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Vitamin D Supplementation in An Area Exposed to Intense Sunlight During Pregnancy: Is It Really Need?

Hamilelikte Yoğun Güneş Işığına Maruz Kalan Bir Bölgede D Vitamini Takviyesi: Gerçekten Gerekli Mi?

Mehmet BULBUL[1], Berna DILBAZ[2], Mustafa KAPLANOGLU[3], Capan KONCA[4], Zelal KAHRAMANER ERDEMİR[5], Abdullah ARPACI[6]

Abstract: Objective: Our aim was to investigate the effect of vitamin-D (vit-D) intake during pregnancy on maternal and fetal serum 25-OHvitD (25-hydroxy vitamin-D) levels and perinatal outcomes in a region exposed to intense sunlight. Methods: In this retrospective case-control study, 192 pregnant women using vit-D and 188 pregnant women not using vit-D were included in the study. Results: Parathyroid hormone level, neonatal respiratory support need and incidence of gestational diabetes mellitus were lower in the Vit-D user group, but vit-D and calcium levels were higher. Conclusion: Although the use of 500 IU / day vit-D slightly improves the results, even in areas with high exposure to sunlight, higher doses of vit-D support are needed to improve perinatal outcomes and blood values.
Keywords: Calcium, Parathyroid hormone, Perinatal outcomes, Pregnancy, Vitamin D.

Öz: Amaç: Yoğun güneş ışığına maruz kalan bir bölgede yaşayan ve gebeliği boyunca vitamin-D (vit-D) alan gebelerde maternal ve fetal serum 25-OHvitD (25-hidroksi vitamin-D) düzeyleri ve perinatal sonuçlar araştırıldı. Gereç ve Yöntem: Bu retrospektif vaka kontrol çalışmasında vit-D kullanan 192 gebe ve vit-D kullanmayan 188 gebe çalışmaya dahil edildi. Bulgular: Vit-D kullanıcı grubunda paratiroid hormon düzeyi, neonatal solunum destek ihtiyacı ve gestasyonel diabetes mellitus insidansı daha düşük iken vit-D ve kalsiyum seviyeleri daha yüksekti. Sonuç: Güneş ışığına yüksek oranda maruz kalan bölgelerde bile, 500 IU/gün vit-D kullanımı sonuçları bir miktar iyileştirse de perinatal sonuçları ve kan değerlerini iyileştirmek için daha yüksek dozlarda vit-D desteği gereklidir.
Anahtar Kelimeler: Kalsiyum, Paratiroid hormon, Perinatal sonuçlar, Gebelik, D vitamini.

[1]Corresponding Author: Dr. Öğr. Üyesi, Kadın Hastalıkları ve Doğum ABD, Adıyaman Üniversitesi, Tıp Fakültesi, ORCID: 0000-0001-5695-2586, mehmetbulbulmd@gmail.com
Assistant Prof. Dr., Department of Obstetrics and Gynecology, Adiyaman University Faculty of Medicine
[2] Prof. Dr. Kadın Hastalıkları ve Doğum ABD., Adıyaman Üniversitesi, Tıp Fakültesi, ORCID: 0000-0003-1137-8650, sdilbazhotmail.com
Prof. Dr., Department of Obstetrics and Gynecology, Adiyaman University Faculty of Medicine, Adiyaman, Turkey.
[3] Doç. Dr. Kadın Hastalıkları ve Doğum ABD., Adıyaman Üniversitesi, Tıp Fakültesi, ORCID: 0000-0002-4658-1336, mustafakaplanoğlu@gmail.com
Associate Prof. Dr., Department of Obstetrics and Gynecology, Adiyaman University Faculty of Medicine, Adiyaman, Turkey.
[4] Doç. Dr. Pediatri ABD., Adıyaman Üniversitesi, Tıp Fakültesi, ORCID: 0000-0001-8625-9045, dr.capan@hotmail.com
Associate Prof. Dr., Department of Pediatrics, Adiyaman University Faculty of Medicine, Adiyaman, Turkey.
[5] Doç. Dr. Pediatri ABD., Adıyaman Üniversitesi, Tıp Fakültesi, ORCID: 0000-0003-4739-875x, zelaldr@hotmail.com
Associate Prof. Dr., Department of Pediatrics, Adiyaman University Faculty of Medicine, Adiyaman, Turkey.
[6] Prof. Dr. Biyokimya ABD., Adıyaman Üniversitesi, Tıp Fakültesi, ORCID: 0000-0002-6077-8258, arpaci57@gmail.com
Prof. Dr., Department of Biochemistry, Adiyaman University Faculty of Medicine, Adiyaman, Turkey.

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Introduction

Vitamin D (vit-D), which is synthesized in the skin with the effect of sunlight, has many functions. Vit-D—mainly responsible for calcium and phosphorus metabolism and bone health—plays a particularly important role during pregnancy in terms of egg fertilization and implantation, cell development, membrane stabilization, nerve conduction, and insulin synthesis (Bikle, 2009; Norman, 2008; Tariq, Tariq and Lone, 2018).

It is known that vit-D deficiency increases the risks of gestational diabetes, preeclampsia, preterm labor, and low-birth-weight infants (Aghajafari et al., 2013; Amraei et al., 2018; Yin, et al., 2020). In addition, vit-D deficiency and insufficiency can lead to hypocalcemia, infantile rickettsia, craniotabes, dental enamel hypoplasia, and increased incidence of temporary tachypnea in the mother-dependent neonate (Konca et al., 2014; Soliman et al., 2013). Considering all these potential effects of vit-D deficiency, supplementation is very important if skin synthesis and intestinal absorption from food are insufficient.

The main source of vit-D in the human is the production in the skin through sunlight. In areas with less sunlight exposure, vit-D synthesis from the skin may stop completely (Webb, Kline and Holick, 1988). Therefore, the need for vit-D in pregnant women may vary depending on the region they live in. The prevalence of vit-D deficiency in developed countries is around 40% (Forrest and Stuhldreher, 2011). In our country, this rate is between 70 and 88% (Taşkıran and Cansu, 2016; Çolak et al., 2015; Bozkaya et al., 2017). Perhaps this is why there is no consensus on the most effective and safe dose of vit-D in pregnant women. Therefore, we aimed to investigate the perinatal effects of 500 IU/day vit-D supplementation during pregnancy in a region with high exposure to sunlight.

Material and Methods

After obtaining ethical approval (Biomedical Ethics Committee, Faculty of Medicine, Adiyaman University, Approval no. 2013/04/04-1.1), this retrospective case-control studywas conducted at the Obstetrics and Gynecology Department, Adiyaman University Hospital, Adiyaman, Turkey, between January and April 2013. During the study period, 1675 babies were born in our unit. After exclusion criteria, 192 pregnant women who had received 500 IU/day vit-D supplementation (cholecalciferol) from the 12th week of pregnancy to birth were included in the study. One hundred and eighty-eight pregnant women who did not receive vit-

D support during pregnancy were included in the study for comparison (Figure 1). Pregnant women with endocrine disorders, intestinal malabsorption or irregular use of vit-D were excluded from the study. Pregnant women in the study and control groups were hospitalized for labor and delivered during the same period, lived in the same geographic region (Between 370 25 'and 380 11' north latitude, 370 and 390 east longitude), and had similar living standards.

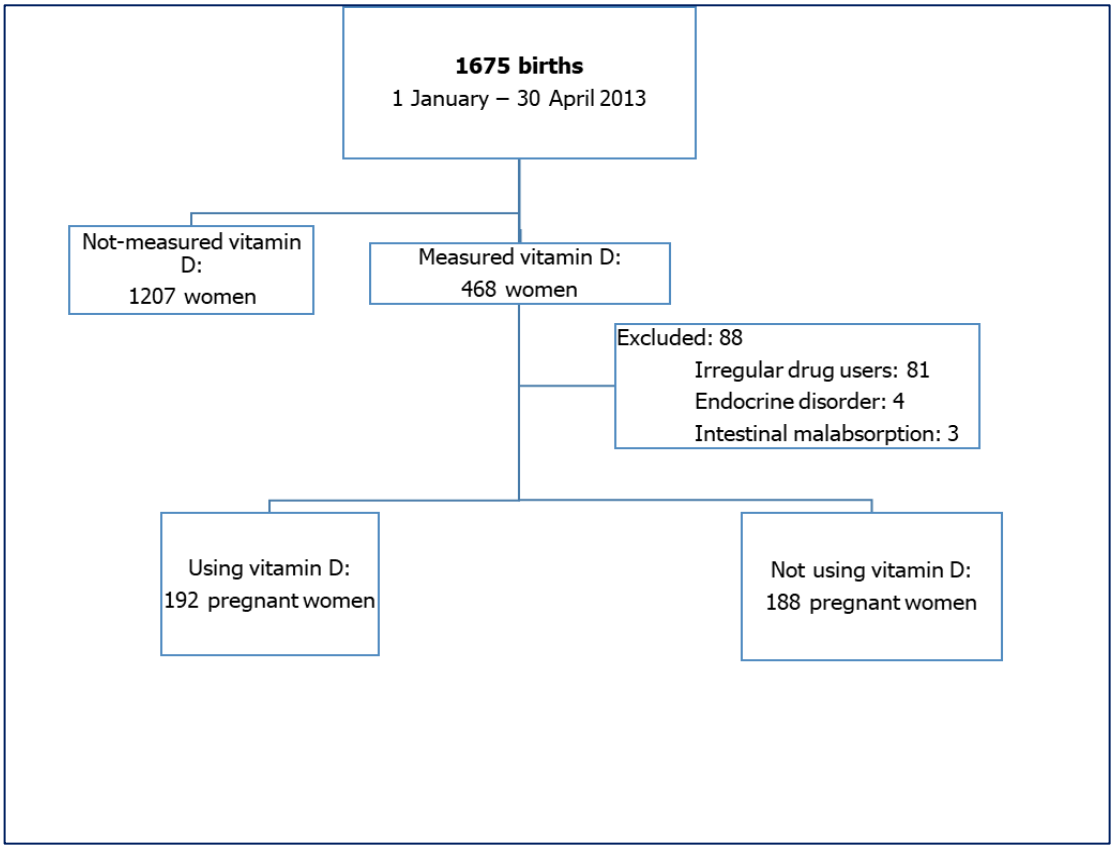

Figure 1: Diagram showing the number of patients included in this study

Blood was taken from mothers by venipuncture before birth. In addition, blood of babies was drawn from fetal cord postnatally. Calcium (Ca), serum 25-hydroxyvitamin D (25-OHvitD), alkaline phosphatase (ALP), parathyroid hormone (PTH), and phosphorus (P) levels were determined from all blood samples. All measurements were performed at the Biochemistry Laboratory, Adıyaman University. Serum 25-OHvitD and PTH levels were determined with Cobas 6000 series (Cobas e 601 module) automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany), and Ca, ALP, and P levels were determined by spectrophotometry with the Cobas c 501 module of the same autoanalyzer. For cord blood, vit-

D deficiency is defined as 25-OHvitD less than 12 ng/ml, insufficiency as 25-OHvitD 12–20 ng/ml, and sufficiency as 25-OHvitD greater than 20 ng/ml. For pregnant women, vit-D deficiency is defined as 25-OHvitD less than 20 ng/ml, insufficiency as 25-OHvitD 20–30 ng/ml, and sufficiency as 25-OHvitD greater than 30 ng/ml.

Demographic data for the pregnant women (i.e., maternal age, gravida, parity, abortus, and number of living children), information related to maternal diseases arising during pregnancy, and characteristics of the newborn (i.e., gestational week, birth weight, gender, type of delivery, and need for neonatal intensive care support) were recorded. Statistical analysis was done using SPSS 21.0 (IBM Corp., Armonk, USA). Variables with continuous values were presented with mean ± standard deviation values in the study. Variables that took continuous values were compared using the independent sample t-test and the Mann-Whitney U test. The statistical significance level was found to be 0.05 and Chi-square test was used to compare categorical variables.

Results

There were no statistically significant differences in terms of maternal age, number of births, abortions, and the number of children between the two groups ($p>0.05$) (Table 1). The total number of pregnancies was higher in the study group (3 [1–12] vs. 3 [1–5]; $p = 0.033$). GDM was found to be lower in the study group (2.1% vs. 6.4%; $p = 0.037$), whereas there was no difference in terms of hypertensive disorders and recurrent pregnancy losses.

The gestational age, delivery type, birth weight, fetal height and fetal gender were similar in the two groups. However, in the follow-up of infants after the birth, 71.9% (n = 138) of the infants in the vit-D user group did not require respiratory support, whereas this rate was 58.5% (n = 110) in the other group group and this was statistically significant ($p = 0.024$) (Table 1).

Maternal 25-OHvitD, Ca, ALP, and P levels were similar in the two groups ($p>0.05$). PTH was found to be lower in the study group (34.7 ± 25.2 vs. 40.7 ± 22.2; $p = 0.025$) and the difference was statistically significant. Although no significant difference was found in the mothers, 25-OHvitD and Ca levels were found to be higher and PTH level was lower in the babies of the study group (respectively 7.9 ± 3.9 vs. 5.7 ± 2.8, $p <0.001$; 9.6 ± 0.8 vs. 9.3 ± 0.6, $p = 0.016$; 19.1 ± 24.4 vs. 28.4 ± 29.6, $p = 0.001$) (Table 2).

Table 1: Maternal Demographic Characteristics and Birth Data of Babies

			Vit-D Users	Vit-D Nonusers	*p*
			n: 192	*n*: 188	
Maternal age (year, mean ± SD)			29.0±6.5	29.6±5.3	0.336
BMI (kg/m2, mean ± SD)			26.69±2.49	26.75±2.71	0.838
Gravida (Median; Min–Max)			3 (1–12)	3 (1–5)	0.033
Parity (Median; Min–Max)			2 (1–10)	2 (0–8)	0.832
Number of abortions (Median; Min–Max)			0 (0–4)	0 (0–3)	0.313
Number of children (Median; Min–Max)			1 (0–8)	1 (0–4)	0.086
Accompanying diseases % (*n*)		GDM	2.1 (4)	6.4 (12)	0.037
		HT	4.2 (8)	6.9 (13)	0.214
		RPL	1.6 (3)	4.3 (8)	0.117
Gestational age (week, mean ± SD)			39.5±1.1	39.5±0.9	0.727
Type of delivery (%) (*n*)		Vaginal	62.5 (120)	52.7 (99)	0.052
		Cesarean	37.5 (72)	47.3 (89)	
Birth weight (g, mean ± SD)			3230.7±456.6	3272.6±464.7	0.383
Fetal height (cm, mean ± SD)			49.9±1.5	49.9±1.4	0.785
IUGR (%) (*n*)			0 (0.0)	2 (1.1)	0.204
LGA (%) (*n*)			6 (3.2)	4 (2.2)	0.568
Fetal gender (%) (*n*)		Female	54.2 (104)	49.5 (93)	0.359
		Male	45.8 (88)	50.5 (95)	
Respiratory support (%) (*n*)	No		71.9 (138)	58.5 (110)	0.024
	O_2 inhalation		14.6 (28)	21.8 (41)	
	Bag-mask ventilation		13.5 (26)	19.7 (37)	

GDM, gestational diabetes mellitus; HT, hypertension; IUGR, Intrauterine growth retardation; LGA, large for gestational age; RPL, recurrent pregnancy loss; SD, standard deviation; vit-D, vitamin D.

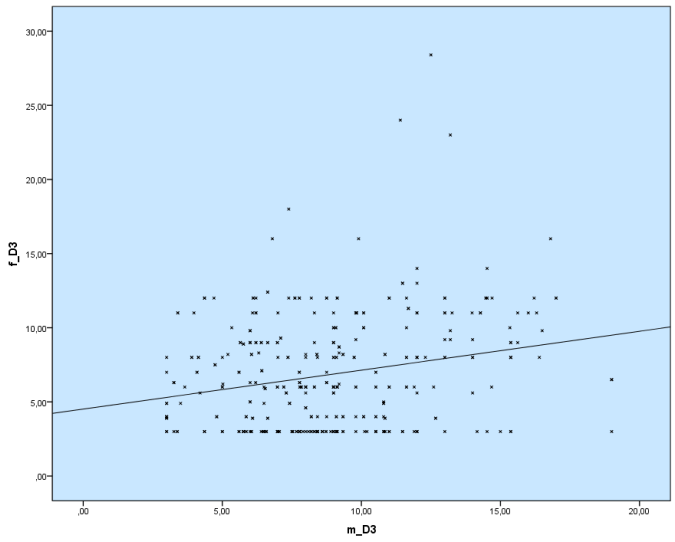

Figure 2: Correlation between maternal and cord blood vitamin D levels (m_D3: maternal vitamin D, f_D3: fetal vitamin D, r = 0.232, p<0.001)

Table 2: Laboratory Data of Maternal and Fetal Calcium Metabolism

		Vit-D Users	**Vit-D Nonusers**	***p***
		n: 192	*n*: 188	
Maternal	25-OHvitD (ng/ml, mean ± SD)	9.2±3.7	8.4±2.7	0.197
	PTH (pg/ml, mean ± SD)	34.7±25.2	40.7±22.2	0.025
	Calcium (mg/dl, mean ± SD)	8.8±0.4	8.8±0.5	0.605
	Phosphorus (mg/dl, mean ± SD)	3.9±0.5	4.0±0.8	0.558
	ALP (IU/L, mean ± SD)	167.9±25.2	171.9±36.5	0.365
	Hemoglobin (g/dl, mean ± SD)	11.3±1.3	12.0±1.1	0.017
Fetal	25-OHvitD (ng/ml, mean ± SD)	7.9±3.9	5.7±2.8	<0.001
	PTH (pg/ml, mean ± SD)	19.1±24.4	28.4±29.6	0.001
	Calcium (mg/dl, mean ± SD)	9.6±0.8	9.3±0.6	0.016
	Phosphorus (mg/dl, mean ± SD)	5.9±1.6	6.3±1.8	0.059
	ALP (IU/L, mean ± SD)	154.7±53.9	154.1±64.1	0.724

25-OHvitD, 25-hydroxy vitamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; SD, standard deviation; vit-D, vitamin D.

There was no statistically significant difference between the vit-D user and non-user groups in terms of neonatal serum phosphorus level. There was also a positively weak relationship between maternal and neonatal serum vit-D levels (r = 0232, p <0.001) (Figure 2).

When the mothers were evaluated for vit-D insufficiency, the frequency of deficiency and insufficiency was found to be lower in the study group (75.0% vs. 91.0%; 25.0% vs. 9.0%; p<0.001) (Table 3). Similarly, in terms of vit-D insufficiency in the infants, the frequency of deficiency and insufficiency in the study group was low (83.3% vs. 94.7%; 15.1% vs. 5.3%, p = 0.001).

Table 3: Prevalence of Vitamin D Deficiency in Pregnant Women and Infants

		Vit-D Users	Vit-D Nonusers	*p*
Maternal	Deficiency *n* (%)	144 (75.0)	171 (91.0)	<0.001
	Insufficiency *n* (%)	48 (25.0)	17 (9.0)	
Fetal	Deficiency *n* (%)	160 (83.3)	178 (94.7)	0.001
	Insufficiency *n* (%)	29 (15.1)	10 (5.3)	
	Sufficiency *n* (%)	3 (1.6)	0 (0.0)	

Vit-D, vitamin D.

Discussion

Low maternal vit-D levels during pregnancy were associated with adverse pregnancy/fetal outcomes, including GDM, preeclampsia, and low-birth-weight infants (Konca et al., 2014; Hossain et al., 2014; Wilson et al., 2014). Also, high vit-D levels are reported to have a protective effect against many diseases, as well as GDM, pregnancy losses, preeclampsia, preterm labor, bacterial vaginosis, low birth weight and transient tachypnea of the neonate, and higher APGAR scores (Aghajafari et al., 2013; Konca et al., 2104; Hossain et al., 2014; Bärebring et al., 2016; Dawodu et al., 2014; Heyden and Wimalawansa, 2018; Holick et al., 2011; Holmes et al., 2009; Moon, Harvey and Cooper 2015; Palacios et al., 2016). Although vit-D is important during pregnancy, the required amount of daily dose is still controversial. The recommended daily dose of vit-D is based on expert opinions in the guidelines published in many countries (Chakhtoura, 2018). This study aimed to review the reports published so far and contribute to the knowledge on this subject with our results.

Holick et al. (2011) suggested that pregnant women require at least 600 IU/day of vit-D and recognized that at least 1500 IU/day of vit-D might be needed to continue a blood level of 25-OHvitD greater than 30 ng/ml. In another study investigating the effectiveness of different doses of vit-D supplements, it was found that 400 IU / day vit-D did not increase basal 25-OHvitD levels (Hollis et al., 2011). However, 25-OHvitD levels at delivery were found to be higher in pregnant women who received vit-D≥2000 IU/day. This finding has been demonstrated in another study. (Wagner et al., 2013). It is not possible to compare our results with this study because of the lack of a control group without vit-D. However, in our study, some improvement was shown in calcium and bone metabolism in mothers and babies who

received vit-D supplements. However, this improvement in these pregnant women was not sufficient despite being exposed to intense sunlight.

A report entitled “Global Consensus Recommendations on Prevention and Management of Nutritional Rickets” was published in order to eliminate the confusion about this issue. The report stated that intake of 600 IU/day of vit-D by pregnant women would provide adequate maternal 25-OHvitD levels (Munns et al., 2016). A recent meta-analysis reported that vit-D supplementation (≤2000 IU/day) during pregnancy is associated with a reduction in the risk of fetal or neonatal morbidity and mortality (Bi et al., 2018). At the same time as this meta-analysis, Ariyawatkul and Lersbuasin (2018) performed a study that compared pregnant women who were given 400 IU/day vit-D with those who were not given vit-D. They showed that the rate of vit-D deficiency was significantly higher in mothers who did not receive vit-D and the babies born to these mothers showed higher vit-D deficiency ratio in cord blood. It has been noted that vit-D given in these doses does not prevent the development of vit-D insufficiency in pregnant women. Also, although vit-D deficiency was significantly reduced in infants born to pregnant women receiving vit-D, vit-D insufficiency remained high around 84%. The present results show that 400 U/day vit-D supplementation is insufficient for both parents and babies in this population. Similarly, in our study, it was observed that 500 IU/day vit-D supplementation did some improvement in calcium and bone metabolism in mothers and babies, but the overall optimal improvement was not achieved.

The World Health Organization (Dalgleish et al., 2016) and the ACOG (American College of Obstetricians and Gynecologists) (2011) did not recommend vit-D supplementation and routine screening in all pregnant women because of the lack of evidence. However, vit-D deficiency is common in women, and this deficiency has detrimental effects for mother and baby. In addition, in every society, there are several factors that affect women's vit-D levels, such as sunlight exposure, dietary habits, religious beliefs, and ethnic, geographic and genetic differences. Therefore, each society should determine prophylaxis during pregnancy according to their basal vit-D levels. Because, even if exposure to sunlight is high, 500 IU/day vit-D supplementation may not provide adequate improvement in mothers and babies. Therefore, pregnant women should be given higher doses of vit-D regardless of sunlight.

The limitations of this study arise from its retrospective nature. Another limitation is that cases have not been compared with data in a region with lower sunlight.

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