

The Association Between 25-Hydroxyvitamin D Levels and Fetal Malnutrition in Term Neonates

Term Yenidoğanlarda 25-Hidroksivitamin D Düzeyleri ve Fetal Malnütrisyon İlişkisi

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ABSTRACT

Objective: The aim of this study is to determine the association between vitamin D deficiency in fetal malnutrition average for gestational age (AGA) neonates.

Materials and Methods: The study was conducted on singleton term infants between March 1 and April 30, 2012. All of the neonates' cord-blood vitamin D levels were measured, and those identified as suffering from fetal malnutrition were placed into the study group, while the cord-blood vitamin D levels of well-nourished term newborns comprised the control group. Fetal malnutrition was detected using the Clinical Assessment of Nutritional Status Score (CANSORE) method. Cord-blood vitamin D levels (ng/mL units) of newborns were measured and anthropometric results were recorded.

Results: Total 110 term newborns were included in the study. Of these, 44 (40%) were part of the well-nourished nutrition group, with 66 (60%) in the malnutrition group. Birth weight, birth height, head circumference, weight gain during pregnancy, CANSORE, and 25-hydroxyvitamin D [25(OH)Vit D] mean levels of the fetal malnourished group were found to be lower compared with the well-nourished group ($p=0.0001$). The maternal skin color and the maternal body mass index of the fetal malnourished group were found to differ significantly compared with the well-nourished group. Low cord-blood 25(OH)Vit D levels ($p=0.002$) and low head circumference ($p=0.002$) were found to be the factors that affect the presence of fetal malnutrition.

Conclusion: 25(OH)Vit D levels are lower in with fetal malnourished AGA neonates compared with well-nourished term AGA neonates.

Keywords: Nutrition assessment, cord blood, vitamin D levels, fetal malnutrition

ÖZ

Amaç: Bu çalışmanın amacı gebelik haftasına göre uygun [average for gestational age (AGA)] yenidoğanlarda fetal malnütrisyon ile D vitamini eksikliği arasındaki ilişkiyi saptamaktır.

Gereç ve Yöntemler: Çalışma, 1 Mart-30 Nisan 2012 tarihleri arasında tek dönem bebeklerde yapıldı. Yenidoğanların tümünün kordon kanı D vitamini düzeyleri ölçüldü ve fetal malnütrisyonu bulunan bebekler çalışma grubuna alındı. İyi beslenen term yenidoğanların kord bebek D vitamini seviyeleri kontrol grubunu oluşturdu. Fetal malnütrisyon, Clinical Assessment of Nutritional Status Score (CANSORE) yöntemiyle tespit edildi. Kord bebek D vitamini seviyeleri (ng/mL ünite) yenidoğanlar ölçülmüş ve antropometrik sonuçlar kaydedilmiştir.

Bulgular: Toplam 110 term yenidoğan çalışmaya alındı. Bunların 44'ü (%40) iyi beslenen beslenme grubunun bir parçasıydı ve malnütrisyon grubunda 66 (%60) idi. Doğum ağırlığı, doğum yüksekliği, baş çevresi, gebelik sırasında kilo alımı, CANSORE ve 25-hidroksivitamin D [25(OH)Vit D] ortalamalarının fetal malnütrisyonlu grupta iyi beslenen gruba kıyasla daha düşük olduğu bulundu ($p=0,0001$). Fetal malnütrisyon grubunun maternal deri rengi ve maternal vücut kitle indeksi, iyi beslenen gruba göre anlamlı olarak farklı bulundu. Fetal malnütrisyon varlığını etkileyen faktörlerin düşük kord kanında 25(OH)Vit D düzeylerinin $p=0,002$ ve düşük baş çevresinin $p=0,002$ olduğu bulundu.

Sonuç: Fetal malnütrisyonlu AGA yenidoğanlarda 25(OH)Vit D düzeyleri iyi beslenen AGA yenidoğanlar ile karşılaştırıldığında daha düşüktür.

Anahtar kelimeler: Beslenme değerlendirmesi, kordon kanı, D vitamini seviyeleri, fetal malnütrisyon

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INTRODUCTION

Fetal malnutrition (FM) is distinguished by loss of muscle volume and subcutaneous adipose tissue during the intrauterine period. However, being small for gestational age (SGA) and intrauterine growth retardation (IUGR) are not analogous with FM. IUGR is defined as a fetus unable to reach its growth potential (1). IUGR fetuses may suffer from FM as a result of events that prevent normal growth potential (2,3). Micronutrients are necessary for normal growth and development of the fetus, and deficiencies have been found to be associated with IUGR and SGA infants (4,5). For this reason, micronutrient deficiency, especially 25-hydroxyvitamin D [25(OH)Vit D] deficiency, may be related to FM. 25(OH)Vit D plays a critical role in intrauterine growth and development, the physiology of brain development, and the central nervous system development, together with thyroid hormones, retinoic acid, and steroid hormones (6).

25(OH)Vit D is one of the most important nutritional factors involved in steroid hormone production. While fetal genetic factors mainly affect fetal growth and development in the first trimester of intrauterine life, hormonal and environmental factors affect fetal growth and development during the following gestational periods, especially in the third trimester (7).

The aim of this study was to determine the association between 25(OH)Vit D deficiency and FM.

MATERIALS AND METHODS

Study Design

This prospective observational study was carried out in neonatal intensive care unit between March 1 and April 30, 2012. The hospital is a third-level neonatal center with almost 2.500 newborns delivered each year. The single, term (37-42 completed gestational weeks), living average for gestational age (AGA) babies born by caesarean section or normal vaginal delivery between the 37th and the 42nd gestational weeks according to ultrasonographic measurements and last menstruation date who were found to have only AGA infants included to study. And all of the neonates were evaluated for FM. FM detected neonates were constituted the FM study group. The control group was composed with term, single, AGA and well nutrition neonates.

Caesarean section, complicated vaginal delivery (obstetric forceps and vacuum extraction), breech presentation,

multiple pregnancies, premature infants (gestational age <37 weeks), post-mature infants (>42 gestational weeks), large for gestational age (LGA) neonates, SGA neonates, newborns that were actively resuscitated postnatally in the delivery room, newborns with major anomalies, and babies requiring intervention due to suspicious lung pathology, cyanotic congenital heart disease, early sepsis-meningitis following clinical examination at the neonatal intensive care unit were not included in the study (Figure 1).

On the basis of previous findings, that birth weight, birth height, and head circumference of FM neonates are lower than that of well-nourished neonates, we hypothesized that 25(OH)Vit D levels are lower in FM infants and may be the cause of the lack of growth in these neonates (8). We calculated that a sample size of 60 neonates with malnourished neonates ($\alpha=0.05$, power=80%). The study protocol was approved by the local ethical committee of the hospital and written informed consent from a parent was obtained for each neonate prior to the study.

Measurements

The number of gestation weeks was determined by different researches one hour after delivery using the last menstrual date and New Ballard scoring, independently of the Clinical Assessment of Nutritional Status score (CANSCORE) (2). The birth weight, height, and head circumference measurements of the neonates were measured by the delivery-room nurse. Using these data and Lubchenko intrauterine growth curves, the newborns were then classified as SGA (below the 10th percentile), AGA (between the 10th and 90th percentile), and LGA (above the 90th percentile) babies. Newborns with AGA with FM were included in the study to exclude factors that could be the cause of SGA and LGA newborns, to minimize the effects on 25(OH)Vit D levels and to achieve more consistent results. The CANSCORE was applied by different researches to each postnatal neonate and FM was diagnosed according to CANSCORE. The sensitivity and specificity of CANSCORE had reported to 51% and 21.5%. CANSCORE features the estimated physical signs of good or bad nutrition (hair, cheeks, neck, and chin fatness; skin furrows with a deficiency of subcutaneous adipose tissue in the arms, legs, back, buttocks, abdomen, and chest). Each of the signs was rated from 4 (best) to 1 (worst). Newborns with a total CANSCORE <25 were considered to suffer from FM, while those with a CANSCORE of 25-36 were considered to

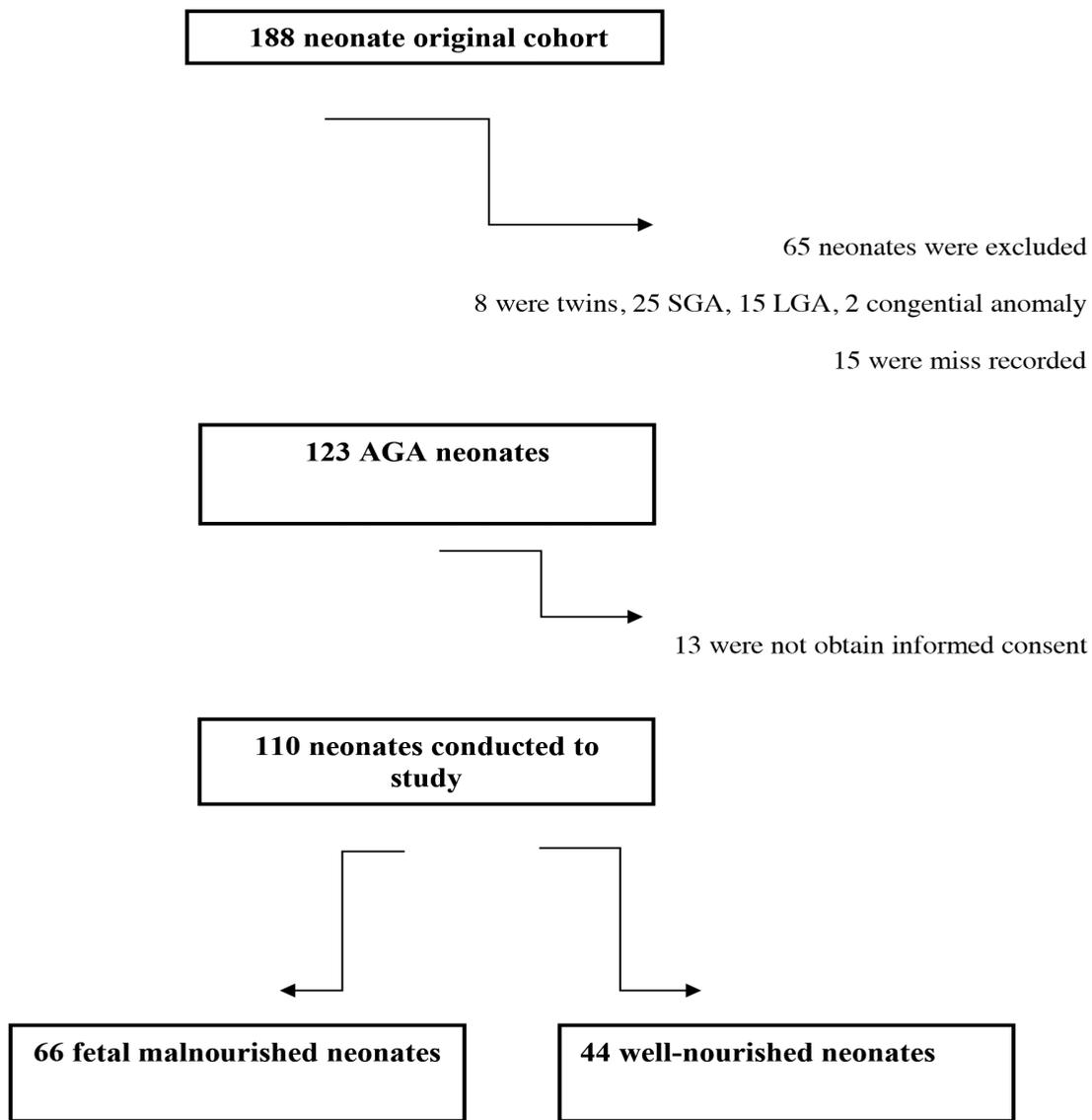


Figure 1: Flow chart of patients

AGA: Average for gestational age, SGA: Small for gestational age, LGA: Large for gestational age

be well nourished (2,7-9). The history of the mothers [e.g., gestational complications, 25(OH)Vit D supplementation, type of delivery, medical care at birth, and identifying style of dress, skin color, and low and excess weight gain] was acquired from medical records. Maternal 25(OH)Vit D status was described by a 25(OH)Vit D supplement being taken as a tablet (minimum 400 IU/day) for a minimum of three months. The scales were divided into three classes

during pregnancy; ≤ 9 kg weighing: low, weighing between 10-19 kg: normal, $20 \text{ kg} \geq$ weighing was defined as high. Maternal skin type of the subjects was classified using the Fitzpatrick skin-type scale and maternal dress style was described as being in two different forms: "open" or "closed". Closed dress style: headscarf (face and hand open from wrist), and open dress style: head, face, hand and arms are open.

Laboratory Analysis

About 2 mL of blood samples obtained from the umbilical cord blood of all neonates at birth were placed into jelly biochemical tubes. The samples were protected from sunlight by aluminium foil, were centrifuged at 4000 rpm for 15 minutes to avoid hemolysis, and the separated serum samples -each with the written name of the patient and protocol inside the tubes- were kept frozen at -80 °C in a refrigerator. The serum samples were preserved for about two months until all analysis samples were collected and analyzed by high-performance liquid chromatography. 25(OH)Vit D deficiency was defined as a 25(OH) 25(OH)Vit D below 20 ng/mL (50 nmol/L), and 25(OH)Vit D insufficiency as a 25(OH) 25(OH)Vit D of 21-29 ng/mL (525-725 nmol/L) (10).

Statistical Analysis

Statistical analyses were performed using the Number Cruncher Statistical System 2007 statistical software (Utah, USA). In the assessment of the data, in addition to the descriptive statistical methods (mean and standard deviation), an independent t-test was used in the comparison of the binary groups with normal distribution variables, the Mann-Whitney U test was used in the comparison of the binary groups with non-normal distribution variables, and the chi-square test was used in the comparison of the qualitative data. The Pearson correlation coefficient was performed to determine the factors that affect the presence

of <25 CANSCORE. The results determined as significant were $p < 0.05$.

RESULTS

A total of 110 term newborns were included in the study. Of these, 44 (40%) comprised the well-nourished (WN) group, 66 (60%) the FM group. Birth weight, birth height, head circumference, weight gain during pregnancy, CANSCORE, and 25(OH)Vit D mean levels of the FM group were found to be lower compared with the WN group ($p = 0.0001$). Birth anthropometric measurements and maternal features of the newborns are shown in Table 1.

History of pregnancy and factors relating to the mother was shown Table 2. The maternal skin color and body mass index in the FM group were found to differ significantly from the WN group. No differences were observed in parity and maternal mean age between the WN and FM groups. No differences were observed in maternal skin color, maternal style of dress, maternal 25(OH)Vit D intake status, and maternal smoking between the WN and FM groups.

Comparison of maternal variables and 25(OH)Vit D levels are presented in Table 3. The correlation of cord-blood 25(OH)Vit D levels of newborns with each of the variables, such as the mother's age, parity, and weight gain during gestation, the birth weight of the newborns, and CANSCORE values are presented separately in Table 4. Low cord-blood 25(OH) 25(OH)Vit D levels were ($p = 0.002$) and low head circumference ($p = 0.002$) were found to be the factors that affect the presence of FM.

Table 1: General characteristics of study and control groups (n=110)

	FM Group (n=66) n (%)	WN Group (n=44) n (%)	p
Gender			
Male	32 (48.5%)	24 (54.5%)	
Female	34 (51.5%)	20 (45.5%)	0.36
Birth weight (g)	2968.15±163.54	3517.73±212.9	0.0001
Gestational age (week)	39.15±0.23	39.91±0.68	0.11
Head circumference (cm)	33.91±1.62	36.71±1.22	0.0001
Birth height (cm)	48.87±2.15	51.34±1.44	0.0001
CANSCORE	23.61±4.17	27.61±4.39	0.0001
25-hydroxyvitamin D (ng/mL)	7.03±5.22	12.18±8.21	0.0001

FM: Fetal malnutrition, WN: Well-nourished, CANSCORE: Clinical Assessment of Nutritional Status Score

Table 2: History of pregnancy and factors relating to the mother

		FM group n (%)		WN group n (%)		P
Age (years)*		27.68±7.13		28.09±5.69		0.751
Parity number*		2.23±1.49		2.39±1.79		0.614
Weight gain (kg)*		12.3±4.74		16.14±5.79		0.0001
Skin color	Light	30	45.50%	33	75.00%	0.002
	Dark	36	54.50%	11	25.00%	
Style of dress	Closed	46	69.70%	31	70.50%	0.932
	Open	20	30.30%	13	29.50%	
Vitamin intake status	Vitamin D (-)	16	24.20%	10	22.70%	0.855
	Vitamin D (+)	50	75.80%	34	77.30%	
Body mass index	Low	14	21.20%	1	2.30%	0.0001
	High	21	31.80%	31	70.50%	
Smoking habit	(-)	48	72.70%	37	84.10%	0.164
	(+)	18	27.30%	7	15.90%	

FM: Fetal malnutrition, WN: Well-nourished *Mean ± standard deviation

Table 3: Comparison of maternal variables and vitamin D levels

	Closed style (n=46)	Open style (n=20)	P
25(OH)Vit D (ng/mL)	8.62±7.01	10.18±7.03	0.083
	Vitamin D intake (-) (n=16)	Vitamin D intake (+) (n=50)	
25(OH)Vit D (ng/mL)	7.02±5.02	9.73±7.44	0.105
	Smoke (-) (n=48)	Smoke (+) (n=18)	
25(OH)Vit D (ng/mL)	7.02±5.02	9.73±7.44	0.358
	Weight gain <9 kg (n=14)	Weight gain ≥20 kg (n=21)	
25(OH)Vit D (ng/mL)	7.23±5.88	10.46±8.28	0.206

25(OH)Vit D: 25-hydroxyvitamin D

Table 4: Correlation analysis in the fetal malnutrition group (n=66)

		Vitamin D level (ng/mL)
Mother age	R ²	0.133
	p	0.165
Parity	R ²	-0.113
	p	0.239
Weight gain of mother (kg)	R ²	-0.006
	p	0.949
Birth weight	R ²	0.115
	p	0.230
CANSORE	R ²	0.290
	p	0.002
Head circumference	R ²	0.219
	p	p=0.021

CANSORE: Clinical Assessment of Nutritional Status Score

DISCUSSION

The CANSORE, as validated by Metcoff, makes an indirect assessment of subcutaneous fat and was able to detect FM in all the neonates during this study; none of the other anthropometric measurements that assess the thickness of subcutaneous tissue were able to do better (2). FM may be related to micro- and macronutrient deficiency (11).

25(OH)Vit D is unique among hormones because it can be made in the skin from exposure to sunlight. The 25(OH)Vit D receptor is present in most tissues and cells in the body. 25(OH) 25(OH)Vit D has a wide range of biological actions (12).

During the last trimester, the fetus's skeleton begins to calcify, thereby increasing maternal demand for calcium. Circulating concentrations of 25(OH) 25(OH)Vit D gradually increase during the first and second trimesters owing to

an increase in 25(OH)Vit D-binding protein concentrations in the maternal circulation. However, the free levels of 25(OH)Vit D, responsible for enhancing intestinal calcium absorption, are only increased during the third trimester. For this reason, there have been numerous studies investigating 25(OH)Vit D levels in pregnant women (12). However, studies of 25(OH)Vit D and measurements of birth weight are less common. Two randomized trials in India testing third-trimester 25(OH)Vit D supplementation and three observational studies of maternal first-trimester and third-trimester 25(OH) 25(OH)Vit D found a positive 25(OH)Vit D and birth weight relationship (13,14). Three randomized supplementation trials and four observational studies found no relation between maternal 25(OH)Vit D and birth weight (12,13,15-19). In the present study, which aimed to detect the relationship between FM and 25(OH) Vit D, a significant correlation was detected between cord-blood 25(OH)Vit D levels and FM. This result suggests that 25(OH)Vit D, apart from its many effects on the musculoskeletal system, also affects intrauterine growth and the development of the fetus, particularly in the last trimester. When the 25(OH)Vit D levels were compared among all the newborns birth length, head circumference, and birth weights, a statistically significant correlation was detected only between head circumference and 25(OH)Vit D levels. Although these results suggest that 25(OH)Vit D, which is one of the steroid hormones, also affects brain development through the homolog receptors, these data should be confirmed by further and more extensive studies. Our results of a positive association between cord-blood 25(OH) 25(OH)Vit D levels and head circumference in term AGA infants supports Gernand et al.'s previous study (13).

In our study, a comparison of the mother's skin type between the study group and the control group showed that more mothers with dark skin or lower weight gain (≤ 9 kg) during pregnancy had newborns with FM. So far, there has been no study in the literature on the relationship between FM and the mother's skin color, although a study by Salihoğlu et al. showed a significant relationship between low gestational weight gain of the mother and the frequency of FM, similarly supporting our study results (8). In the present study, no statistically significant difference was detected in newborns in respect of the mother's style of dress. In a study by Fenercioğlu et al. on 266 newborns, comparing the babies of mothers who smoke with passive smokers and non-smokers, FM clinical features were detected in babies whose mothers smoked and in passive

smokers, demonstrating that babies exposed to tobacco smoke during their intrauterine life are significantly at risk of FM (20). However, in our study, while observing FM in the babies of smoking mothers, no statistically significant relationship was detected. But, as smoking affects fetal nutrition and growth and is dose-dependent, these results may be related to the fact that the number of cases and the number of cigarettes were not determined. Assessments of the mother's gestational weight gain have shown that the mothers of well-nourished newborns are more likely to be in the excess gestational weight-gain group; in the present study, however, no correlation could be detected between cord-blood 25(OH)Vit D levels and average mother gestational weight-gain values (21).

The Institute of Medicine report recommends a 25(OH) Vit D intake of 400 to 600 IU/d and states that this level can be obtained solely from the diet. Further, this intake level should be sufficient to meet their circulating 25(OH) 25(OH)Vit D target of 20 ng/mL (50 nmol/L) (21-23). Furthermore, no statistically significant relationship was detected between those mothers taking a 25(OH)Vit D supplement of 400 IU/day for at least three months and those who did not take the supplement. However, a significant relationship between cord-blood 25(OH)Vit D levels and FM was detected in our study: 80% of newborns with sufficient 25(OH)Vit D levels did not suffer from FM, suggesting that there is a strong relationship between FM and 25(OH)Vit D levels. The Salihoğlu et al. study featured 10.7% of mothers and a high percentage of their newborns were detected as having FM (8). In mothers aged older than 35 (15.1% of that study group), 70% of their babies had FM. In a 2006 study performed in Greece, a country with similar geographic and cultural features to Turkey, 25(OH)Vit D levels in the last gestational trimester and the levels of newborns were found to correlate, detecting that newborns with dark-skinned mothers had much lower 25(OH)Vit D levels (25). Currently, some studies have reported that daily doses of 600 IU do not prevent 25(OH)Vit D deficiency in pregnant women. Their daily regimen should at least include a prenatal vitamin containing 400 IU 25(OH)Vit D with a supplement that contains at least 1000 IU 25(OH)Vit D (24). Manson et al. reported that the recommended daily allowances (RDA) will nearly always meet the needs of generally healthy people (22). For patients who are at high risk or who have a disorder related to calcium metabolism, targeted 25(OH)Vit D assessment would be appropriate

and 25(OH)Vit D supplementation at levels above the RDA may be necessary. Pregnancy is a special condition for mothers and their neonates. For this reason, the question of the intake of 25(OH)Vit D in pregnancy and the necessity seems to be important for both mother and baby (24-26).

Study Limitations

There were some limitations of the study. Firstly, there is a lack of information on some potential confounders, in particular maternal sun exposure and standardization of photo type. Secondly, the study was conducted at the end of the winter, which could influence the mother's 25(OH)Vit D status and serum 25(OH)Vit D levels.

CONCLUSION

As a result of the study, there was an weak association between head circumference and vitamin D levels (R^2 : 0.219) but this doesn't mean that there is a cause-effect relationship between vitamin D and head circumference. Additionally the CANSORE was slightly below the threshold of 25 points in the FM group which and also the mean weight of the infants was within the normal range probably mean that the malnourishment may limited our study group neonates. We consider that newborns should be assessed by standard fetal-growth curves as well as FM evaluation, that 25(OH)Vit D deficiency in these babies might be related to fetal growth, but that more cases and similar parameters should be evaluated.

Informed Consent: Written informed consent from a parent was obtained for each neonate prior to the study.

Authorship Contributions

Surgical and Medical Practices: D.E., Ö.S., E.C., Concept: Ö.S., S.H., Design: Ö.S., E.C., Data Collection or Processing: D.E., E.C., Analysis or Interpretation: Ş.T.L., E.C., S.H., Literature Search: Ş.T.L., D.E., Writing: D.E., Ö.S., E.C., Ş.T.L., S.H.

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REFERENCES

1. Sankhyan N, Sharma VK, Singh S. Detection of fetal malnutrition using CAN score. *Indian J Pediatr* 2009;6:903-6.
2. Metcalf J. Clinical assessment of nutritional status at birth. Fetal malnutrition and SGA are not synonymous. *Pediatr Clin North Am* 1994;41:875-91.
3. Scott KE, Usher R. Fetal malnutrition: Its incidence, causes and effects. *Am J Obstet Gynecol* 1966;94:951-63.
4. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of 25OH Vit D deficiency in pregnancy and lactation. *Am J Obstet Gynecol* 2010;202:429.
5. Walker VP, Modlin RL. The 25OH Vit D connection to pediatric infections and immune function. *Pediatr Res* 2009;65:106-13.
6. Thomas SD, Fudge AN, Whiting M, Coates PS. The correlation between third-trimester maternal and newborn-serum 25-hydroxy-25OH Vit D in a selected South Australian group of newborn samples. *BMJ Open* 2011;1:e000236.
7. Salihoğlu Ö, Karatekin G, İlhan R, Nuhoğlu A. Placental findings in malnourished term neonates. *Pediatr Int* 2009;51:494-7.
8. Salihoğlu Ö, Karatekin G, Baksu B, Uslu S, Baksu A, Can G, et al. Frequency and risk factors of fetal malnutrition among liveborn singleton term neonates using a computerised perinatal database, 2000-2006. *J Paediatr Child Health* 2012;48:926-30.
9. Adebami OJ, Owa JA. Comparison between CANSORE and other anthropometric indicators in fetal malnutrition. *Indian J Pediatr* 2008;75:439-42.
10. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of 25OH Vit D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911-30.
11. Tongo OO, Ajayi SO, Ogunbosi BO, Orimadegun AE, Akinyinka OO. Static skinfold thickness in African newborns as an index of fetal nutritional assessment. *Paediatr Int Child Health* 2013;33:161-4.
12. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: Double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res* 2011;26:2341-57.
13. Gernand AD, Simhan HN, Klebanoff MA, Bodnar LM. Maternal serum 25-hydroxy25OH Vit D and measures of newborn and placental weight in a U.S. multicenter cohort study. *J Clin Endocrinol Metab* 2013;98:398-404.
14. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy 25OH Vit D status in relation to fetal and neonatal growth: Results of the multi-ethnic Amsterdam-born children and their development cohort. *Br J Nutr* 2010;104:108-17.
15. Morley R, Carlin JB, Pasco JA, Wark JD, Ponsonby AL. Maternal 25-hydroxy25OH Vit D concentration and offspring birth size: Effect modification by infant VDR genotype. *Eur J Clin Nutr* 2009;63:802-4.
16. Prentice A, Jarjou LM, Goldberg GR, Bennett J, Cole TJ, Schoenmakers I. Maternal plasma 25-hydroxy25OH Vit D concentration and birthweight, growth and bone mineral accretion of Gambian infants. *Acta Paediatr* 2009;98:1360-2.

17. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin status during pregnancy and child outcomes. *Eur J Clin Nutr* 2008;62:68–77.
18. Farrant HJ, Krishnaveni GV, Hill JC, Boucher BJ, Fisher DJ, Noonan K, et al. Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. *Eur J Clin Nutr* 2009;63:646–52.
19. Morley R, Carlin JB, Pasco JA, Wark JD. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *J Clin Endocrinol Metab* 2006;91:906–12.
20. Fenercioğlu A, Karatekin G, Nuhoğlu A. Fetal malnutrition in infants of smokers and passive smokers assessed by clinical assessment of nutritional status scoring. *Turk J Med Sci* 2009;39:849–55.
21. Grieger JA, Clifton VL. A review of the impact of dietary intakes in human pregnancy on infant birthweight. *Nutrients* 2014;29:7:153–78.
22. Manson JE, Brannon PM, Rosen CJ, Taylor CL. 25OH Vit D deficiency – is there really a pandemic? *N Engl J Med* 2016;375:1817–20.
23. IOM (Institute of Medicine). Dietary reference intakes for calcium and 25OH Vit D. Washington, DC: The National Academies Press; 2011.
24. Food and Nutrition Board. Standing committee on the scientific evaluation of dietary reference intakes. Dietary reference intakes for 25OH Vit D and calcium. Washington, DC: The National Academies Press; 2010.
25. Nicolaidou P, Hatzistamatiou Z, Papadopoulou A, Kaleyias J, Floropoulou E, Lagona E, et al. Low 25OH Vit D status in mother pairs in Greece. *Calcif Tissue Int* 2006;78:337–42.
26. Kovacs CS. Bone development and mineral homeostasis in the fetus and neonate: Roles of the calcitropic and phosphotropic hormones. *Physiol Rev* 2014;94:1143–218.