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Serum Vitamin D Concentrations Among Pregnant Women and Its Influence on the Fetal Anthropometric Measurements

Gebe Kadınlarda Serum D Vitamin Konsantrasyon Düzeyi ve Bunun Fetal Antropometrik Ölçümler Üzerine Etkisi

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Abstract

Objectives: Vitamin D is a fat-soluble vitamin which comes primarily from exposure to sunlight. Vitamin D deficiency (VDD) in pregnancy is found to be related to adverse pregnancy outcomes including preeclampsia, hypertension, caesarean section, preterm birth, etc. In this current study, we aimed to evaluate the relationship between VDD and fetal anthropometric measurements, amniotic fluid abnormalities, and placental location in pregnant women with singleton pregnancies.

Materials and Methods: This prospective study consisted of 268 pregnant women who attended to the antenatal clinics for their routine second trimester prenatal ultrasound screening. VDD is defined as <30 nmol/L (equals to 12 ng/ml) based on the criteria regarding the vitamin D status. Study population was subdivided into two groups with respect to their serum 25(OH)D levels: Group 1 - VDD group (n= 190); 25(OH)D <12 ng/ml, and Group 2 - normal vitamin D (NVD) group (n= 78); 25(OH)D ≥12 ng/ml. Fetal anthropometric measurements, placental location, and amniotic fluid abnormalities were compared between groups. A p-value < 0.05 was considered statistically significant.

Results: The mean vitamin D was 7.52±2.26 ng/ml in VDD group, and 22.61±19.40 ng/ml in NVD group (p=0.001). There were no differences in the measurements of fetal biparietal diameter, femur length, abdominal circumference, cisterna magna, lateral ventricles and transverse cerebellar diameter between groups (p> 0.05). Fifty five % of women in VDD group and 46.6% of the cases in NVD group had their placenta located in corpus posterior of the uterus (p= 0.145). Ten out of 190 women in VDD group and 7 out of 78 women in NVD group had polyhydramnios in the study (p= 0.457).

Conclusion: The current study failed to demonstrate the relationship between VDD and fetal anthropometric measurements, amniotic fluid abnormalities, and placental location in pregnant women at 20-25 weeks of gestation. Based on the findings in literature, we can assume that other protective mechanisms may play role in preventing fetus from the influence of VDD during the second trimester or fetus has not been affected from the disease, because fetus does not require much calcium and vitamin D due to its small bone mass during this period. The adverse impact of VDD on the fetal bone development can be prevented by appropriate treatment in pregnancy.

Key words: Vitamin D, pregnancy, fetal measurement, vitamin D deficiency

Öz

Amaç: D vitamini yağda çözünen bir vitamin olup güneş ışığından elde edilir. Gebelikte D vitamini eksikliği (DVE) preeklampsi, hipertansiyon, sezaryen doğumlar, preterm doğum gibi kötü gebelik sonuçları ile ilişkili bulunmuştur. Bu çalışmada tekil gebeliği olan kadınlarda DVE ile fetal antropometrik ölçümler, amnion sıvısı anormallikleri ve plasental lokalizasyonu arasında ilişki incelendi.

Materyal ve Metot: Bu prospektif çalışma ikinci trimesterde rutin ultrason değerlendirmesi için antenatal kliniğe başvuran 268 gebeden oluşmaktadır. D vitamini ile ilgili kriterlere dayanılarak DVE serum vitamin D <30 nmol/L (12 ng/ml) olarak tanımlandı. Çalışma popülasyonu D vitamini düzeylerine göre 2 gruba ayrıldı. Grup 1 - DVE grubu (n= 190); 25(OH)D <12 ng/ml, ve grup 2 - normal D vitamini (NVD) grup (n= 78); 25(OH)D≥12 ng/ml. Fetal antropometrik ölçümler, plasental lokalizasyon ve amniotik sıvı anormallikleri iki grup arasında karşılaştırıldı. P <0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Ortalama D vitamin düzeyi DVE grubunda 7,52±2,26 ng/ml ve NVD grubunda 22,61±19,40 ng/ml idi. İki grup arasında fetal biparyetal çap, femur uzunluğu, abdominal çap, sisterna magna, lateral ventrikül, ve transserebellar çap ölçümleri bakımından farklılık tespit edilmedi (p> 0,05). DVE grubunun %55 inde ve NVD grubunun %46,6 sında korpus posteriorda lokalize plasenta tespit edildi (p=0,145). DVE grubunda 190 kadının 10 unda ve NVD grubunda 78 kadının 7 sinde polihidramniyoz tespit edildi (p= 0,457).
Sonuç: Bu çalışmada 20-25. haftadaki gebe kadınlarda DVE ile fetal antropometrik ölçümler, plasental lokalizasyon ve amniotik sıvı anormallikleri arasında ilişki tespit edilemedi. Literatürdeki çalışmalara dayanarak, DVE den fetüsü koruyan başka mekanizmaların varlığı olduğunu düşünebilir ya da bu dönemde fetüsün kemik kütlesi küçük olduğundan, çok fazla Ca ve D vitaminine ihtiyaç duymuyor olabilir. Bununla beraber DVE nin fetal kemik gelişimine olan negatif etkisini önlemek için gebelikte uygun tedavi verilmelidir.
Anahtar kelimeler: D vitamini, gebelik, fetal ölçümler, D vitamini eksikliği

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Introduction

Vitamin D is a fat-soluble vitamin which is obtained primarily from sun exposure. In order to become activated, it undergoes two hydroxylation reactions in the body. First, vitamin D is converted to 25-hydroxyvitamin D [25(OH)D] in the liver, and second reaction occurs in the kidney as 25(OH)D is hydroxylated to form active 1,25-dihydroxyvitamin D [1,25(OH)2D].[1,2] Vitamin D status can be assessed by measuring serum concentration of 25(OH)D (1) which has a reasonably long half-life in the circulation.[3] The importance of vitamin D for skeletal development, modulation of calcium homeostasis, bone formation, and resorption has been well described in literature.[1,4] It has also other vital roles in regulation of immune function, cell growth, and inflammation in the body.[1,4,5] Adequate vitamin D status is defined as having serum 25(OH)D concentrations greater than 50 nmol/L (or 20 ng/mL) in general population.[1] In addition, vitamin D insufficiency is described as having serum 25(OH)D below 12 ng/ml (30 nmol/liter) in the body.[6]

Vitamin D deficiency (VDD) is a common worldwide health problem with a high prevalence among infants, children, adolescents, adults and elders.[7] If severe enough, it can preclude normal bone mineralization leading to clinical manifestations such as rickets or osteomalacia.[8] Vitamin D levels in the body fluctuate with the changing seasons. Manifestations of VDD are more common during the winter season when vitamin D levels reach their lowest levels.[9]

VDD in pregnancy is found to be related to an increased risk of pre-eclampsia, hypertension, caesarean section, preterm birth, and gestational diabetes mellitus etc.[10-14] Studies have shown that there is a strong relationship between maternal VDD and adverse maternal and fetal outcomes including lower maternal weight gain and reduced bone mineral acquisition during early postnatal life.[15,16] Inadequate vitamin D intake

during pregnancy has been found to be related to low infant birth weight.[17] Another study investigating the relationship between maternal vitamin D status and postnatal growth reported significantly higher weights during the first year of life for children whose mothers received vitamin D supplementation during pregnancy.[18] Recent study has suggested that the bone mass of newborn is closely related to the maternal serum vitamin D concentrations during pregnancy[19] and maternal vitamin D intake has been shown to decrease the risk of wheezing symptoms in early childhood. [20]

The present study set out to evaluate the association between maternal vitamin D status measured in the second trimester in pregnancy and fetal anthropometric measurements, amniotic fluid index, and placental location in pregnant women with singleton pregnancies.

Materials and Methods

This prospective cross sectional study was carried out at Ankara Ataturk Training and Research Hospital, Obstetrics and Gynecology Clinic. The project is approved by the Institutional Ethical Committee of the hospital and written informed consent was obtained from all participating women. The study population consisted of 268 pregnant women who attended to the antenatal clinics for their routine second trimester prenatal ultrasound screening at 20-25 weeks of gestation. The gestational age was determined based on the combination of last menstrual period and ultrasound findings during early pregnancy in all cases. BMI was calculated as weight (kg)/height squared (m^2) in the study. Inclusion criteria for participants were maternal ages between 18–40 years, singleton pregnancies with a live fetus, gestational age between 20 and 25 weeks, and healthy pregnant women without any medical disorders. Since Vitamin D metabolism is affected by obesity,[21] pregnant women with normal BMI (18-25 kg/m^2) were included in the study. Pregnant women with disorders such as rheumatoid arthritis, thyroid, adrenal, or parathyroid diseases, hepatic or renal failure, bone disease, type 1 diabetes mellitus, malabsorption, alcohol consumption, illicit drug use, blood transfusion, and multiple pregnancies were excluded from the study. Venous blood samples were withdrawn from the brachial vein of the patients in the morning, after overnight fasting in order to determine serum calcium (Ca), 25(OH)D levels. Serum 25(OH)D concentration was measured by a high-performance liquid chromatography (HPLC) method with use of a Chromsystems kit (recovery: >85% (Coefficient of variation (CV): 4%). Serum Ca was both measured by colorimetry using the Siemens-advia kit. VDD is defined as < 30 nmol/L (equals to 12 ng/ml) based on criteria regarding the vitamin D status.[22] Study population was subdivided in to two groups based on their serum 25(OH)D levels group1- VDD group (n= 190) ; 25(OH)D <12 ng/ml, and group 2- normal vitamin D (NVD) group (n= 78) ; 25(OH)D ≥ 12 ng/ml. Routine ultrasound examination carried out at 20 to 25 weeks of gestation with a Logic 9 sonographic equipment using a 7.5 MHz convex transabdominal probe (General Electric, Milwaukee, WI, USA). Placental location in the uterine cavity, amniotic fluid index, fetal anthropometric measurements including biparietal diameter (BPD), abdominal circumference, femur length, transcerebellar diameter (TCD), cisterna magna (CM), lateral ventricles, nasal bone were determined during the ultrasound screening. These measurements were compared between two

groups. Data were analyzed using the SPSS software package Version 21.0 (released 2012, IBM Corp., Armonk, N.Y., USA). The Kolmogorov-Smirnov test was performed to test the normality of distribution of the variables. Continuous variables with normal distribution were presented as mean ± SD. Fetal anthropometric measurements, serum Ca and Vitamin D levels were compared between two groups by using Student`s T test. Placental location and amniotic fluid abnormalities were compared between groups by using Chi square test. A p-value < 0.05 was considered statistically significant.

Results

The mean maternal age was 26.56± 5.18 years in VDD group and 27.45±5.06 years in NVD group (p=0.331) (Table 1). The mean gestational age was 21.69±1.62 weeks in VDD group and 21.92±1.82 weeks in VND group. The mean pregestational BMI was found as 24.19±4.45 kg/m^2 in VDD group and 23.93±4.53 kg/m^2 in NVD group (p=0.705). The mean vitamin D concentrations were measured as 7.52±2.26 ng/ml and 22.61±19.40 ng/ml in VDD and NVD groups respectively. Serum Ca concentrations were 8.71±0.67 mg/dl in VDD group and 8.69±0.73 mg/dl in NVD group in the study (p=0.325). There were no differences of the measurements of fetal biparietal diameter, femur length, abdominal circumference, cisterna magna, lateral ventricles, transverse cerebellar diameter between groups (p > 0.05) (Table 1). Fifty five % of women in VDD group and 46.6% of the cases in NVD group had their placenta located in corpus posterior of the uterus (p= 0.145). Ten out of 190 women in VDD group and 7 out of 78 women in NVD group had polyhydramnios in the study (p= 0.457). No oligohydramnios was observed in the study.

Table 1. Patient characteristics, fetal anthropometric measurements and blood values for two groups

	Vitamin D <12ng/mL n=190	**Vitamin D ≥12ng/mL n=78**	**p-value**
Pregestational BMI (kg/m2)	24.19±4.45	23.93±4.53	0.705
BMI 20-25. weeks (kg/m2)	25.90±4.38	25.86±4.47	0.951
Maternal age (years)	26.56± 5.18	27.45±5.06	0.331
Gravida (n)	2.03±1.10	2.0 ±1.05	0.918
Parity (n)	0.81± 0.83	0.71 ±0.79	0.373
Gestational age (weeks)	21.69±1.62	21.92±1.82	0.503
BPD (mm)	51.34±5.44	52.26±5.83	0.245
FL (mm)	36.66±4.39	37.51±5.09	0.313
AC (mm)	168.65±21.42	172.04±21.36	0.320
Fetal weight (g)	470.65±132.42	489.82±161.11	0.491
Lateral ventricle (mm)	6.85±0.75	6.90±0.73	0.729
Sisterna magna (mm)	4.69±0.87	4.76±0.90	0.584
Cerebellum (mm)	22.63±2.32	22.97±2.85	0.415
Nasal bone (mm)	7.39±0.79	7.59±0.86	0.061

Discussion

In this current study, no differences of fetal anthropometric measurements, amniotic fluid abnormalities, and placental location were observed between VDD and NVD groups. There is conflicting evidence in literature that maternal 25-(OH)D deficiency may impair fetal growth inutero.[18,23-25] Placental 1,25-(OH)2D is produced by using maternal 25-(OH)D in the body. It is postulated that 25-(OH)D and 1,25-(OH)2D concentrations in fetal circulation may be affected leading to reduced fetal bone growth in severe maternal VDD [26]. The recent study showed that infants born to mothers with early pregnancy vitamin D levels ≤ 29.9 nmol/l (12 ng/ml) had significantly lower birth weights and an increased risk of small for gestational ages compared with infants born to mothers with levels ≥50 nmol/l (20 ng/ml).[18] In this report, cases were different from ours as they included pregnant women with a pregnancy duration of 37 weeks or more. Therefore they measured serum vitamin D levels during the third trimester of pregnancies. On the other hand we evaluated the relationship between fetal measurements and VDD in the second trimester. In another study they found that low maternal 25-(OH)D in late pregnancy was associated with reduced intrauterine long bone growth and slightly shorter gestation. They also found that infants of mothers who were vitamin D deficient (<28 nmol/l) at 28–32 wk gestation had shorter knee-heel length than other babies during the postnatal period.[23] Unlike to this study, we measured serum vitamin D levels at 20-25 weeks of gestation in our study and found no correlation between VDD status and fetal growth. We assumed that fetal growth might not be affected from VDD due to the need of small amount of Ca and vitamin D for a small fetus during the second trimester. As the body weight of fetus increases with gestational age, it leads to increased demand for vitamin D and Ca in order to accommodate appropriate fetal bone development later in pregnancy.

Recent study has demonstrated that restricting fortified milk or vitamin D intake causing VDD during pregnancy lowers infant birth weight in otherwise healthy, nonsmoking mothers.[27]

However, these findings have not been consistently replicated by others. Farrant et al. have found that although VDD at 30 weeks gestation is common among pregnant women, it is not associated with an impaired fetal growth in their study.[28] Similar to what we found our study, Prentice et al. have observed that there is no influence of vitamin D status during pregnancy on infant growth and bone mineral increase.[29] In this present study we did not find any significant differences in terms of amniotic fluid abnormalities and placental location between groups. There is no data regarding the amniotic fluid abnormalities and placental location in pregnant women with VDD in literature.

This cross sectional study has some limitations. First, we measured maternal serum vitamin D levels and fetal growth at 20-25 weeks of gestation. Since we did not evaluate these women later in pregnancy we hardly anticipate whether SGA or growth restriction will develop in these fetuses. Therefore we cannot confidently tell that VDD won`t affect fetal development. However we can at least declare that the effect of VDD has not emerged during the second trimester, so we can still treat the pregnant women. Thus the

impact of VDD on the development of the diseases such as rickets can be to some extent prevented by appropriate treatment. In addition to that some debate remains as to what blood level of 25(OH)D should be for an most favorable skeletal development and health.[1,30] Studies have noted that to maximize bone health in children and adults, the blood level of 25(OH)D should be at least 20 ng/mL.[1]

In conclusion, the current study failed to demonstrate relationship between vitamin D deficiency and fetal anthropometric measurements, amniotic fluid abnormalities, and placental location in pregnant women at 20-25 weeks of gestation. Based on the findings in literature, we can assume that other protective mechanisms may play role in preventing fetus from the influence of VDD during the second trimester or fetus has not been affected from the disease, because fetus does not require much calcium and vitamin D due to its small bone mass during this period. However, the adverse impact of VDD on the fetal bone development can be prevented by appropriate treatment in pregnancy. In order to confirm our findings, longitudinal studies with repeated measurements during pregnancy should be performed.

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