivery, fetal weight, Apgar scores, smoking, hemoglobin levels (Table 1, $p<.05$). PROM, preterm delivery, macrosomia, intrauterine growth restriction, polyhydramnios, preeclampsia, gestational diabetes mellitus are considered as adverse pregnancy outcomes.

We observed PROM in 17 patients (19.76%), preterm delivery in 6 patients (6.9%), macrosomia in 2 patients (2,32%), intrauterine growth restriction in 7 (8.13%) patients, polyhydramnios in 2 patients (2.32%), preeclampsia in 2 patients (2.32%) and gestational diabetes mellitus in 8 patients (9.3%). Where required Overall 86 participants, vaginal delivery rate was 54.6% ($n = 47$) and cesarean delivery rate was 45.3% ($n = 39$). Cesarean section was performed for different obstetric indications.

Mean gestational age and birth weight of the neonates at the time of delivery were 39 ± 1.68 weeks and 3391 ± 395 g, respectively. The results revealed statistically significant increase in adverse outcomes through the participants with severe vitamin D deficiency (group 1) (Table 1, $p<.018$).

Discussion

The literature focusing on vitamin D insufficiency in pregnancy is growing rapidly, with several studies pointing on the association with adverse pregnancy outcomes and infantile deficiency. The present study has shown that the pregnancies with severe vitamin D insufficiency are complicated with adverse outcomes such as PROM, preterm delivery, macrosomia, intrauterine growth restriction, polyhydramnios, preeclampsia, and gestational diabetes mellitus.

A previous study has shown that maternal 25 (OH)D levels are four times higher in elective/emergency cesarean section than vaginal delivery [13]. Our study does not support these findings as we found no association between maternal serum vitamin D levels and mode of delivery. This difference could be as a result of the time when the level of vitamin D has calculated. In this study, the value of vitamin D has calculated at the time of delivery and differs from our study with this point. In our study, we took into consideration the first trimester levels of vitamin D and it has possibly dynamic changes during the pregnancy. We believe that levels of vitamin D can still affect the delivery mode if serial measurements have been performed. It can affect the bone structure, pelvic muscles' contractility and function due to the change in calcium levels [14,15]. Another study from Pakistan has demonstrated that maternal vitamin D levels between women with a vaginal delivery and cesarean section due to the cephalopelvic disproportion have no significant difference which is supporting our study [16].

In studies by Merewood et al. and Powe et al. the risk of developing preeclampsia was higher in the patients whose vitamin D levels are less than 15 ng/Ml [13–17]. Although there are several reports suggesting the relationship between low serum vitamin D levels and preeclampsia, especially early onset (before 34 weeks) severe preeclampsia [18], conflicting results are possible due to the effect of sample size, study design, ethnic-genetic factors, lifestyle, the season, and trimester of collecting the samples. Shand et al. have found no significant difference in terms of vitamin D levels between preeclamptic women and control group who has evaluated in first and second trimester [19]. More comprehensive studies are needed in this regard.

The serum vitamin D levels seem to be associated with insulin sensitivity and circulating insulin levels due to the pancreatic cell function [20] but it is not clear that the correlation between gestational diabetes and vitamin D insufficiency. A study by Zhang C et al. revealed a strong correlation between GDM and low vitamin D levels [21] similarly the case-control study by Soheilykhah et al. suggesting 2.7 times higher risk for GDM regarding BMI, age and gestational age [20].

Low vitamin D levels are also been implicated in the risk of preterm labor. In a Japanese study, the women with high risk of preterm labor are likely to have co-occurrence with inadequate vitamin D status [22]. Hollis et al. reported that preterm labor can be precluded by vitamin D supplementation at 12–16 weeks of pregnancy [5]. Although there are several studies supporting this hypothesis, further investigations are needed.

An Amsterdam study including 3730 women with various ethnicities has shown that lower vitamin D levels are associated with higher risk of delivering SGA infants. The birth weights are lower when we compare the patients with vitamin D levels <12 ng/ml with >20 ng/ml or more [23]. Bodnar et al. have presented a study claiming that maternal vitamin D levels, especially at 22 weeks of pregnancy are associated with lower birth weights of infants [24]. Alonso et al. have found no significant difference between the women who have vitamin D insufficiency and not [25].

In a study from Turkey, vitamin D deficiency was found to be 81.4% for pregnant women and 97.2% for their newborns [3] suggesting that vitamin D deficiency of infants can be prevented by supplementation of pregnant women. Since the vitamin D content of the human milk is very low, main vitamin D requirement of newborn is obtained from mother by crossing from placenta [26,27]. Rickets related vitamin D deficiency is more likely to occur in pregnancies complicated by inadequate vitamin D and may be reduced by sufficient intake [28].

The limitations of this study include the small number of patients and also adverse outcomes which results in difficulties for present comparisons. Since it was not possible to compare adverse outcomes particularly, we examined all the adverse outcomes together. Vitamin D status is variable according to the season, nutritional status, wearing habits and gestational age. Vitamin D insufficiency is common in pregnancy, especially for high-risk women like vegetarians, dark-skinned people, women who are living in cold climate and wearing protective clothing. This variation should be kept in mind and vitamin D supplementation needs to be individual.

Dose–response relation between vitamin D and pregnancy outcomes is not clear and it complicated to determine cut off levels of vitamin D. Although the effect of vitamin D supplementation is based on limited evidence, supplementation may be a simple way to reduce adverse pregnancy outcomes according to the present study. Pregnant women should be encouraged to follow current guidelines recommending daily vitamin D intake to prevent adverse pregnancy outcomes.

Finally, our study has demonstrated that vitamin D deficiency is a major health problem in Turkish pregnant women. Although Turkey is a member of temperate climate geographic region with sufficient sunshine, 39.5% of pregnant women have severe vitamin D insufficiency and 55.8% of these pregnancies are associated with poor prenatal outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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