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**Original Article**

# Serum 25-Hydroxyvitamin D Levels in Preterm Infants Born at Gestational Age of ≤32 Weeks and Prematurity-related Morbidities and Complications

## *Gebelik Yaşı ≤32 Hafta Olan Preterm İnfantlarda Serum 25-Hidroksivitamin D Düzeyleri ve Prematürite İlişkili Morbidite ve Komplikasyonlar*

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## ABSTRACT

**Objective:** To investigate the association between vitamin D levels and prematurity-related morbidities and complications in preterm infants born at ≤32 gestational weeks

**Method:** Newborns having a gestational age of ≤32 weeks were included in the study. Lower 25-hydroxyvitamin D (25-OHD) levels (≤15 ng/mL) were detected in the study, and normal 25-OHD levels (>15 ng/mL) were in the control group. Neonatal and maternal demographic features, laboratory findigs, clinical outcomes, prematurity-related morbidities and complications were investigated for two groups.

**Results:** A total of 122 preterm infants were evaluated in the study. The study group consisted of 73 (60%) and the control group comprised 49 (40%) infants. The study group more frequently used antenatal steroid (p=0.046). First and fifth minute - Apgar scores were lower in the study group (p=0.001 and p=0.003, respectively). Duration of invasive mechanical ventilation was longer in the study group (p=0.02). Late-onset sepsis (LOS) was more often detected in the study group (p=0.0001). The incidence of hemodynamically significant patent ductus arteriosus (hsPDA) and metabolic bone disease of prematurity (MBD) was higher in the study group (p=0.001 and p=0.04, respectively).

**Conclusion:** Significant relationships were found between low vitamin D levels and LOS, hsPDA and MBD. Vitamin D usage during pregnancy is important to avoid maternal and neonatal vitamin D deficiency and its consequences.

**Keywords:** Preterm infant, morbidity, 25-hydroxyvitamin D level

## ÖZ

**Amaç:** Bu çalışmanın amacı, ≤32 gebelik haftasında doğan prematüre bebeklerde vitamin D düzeyleri ile prematüriteye bağlı morbidite ve komplikasyonlar arasındaki ilişkiyi değerlendirmektir.

**Yöntem:** Gebelik yaşı ≤32 hafta olan yenidoğanlar çalışmaya dahil edildi. Düşük 25-hidroksivitamin D düzeyi (≤15 ng/mL) çalışma grubu, normal 25- hidroksivitamin (>15 ng/mL) kontrol grubu olarak tanımlandı. Her iki grup için neonatal ve maternal demografik özellikler, laboratuvar bulguları, klinik sonuçlar, prematürite morbiditeleri ve komplikasyonları değerlendirildi.

**Bulgular:** Toplam 122 preterm infant çalışmada değerlendirildi. Çalışma grubunu 73 (%60) infant, kontrol grubunu ise 49 (%40) infant oluşturdu. Çalışma grubunda antenatal steroid kullanımı daha sıktı (p=0,046). Birinci ve beşinci dakika Apgar skorları çalışma grubunda daha düşüktü (sırasıyla; p=0,001 ve p=0,003). Çalışma grubunda invaziv mekanik ventilasyon süresi daha uzundu (p=0,02). Geç başlangıçlı sepsis çalışma grubunda daha sık saptandı (p=0,0001). Hemodinamik anlamlı patent duktus arteriyozus ve prematürenin metabolik kemik hastalığı insidansı çalışma grubunda daha yüksekti (sırasıyla; p=0,001 ve p=0,04).

**Sonuç:** Düşük vitamin D seviyesi ile geç başlangıçlı sepsis, hemodinamik anlamlı patent duktus arteriyozus ve prematürenin metabolik kemik hastalığı arasında anlamlı ilişki saptandı. Gebelik sırasında vitamin D kullanımı, maternal ve neonatal vitamin D eksikliğini ve sonuçlarını önlemek için önemlidir.

**Anahtar kelimeler:** Preterm infant, morbidite, 25-hidroksivitamin D seviyesi

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## INTRODUCTION

Vitamin D has functional roles in many systems, such as bone metabolism and fetal growth [1,2]. Vitamin D receptors (VDRs), which are found in osteoblasts, bronchial epithelial cells, alveolar type II cells, intestinal and skin epithelial cells, kidney tubules, parathyroid gland epithelium, pancreatic beta cells and immune system cells, are responsible for its effects [3]. It is best known for its effects on phosphorus (P) and calcium (Ca) homeostasis; but it also has considerable functions in fetal lung development, supporting the functions of the innate and adaptive immune system, intestinal cell proliferation, and differentiation, induction of apoptosis, stabilization of vascular smooth muscle and endothelial cells [4-9].

Deliveries occurring before the 37th gestational weeks is defined as preterm birth. There are approximately 15 million preterm births in the world every year, and approximately one million of these newborns die due to various complications [10,11]. Patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), early-onset sepsis (EOS), late-onset sepsis (LOS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), periventricular leukomalacia, metabolic bone disease of prematurity (MBD) are the major morbidities [12,13].

This study aimed to investigate the association between vitamin D levels and prematurity-related morbidities and complications in preterm infants born at gestational age (GA) of ≤32 weeks.

## MATERIALS and METHODS

This single center retrospective study was carried out between April 2019 and April 2021 in Dörtçelik Children's Hospital, neonatal intensive care unit (NICU) in Bursa, Turkey. Ethical committee approval was received from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2021-11/17, date: 11.08.2021).

Newborns with a GA of ≤32 weeks were included in the study. The 25-hydroxyvitamin D (25-OHD) levels measured at postnatal six hours in the NICU, were used for the categorization of preterm infants. The infants with low (≤15 ng/mL), and normal (>15 ng/mL) 25-OHD levels were allocated into the study, and the control groups, respectively [8]. Maternal demographic data related to maternal age, presence of concomitant disease and multiple pregnancies were used. The characteristics of the newborns such as birth weight (BW), GA, sex, GA-adjusted BW, mode of delivery, Apgar scores, antenatal steroid use, duration of invasive and noninvasive mechanical ventilation (MV), oxygen support, and hospitalization, total parenteral nutrition (TPN) and body weight at discharge and were recorded.

Blood samples for the measurement of alkaline phosphatase (ALP), parathyroid hormone (PTH), P, magnesium (Mg) and Ca were obtained from all participants at postnatal six hours in the NICU. Serum PTH and 25-OHD levels were measured by chemiluminescent immunoassay analyzer (Abbott i2000, Abbott Laboratories, USA). The photometry method on the Beckman Coulter AU680 analyzer (Danaher Corporation, Brea, CA, USA) was used to measure Mg, P, Ca and ALP levels.

Prematurity - related morbidities and complications such as RDS, pulmonary hemorrhage, EOS, LOS, hemodynamically significant patent ductus arteriosus (hsPDA), MBD, NEC, ROP, IVH, BPD and mortality were recorded.

### Statistical Analysis

SPSS version 20.0 software (SPSS Inc. Chicago, IL, USA) was used for statistical analysis. Categorical values were summarized as numbers and percentages. Continuous data with nonnormal distribution were presented as median [interquartile range (IQR)]. Mann-Whitney U test was used for non-normal distributions. The Fisher's Exact and chi-squared tests were used for categorical variables. A p value of <0.05 was accepted for statistical significance.

## RESULTS

Between April 2019 and April 2021, 122 preterm infants were evaluated including 73 (60%) infants in the study and 49 (40%) in the control group. The study group used antenatal steroids more frequently (p=0.046). The study group had lower 1 and 5- minute Apgar scores compared to the control group (p=0.001 and p=0.003, respectively). Other demographic characteristics were similar between the groups. All demographic characteristics are given in Table 1.

All laboratory findings were similar between the groups. When the groups were evaluated for the clinical outcomes, only duration of invasive MV was longer in the study group (p=0.02). The other clinical outcomes were similar between the groups (Table 2).

While the frequency of EOS was similar in both groups, the frequency of LOS was higher in the study group (p=0.0001). Also, hsPDA and MBD were more frequently detected in the study group (p=0.001 and p= 0.04, respectively). Other morbidities and complications were similar between the groups (Table 3).

## DISCUSSION

Effects of vitamin D on mineral and bone metabolism have been known for a long time. Recent studies have shown that VDRs are found in many tissues and vitamin D affects many systems [14,15]. Maternal vitamin D, which shows transplacental transmission throughout pregnancy, is the most important determinant of fetal and neonatal vitamin D levels [16,17]. In the literature, low vitamin D levels in the neonatal period have been linked to an increased risk of wheezing and asthma in later childhood [18].

Neonatal sepsis causes seriuos morbidity and mortality in the neonatal period. While EOS is associated with maternal transmission of microorganisms, LOS is encountered as a complication of prolonged NICU stay, especially in preterm infants [19,20]. Vitamin D affects cells of the immune system [21]. It has been reported that vitamin D deficiency in cord blood increases the risk of neonatal sepsis in preterm infants, but vitamin D deficiency was not found to be an independent risk factor for sepsis [8]. Contrary to that finding, low maternal and neonatal vitamin D levels were found to be associated with EOS in term infants [19]. In an another study, vitamin

**Table 1. Neonatal and maternal demographic features of the groups**

| Variables | Study group n=73 | Control group n=49 | p |
|---|---|---|---|
| GA at birth, weeks, median (IQR) | 31 (30-32) | 30 (30-31) | 0.88[a] |
| Birth weight, g, median (IQR) | 1400 (1148-1733) | 1570 (1200-1700) | 0.91[a] |
| Sex, male, n (%) | 39 (53) | 21 (43) | 0.25[b] |
| Type of delivery, C/S, n (%) | 66 (90) | 42 (86) | 0.42[b] |
| SGA, n (%) | 21 (29) | 11 (22) | 0.53[b] |
| Antenatal steroid usage, n (%) | 34 (47) | 14 (29) | 0.046[b] |
| 1- minute Apgar score, median (IQR) | 7 (6-8) | 8 (7-9) | 0.001[a] |
| 5- minute Apgar score, median (IQR) | 8 (8-9) | 9 (9-10) | 0.003[a] |
| Multiple pregnancies, n (%) | 21 (29) | 7 (14) | 0.06[b] |
| Maternal age, year, median (IQR) | 30 (23-33) | 27 (23-35) | 0.97[a] |
| Concomitant diseases, n (%) | 37 (51) | 30 (61) | 0.25[b] |

[a]Mann-Whitney U test, [b]Chi-square test, GA: Gestational age, IQR: Interquartile range, g: gram, C/S: Cesarean section, SGA: Small for gestational age

**Table 2. Laboratory findings and clinical outcomes of the groups**

| Variables | Study group n=73 | Control group n=49 | p |
|---|---|---|---|
| Ca, mg/dL, median (IQR) | 8.3 (7.7-9.1) | 8.5 (8.2-9.4) | 0.08[a] |
| P, mg/dL, median (IQR) | 5.5 (4.7-6.3) | 5.6 (4.7-6.1) | 0.66[a] |
| Mg, mg/dL, median (IQR) | 2 (1.8-2.6) | 2 (1.8-2.7) | 0.74[a] |
| ALP, IU/L, median (IQR) | 191 (147-244) | 192 (155-210) | 0.26[a] |
| PTH, pg/mL, median (IQR) | 49 (31-160) | 45 (26-110) | 0.11[a] |
| TPN, day, median (IQR) | 24 (14-44) | 23 (14-30) | 0.36[a] |
| Noninvasive MV, day, median (IQR) | 2 (0-7) | 1 (0-4) | 0.18[a] |
| Invasive MV, day, median (IQR) | 0 (0-6) | 0 (0-4) | 0.02[a] |
| $O_2$ support, day, median (IQR) | 2 (1-6) | 2 (1-3) | 0.43[a] |
| Body weight*, g, median (IQR) | 2345 (2073-2645) | 2400 (2050-2505) | 0.64[a] |
| Hospitalization**, day, median (IQR) | 41 (29-60) | 36 (28-52) | 0.4[a] |

[a]Mann-Whitney U test, *Body weight at discharge, **Duration of hospitalization, Ca: Calcium, IQR: Interquartile range, P: Phosphorus, Mg: Magnesium, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, TPN: Total parenteral nutrition, MV: Mechanical ventilation, $O_2$: Oxygen

| Table 3. Prematurity - related morbidities and complications of the groups | | | |
|---|---|---|---|
| **Variables** | **Study group n=73** | **Control group n=49** | **p** |
| RDS, n (%) | 38 (52) | 18 (36) | 0.09[a] |
| EOS, n (%) | 12 (16) | 5 (10) | 0.33[a] |
| LOS, n (%) | 50 (68) | 8 (16) | 0.000[a] |
| Pulmonary hemorrhage, n (%) | 5 (7) | 0 (0) | 0.08[a] |
| hsPDA, n (%) | 22 (30) | 3 (6) | 0.00[a] |
| MBD, n (%) | 16 (22) | 4 (8) | 0.04[a] |
| NEC, n (%) | 13 (18) | 13 (26) | 0.25[a] |
| ROP, n (%) | 16 (22) | 12 (24) | 0.74[a] |
| IVH, n (%) | 16 (22) | 18 (36) | 0.07[a] |
| BPD, n (%) | 4 (5) | 0 (0) | 0.15[a] |
| Mortality, n (%) | 4 (5) | 0 (0) | 0.15[a] |

[a]Chi-square test, RDS: Respiratory distress syndrome, EOS: Early - onset sepsis, LOS: Late - onset sepsis, hsPDA: Hemodynamically significant patent ductus arteriosus, MBD: Metabolic bone disease, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, IVH: Intraventricular hemorrhage, BPD: Bronchopulmonary dysplasia

D levels was lower in preterm infants diagnosed with LOS and the risk of LOS increased in case of vitamin D levels of ≤9.5 ng/mL [5]. Dhandai et al. [22] demonstrated that low vitamin D levels increase the risk of LOS in the late preterm and term infants. In the present study, while there was no relationship between vitamin D levels and EOS, vitamin D levels were lower in preterm infants who developed LOS. In studies evaluating the effects of vitamin D on the immune system and its association with neonatal sepsis, low vitamin D levels were found to increase the risk of both EOS and LOS. Similar to the literature, our study has found that preterm infants with low vitamin D levels had a higher risk of LOS. However, no relationship was identified between vitamin D levels and EOS.

BPD and RDS are major respiratory complications of preterm infants [23]. Surfactant is synthesized in alveolar type II cells and decreases alveolar surface tension. RDS is a neonatal respiratory system disorder caused by impared or decreased secretion of surfactants [24]. BPD is a disease characterized by long - term respiratory failure and its etiology and mechanism are not fully understood [25]. Vitamin D effects surfactant synthesis and secretion through VDRs in alveolar type II cells [26,27]. Low vitamin D levels were reported to be an independent risk factor for RDS [28]. Similar to that finding, maternal and neonatal vitamin D levels were lower in patients with BPD [29]. In another study evaluating RDS and BPD, vitamin D levels were lower in preterm infants with RDS (≤30 GA) and BPD (<34 GA) [23]. Contrary to that, Matejek et al. [17] found no association between vitamin D levels and RDS and BPD. We found that low vitamin D levels were not risk factors for these diseases.

Requirement for respiratory support in newborns is inversely proportional to GA [30]. Two studies reported that duration of invasive MV did not differ significantly according to vitamin D levels [17,31]. In addition, Matejek et al. [17] stated that the duration of noninvasive MV did not differ between vitamin D groups. Contrary to these studies, two studies reported that the duration of both invasive and noninvasive MV was longer in groups with low vitamin D levels [18,23]. Another study showed that the duration of invasive MV was longer in the lower vitamin D group [28]. Some studies in the literature have shown that the duration of oxygen support is longer in preterm infants with low vitamin D levels [18,23]. In our study, duration of invasive MV is longer in the study group, but without any intergroup difference in terms of duration of noninvasive MV and oxygen support. Prolonged exposure to high oxygen concentrations causes lung damage which plays a role in the development of BPD [25]. The similarity in the duration of oxygen support between the groups may explain the lack of difference in BPD.

MBD is mainly caused by abnormalities in Ca and P metabolism due to nutritional, environmental and biomechanical factors [32,33]. In MBD, abnormal bone mineralization, cortical and trabecular damage to the bones are observed. In severe cases, it can cause osteopenia and pathological fractures [32,34]. The usage of fortified breast milk, preterm formulas and advances in neonatal care has reduced the incidence of MBD in recent

years [34,35]. Ca and P are transmitted from the mother to the fetus most frequently in the third trimester [34]. Vitamin D deficiency and prolonged parenteral nutrition are other important risk factors for MBD [32]. In our study, although neonatal cholestasis was similar in both groups, the frequency of MBD was higher in the study group. Although there are studies for determining the optimal vitamin D supplementation to prevent MBD in preterm infants, there are no studies about relationship between vitamin D levels in first day after birth and MBD.

NEC is a multifactorial disease whose pathophysiology is not fully understood [36,37]. Genetic predisposition, inadequate intestinal function, excessive inflammatory response and alterations in microbiota play a role in the pathophysiology [36]. In a recent study, the incidence of NEC was 7% in very low birth weight infants followed in the NICU [38]. Vitamin D exerts its function in intestinal tissue by induction of cell proliferation, differentiation and apoptosis through VDRs [6]. In a study, maternal and neonatal vitamin D levels were found to be lower in the NEC group but only maternal vitamin D level was detected to be a significant predictor for NEC [39]. In another study, no association was found between vitamin D levels and NEC [17]. In our study any significant difference was not observed between the groups in terms of NEC.

PDA is an important congenital heart disease in preterm infants. While the ductus arteriosus is functionally closed within postnatal 72 hours in term infants, this closure may be delayed in preterm infants [40]. GA and BW are inversely related to the risk of PDA [41]. After birth, increased partial pressure of oxygen in the arterial blood, decreased prostaglandin E2 and prostacyclin 2 levels negatively effect ductal closure [42,43]. An animal study, showed that Ca flow through Ca channels and increased Ca sensitivity play a role in ductal closure. In the same study, it was observed that closure was delayed with Ca channel blockers [44]. Cakir et al. [41] measured ionized Ca (iCa) at the 1st and 48th postnatal hours in the hsPDA and non-hsPDA groups, and found that iCa levels was lower in the group with hsPDA. A study examining the association between vitamin D levels and PDA, showed that low vitamin D does not increase the risk of PDA [18]. In our study, although GA, BW and Ca levels were similar between the groups, hsPDA was higher in the study group.

ROP is another morbidity of preterm infants closely related to low BW and low GA. RDS, BPD, prolonged high oxygen delivery are other important risk factors [45,46]. In a study, it was stated that vitamin d deficiency may be effective in the development of ROP [45]. Similarly, Kim et al. [18] found that ROP was more common in patients with severe vitamin D deficiency. On the other hand, in our study, no relationship was found between vitamin D levels and ROP which may be related to similarities between our groups in terms of the most important ROP risk factors such as GA, BW, RDS, BPD and duration of oxygen support.

The risk of IVH increases with prematurity and low BW. Immature germinal matrix, hypoxic and ischemic brain damage, fluctuations in cerebral blood pressure, hemostatic abnormalities play a role in the pathogenesis [4]. Vitamin D exerts its effect on vascular smooth muscle cells by reducing angiogenesis, inflammation, proliferation and providing vascular endothelium stability [4,47]. Boskabadi et al. [4] found that preterm infants with IVH had lower serum vitamin D levels. In our study, the development of IVH was similar between the groups.

The present study focused on the relationships between neonatal 25-OHD levels and prematurity-related morbidities and complications.

### Study Limitations

This study has several limitations. Firstly, the maternal 25-OHD levels at the time of delivery were not evaluated. Secondly, pregnant women were given vitamin D supplementation beginning from the 12th weeks of gestation. The usage patterns of vitamin D (no usage, irregular use, regular use) were not examined in the study. 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 which were not examined in the study. Another limitation was the small sample size of the study population.

## CONCLUSION

In this study, significant relationships were found between low vitamin D levels and LOS, hsPDA and MBD. Our study shows similar results as well as differences when compared with the studies in the literature, Further studies with larger sample size are required to achieve precise results. The advances in prenatal and neonatal care increase the chance of survival of newborns. This condition also causes an increase in morbidity due to prematurity. The main aim should be to prevent these morbidities before they occur. Therefore, vitamin D

usage during pregnancy is important to avoid vitamin D deficiency and its consequences.

### Ethics

**Ethics Committee Approval:** Ethical committee approval was received from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2021-11/17, date: 11.08.2021).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Author Contributions

Surgical and Medical Practices: E.B., E.Y., Concept: E.B., E.Y., Design: E.B., E.Y., Data Collection and/or Processing: E.B., E.Y., Analysis and/or Interpretation: E.B., E.Y., Literature Search: E.B., E.Y., Writing: E.B., E.Y.

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