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Vitamin D levels in pregnancies and neonatal outcomes

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Abstract

Objective: We aimed to evaluate the differences in obstetrics and neonatal outcomes, such as mode of delivery, gestational diabetes mellitus, preeclampsia, and infant birth weight between pregnancies with normal and insufficient vitamin D levels.

Methods: The study was designed as a retrospective study. One hundred and seventy-nine pregnant women who were followed up at our clinic and whose vitamin D levels were evaluated in each trimester were included. All patients were administered 1200 IU/day beginning from the 12 weeks of gestation in accordance with the national guidelines. Vitamin D levels above 20 ng/ml were defined as sufficient, and those below 20 ng/ml were defined as insufficient.

Results: The median vitamin D level in the third trimester was significantly higher than that in the first and second trimesters ($p<0.001$). There was a moderate positive correlation between vitamin D levels in infant cord blood at the time of birth and vitamin D levels in the third trimester ($p<0.001$, $R=0.496$). Birth weights of the patients with insufficient vitamin D levels in the first trimester but with sufficient neonatal cord blood levels as a result of treatment were significantly higher compared to those in patients with insufficient cord blood vitamin D levels (3327 g vs. 3133 g, $p=0.030$).

Conclusion: This study observed that neonatal cord blood vitamin D level is a better indicator than antenatal vitamin D levels. Regardless of first-trimester vitamin D levels, infant birth weights were significantly higher in the group with sufficient neonatal cord blood levels.

Keywords: Fetal growth, pregnancy, perinatal outcome, vitamin D.

Introduction

Vitamin D receptors are present in many different types of cells and control mineral metabolism.[1,2] Maternal vitamin D levels during pregnancy affect maternal and fetal calcium homeostasis. The fetus receives vitamin D from the mother through the placenta.[3] Vitamin D affects placental implantation, immune functions, inflammatory response and glucose homeostasis.[4–7] The total amount of calcium absorbed gradually increases during pregnancy and reaches a level of approximately 400 mg/day in the third trimester. Increased calcium absorption is provided by elevated concentrations of 1,25 dihydroxyvitamin D.[8] In studies which monitored vitamin D levels, it was found that neonatal vitamin D levels were well correlated with maternal vitamin D levels.[9]

Vitamin D deficiency is a common health problem around the world. Vitamin D deficiency has been associated with many diseases and numerous studies have been conducted on it. In terms of maternal results, there are studies that associate low vitamin D levels and obstetric complications such as preeclampsia, gestational diabetes, mode of delivery and low birth weight.[10–14] Therefore, standard vitamin D replacements are recommended by the Ministry of Health for pregnant women in Türkiye. The recommended daily amount of vitamin D is 1200 IU.

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In this study, we aimed to investigate the effect of standard treatment for pregnant women with normal or insufficient vitamin D level on vitamin D levels in the following pregnancy weeks and in the neonatal cord blood, in addition to evaluating the perinatal results.

Methods

The study was planned as a retrospective and single-center study. One hundred and seventy-nine patients who were followed up in the Gynecology and Obstetrics Clinic at Gazi University Faculty of Medicine between January 2016 and December 2017 were included in the study. Inclusion criteria were determined as the evaluation of vitamin D levels in each trimester and gave birth in our clinic. All patients received vitamin D supplements in accordance with the national guidelines of the Turkish Ministry of Health. The exclusion criteria were pregnancies that did not use the recommended vitamin D replacement. Patients with multiple pregnancy were also excluded from study. Taking into account the reference value of our laboratory, vitamin D levels above 20 ng/ml were defined as sufficient and those below 20 ng/ml were defined as vitamin D deficiency. The Institute of Medicine (IOM) stated in 2011 that a blood level of 25 (OH) D 20 ng/mL and above was sufficient.[15]

Laboratory values, pregnancy information, pregnancy outcomes, pregnancy complications (GDM, preeclampsia) and infant birth weight measurements, were retrieved from archives and electronic data analyses, and they were recorded. Small for gestational age (SGA) was defined as a birth weight less than 2500 g. IBM SPSS (Statistical Package for the Social Sciences) v. 20 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to analyze the normal distribution of the data. Continuous data with normal distribution were expressed as mean ± standard deviation; continuous data without normal distribution were expressed as median and min–max, and categorical data were expressed as percent (%). Student's t-test was used to compare the data of two groups with normal distribution between independent groups. Friedman test was used to compare more than two dependent variables without normal distribution, and when there was a difference between variables, the groups were compared in pairs using the Wilcoxon test to determine the group that caused the difference. Spearman's correlation analysis was used to determine correlation between variables. Chi-squared or Fisher's exact test was used to compare independent categorical variables, and $p<0.05$ was considered statistically significant.

Results

One hundred and seventy-nine patients were enrolled in the study. All patients used 1200 IU/day vitamin D starting from the 12 weeks of gestation. The characteristics of patients such as age, gravida, parity and birth mode are shown in **Table 1**.

The median vitamin D level of each trimester was determined and compared. The median vitamin D level measured in the third trimester was significantly higher than that in the first and second trimesters ($p<0.001$). Vitamin D levels measured in the first and second trimesters were similar ($p=0.961$). There was a moderate positive correlation between neonatal vitamin D level and third-trimester maternal vitamin D level ($p<0.001$, $R=0.496$).

The first-trimester vitamin D level was sufficient for 73 patients. The first- and third-trimester vitamin D level was sufficient for 34 patients. Vitamin D levels were insufficient in the first and third trimesters of 73 patients. Approximately 52% of 73 patients with vitamin D levels above 20 ng/dl in the first trimester had a vitamin D level below 20 ng/dl in the third trimester despite the treatment. Of 106 patients with vitamin D levels below 20

Table 1. Demographic and clinical characteristics of patients.

		n=179
Age, mean (sd)		29±5.4
Gravida, mean (sd)		2±0.9
Parity, mean (sd)		1±0.7
Smoker, n (%)		21 (11.7)
Mode of delivery	NVYD, n (%)	101 (56.4)
	C/S, n (%)	78 (43.6)
Median vitamin D level (IQR)	First trimester	12 (10–21)
	Second trimester	15 (10–20)
	Third trimester	17 (12–23)
GDM, n (%)		8 (4.5)
Preeclampsia, n (%)		5 (2.8)
Birth weight, g (sd)		3270±440
Macrosomia, n (%)		14 (7.8)
SGA, n (%)		7 (39)

Table 2. Comparison of perinatal results.

		Sufficient (first trimester) (n=73) Sufficient vs. insufficient (three trimesters or cord blood)	Insufficient (first trimester) (n=106) Sufficient vs. insufficient (three trimesters or cord blood)
Mode of delivery	Third trimester	0.918	0.661
	Cord blood	0.452	0.673
GDM	Third trimester	0.713	0.904
	Cord blood	0.220	0.690
Preeclampsia	Third trimester	0.953	0.248
	Cord blood	0.330	**0.049***
Macrosomia	Third trimester	0.608	0.108
	Cord blood	0.654	0.195
SGA	Third trimester	0.169	0.097
	Cord blood	**0.046***	**0.016***

*Fisher's test.

ng/dl in the first trimester, only 31% were able to reach a sufficient level in the third trimester after the treatment, and 69% remained at an insufficient level. The rate of patients whose vitamin D level was sufficient in the first trimester and continued adequately in the cord blood was 79%. The rate of patients whose vitamin D level was sufficient in the first trimester and whose cord blood vitamin D was insufficient was 21%. In the patients with sufficient vitamin D levels in the first trimester who received treatment, SGA was significantly lower in the group with sufficient neonatal cord blood vitamin D level, compared to those in the group with insufficient neonatal cord blood vitamin D level (p=0.046) (**Table 2**). In the group with insufficient vitamin D levels in the first trimester, preeclampsia rate (p=0.049) and birth rate below 2500 g (p=0.016) were significantly lower as shown in **Table 2**. The mean birth weight of 34 patients with sufficient first- and third-trimester vitamin D levels was 3401 g, and the mean birth weight of 73 patients with insufficient first- and third-trimester vitamin D levels was 3227 g (**Table 3**).

There was a significant difference between the birth weights of these two groups (p=0.03). Although there was no significant difference in terms of small for gestational age (SGA) in the subgroups categorized to obtain secondary results, birth weights were higher in women who had sufficient vitamin D levels in the first trimester (p=0.057 and p=0.096). Birth weights for patients with insufficient vitamin D levels in the first trimester but with sufficient neonatal cord blood levels as a result of treatment were significantly higher compared to those in patients with insufficient cord blood vitamin D levels (3327 g vs. 3133 g, p=0.030) as shown in **Table 3**.

Discussion

The main purposes of our study were to determine vitamin D levels measured in all trimesters of pregnancy in

Table 3. Comparison of birth weights.

Maternal blood in the first trimester	Third-trimester or cord blood	Third-trimester blood: Birth weight (mean, Std)	Third-trimester blood: p-value	Cord blood: Birth weight (mean, Std)	Cord blood: p-value
Sufficient	Sufficient	3401±384 (n=35)	0.057	3345±345 (n=58)	0.096
	Insufficient	3208±458 (n=38)		3141±647 (n=16)	
Insufficient	Sufficient	3307±484 (n=32)	0.402	3327±391 (n=66)	**0.030***
	Insufficient	3227±430 (n=74)		3133±511 (n=39)	

*Student's t-test.

patients who received vitamin D replacement in accordance with the national health guidelines, and to monitor the changes between trimesters. The secondary purpose of the study was to compare perinatal results. We demonstrated the importance of controlled and regular vitamin D replacement in pregnant women. Despite replacement therapy, vitamin D levels did not increase to desired levels in a significant number of patients during the following weeks of gestation. In this study, there was a correlation between third-trimester vitamin D levels and neonatal cord blood vitamin D levels. Birth weights were lower in the group with insufficient vitamin D level in the beginning of the pregnancy and insufficient neonatal cord blood vitamin D level. We observed that the standard dose of vitamin D replacement therapy used in Türkiye was insufficient.

There are many studies in the literature that evaluate the effect of vitamin D deficiency in pregnancy on poor prenatal results.[16–18] Increased levels of vitamin D deficiency in cord blood are clinically important due to the risk of health complications in newborns. In 2016, Dangard et al.[16] investigated the relationship between 25(OH) vitamin D levels in the third trimester and fetal development. They observed the infant birth weight and height measured in the first 14 days. They demonstrated that maternal third-trimester 25(OH) vitamin D level was correlated with infant height measurement but not with infant weight. They showed that the concentration of vitamin D in maternal blood was higher in the late stages of pregnancy than that in the cord blood. In a study involving 7098 pregnant women in which Miliku et al.[17] measured 25(OH) vitamin D levels in the second trimester in Netherlands, they found that low vitamin D concentrations were associated with proportional fetal growth restriction, SGA, and an increase in the frequency of preterm births. In the meta-analysis including 13 randomized controlled trials published in 2015, it was shown that vitamin D supplementation increased 25(OH) vitamin D levels, birth weight, and birth height.[18] In our study, the birth weight was lower in the group with insufficient vitamin D levels at the beginning of the pregnancy and insufficient neonatal cord blood vitamin D levels. Fetal growth is a complex process. Many factors affect the development, such as genetic structure, trophoblast implantation, placental development, nutrition and physical activity.

World Health Organization (WHO) recommends 200 IU vitamin D supplement per day for pregnant women with vitamin D deficiency.[19] While American College of Obstetricians and Gynecologists (ACOG) recommends routine supplementation at a standard vitamin D dose, it states that it is safe to use 1000–2000 IU vitamin D per day in accordance with expert opinions in case of vitamin D deficiency during pregnancy. Although there is no consensus on optimal vitamin D levels, there is an opinion that blood vitamin D levels should be at least 20 ng/dl to avoid bone problems.[20] The Institute of Medicine (IOM) states that pregnant women should take 600 IU of vitamin D, that the daily intake for pregnant women with vitamin D deficiency can increase up to 4000 IU, and that they should continue the same dose during breastfeeding in order to maintain their own health and the health of their infants. In addition, it is stated that blood levels of 25(OH) vitamin D of 20 ng/mL and above are sufficient.[15] As per the protocol of the Ministry of Health in Türkiye, it is recommended to start vitamin D support in pregnant women regardless of their blood level. Approximately 1200 IU of vitamin D is recommended to be taken as a single daily dose for pregnant women in the prenatal period and for postpartum period for 6 months.[21] Although this standard treatment was administered in our study, third-trimester and neonatal cord blood values did not reach desired levels in most patients.

There are many possible biological mechanisms that underlie the potential contribution of maternal vitamin D deficiency to the pathophysiology of preeclampsia, such as abnormal placental implantation, vascular endothelial dysfunction at the maternal-fetal interface, and excessive inflammation characterize preeclampsia.[22] In our study, preeclampsia rate was significantly lower in the group with sufficient neonatal vitamin D levels. In the review conducted by Callaghan and Kiely[23] in 2018, 37 systematic reviews and observational studies were discussed. The purpose of their review was to demonstrate the effect of maternal vitamin D status or dietary vitamin D replacement on the prevalence of hypertensive diseases during pregnancy. Systematic studies have not reached definite conclusions regarding the potential of vitamin D to protect against gestational hypertensive diseases. Observational cohort studies show a positive association between vitamin D deficiency and increased risk of preeclampsia; however, the results cannot be relied upon to draw conclusions due to suboptimal clinical phenotyping, incomplete subject characterization, and large heterogeneity between studies.

Possible biological mechanisms of the relationship between vitamin D and gestational diabetes mellitus (GDM) are based on insulin-sensitive tissues, calcium pool in the pancreas, genetic diversity and inflammation.[24] In a meta-analysis of 29 observational studies by Hu et al.,[12] 28,982 patients were included. Although GDM diagnostic criteria and vitamin D cut-off values differed between the studies, 25(OH) vitamin D levels were significantly lower in patients with GDM. As in our study, in the study by Eggemoen et al.[25] with 745 pregnant women of different ethnic origins, the authors showed that vitamin D deficiency had no effect on GDM and glucose metabolism. Based on literature review, vitamin D deficiency has been associated with GDM more frequently. In this study, we did not associate vitamin D deficiency with GDM, mode of delivery, and gestational age. We observed that the third-trimester 25(OH) vitamin D level was correlated with cord blood level. We also found that there was a relationship between vitamin D deficiency and SGA. In our study, there was no significant difference in the group with insufficient 25(OH) vitamin D levels in all trimesters, although the number of births with C/S was higher. There are publications in the literature showing that birth rate with C/S is higher in case of low blood vitamin D levels.[14]

Some limitations of our study were that it was retrospective in nature, was designed in a clinic where risky pregnancies are followed up intensively, and had insufficient number of patients. The strengths of the study were that it was a single-center study and all patients received a standard treatment.

Conclusion

Vitamin D levels in neonatal cord blood predicted SGA better compared to third-trimester cord blood vitamin D levels. There was a moderate positive correlation between third-trimester and neonatal cord blood levels. Regardless of first-trimester vitamin D value, infant birth weight was significantly higher and the SGA rate was significantly lower in the group with sufficient neonatal cord blood level.

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