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Vitamin D Status in Early Preterm Infants

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ABSTRACT

Purpose: Vitamin D deficiency is still common in pregnant women and infants, especially preterm infants. This study evaluated the prevalence, characteristics, and prenatal and postnatal complications associated with vitamin D deficiency in preterm infants.

Methods: Preterm infants (gestational age of <32 weeks, delivered between January 2014 and December 2014) were divided into two groups according to umbilical cord blood 25-hydroxyvitamin D concentrations (deficiency group, <20 ng/mL; non-deficiency group, ≥20 ng/mL), and associated factors were evaluated.

Results: The mean concentration of 25-hydroxyvitamin D in the preterm infants was 14.3±9.7 ng/mL. 80% (78 out of 98) of subjects had vitamin D deficiency (<20 ng/mL), and 45% (44 out of 98) of preterm infants had a severe vitamin D deficiency (<10 ng/mL). No seasonal variation was observed in 25-hydroxyvitamin D concentration. Mean gestational age and birth weight were lower in the deficiency group. The serum calcium and alkaline phosphatase (ALP) concentrations, which reflect bone metabolism, were significantly different between the two groups, but not the serum phosphorous concentrations. Maternal prenatal complications and infant complications were not significantly different between the two groups.

Conclusion: The prevalence of vitamin D deficiency is high, and it is a persistent problem among Korean mothers and their newborn infants, especially preterm infants. Thus, it is important to prevent vitamin D deficiency by early detection of the deficiency and supplementation of vitamin D.

Key Words: Preterm infant, Vitamin D, Vitamin D deficiency

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INTRODUCTION

The prevalence of vitamin D deficiency seems to have disappeared as socioeconomic and nutritional statuses have been improved. However, it is still common in pregnant women and infants, especially preterm infants. Vitamin D status in newborn infants is associated with maternal vitamin D status during pregnancy[1]. Vitamin D deficiency in pregnant women is associated with pregnancy-induced hypertension (PIH)[2], gestational diabetes mellitus (GDM)[3], intrauterine growth retardation[4,5], and other ailments. The above-

mentioned perinatal complications, including PIH, GDM, and intrauterine growth retardation, may hasten preterm delivery, putting preterm infants at high risk of vitamin D deficiency[6,7]. Maternal vitamin D supplementation during pregnancy improved maternal and neonatal vitamin D status, which is negatively associated with preterm birth by attenuating preterm labor[8].

Preterm infants at a gestational age of < 28 weeks or birh weight of <1,000 g are born prior to the time that the bulk transplacental transport of vitamin D from the mother to the fetus usually occurs during the third trimester. In fact, 80% of calcium and phosphorus retained in newborn infants is transferred during the third trimester[9]. This can result in deficient vitamin D storage in preterm infants, finally resulting in a more severe vitamin D deficiency and rickets[10,11]. In addition, vitamin D deficiency in preterm infants admitted to neonatal intensive care units is aggravated by deficient vitamin D synthesis in the skin due to lack of sun exposure, reduced vitamin D absorption from the intestine, reduced supplementation with milk caused by inadequate enteral nutrition or delayed fortification of human breast milk, and insufficient phosphorus supply and relatively increased requirement[6]. As a result, preterm infants are at a high risk of vitamin D deficiency.

Although the relationship between gestational ages and serum vitamin D levels in preterm infants is unknown, the prevalence of vitamin D deficiency in high-risk preterm infants differs in various research results[6,12-17]. Vitamin D deficiency is more frequent in infants born in Asia than those born in Western countries, but the information on the vitamin D status of preterm infants born in Asian countries is limited[18].

This study was conducted to evaluate the prevalence, characteristics, and complications related to vitamin D deficiency in preterm infants and to suggest ways to reduce vitamin D deficiency and associated complications in preterm infants.

MATERIALS AND METHODS

1. Patients

The protocol of this study was reviewed and approved by the Institutional Review Board of the Inje University Busan Paik Hospital. Preterm infants who had been delivered before 32 weeks gestation and admitted to the neonatal intensive care unit of Inje University Busan Paik Hospital, Busan, Korea from January 2014 to December 2014, were enrolled. The infants were allocated to two groups depending on their 25-hydroxyvitamin D concentrations (deficiency group <20 ng/mL; non-deficiency group ≥20 ng/mL).

2. Study protocol

Clinical data were collected retrospectively from medical records. Various demographic factors and prenatal maternal complications were evaluated to identify factors that might influence vitamin D deficiency. Postnatal complications resulting from vitamin D deficiency were evaluated. Blood samples were taken from infants within one hour after birth or from their umbilical cord blood. Concentrations of 25-hydroxyvitamin D were measured using radioimmunoassay (DIAsource 25OH-Vit.D3-RIA-CT, DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium). Demographic factors considered were season of birth, gestational age, birth weight, gender, Apgar score at 1 and 5 minutes, small for gestational age (SGA), antenatal corticosteroids therapy, singleton or multiple birth, maternal age, and maternal body mass index (BMI). Prenatal factors were maternal GDM, PIH, and premature rupture of membrane (PROM). Outcome factors that were associated with prematurity included respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and sepsis.

The definition of SGA was any birth weight below the 10th percentile on the Lubchenco growth curve[19]. IVH and PVL were diagnosed by brain ultrasound and limited to high grade (≥grade III) IVH[20]. The definition of BPD was an oxygen dependency at 36 weeks post-menstrual age with oxygen treatment for at least the first 28 days of life and categorized as mild, moderate, or severe[21]. NEC was limited to a modified bell stage≥II[22]. ROP was limited to a high stage requiring laser therapy. Sepsis was limited to a positive blood culture with clinical signs of systemic infection[23].

3. Statistical analysis

Statistical analysis was performed using *t*-tests or Mann-Whitney *U* tests for continuous variables and one-way ANOVA, chi-square tests, and Fisher's exact test for categorical variables. Potential confounding factors that affected the severity of vitamin D deficiency were analyzed using logistic regression. Statistical analysis was performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA). Data are given as mean±standard deviation.

Neonatal Med 2016 August;23(3):143-150
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P-values of <0.05 were considered statistically significant.

RESULTS

From January 2014 to December 2014, 98 preterm infants born before 32 weeks gestation were enrolled and categorized into two groups (deficiency group, n=78, 25-hydroxyvitamin D concentrations <20 ng/mL; non-deficiency group, n=20, 25-hydroxyvitamin D concentrations ≥20 ng/mL).

We found that the 25-hydroxyvitamin D concentrations in preterm infants less than 32 weeks of gestation were quite low (Figure 1); the mean concentration was 14.3±9.7 ng/mL. More than two-thirds of the enrolled preterm patients (80%, 78 out of 98) had a vitamin D deficiency (25-hydroxyvitamin D concentrations <20 ng/mL). Nearly half of the enrolled preterm patients (45%, 44 out of 98) had severe vitamin D deficiency (25-hydroxyvitamin D concentrations <10 ng/mL).

The concentration of 25-hydroxyvitamin D has a tendency to be higher during summer time (16.3 ng/mL) and lower during winter (13.3 ng/mL). The concentrations were lowest from January to April and increased from May through August. However, seasonal variation of 25-hydroxyvitamin D was not statistically significant (see Table 1, and Figure 2).

Mean gestational age and birth weight were lower in the deficiency group than in the non-deficiency group, with a statistically significant difference (*P*=0.040 and *P*=0.031). The serum calcium and ALP concentrations were significantly different between the two groups (*P*=0.047 and *P*=0.014).

Prenatal complications (maternal GDM, PIH, and PROM) were not significantly different between the two groups (Table 2), and 25-hydroxyvitamin D concentrations did not differ based on

Table 1. 25-hydroxyvitamin D Concentration According to Associated Factors

	n (%)	25(OH)D(ng/mL)	*P*-value
All subjects	98 (100)	14.3±9.7	
Season of birth			0.577
Spring	18 (18.4)	13.6±10.4	
Summer	32 (32.7)	16.3±11.4	
Fall	29 (29.6)	13.1±7.2	
Winter	19 (19..4)	13.3±9.4	
Infant sex			0.776
Male	60 (61.2)	14.5±9.5	
Female	38 (38.8)	13.9±10.1	
Gestational age (wks)			0.375
<28	37 (37.8)	12.8±8.0	
28-29	32 (32.7)	14.2±9.8	
30-31	29 (29.6)	16.2±11.4	
Singleton or multiple birth			0.937
Singleton	67 (68.4)	14.3±9.7	
Multiple	31 (31.6)	14.2±9.9	

The values are presented as number (%) or mean±SD.
Abbreviation: 25(OH)D, 25 hydroxyvitamin D.

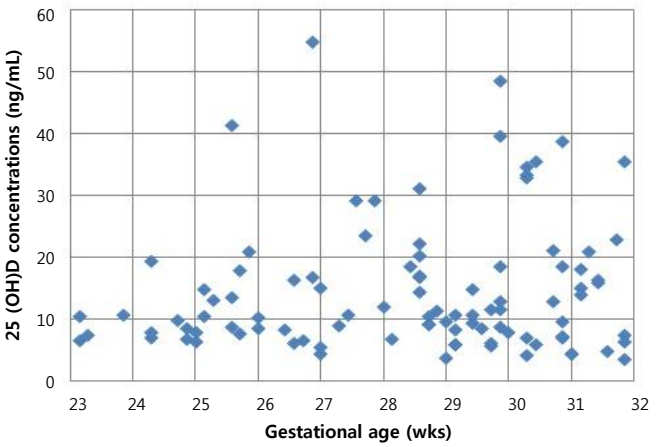

Figure 1. 25-hydroxyvitamin D concentration according to gestational age. 25-hydroxyvitamin D concentration was not significantly related to gestational age, though the concentration did increase with increased gestational age. Abbreviation: 25(OH)D, 25 hydroxyvitamin D.

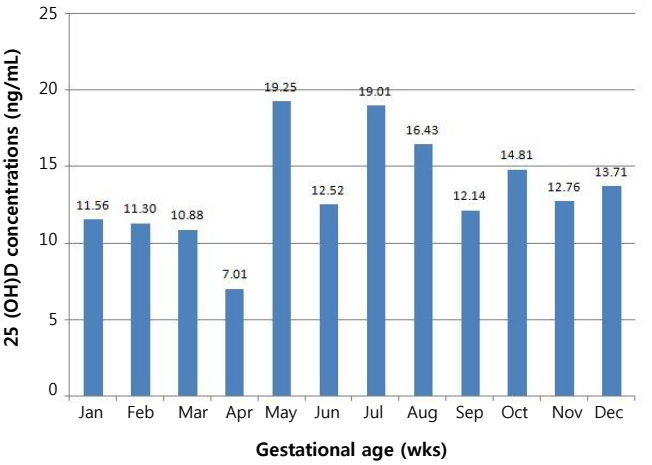

Figure 2. 25-hydroxyvitamin D concentration according to the month of birth. Monthly 25-hydroxyvitamin D concentration was higher during summer and lower during winter, with the lowest concentrations from January to April and highest concentrations from May through August. However, the variations were not statistically significant. Abbreviation: 25(OH)D, 25 hydroxyvitamin D.

Table 2. Influencing Factors to Vitamin D Deficiency

	25 (OH)D <20 ng/mL (n=78)	25 (OH)D ≥20 ng/mL (n=20)	*P*-value
Gestational age (wks)	28.1±2.5	29.2±1.9	0.040
Birth weight (g)	1116±361	1309±334	0.031
Male, n (%)	45 (57.7)	15 (75.0)	0.202
Apgar score at 1 min	4.3±1.6	5.0±1.6	0.106
Apgar score at 5 min	6.9±1.0	7.3±1.1	0.122
SGA, n (%)	10 (12.8)	0 (0)	0.206
Antenatal corticosteroids therapy, n (%)	74 (94.9)	19 (95.0)	0.981
Gestational number, n (%)			0.594
Singleton	52 (66.7)	15 (75.0)	
Multiple	26 (33.3)	5 (25.0)	
Maternal age (yr)	33.1±4.0	32.4±1.8	0.221
Maternal BMI (kg/m^2)	23.0±4.9	21.4±2.8	0.060
GDM, n (%)	8 (10.3)	3 (15.0)	0.691
PIH, n (%)	6 (7.7)	1 (5.0)	0.677
PROM, n (%)	19 (24.4)	8 (40.0)	0.162
Calcium (mg/dL)	8.6±0.8	9.3±0.8	0.047
Phosphorous (mg/dL)	6.7±1.0	6.5±1.2	0.520
Alkaline phosphatase (U/L)	1,168±437	989±214	0.014
RDS, n (%)	73 (93.6)	17 (85.0)	0.354
IVH, n (%)	10 (12.8)	1 (5.1)	0.452
PVL, n (%)	3 (3.8)	0 (0)	0.373
BPD, n (%)	19 (24.4)	3 (15)	0.550
NEC, n (%)	4 (5.1)	1 (5)	0.981
ROP, n (%)	8 (11.5)	2 (20)	0.973
Sepsis, n (%)	9 (10.3)	4 (15.8)	0.458

The values are presented as number (%) or mean±SD.
Abbreviations: 25 (OH)D, 25 hydroxyvitamin D; SGA, small for gestational age; BMI, body mass index; GDM, gestational diabetes mellitus; PIH, pregnancy induced hypertension; PROM, premature rupture of membrane; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

the presence of these complications (Table 3).

There were no differences in gender, Apgar score at 1 and 5 minutes, SGA, antenatal corticosteroids therapy, gestational number (singleton or multiple), maternal age, or maternal body mass index between the deficiency and non-deficiency groups (Table 2). There were no differences in the rates of RDS, IVH (≥grade III), PVL, BPD (≥moderate), NEC (≥stage II), ROP (requiring laser therapy), or sepsis between the two groups (Table 2).

Table 3. 25-hydroxyvitamin D Concentration According to Prenatal Complications

	n	25(OH)D(ng/mL)	*P*-value
PROM			0.569
Yes	27	15.4±9.9	
No	71	13.9±9.7	
PIH			0.786
Yes	7	12.7±10.7	
No	91	14.4±9.7	
GDM			0.324
Yes	11	16.5±11.7	
No	87	14.0±9.4	

The values are presented as number (%) or mean±SD.
Abbreviations: 25(OH)D, 25 hydroxyvitamin D; PROM, premature rupture of membrane; PIH, pregnancy induced hypertension; GDM, gestational diabetes mellitus.

DISCUSSION

Seven-dehydrocholesterol in the skin is converted to previtamin D_3 by sun exposure, especially ultraviolet radiation, and previtamin D_3 is rapidly converted to vitamin D_3. Vitamin D_2 is made from ergosterol from yeast by ultraviolet radiation; humans cannot produce ergosterol. Thus, vitamin D (vitamin D_2 or D_3) is made in the skin by sun exposure or from diet or dietary supplementation[24]. It is converted to 25-hydroxyvitamin D in the liver. Serum 25-hydroxyvitamin D concentration is the best indicator of a patient's vitamin D status; 25-hydroxyvitamin D is converted in the kidneys to 1,25-dihydroxyvitamin D, an active form of vitamin D[24]. The concentration of 25-hydroxyvitamin D is related to bone mineralization, which is essential for calcium absorption; only 10-15% of calcium is absorbed from the intestine in the absence vitamin D[25]. Calcium absorption from the intestine is restricted dramatically with 25-hydroxyvitamin D concentrations <30 ng/mL[24]. Parathyroid hormone concentration then increases, which enhances calcium resorption from the kidneys and activates osteoblasts, ultimately activating mature osteoclasts. Mature osteoclasts increase the removal of calcium and phosphorus from the bone to maintain serum calcium and phosphorus concentration, resulting in osteopenia, osteoporosis, and fracture[25]. Vitamin D receptors are present in the brain, lungs, and immune cells, aiding in non-skeletal, vitamin D-related functions, such as autoimmune disease or respiratory tract disease[24].

Vitamin D deficiency is subdivided into vitamin D deficiency

Neonatal Med 2016 August;23(3):143-150
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(10-20 ng/mL, or 25-50 nmol/L), and severe vitamin D deficiency (<10 ng/mL, or <25 nmol/L)[26]. There is considerable discussion that the serum concentrations of 25-hydroxyvitamin D are associated with deficiency, adequacy for bone health, and optimal overall health by the Institute of Medicine (Dietary Reference Intakes (DRIs), 2010). Based on its review of data on vitamin D, generally all people have sufficient levels, ≥20 ng/mL[27]. The concentration of 25-hydroxyvitamin D in infants at the time of delivery is determined by the maternal vitamin D status during gestation, and is 50-70% of maternal concentration[28,29]. Thus, the risk of having a newborn infant with a vitamin D deficiency is higher for pregnant women who have an newborn infants increased risk of vitamin D deficiency, such as those who have a dark complexion, live at high latitudes, and have decreased exposure to sunlight[30].

Weiler et al. reported that 46% of mothers and 36% of term newborn infants were vitamin D deficient in Winnipeg, Canada, and vitamin D deficiency was more frequent in non-Caucasian mothers and infants[30]. Basile et al. reported that 46% of newborn infants were vitamin D deficient, and 25-hydroxyvitamin D concentrations were lower in African-American infants than in Caucasian infants (10.5 ng/mL vs. 19.5 ng/mL) in the southeastern United States[31]. Among 220 pregnant Korean women, 77.3% were vitamin D deficient, and 28.6% were severely deficient[32]. Vitamin D deficiency was more frequent during the winter (up to 100%) than the summer (up to 45.5%) and much higher in the pregnant Korean women than among Caucasian mothers in Western countries[32].

Park et al. reported that 91.7% of preterm infants (gestational age <37 weeks) were vitamin D deficient, 51.5% were severely deficient in Kyungpook, Korea, and 25-hydroxyvitamin D concentration in preterm infants (gestational age <32 weeks) was 10.8 ng/mL[33]. Seasonal variation in 25-hydroxyvitamin D concentration was significant, but there was no statistically significant difference in gestational age and birth weight between the severe vitamin D deficient group and non-severe vitamin D deficient group[33]. In our study, 80% of early preterm infants (gestational age <32 weeks) were vitamin D deficient, 45% were severely deficient, and the concentration of 25-hydroxyvitamin D was 14.3 ng/mL. Gestational age and birth weight were significantly lower in the deficiency group, whereas seasonal variation was not significant. Vitamin D deficiency was more frequent and severe in Middle Eastern and Asian mothers and infants than it was among Western mothers and infants[12]. 44% of preterm infants (gestational age of 26-34 weeks) in the United Arab Emirates were severely vitamin D deficient, or rachitic. The 25-hydroxyvitamin D concentration of mothers who had taken vitamin D supplements during pregnancy was 17.3 nmol/L (6.92 ng/mL), which is also rachitic.

Umbilical cord blood 25-hydroxyvitamin D concentration was lower than the maternal concentration (31 vs. 45 nmol/L, $P<0.001$), but the cord blood concentration was determined by the maternal concentration during pregnancy in Oslo, Norway[34]. Umbilical cord blood 25-hydroxyvitamin D concentration in term infants was 22.4 ng/mL. Over three-quarters (84.1%) of the enrolled newborn infants were vitamin D deficient, and 36.3% were deficient in Shanghai, China[17]. We did not check maternal vitamin D status in our present study. However, most mothers of the enrolled preterm patients may be vitamin D deficient because the vitamin D status in the newborns is determined by maternal vitamin D status. Choi et al. reported that a higher risk of vitamin D deficiency was observed in the first trimester than in the third trimester[32].

In previously reported studies of vitamin D deficiency in infants, seasonal variation in vitamin D status was found. Maternal and umbilical cord blood 25-hydroxyvitamin D concentration in term infants varied significantly according to seasons, with the highest levels present during the summer (June-September) and the lowest levels present in the winter (December-March) in one study from Oslo, Norway[34]. Similar seasonal variation was found in another study in Shanghai, China; the highest 25-hydroxyvitamin D concentrations occurred from June to August, and then decreased from September through February[17]. In another study conducted in the southeastern United States, seasonal variation was found only in Caucasian mothers and infants; it was higher during the summer and lower during winter and early spring, but this variation was not found in the African-American mothers and infants[31]. The authors concluded that the differences came from the individual differences in skin pigmentation, season, and latitude and their effects on vitamin D production in the skin by sun exposure. In our study, 25-hydroxyvitamin D concentrations were higher during summer and lower during winter, with the lowest concentrations from January to April; they increased from May through August, but the increase was not statistically significant.

Our study reports that 25-hydroxyvitamin D concentrations were 12.8 ng/mL, 14.2 ng/mL, and 16.2 ng/mL in gestational ages of <28 weeks, 28-29 weeks, and 30-31 weeks, respectively.

Additionally, gestational age and birth weight were lower in the deficiency group than in the non-deficiency group. Some researchers have concluded that vitamin D concentration is not correlated with gestational age in preterm infants, and they have not found a clear linear association between 25-hydroxyvitamin D concentration and gestational age[6,17,33]. In contrast, other researchers have reported the risks of developing vitamin D deficiency in preterm infants compared to full-term infants[6,13,16]. Burris et al reported that 25% of infants at gestational age <32 weeks and 7% of infants at gestational age of 32-36 weeks had vitamin D deficiency, and infants at gestational age <32 weeks had higher odds of having a vitamin D deficiency[6]. More studies about the relationship between gestational age and vitamin D status are needed.

Onwuneme et al. reported that a low vitamin D level in preterm infants at birth was associated with an increased oxygen requirement, increased duration of intermittent positive-pressure ventilation during resuscitation at delivery, and greater need for assisted ventilation[35]. In addition, Çetinkaya et al. demonstrated that lower maternal and neonatal vitamin D levels were associated with BPD development in preterm infants[36]. In our study, the prevalence of BPD was not significantly high in the vitamin D deficiency group.

Human breast milk contains only 20 IU/L of vitamin D, and it is much lower if the nursing mother is vitamin D deficient[18]. Therefore, exclusively breast-fed infants need vitamin D supplementation even if they were born at full term. The World Health Organization recommends a daily intake of 400–1,000 IU of vitamin D[37], although the recommended dose varies among other organizations; the American Academy of Pediatrics recommends 400 IU[38], but the European Society of Pediatric Gastroenterology recommends 800–1,000 IU[10]. Mitigating vitamin D deficiency in high-risk preterm infants is necessary, specifically by giving vitamin D supplements to pregnant mothers and providing early postnatal fortified human milk and vitamin D supplements to infants; this is important in preventing severe vitamin D deficiency.

A limitation of our study is that we were unable to follow up with study participants to measure their 25-hydroxyvitamin D level. Cord blood 25-hydroxyvitamin D level can change, depending on vitamin D supplementation after birth. Therefore, our study has the limited ability to show the relationship between 25-hydroxyvitamin D and postnatal complications. Further studies are needed to elucidate the role of vitamin D, which contributes to neonatal complications.

In summary, the prevalence of vitamin D deficiency is high, and it is a persistent problem among mothers and their newborn infants, especially preterm infants. Therefore, early detection of vitamin D deficiency and supplementation of vitamin D are important. Vitamin D deficiency is not completely preventable. However, our results may increase the awareness of vitamin D deficiency and vitamin D supplementation in preterm infants as well as in pregnant women. Additional prospective, randomized studies that compare Korean mothers' vitamin D status during pregnancy, sun exposure, and latitudes with the vitamin D status in their newborn preterm infants are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Neonatal Med 2016 August;23(3):143-150
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