Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2021.21166

The Effect of Vitamin D Prophylaxis on 25-OH Vitamin D Levels in Children

İhsan Gül[1], Emel Gür[2], Tuğba Erener-Ercan[3], Günay Can[4]

[1]Department of Pediatrics, Suleymaniye Maternity and Women's Hospital, Istanbul, Turkey
[2]Department of Social Pediatrics, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey
[3]Department of Pediatrics, Maltepe University, Medical Faculty, Istanbul, Turkey
[4]Department of Public Health, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

What is already known on this topic?

- *Vitamin D deficiency is a major public health problem worldwide.*
- *Adequate VD status is important for mothers, neonates, and children, and vitamin D deficiency is common among breastfed infants who do not receive VD supplementation due to inadequate vitamin D in human milk.*
- *In the context of national vitamin D supplementation to infants, Turkish Ministry of Health recommends 400 IU of vitamin D during the first year of life.*

What this study adds on this topic?

- *Children on VD prophylaxis had higher levels of 25-OHD than those who were not on prophylaxis.*
- *Infants of mothers who used vitamin D supplementation regularly during pregnancy and lactation were found to be more likely to have 25-OHD levels in the sufficiency range.*
- *Receiving VD prophylaxis and supplementation of mothers with VD during lactation had a significant effect on 25-OHD levels.*
- *Vitamin D supplementation at a dose of 400 IU seems to be sufficient to prevent vitamin D deficiency.*

Corresponding author:
Tugba Erener-Ercan
✉terenercan@gmail.com
Received: May 23, 2021
Accepted: August 19, 2021

ABSTRACT

Background: Vitamin D deficiency is a major public health problem. The aim of our study was to determine serum 25-hydroxyvitamin D levels among healthy children aged 3-36 months in a setting where vitamin D prophylaxis is a national policy for infants during the first year of life and among pregnant women.

Methods: A total of 190 healthy children with a mean age of 15.9 ± 10.4 months were prospectively enrolled.

Results: The mean 25-hydroxyvitamin D level of children was 38.1 ± 16.2 ng/mL. 25-Hydroxyvitamin D level was ≥20 ng/mL in 87.4% of children while it was between 12 and 19 ng/mL in 10.5% and <12 ng/mL in 2.1% of the children. Children who were on vitamin D prophylaxis were found to have significantly higher 25-hydroxyvitamin D levels than those who were not on prophylaxis (41.6 ± 17.6 vs 33.6 ± 13.1 ng/mL; $P = .001$). None of the children >1 year of age who were on prophylaxis had 25-hydroxyvitamin D levels <20 ng/mL. No significant difference in 25-hydroxyvitamin D levels was found between children who were receiving different vitamin D doses (400 IU vs >400 IU). Analysis of covariance revealed that vitamin D prophylaxis and vitamin D supplementation of the mother during lactation had significant effects on 25-hydroxyvitamin D levels ($P = .034$ and $P = .009$, respectively).

Conclusion: Although vitamin D prophylaxis at a dose of 400 IU seems to be sufficient to prevent vitamin D deficiency, we suggest that continuing vitamin D supplementation beyond 1 year of age with supplementation of pregnant and especially lactating mothers could have an impact on a replete vitamin D status among infants.

Keywords: Children, vitamin D deficiency, vitamin D status, 25-OH vitamin D

INTRODUCTION

Vitamin D (VD) deficiency is a major public health problem worldwide. Vitamin D deficiency has been reported to lead to a variety of adverse effects in mothers, neonates, and children such as rickets in infants and children and osteomalacia, hypocalcemia, preeclampsia, preterm birth, an increased risk of gestational diabetes, and hypertension among mothers.[1,2] Vitamin D deficiency has also been associated with an increased rate of lower respiratory tract infections in infancy and childhood and autoimmune diseases, such as type 1 diabetes.[3] Some studies reported that lower maternal and neonatal VD levels have been associated with neonatal sepsis and prematurity complications such as bronchopulmonary dysplasia and necrotizing enterocolitis.[4-6] Therefore, adequate VD status seems to be important for mothers, neonates, and children. Vitamin D deficiency is common among breastfed infants who do not receive VD supplementation due to inadequate VD in human milk. Maternal VD

Cite this article as: Gül İ, Gür E, Erener-Ercan T, Can G. The effect of vitamin D prophylaxis on 25-OH vitamin D levels in children. *Turk Arch Pediatr.* 2021; 56(6): 618-623.

status is also a determinant of neonatal VD levels.[7,8] Studies among pregnant women have shown a high prevalence of VD deficiency worldwide.[9,10] Therefore, VD supplementation of breastfeeding mother–infant pairs should be a global concern. In the context of national VD supplementation to infants, Turkish Ministry of Health recommends 400 IU of VD during the first year of life in order to prevent rickets and VD deficiency similar to the recommendations of European Academy of Pediatrics and American Academy of Pediatrics.[11,12] Vitamin D has been started to be supplemented free of charge to all infants under 1 year of age since 2005. Maternal VD supplementation has also been recommended by Turkish Ministry of Health, starting at 12th gestational week until 6 months postpartum for all pregnant women at a dose of 1200 IU/day since May 2011.

The aim of our study was to determine the serum 25-hydroxyvitamin D (25-OHD) levels, the prevalence of VD deficiency and insufficiency, and the factors that may influence the VD status among healthy children aged 3-36 months in a setting where VD prophylaxis is a national policy for infants during the first year of life and among pregnant women.

METHODS

Study Participants

The study group consisted of healthy children aged 3-36 months who were admitted to the outpatient Healthy Child Clinics of Istanbul University, Cerrahpasa Medical Faculty, Istanbul (latitude 41°N), Turkey, for their routine control and vaccination between September 01, 2013, and November 31, 2013, and whose parents gave informed consent for the study. Patients with clinical findings of rickets, patients with chronic diseases such as neurological, cardiovascular, respiratory, renal, and hepatic, or patients who were using anticonvulsant drugs and who were born preterm were excluded from the study.

Questionnaires About Vitamin D Prophylaxis, Nutrition, and Lifestyle

A questionnaire regarding the duration of VD prophylaxis, dosage, duration of sun exposure, duration of breastfeeding, consumption of vitamin D-rich foods, maternal VD prophylaxis during pregnancy and lactation, the educational status and clothing style of the mother was given to the parents of each child at the well-child visit.

Definitions

Regular VD consumption by mothers was defined as using VD or VD-containing vitamin preparations >5 days/week for >3 weeks. Infants who were not breastfed for 1 month were defined as not taking breast milk. Vitamin D-rich food (such as fish, egg, milk, and liver) consumption was defined as consuming foods rich in VD at least 3 days a week. Vitamin D deficiency has been defined as a 25-OHD level <12 ng/mL (30 nmol/L), while VD insufficiency is defined as a 25-OHD level between 12 and 19 ng/mL (30-50 nmol/L) and VD sufficiency is defined as 25-OHD ≥20 ng/mL (≥50 nmol/L) according to the Global Consensus Recommendations.[13]

Laboratory Measurements

The levels of 25-OHD, parathyroid hormone (PTH), calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) were determined in every child. Blood samples of the enrolled infants were obtained at the time of admission to the outpatient clinics. Plasmas of blood samples were separated and stored at −80°C. Levels of 25-OHD and PTH were determined using Roche Cobas 8000 analyzer (Roche Diagnostics, Basel, Switzerland) by chemiluminescence method, and Ca, P, and ALP levels were determined using the same analyzer by spectrophotometric method.

The study protocol was approved by the Ethical Committee of Istanbul University, Cerrahpasa Medical Faculty (2013/11263). Informed parental consent was obtained for all enrolled infants.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Windows 21.0 software (IBM Corporation, Armonk, NY) was used to evaluate the data. Categorical variables were summarized as count and percentage, whereas continuous ones were summarized as mean, SD, median, minimum, and maximum. Categorical ones were compared using chi-square and Fisher's exact test. Logistic regression analysis and analysis of covariance were performed to determine the influence of the variables on VD levels. Statistical significance was considered at $P < .05$.

RESULTS

Clinical Characteristics

A total of 190 healthy term children (102/88: males/females) with a mean age of 15.9 ± 10.4 months (3-36 months) were enrolled. Of those 190 children, 101 (53.2 %) were between 3 and 12 months of age and 89 (46.8 %) were >12 months of age. Mean body weight and mean length were 10 345 ± 3135 g and 79.2 ± 12.3 cm, respectively.

PREVALENCE OF VITAMIN D DEFICIENCY

The mean 25-OHD level of the enrolled subjects was 38.1 ± 16.2 ng/mL. 25-Hydroxyvitamin D level was ≥20 ng/mL in 87.4% of children while it was between 12 and 19 ng/mL in 10.5% and <12 ng/mL in 2.1% of the enrolled subjects. 25-Hydroxyvitamin D levels <10 ng/mL were detected only in 2 of the enrolled patients (1.05%); however, none of the patients had a 25-OHD level <5 ng/mL. Mean Ca, P, ALP, and PTH levels of patients were found to be normal (Table 1). 25-Hydroxyvitamin D levels in the sufficiency range were found in 86.1% and 88.8% of subjects ≤12 months and >12 months of age, respectively. Vitamin D levels with regard to age are presented in Table 2.

Variables Associated With Vitamin D Sufficiency Using Statistical Comparisons

Since Turkish Ministry of Health recommends 400 IU of vitamin D during the first year of life, enrolled subjects were divided into

Table 1. Mean Levels of 25-Hydroxyvitamin D (25-OHD), Parathyroid Hormone (PTH), Calcium (Ca), Phosphorus (P), and Alkaline Phosphatase (ALP)

Age (months)	15.9 ± 10.4
25-OHD (ng/mL)	38.15 ± 16.2
PTH (pg/mL)	20.5 ± 8.5
Ca (mg/dL)	9.2 ± 0.9
P (mg/dL)	5.2 ± 0.9
ALP (IU/L)	198.8 ± 59.3

Table 2. 25-Hydroxyvitamin D (25-OHD) Levels With Regard to Age Among Enrolled İnfants

	Number of Infants With VD Deficiency, <20 ng/mL	Number of Infants With VD Sufficiency, ≥20 ng/mL	*P*
≤12 months	14 (13.9%)	87 (86.1%)	.587
>12 months	10 (11.2%)	79 (88.8%)	

2 groups as those ≤1 year of age and those over 1 year of age. Of 101 children who were ≤1 year of age, 90 (89.1%) were on vitamin D prophylaxis while 18 of 89 children (20.2%) >1 year of age were on prophylaxis. Children who were on VD prophylaxis were found to have a mean 25-OHD level of 41.6 ± 17.6 while those who were not on prophylaxis had a mean 25-OHD level of 33.6 ± 13.1. Children who were on prophylaxis were found to have significantly higher 25-OHD levels ($P = .001$). Although a higher percentage of infants ≤1 year of age who were on prophylaxis had 25-OHD levels in the sufficiency range (≥20 ng/mL), there was no statistically significant difference when compared to those who were not on prophylaxis. None of the children >1 year of age who were on prophylaxis was found to have 25-OHD levels in the deficiency range (<20 ng/mL). Among the whole cohort, a higher percentage of subjects who were on prophylaxis had 25-OHD levels in the sufficiency range than those who were not on prophylaxis, although it did not reach a statistical significance (Table 3). 25-Hydroxyvitamin D levels were in the sufficiency range (≥20 ng/mL) in 84.7% and 94.1% of children who received vitamin D at a dose of 400 IU or >400 IU, respectively. In the group with VD supplementation >400 IU, 8 subjects were recorded to receive VD at a dose of 800 IU. Vitamin D status of children with regard to dosage of VD prophylaxis is presented in Table 4. There was no statistical difference in percentage of infants with VD level ≥20 ng/mL between subjects with regard to consumption of VD-rich or -poor diet and exposure to sunlight. There was also no statistical difference in VD status of subjects with regard to educational level and clothing type of mothers. Infants of mothers who used VD supplementation during pregnancy were more likely to have 25-OHD levels in the sufficiency range ($P = .037$). When infants of mothers who used VD supplementation during lactation were compared to those whose mothers did not use VD during lactation, they were more likely to have a VD level ≥20 ng/mL ($P = .048$). None of the infants whose mothers were receiving VD during lactation had 25-OHD levels <20 ng/mL (Table 5). Logistic regression analysis was performed to determine the effect of receiving VD prophylaxis, age, maternal VD intake during pregnancy and lactation on having a 25-OHD level in the sufficiency range (≥20 ng/mL), and no variable was found to have an effect on having 25-OHD level in the sufficiency range by multivariate regression analysis. However,

Table 3. 25-Hydroxyvitamin D (25-OHD) Levels With Regard to VD Intake

VD Intake	Number of Infants With VD Levels, <20 ng/mL	Number of Infants With VD levels, ≥20 ng/mL	*P*
Infants ≤12 months			
No	3 (27.3%)	8 (72.7%)	.178
Yes	11 (12.2%)	79 (87.8%)	
Infants >12 months			
No	10 (14.1%)	61 (85.9%)	.203
Yes	0	18 (100%)	
All infants			
No	13 (15.9%)	69 (84.1%)	.244
Yes	11 (10.2%)	97 (89.8%)	

Table 4. VD Status of Children With Regard to Dosage of VD Prophylaxis

VD Dosage (IU)	Number of Infants	Number of Infants With VD Deficiency, <20 ng/mL	Number of Infants With VD Sufficiency, ≥20 ng/mL	*P*
400	59	9 (15.3 %)	50 (84.7%)	.137
>400	51	3 (5.9 %)	48 (94.1 %)	

VD, Vitamin D.

Table 5. Distribution of 25-OHD Levels With Regard to VD Supplementation During Pregnancy and Lactation

	Number of Infants With 25-OHD Level, <20 ng/mL	Number of Infants With 25-OHD Level, ≥20 ng/mL	*P*
VD supplementation during pregnancy			
No	14 (18.9%)	60 (81.1%)	.037
Yes	10 (8.6%)	84 (91.4%)	
VD supplementation during lactation			
No	24 (14.5%)	142 (85.5%)	.048
Yes	0	24 (100.0%)	

VD, Vitamin D; 25-OHD, 25-hydroxyvitamin D.

analysis of covariance revealed that receiving VD prophylaxis and supplementation of mothers with VD during lactation had a significant effect on 25-OHD levels (P = .034 and P = .009, respectively).

DISCUSSION

In this study, we investigated the VD status in a group of healthy Turkish children aged 3-36 months in a setting where VD supplementation is a national policy for infants during the first year of life and among pregnant women. In our study cohort, 87.4% of children were found to have a 25-OHD level ≥20 ng/mL and 10.5% had levels between 12 and 19 ng/mL despite VD prophylaxis. Vitamin D insufficiency or deficiency is a global problem which has been reported not only in infants but also in pregnant and lactating mothers, and contemporary studies from different parts of the world have reported different prevalence rates of VD deficiency and nutritional rickets.[14] Vitamin D deficiency is also said to be widespread across Europe.[14] In a metaanalysis of studies of European children, teenagers, adults, and older adults encompassing 55 844 individuals living in latitudes ranging between 35˚N and 69˚N, the prevalence of VD deficiency (<20 ng/mL) was found to be 40.4%.[15] In a systemic review of VD status extracting data from 107 studies that represent 630 093 individuals in southern European countries, more than one-third of the studies reported mean 25-OHD concentrations <20 ng/mL and ~10% reported mean serum 25-OHD concentrations <10 ng/mL with the finding that females, neonates/infants, and adolescents had the higher prevalence of poor VD status.[16] In studies investigating VD levels in children and adolescents in Turkey, Andiran et al.[17] found that 40% of 440 children aged 0-16 years had VD levels <20 ng/mL, and among 849 children aged 1-16 years, this rate was 8% in the study of Akman et al.[18] In a study investigating VD status across different age groups in Turkey, mean 25-OHD levels of children <1 year were found to be 37.3 ng/mL, and the prevalence of VD levels <20 ng/mL was found to be lowest also in this age group when compared to older age groups which was attributed to the beneficial effects of the vitamin D supplementation program in the 0- to 1-year-old age group in Turkey.[19] In a study from Boston, Gordon et al.[20] found that the prevalence of VD deficiency (≤20 ng/mL) among 380 infants aged 8-24 months was 12.1%, and 40.0% had levels <30 ng/mL similar to the rates in our study. In Turkey, after implementation of VD supplementation for infants <1 year of age in 2005, there has been a notable reduction in rickets from 6% in 1998 to 0.1% in 2008 in children <3 years of age.[21,22] In our study, of the enrolled children who were ≤1 year of age, 89.1% were on vitamin D prophylaxis which may be a reflection of the well-adopted national recommendations. We found that a higher percentage of infants who were on VD prophylaxis had 25-OHD levels in the sufficiency range, and those on prophylaxis were found to have significantly higher 25-OHD levels compared to those who were not on prophylaxis. In fact, among subjects over 1 year of age who were on prophylaxis, none of them had VD levels in the deficiency range (<20 ng/mL) which might reflect a beneficial role of continuing prophylaxis beyond the first year of life for maintaining a sufficient VD level in children.

In the study of Gallo et al.,[23] 132 healthy term 1-month-old infants were randomized to 4 different doses of VD (400, 800, 1200, and 1600 IU) with the primary outcome of 25-OHD level ≥30 ng/mL at 3 months of age. This outcome was achieved in 55%, 81%, 92%, and 100%, respectively, but this concentration was not sustained in 97.5% of infants at 12 months in any group, and the 1600 IU/day dosage was discontinued due to elevated 25-OHD levels. However, all dosages established 25-OHD concentrations ≥20 ng/mL which was sustained in 98% at 12 months. They found no difference in growth and mineral content with regard to dosage. Gallo et al.[24] in a recent study reported that longer-term outcomes of their 2013 article found no significant differences among groups of different doses of VD supplementation with regard to lumbar spine or whole-body bone mineral density, bone mineral content, and mineral accretion. In our study, 8 patients were on a VD supplementation of 800 IU, and all were found to have 25-OHD levels in the sufficiency range. Although more infants who were receiving VD at a dose >400 IU were found to have 25-OHD levels in the sufficiency range than those who were on prophylaxis at a dose of 400 IU, there was no statistical difference between the groups which may reflect the adequacy of VD prophylaxis at a dose 400 IU. In the study by Mutlu et al.[25] from Turkey, it was also suggested that 400 IU/day vitamin D was adequate to prevent vitamin D deficiency. In a systemic review by Mimouni et al.[26] published in 2017, randomized controlled trials since 2009 that investigated VD doses in infancy were reviewed, and the authors concluded that there was no additional evidence that larger daily doses of VD beyond the recommended dose of 400 IU affected any significant outcome.

In our study, infants of mothers who used VD supplementation regularly during pregnancy were more likely to have 25-OHD levels in the sufficiency range which was in accordance with other studies.[27-29] In the study of Við Streym et al.,[28] infants born to mothers who used VD supplements had higher cord blood 25-OHD levels than those who did not use. Grant et al.[27] also found that daily VD supplementation during pregnancy and then infancy increased the proportion of infants with 25-OHD levels ≥30 ng/mL. In our study, 91.4% of the infants of mothers who were using VD during pregnancy and 100% of the infants of mothers who were using VD during lactation had 25-OHD levels ≥20 ng/mL. In our study, covariance analysis revealed that receiving VD prophylaxis and supplementation of mothers with VD during lactation had a significant effect on 25-OHD levels.

European Academy of Pediatrics recommends that all infants should receive an oral supplementation of 400 IU of VD, and the upper limit of safety is set at 1000 IU/day for infants.[11] However, data from contemporary studies suggest that doses in excess of 400 IU did not cause hypercalcemia. In the study of Gallo et al.,[23] VD dosage of 1600 IU/day was discontinued not due to hypercalcemia but due to 25-OHD levels exceeding the normal healthy range of 20-50 ng/mL. However, Endocrine Society states that 25-OHD concentrations ≥100 ng/mL (≥250 nmol/L) are safe for children, whereas concentrations >150 ng/mL (>375 nmol/L) are excessive.[30] In other 2 studies from Finland,[31,32] VD supplementation of 1200 IU or 1600 IU/day during infancy caused no severe hypercalcemia and was considered safe in term infants; in fact, 1600 IU dose maintained 25-OHD levels >30 ng/mL in all infants.[31]

There are some limitations of our study. First of all, VD level was not measured in all months of the year but only during a 3-month period which was the autumn period, and determination of the duration of exposure to sunlight depended on caregivers' subjective verbal statements which were subject to under- or over-reporting. This might be the reason for not finding any effect of exposure to sunlight on VD levels. Data on VD intake from diet also depended on subjective verbal statements of the caregivers which might not reflect the exact amounts of consumption. In Turkey, there is no fortification of foods and drinks with VD. We did not have any data about maternal 25-OHD levels. The study cohort consisted of infants with a wide age range between 3 and 36 months, not including only those <1 year of age. This might be a plausible explanation of not finding any effect of maternal VD intake during pregnancy on the infants' level of 25-OHD in the logistic regression model. In the study of Við Streym et al.,[28] maternal plasma 25-OHD level was found to be a significant determinant of infant plasma 25-OHD levels at birth and at 4 months of age but not at age of 9 months.

CONCLUSION

Despite a high compliance of VD prophylaxis among our study cohort, VD deficiency determined as 25-OH levels <20 ng/mL was still apparent in a small percentage of infants (12.6% of the study cohort). Although there has been an ongoing debate about the dosage or duration of VD supplementation, based on the currently available evidence, we can suggest that 400 IU of VD prophylaxis during the first year of life is adequate. However, besides this routine practice, continuing VD supplementation beyond 1 year of age with VD supplementation of pregnant and lactating mothers might be a reasonable approach to ensure a replete VD status among infants. Therefore, supplementation of infants in the first year of life and beyond and supplementation of mothers with VD especially during lactation should be a primary global public health concern.

Ethical Committee Approval: Ethics committee approval was received from the Ethical Committee of Istanbul University, Cerrahpasa Medical Faculty (2013/11263).

Informed Consent: Informed parental consent was obtained for all enrolled infants.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – I.G., E.G.; Design - I.G., E.G.; Supervision - E.G.; Data Collection and/or Processing - I.G.; Analysis and/or Interpretation - G.C.; Writing - T.E.E.

Acknowledgments: We thank the Scientific Project Department of Istanbul University for their financial support.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study is supported by the Scientific Project Department of Istanbul University with project no. 32982.

REFERENCES

1. Elsori DH, Hammoud MS. Vitamin D deficiency in mothers, neonates and children. *J Steroid Biochem Mol Biol*. 2018;175:195-199. [CrossRef]
2. Nassar N, Halligan GH, Roberts CL, Morris JM, Ashton AW. Systematic review of first-trimester vitamin D normative levels and outcomes of pregnancy. *Am J Obstet Gynecol*. 2011;205(3):208.e1-208.e7. [CrossRef]
3. Camargo CA Jr, Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics*. 2011;127(1):e180-e187. [CrossRef]
4. Cetinkaya M, Cekmez F, Buyukkale G, et al. Lower vitamin D levels are associated with increased risk of early-onset neonatal sepsis in term infants. *J Perinatol*. 2015;35(1):39-45. [CrossRef]
5. Çetinkaya M, Çekmez F, Erener-Ercan T, et al. Maternal/neonatal vitamin D deficiency: a risk factor for bronchopulmonary dysplasia in preterms? *J Perinatol*. 2015;35(10):813-817. [CrossRef]
6. Cetinkaya M, Erener-Ercan T, Kalayci-Oral T, et al. Maternal/neonatal vitamin D deficiency: a new risk factor for necrotizing enterocolitis in preterm infants? *J Perinatol*. 2017;37(6):673-678. [CrossRef]
7. Salameh K, Al-Janahi NS, Reedy AM, Dawodu A. Prevalence and risk factors for low vitamin D status among breastfeeding mother-infant dyads in an environment with abundant sunshine. *Int J Womens Health*. 2016;8:529-535. [CrossRef]
8. Dawodu A, Tsang RC. Maternal vitamin D status: effect on milk vitamin D content and vitamin D status of breastfeeding infants. *Adv Nutr*. 2012;3(3):353-361. [CrossRef]
9. Holmes VA, Barnes MS, Alexander HD, McFaul P, Wallace JM. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. *Br J Nutr*. 2009;102(6):876-881. [CrossRef]
10. Perampalam S, Ganda K, Chow KA, et al. Vitamin D status and its predictive factors in pregnancy in 2 Australian populations. *Aust N Z J Obstet Gynaecol*. 2011;51(4):353-359. [CrossRef]
11. Grossman Z, Hadjipanayis A, Stiris T, et al. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). *Eur J Pediatr*. 2017;176(6):829-831. [CrossRef]
12. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142-1152. [CrossRef]
13. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab*. 2016;101(2):394-415. [CrossRef]
14. Creo AL, Thacher TD, Pettifor JM, Strand MA, Fischer PR. Nutritional rickets around the world: an update. *Paediatr Int Child Health*. 2017;37(2):84-98. [CrossRef]
15. Cashman KD, Dowling KG, Škrabáková Z, et al. Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr*. 2016;103(4):1033-1044. [CrossRef]
16. Manios Y, Moschonis G, Lambrinou CP, et al. A systematic review of vitamin D status in southern European countries. *Eur J Nutr*. 2018;57(6):2001-2036. [CrossRef]
17. Andıran N, Çelik N, Akça H, Doğan G. Vitamin D deficiency in children and adolescents. *J Clin Res Pediatr Endocrinol*. 2012;4(1):25-29. [CrossRef]
18. Akman AO, Tumer L, Hasanoglu A, Ilhan M, Caycı B. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. *Pediatr Int*. 2011;53(6):968-973. [CrossRef]
19. Yeşiltepe-Mutlu G, Aksu ED, Bereket A, Hatun Ş. Vitamin D status Across age groups in Turkey: results of 108,742 samples from a single laboratory. *J Clin Res Pediatr Endocrinol*. 2020;12(3):248-255. [CrossRef]
20. Gordon CM, Feldman HA, Sinclair L, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. *Arch Pediatr Adolesc Med*. 2008;162(6):505-512. [CrossRef]
21. Hatun S, Bereket A, Ozkan B, et al. Free vitamin D supplementation for every infant in Turkey. *Arch Dis Child*. 2007;92(4):373-374. [CrossRef]

22. Hatun Ş, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. *Acta Paediatr*. 2011;100(9):1195-1199. [CrossRef]
23. Gallo S, Comeau K, Vanstone C, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *JAMA*. 2013;309(17):1785-1792. [CrossRef]
24. Gallo S, Hazell T, Vanstone CA, et al. Vitamin D supplementation in breastfed infants from Montréal, Canada: 25-hydroxyvitamin D and bone health effects from a follow-up study at 3 years of age. *Osteoporos Int*. 2016;27(8):2459-2466. [CrossRef]
25. Mutlu GY, Kusdal Y, Ozsu E, Cizmecioglu FM, Hatun S. Prevention of vitamin D deficiency in infancy: daily 400 IU vitamin D is sufficient. *Int J Pediatr Endocrinol*. 2011;2011(1):4. [CrossRef]
26. Mimouni FB, Huber-Yaron A, Cohen S. Vitamin D requirements in infancy: a systematic review. *Curr Opin Clin Nutr Metab Care*. 2017;20(3):232-236. [CrossRef]
27. Grant CC, Stewart AW, Scragg R, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics*. 2014;133(1):e143-e153. [CrossRef]
28. Við Streym S, Kristine Moller U, Rejnmark L, et al. Maternal and infant vitamin D status during the first 9 months of infant life-a cohort study. *Eur J Clin Nutr*. 2013;67(10):1022-1028. [CrossRef]
29. Yesiltepe Mutlu G, Ozsu E, Kalaca S, et al. Evaluation of vitamin D supplementation doses during pregnancy in a population at high risk for deficiency. *Horm Res Paediatr*. 2014;81(6):402-408. [CrossRef]
30. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD, Drugs, and Therapeutics Committee of The Pediatric Endocrine Society. Vitamin D supplementation and risk of toxicity in pediatrics: a review of current literature. *J Clin Endocrinol Metab*. 2014;99(4):1132-1141. [CrossRef]
31. Holmlund-Suila E, Viljakainen H, Hytinantti T, et al. High-dose vitamin D intervention in infants: effects on vitamin D status, calcium homeostasis, and bone strength. *J Clin Endocrinol Metab*. 2012;97(11):4139-4147. [CrossRef]
32. Valkama S, Holmlund-Suila E, Enlund-Cerullo M, et al. No severe hypercalcemia with daily vitamin D3 supplementation of up to 30 µg during the first year of life. *Horm Res Paediatr*. 2017;88(2):147-154. [CrossRef]