ORIGINAL ARTICLE
Özgün Araştırma

Yazışma Adresi
Correspondence Address

Erbu YARCI
Department of Neonatology,
Dortcelik Children's Hospital,
Bursa, Turkey
erbuyarci@yahoo.com

Geliş Tarihi : 01 December 2021
Received
Kabul Tarihi : 03 February 2022
Accepted
E Yayın Tarihi : 01 September 2023
Online published

Bu makalede yapılacak atıf
Cite this article as

Yarci E, Baldan E.
25-Hydroxyvitamin D Levels in Preterm Infants ≤32 Weeks Gestational Age and Respiratory Distress Syndrome
Akd Med J 2023; 9(3): 259-264

Erbu YARCI
Department of Neonatology,
Dortcelik Children's Hospital,
Bursa, Turkey
ORCID ID: 0000-0003-4434-0958

Emre BALDAN
Department of Pediatrics,
Dortcelik Children's Hospital,
Bursa, Turkey
ORCID ID: 0000-0003-2305-870X

DOI: 10.53394/akd.1031158

25-Hydroxyvitamin D Levels in Preterm Infants ≤32 Weeks Gestational Age and Respiratory Distress Syndrome

Gebelik Yaşı ≤32 Hafta Olan Preterm Bebeklerde 25-Hidroksivitamin D Düzeyleri ve Respiratuvar Distres Sendromu Arasındaki İlişki

ABSTRACT

Objective:

This study aimed to evaluate effect of vitamin D levels on the development of respiratory distress syndrome (RDS) in preterm infants with a gestational age of ≤ 32 weeks. The association between RDS and severity of vitamin D deficiency was secondary outcome of this study.

Material and Methods:

Newborns having a gestational age of ≤32 weeks with RDS constituted the study group, while newborns hospitalized in the neonatal intensive care unit having ≤32 weeks of gestational age with no signs of RDS were the control group.

Results:

During the study period, 122 preterm infants having a gestational age of ≤ 32 weeks were included. From these, 56 (46%) had RDS (study group), while 66 (54%) newborns (control group) did not have RDS. The groups were similar in terms of maternal age, multiple pregnancy, use of antenatal steroid, mode of delivery, sex accompanying maternal diseases and birth season. Median 25-OHD levels of study group and control group were similar (12.3 ng/ml vs 15.6 ng/ml; p=0.38). The rates of preterm infants having low vitamin D levels (25-OHD level<15 ng/ml) did not differ between the groups (38/56, 68% vs 35/66, 53%; p=0.09).

Conclusions:

There is no established optimal 25-OHD level for both term and premature infants. Besides, taking into account possible unfavorable both maternal and neonatal effects of vitamin D deficiency, adequate vitamin D supplementation should be provided in countries where vitamin D deficiency is common.

Key Words:

25-hydroxyvitamin D, Preterm infant, Respiratory distress syndrome

ÖZ

Amaç:

Bu çalışmanın amacı, gebelik yaşı ≤ 32 hafta olan prematüre bebeklerde D vitamini durumunu ve D vitamini düzeylerinin respiratuvar distres sendromu (RDS) gelişimine etkisini değerlendirmektir. RDS ile D vitamini eksikliğinin şiddeti arasındaki ilişki bu çalışmanın ikincil sonucunu oluşturmaktadır.

Gereç ve Yöntemler:
RDS'li gebelik yaşı ≤32 hafta olan yenidoğanlar çalışma grubunu oluştururken, yenidoğan yoğun bakım ünitesinde yatan ve RDS bulgusu olmayan ≤32 hafta olan yenidoğanlar kontrol grubunu oluşturmakta idi.

Bulgular:
Çalışma süresi boyunca gebelik yaşı ≤ 32 hafta olan 122 erken doğmuş bebek dahil edildi. Bunlardan 56'sında (%46) RDS (çalışma grubu) varken, 66 yenidoğanda (%54) (kontrol grubu) RDS saptanmadı. Gruplar arasında anne yaşı, çoğul gebelik, antenatal steroid kullanımı, cinsiyet, doğum şekli, anne yaşı, antenatal steroid kullanımı, eşlik eden anne hastalıkları ve doğum mevsimi açısından anlamlı fark yoktu. Çalışma grubu ve kontrol grubunun medyan 25-OHD seviyeleri benzerdi (12,3 ng/ml'ye karşı 15,6 ng/ml; p=0.38).
Gruplar arasında D vitamini düzeyi düşük olan (25-OHD düzeyi <15 ng/ml) erken doğmuş bebeklerin oranları açısından farklılık saptanmadı (38/56, %68'e karşı 35/66, %53; p=0,09).

Sonuç:
Hem zamanında doğan hem de prematüre bebekler için belirlenmiş bir optimal 25-OHD seviyesi yoktur. Buna karşın, D vitamini eksikliğinin hem maternal hem de neonatal olası olumsuz etkileri göz önünde bulundurularak, D vitamini eksikliğinin yaygın olduğu ülkelerde yeterli D vitamini desteği sağlanmalıdır.

Anahtar Sözcükler:
25-hidroksivitamin D, Preterm bebek, Respiratuvar distres sendromu

INTRODUCTION

Vitamin D is the key regulator of calcium and phosphate homeostasis. Also, it acts on induction of cell differentiation and inhibition of cancer cells, regulation of cardiovascular function and the innate and adaptive immune responses (1). Development of the lung is an ongoing process which begins as soon as third week of gestational age and continues until early adulthood. Vitamin D plays a prominent role in lung development in branching morphogenesis, proliferation of alveolar type-2 cells, surfactant phospholipid secretion and lung maturation (2).
In the premature newborns, the most common respiratory problem is respiratory distress syndrome (RDS). Especially, surfactant deficiency and lung immaturity are foremost factors causing RDS (3). The relationship between vitamin D levels and many common neonatal morbidities especially encountered in the premature infants such as; RDS, sepsis, necrotizing enterocolitis and bronchopulmonary dysplasia have been investigated in the last few years (4). There is limited data on the effect of vitamin D deficiency and development of RDS in preterm newborns (5,6). This study aimed to evaluate effect of vitamin D levels on the development of RDS in preterm infants with a gestational age of ≤ 32 weeks. The association between RDS and severity of vitamin D deficiency was secondary outcome of this study.

MATERIAL and METHODS

This single center retrospective study was performed between April 2019 and April 2021 at Dortcelik Children's Hospital. The research has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. Parental informed consent was obtained from each patient included in the study. The present study was approved by the Ethics Committee of Uludag University Medical School. The Ethics committee certificate date and no was 11.08.2021: 2021-11/17.
Newborns with a gestational age of ≤32 weeks were included in the study. Gestational age was determined primarily by ultrasonographic evaluation performed in the first trimester and by calculation based on the last menstrual period in follow-up of pregnancies or by clinical evaluation after delivery. Newborns having a gestational age of ≤32 weeks with RDS consisted the study group, while newborns hospitalized in the NICU having ≤ 32 weeks of gestational age with no signs of RDS were the control group. The diagnosis of RDS was considered by x-ray and clinical findings. Nasal continuous positive airway pressure with a mean airway pressure of 7 cm H2O was applied to all newborns. Infants aged ≤26 weeks needed an inspired oxygen fraction (FiO2) of 0.3 and infants aged >26 weeks needed a FiO2 of 0.4, for a target of of arterial oxygen pressure > 60 mm Hg. Beractant alfa (Survanta, Abbvie Inc, North Chicago/ABD) at a dose of 200 mg/kg was used for the infants who needed FiO2 above 0.4. Six hours after the first dose, surfactant treatment were administered to those infants who had no improvement in the clinical course and needing a FiO2 ≥0.4.
Blood sampling for alkaline phosphatase (ALP), calcium (Ca), magnesium (Mg), phosphorus (P), parathyroid hormone (PTH) and 25-hydroxyvitamin D (25-OHD), have been performed from all participants at postnatal six hours of life in the NICU. Serum levels of PTH and 25-OHD were measured by chemiluminescent immunoassay analyzer (Abbott i2000, Abbott Laboratories, USA). The photometry method was used for measuring Ca, Mg, P and ALP levels on the Beckman Coulter AU680 analyzer (Danaher Corporation, Brea, CA, USA). Render BC64 device (Render Biotech Co. Ltd. Shenzen, China) was used for analyzing blood cultures. Maternal demographic data were obtained from medical records. Accompanying maternal diseases, multiple pregnancies, maternal age at the time of delivery and medications used were recorded. Newborns' characteristics such as mode of delivery, birth weight, gestational age, sex, Apgar scores, antenatal steroid use, duration of total parenteral nutrition (TPN), non-invasive and invasive mechanical ventilation (MV) and body weight at discharge and duration of hospitalization were recorded. Also, microorganisms that grew in the blood culture were recorded in the study group. The classification of birth season was; spring (March, April, May), summer (June, July, August), fall (September, October, November) and winter (December, January, February). According to neonatal 25-OHD levels, preterm infants were classified into three groups: Severe vitamin D deficiency (25-OHD levels ≤5 ng/ml), Vitamin D insufficiency (25-OHD levels 5-15 ng/ml) and normal vitamin D (25-OHD levels>15 ng/ml). 25-OHD level ≤ 15 ng/ml was defined as low vitamin D level (6,7).

RESULTS

During the study period, 122 preterm infants having a gestational age of ≤ 32 weeks were included. From these, 56 (46%) had RDS (study group), while 66 (54%) newborns (control group) did not have RDS. The groups did not differ in terms of maternal age, multiple pregnancy, use of antenatal steroid, mode of delivery, sex, maternal age, accompanying maternal diseases, small for gestational age (SGA) infants and body weight at discharge and birth season. In contrast to that, control group had higher gestational age, birth weight, first minute and fifth minute Apgar scores compared to the study group. The study group had longer duration of invasive MV, non-invasive MV and TPN compared to control group. Also, study group was found to have a significantly longer length of hospital stay compared to control group (Table I).

Table I. The maternal and neonatal characteristics of the study and control groups

	Control Group n=66	Study Group n=56	p
Maternal age, year Median(min-max)	28 (16-44)	30 (15-38)	0.13
GA, week Median (min-max)	31 (28-32)	30 (24-32)	0.001
Birth weight, gr Median (min-max)	1670 (740-2200)	1222 (730-1860)	0.001
SGA, n %	22 (33)	10 (18)	0.05
Multiple pregnancy, n %	17 (26)	11 (20)	0.42
Male sex, n %	29 (44)	31 (55)	0.20
Use of antenatal steroid, n %	26 (39)	22 (39)	0.99
Delivery with CS, n%	57 (86)	51 (91)	0.41
1st min Apgar, median (IQR)	8 (4-10)	6 (4-9)	0.001
5th min Apgar, median (IQR)	9 (6-10)	8 (6-10)	0.001
Birth season, n%			0.20
Summer	9 (13)	7 (13)	
Fall	21 (32)	10 (18)	
Winter	13 (20)	19 (34)	
Spring	23 (35)	20 (35)	
Duration of invasive MV, day Median (min-max)	1 (0-5)	4 (0-42)	0.0001
Duration of non-invasive MV, day Median (min-max)	1 (0-18)	4.5 (0-45)	0.0001
Duration of oxygen treatment, day Median (min-max)	1 (0-15)	3 (0-40)	0.001
Length of hospital stay, day Median (min-max)	30 (11-115)	48.5(2-280)	0.0001
Body weight at discharge, gr Median (min-max)	2342 (1600-3480)	2400 (1200-4220)	0.76
Maternal disease, n (%)	31 (47)	36 (64)	0.05
Preeclampsia	8 (12)	22 (39)	
Gestational Diabetes	8 (12)	3 (5)	

p: < 0.05 statistically significant

CS: Cesarean section, GA: Gestational age, IQR: Interquartile range, MV: Mechanical ventilation, SGA: Small for gestational age,

When the groups were compared for laboratory parameters; Ca levels were found to be higher in the control group, while levels of P and Mg were higher in the study group. In contrast to that, median 25-OHD levels of study group and control group were similar (12.3 ng/ml vs 15.6 ng/ml; p=0.38). Also, median ALP and PTH levels were similar between the groups. The rates of preterm infants having low vitamin D levels (25-OHD level<15 ng/ml) did not differ between the groups (38/56, 68% vs 35/66, 53%; p=0.09). In the study group, 5 (9%) preterm infants had severe vitamin D deficiency, 33 (%59) had vitamin D insufficiency and 18 (32%) had normal vitamin D levels. In the control group, 5 (8%) preterm infants had severe vitamin D deficiency, 30 (45%) had vitamin D insufficiency and 31 (47%) had normal vitamin D levels (Table II).

Table II. Comparison of laboratory findings of the study and control groups

Variables	Control group n=66	Study Group n=56	p
Ca (mg/dl), mean ± SD	8.6 ± 0.78	8.2 ± 0.89	0.003
P (mg/dl), Median (min-max)	5.5 (3.4-7.2)	5.6 (2-8.5)	0.02
Mg (mg/dl), Median (min-max)	1.95 (1.4-4.5)	2.1 (1.4-4.7)	0.02
ALP (U/L), Median (min-max)	193 (81- 491)	191 (87-395)	0.95
PTH (pg/ml), Median (min-max)	48 (10-333)	43.5 (15-367)	0.55
25-OHD (ng/ml), Median (min-max)	15.6 (4.4-47.2)	12.3 (4.2-38)	0.38
25-OHD levels, n (%)			0.09
Low (<15 ng/ml)	35 (53)	38 (68)	
Normal (≥15 ng/ml)	31 (47)	18 (32)	
25-OHD levels, n (%)			0.25
Severe deficiency	5 (8)	5 (9)	
Insufficiency	30 (45)	33 (59)	
Normal	31(47)	18 (32)	

p: < 0.05 statistically significant.

Ca: Calcium, P: Phosphorus, Mg: Magnesium, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, 25-OHD: 25-hydroxyvitamin D.

When groups were compared for vitamin D levels in terms of birth season, control group had significantly lower vitamin D levels compared to study group in the winter (10.2 ng/ml vs 16.2 ng/ml; p=0.003), but there was no difference between the groups for other seasons (Table III).

Table III. Comparison of neonatal 25-hydroxyvitamin D levels in terms of season and group at birth

Season	25-hydroxyvitamin D level (ng/ml)		p
	Control Group n=66	Study Group n=56	
	Median (min-max)	Median (min-max)	
Spring	16.4 (6.2-47.2)	11.5 (4.2-18.8)	0.05
Summer	15.7 (4.4-26)	8.8 (4.2-38)	0.25
Fall	16.9 (4.7-20.5)	9.9 (7-17.6)	0.09
Winter	10.2 (5.7-32.3)	16.2 (9.6-29.9)	0.003

P: < 0.05 statistically significant

DISCUSSION

Preterm delivery is the most common cause of surfactant deficiency. In the premature newborns, decreased quantity and quality of surfactant results in RDS (8). Also, the surfactant produced in preterm infants compared with surfactant from term infants has reduced activity because of differences in lipid and protein compositions (9). Experimental animal studies suggested the role of inflammation in the pathogenesis of RDS related to the rapid accumulation of neutrophils in the lung and pulmonary edema. Atelectasis related to surfactant deficiency may result in respiratory epithelial and alveolar capillary endothelial injury, which can trigger a cytokine-mediated inflammatory response (10). Also synthesis of a less active surfactant, reduced surfactant production, and surfactant inactivation decreases the effective surfactant pool size.

Some key hormones have an important role in the development and maturation of organs such as thyroid hormones, glucocorti-

coids and insulin. Growth factors and many other hormones interact with each other in this development process. Recently, new hormones including ghrelin, leptin, glucagon like peptid-1 and gene regulating-hormones such as cholecalciferols and retinoids were found to have a key role in the development of several organs, including the lung (2).
The key regulator of calcium homeostasis is Vitamin D. Calcitriol (1,25-dihydroxyvitamin D) is the active form of vitamin D and produced first by hepatic 25-hydroxylation with the cytochrome P450 2R1 and other enzymes, followed by peripheral tissue 1α-hydroxylation with CYP27B1 enzyme (11). Calcitriol interacts with vitamin D receptor. After binding, it requires a heterodimer formation with retinoid X receptor to interact with vitamin D response elements presenting in the DNA to regulate gene expression (2). The lung is one of the main target tissues of calcitriol during fetal development. Vitamin D receptor is expressed in fetal alveolar type II cells, where its activation induces proliferation and the synthesis and secretion of surfactant.

In animal studies, maternal calcitriol deficiency during lung development was found to have negative effects on development of many organs including the lung which may affect the normal lung physiology (12). Calcitriol supplementation during lactation in rodents with previous deficiency during gestation improves alveolar septation and lung function (13).
Compared to past few years, survival rates of preterm infants have evidently raised with advances in perinatal and neonatal care (14). As a result, rates of extremely low birth (ELBW) and very low birth weight (VLBW) infants have increased. These resulted in an increase of prematurity related morbidities and complications. Therefore, more effort has been given for the prevention rather than the treatment of these morbidities and complications. The incidence of RDS increases with decreasing gestational age. A recent study from Turkey reported the incidence of RDS 95% in the same gestational age group (14). Stoll et al., reported the incidence of RDS as 93% having a gestational age of 28 weeks or below (15).

Vitamin D can be synthesized from the fetal tissues, but maternal vitamin D status is the most important factor on the neonatal 25-OHD levels until neonates are supported for vitamin D from external sources (16). As vitamin D has many important functions in many systems in the human body, supplementation of vitamin D is given during pregnancy all over the world. In Turkey, regardless of blood 25-OHD levels vitamin D supplementation is given beginning from the 12th week of pregnancy to end of pregnancy and continued for six months after delivery. The dose of vitamin D is 1200 IU per day given orally (17).
In this study, premature infants with a gestational age of ≤32 weeks with RDS were found to have lower 25-OHD levels compared to premature infants at the same gestational age without RDS but this was not statistically significant. In contrast to our finding, Dogan et al., reported lower vitamin D levels in RDS patients, but RDS patients had lower gestational age and birth weight compared to control patients (5). Also, RDS patients had higher rates of cesarean section in this study, and cesarean section was reported to be an independent predictor of RDS (5,18,19). In our study, RDS patients had lower birth weight and gestational age compared to control group, but there was no difference for mode of delivery between the groups. In the literature, there are few studies evaluating the association of vitamin D deficiency and its effect on RDS development. These studies concluded vitamin D deficiency as an independent risk factor for RDS development, contrary to our findings (8,19,20). The duration of oxygen treatment, non-invasive and invasive MV were shorter in the control group compared to RDS group, similar to reported in the literature (4,5). In contrast to that, there were no difference in terms of duration of oxygenation and MV in a study examining the association between deficient serum 25-OHD levels at birth and respiratory morbidity which evolved during hospitalization among very low birth weight (VLBW) infants (20). Duration of hospitalization was found to be longer in RDS patients compared to control group, similar to reported in the literature (4-6,21). The RDS patients had lower gestational age and birth weight in the present study. In our opinion, the most important factors for longer duration of oxygen treatment, non-invasive and invasive MV were low gestational age and birth weight, which also caused longer duration of hospital stay. Dogan et al., reported a significant effect of bronchopulmonary dysplasia on the duration of hospitalization and the rate of bronchopulmonary dysplasia was found significantly higher in severe vitamin D deficiency group in that study (5). Similarly Cetinkaya et al. reported a severe vitamin D deficiency in all premature BPD patients (22). In the present study, BPD was not evaluated.

A study including VLBW infants reported higher ALP concentrations in patients with severe vitamin D deficiency compared to vitamin D deficiency and insufficiency groups but in that study, cut-off vitamin D levels were different from the present study (4). ALP levels were similar between the groups in this study.
In the present study, there was no difference between the groups in terms of birth season, but Dogan et al. reported higher birth rates in summer and spring in RDS patients compared to patients without RDS (5).

The present study focused on the relation between neonatal 25-OHD levels and the development of RDS. This study has several limitations. Firstly, due to its retrospective nature, the maternal 25-OHD levels at the time of delivery were not evaluated. Secondly, pregnant women are given vitamin D supplementation beginning from the 12th week of gestation. In the present study, the use of vitamin D supplementation (no usage, irregular use, regular use) was not included. As exposure to sunlight is the most important factor for vitamin D synthesis and use of sun-protective clothing is a major factor in this process, these were not included in the study. Another limitation was the small sample size of the study population. Lastly, the primary focus of this study was the relationship between neonatal 25-OHD levels and development of LOS; maternal 25-OHD levels and use of vitamin D supplementation were not recorded. This was another limitation of the study.

CONCLUSION

In conclusion, the present study found no correlation between 25-OHD deficiency and RDS development. This is the first study declaring no association between vitamin D deficiency and development of RDS having similar sample size with studies declaring contrary results. Up to now, there is no established optimal 25-OHD level for both term and premature infants. Further studies with larger sample size are needed to achieve precise results. Besides, taking into account possible unfavorable both maternal and neonatal effects of vitamin D deficiency, adequate vitamin D supplementation should be provided in countries where vitamin D deficiency is common.

Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethics Committee Approval:

The present study was approved by the Ethics Committee of Uludag University Medical School. The Ethics committee certificate date and no was 11.08.2021: 2021-11/17.

Author Contributions:

Erbu Yarci and Emre Baldan were responsible for the conception, design, analysis, and interpretation of data, data collection, writing the draft of the manuscript, and final approval of the manuscript. All authors have read and approved the final version of the article. All authors contributed to the study conception and design.

Financial Disclosure:

The authors received no financial support for the authorship and publication of this article.

Conflict of Interest:

EY and EB declare that they have no conflict of interest.

REFERENCES

1. Di Rosa M, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immuno-modulator. Immunology. 2011; 134(2):123–39.

2. Fandiño J, Toba L, González-Matías LC, Diz-Chaves Y, Mallo F. Perinatal Undernutrition, Metabolic Hormones, and Lung Development. Nutrients 2019;11(12):2870.

3. Rodriguez RJ. Management of respiratory distress syndrome: an update. Respir Care. 2003;48(3): p. 279-86.

4. Kim I, Kim SS, Song JI, Yoon SH, Park GY, Lee YW. Association between vitamin D level at birth and respiratory morbidities in very-low-birth-weight infants. Korean J Pediatr 2019;62(5):166-72.

5. Dogan P, Ozkan H, Koksal N, Bagci O, Varal IG. Vitamin D deficiency and its effect on respiratory distress syndrome in premature infants: results from a prospective study in a tertiary care centre. Afr Health Sci. 2020; 20(1): 437- 43.

6. Fettah ND, Zenciroğlu A, Dilli D, Beken S, Okumus N. Is Higher 25-Hydroxyvitamin D Level Preventive for Respiratory Distress Syndrome in Preterm Infants? Am J Perinatol 2015; 32(03): 247-50.

7. Say B, Uras N, Sahin S, Degirmencioglu H, Oguz SS, Canpolat FE. Effects of cord blood vitamin D levels on the risk of neonatal sepsis in premature infants. Korean J Pediatr 2017; 60:248-53.

8. Frank L, Sosenko IR. Development of lung antioxidant enzyme system in late gestation: possible implications for the prematurely born infant. J Pediatr. 1987;110(1):9.

9. Hallman M, Kulovich M, Kirkpatrick E, Sugarman RG, Gluck L. Phosphatidylinositol and phosphatidylglycerol in amniotic fluid: indices of lung maturity. Am J Obstet Gynecol. 1976;125(5):613-7.

10. Carlton DP, Albertine KH, Cho SC, Lont M, Bland RD. Role of neutrophils in lung vascular injury and edema after premature birth in lambs
J Appl Physiol 1997;83(4):1307-17.

11. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, Lips P, Munns CF, Lazaretti-Castro M, Giustina A, Bilezikian J. Skeletal and extraskeletal actions of Vitamin D: Current evidence and outstanding questions. Endocr. Rev.2019;40:1109–51.

12. Foong RE, Bosco A, Jones AC, Gout A, Gorman S, Hart PH, Zosky GR. The effects of in utero vitamin D deficiency on airway smooth muscle mass and lung function. Am. J. Respir. Cell Mol. Biol. 2015;53:664–75.

13. Saadoon A, Ambalavanan N, Zink K, Ashraf AP, MacEwen M, Nicola T, Fanucchi MV, Harris WT. Effect of Prenatal versus Postnatal Vitamin D Deficiency on Pulmonary Structure and Function in Mice. Am. J. Respir. Cell Mol. Biol. 2017;56: 383–92.

14. Yarci E, Canpolat FE. Evaluation of Morbidities and Complications of Neonatal Intensive Care Unit Patients with Respiratory Disorders at Different Gestational Ages. Am J Perinatol. 2022;29(14):1533-40.

15. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz 3rd ID, Watterberg KL, Saha S, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Devolopment Neonatal Research Network. Neonatal outcomes of extremely preterminfants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3):443-56.

16. Marshall I, Mehta R, Petrova A. Vitamin D in the maternal-fetal-neonatal interface: clinical implications and requirements for supplementation. J Matern Fetal Neonatal Med 2013; 26: 633–8.

17. Turkiye Cumhuriyeti Sağlık Bakanlığı, Halk Sağlığı Genel Müdürlüğü, Gebelere D Vitamini Destek Programı, Güncelleme tarihi: 25/04/2011. https://www.saglik.gov.tr/TR,11161/gebelere-d-vitamini-destek-programi-rehberi.html

18. Tochie JN, Choukem SP, Langmia RN, Barla E, Koki-Ndombo P. Neonatal respiratory distress in a reference neonatal unit in Cameroon: an analysis of prevalence, predictors, etiologies and outcomes. Pan Afr Med J 2016;24: p. 152.

19. Yu RQ, Chen DZ, Hao XQ, Jiang SH, Fang GD, Zhou Q. Relationship between serum 25(OH)D levels at birth and respiratory distress syndrome in preterm infants. Zhongguo Dang Dai Er Ke Za Zhi 2017; 19(11): p. 1134-7.

20. Kazzi SNJ, Karnati S, Puthuraya S, Thomas R. Vitamin D deficiency and respiratory morbidity among African American very low birth weight infants. Early Hum Dev. 2018;119:19-24.

21. Zhang X, Luo K, He X, Chen P. Association of vitamin D status at birth with pulmonary disease morbidity in very preterm infants. Pediatr Pulmonol. 2021;56(5):1215-20.

22. Cetinkaya M, Çekmez F, Erener-Ercan T, Buyukkale G, Demirhan A, Aydemir G, Aydin FN. Maternal/neonatal vitamin D deficiency: a risk factor for bronchopulmonary dysplasia in preterms? J Perinatol 2015;35(10): p. 813-7.