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# Maternal and perinatal factors affecting vitamin D status of very low birth weight infants hospitalized in neonatal intensive care unit

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**ABSTRACT**

***Background:*** *Vitamin D deficiency is a global problem in premature infants. Vitamin D deficiency is associated with skeletal and non-skeletal disease. In premature infants, vitamin D deficiency is primarily associated with metabolic bone disease.* ***Objective:*** *The study aims to investigate the prevalence and risk factors of vitamin D deficiency in very low birth weight (VLBW) infants who were hospitalized in the neonatal intensive care unit (NICU) of a tertiary hospital in a developing country.* ***Methods:*** *A retrospective cohort was conducted at the NICU of Dr. Sardjito General Hospital, Yogyakarta. VLBW infants (inborn and outborn), hospitalized between January 1, 2018, and December 31, 2020, were enrolled in this study. Data on maternal (age (years), parity, education level, and socio-economic status) and neonatal (birth weight, birth length, and head circumference), gestational age, age of serum 25 hydroxy-vitamin D (25-OHD), sex, type of feeding, postnatal steroid) was taken from the medical records. Serum 25-OHD measurement was conducted at the age of around 4 weeks. Throughout the first 24 hours following birth, all infants at Dr. Sardjito General Hospital weighing <1,500g would receive total parenteral nutrition (TPN). For infants who were referred to Sardjito General Hospital, nutritional and feeding history including TPN was assessed through anamnesis from the nurses or midwives who transport the patient and from referral records.* ***Results:*** *A total of 165 very low birth weight infants consisting of 88 male and 77 female newborns were included in this study. The mean ± SD of the vitamin D level was 11.5 ± 7.6 ng/ml (range 2.9 - 45.5 ng/ml). The prevalence of Vitamin D insufficiency, deficiency, and severe deficiency were 12.1; 55.2; and 23%; respectively. Receiving TPN was positively and independently associated with vitamin D levels (p=0.006).* ***Conclusions:*** *There is a positive relationship between the administration of TPN and serum 25-OHD level in VLBW infants hospitalized in the NICU.*

**KEYWORDS:** maternal factor; perinatal factor; total parenteral nutrition; very low birth weight infant; vitamin D deficiency

## INTRODUCTION

Vitamin D deficiency is a global problem in premature infants. However, due to the lack of facilities and research related to vitamin D deficiency, the examination of serum 25-OHD levels in newborns, especially premature babies, is not carried out routinely [1]. A study in Tanzania found a high prevalence of hypovitaminosis D in preterm and low birth weight infants i.e., 77.4% and 81.1%, respectively [2]. Another study in India found that at birth only 12.6% of the babies were vitamin D insufficient, however, 52.2% became insufficient by 6 weeks [3]. In Yogyakarta, Indonesia, a community survey revealed that 90% of cord blood samples had vitamin D deficiency, while 13% of venous blood samples still had vitamin D deficiency at 6 months of age [4].

Vitamin D deficiency is associated with various diseases, especially bone-related diseases, such as growth disorders and rickets. Vitamin D deficiency can also lead to non-skeletal diseases such as cancer, hypertension, type 1 diabetes mellitus, multiple sclerosis and severe tuberculosis [5]. In premature infants, vitamin D deficiency is primarily associated with metabolic bone

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disease [6]. Osteopenia and rickets are common among low birth weight infants especially extreme low birth weight infants (ELBW, <1000 g birth weight) despite current practices of vitamin and mineral supplementation. A hospital-based study in Texas found that 10% to 20% of extremely low birth weight infants have radiological evidence of rickets with metaphyseal changes despite current nutritional practices [7]. However, study in Kenya found that incidence of rickets of prematurity by six months of age was 58.8% [8].

Risk factors for vitamin D deficiency in neonates are HIV infection, pregnancy in mothers who are too young, premature babies, and babies with low birth weight. Several other factors that are also associated with vitamin D include antenatal and postnatal maternal vitamin D status, vitamin D supplementation in infants, weather variations, UV exposure, geographical factors, as well as genetic and ethnic factors.

In premature infants during hospitalization, maternal vitamin D levels and vitamin D intake are important determinants of vitamin D levels [9,10]. Vitamin D intake vary from different centers. For premature infants, the American Academy of Pediatrics advises a daily dosage of 200–400 IU of vitamin D. In contrast, The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition suggests 800-1000 IU [11]. By knowing the factors associated with vitamin D levels, appropriate interventions can be made to prevent vitamin D deficiency [12]. Therefore, this study aims to investigate the prevalence and risk factors of vitamin D deficiency in very low birth weight who were hospitalized in Neonatal Intensive Care Unit (NICU) of tertiary hospital in developing country.

## METHODS

### Study design and participants

A retrospective cohort was conducted at the NICU of Dr. Sardjito General Hospital, Yogyakarta. Very low birthweight (VLBW) inborn and outborn infants, hospitalized between January 1, 2018, and December 31, 2020 were enrolled into this study. Data of serum 25-OHD level, maternal and neonatal characteristics were taken from the medical records. Infants who died before serum 25-OHD measurement, or those with congenital abnormalities, bone disorders, or suspected to have inborn error of metabolism were excluded from this study. The study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta. The reading of medical records was approved by the Education and Research Department, Dr. Sardjito General Hospital, Yogyakarta (Ref. No.: KE/FK/1333/EC/2020).

### Measures

*Maternal characteristics.* The data for maternal characteristics were collected from the medical record. Data of maternal characteristics consisted of maternal age (years), parity, education level, and socio-economics status. Parity is defined as the number of times that the mother has given birth, i.e., primiparous if the mother has given birth once and multiparous if the mother has given birth more than once. Maternal education level was grouped into the lower level and higher level. The lower education level was defined if the last level of education were senior high school or below. In contrast, the higher education level was determined if the last level of education were above senior high school. The socioeconomic status was defined based on the insurance. Patients/mothers enrolled in the hospital using government-subsidized health insurance are classified as low/poor socioeconomics, while private insurance, non-subsidized insurance, or self-pay are classified as high/wealth socioeconomics.

*Neonatal characteristics.* Neonatal characteristics consisted of anthropometric measurements (birth weight, birth length, and head circumference), gestational age, age of serum 25-OHD measurement, sex, type of feeding, postnatal steroid, and gestational age appropriateness. Weight in grams (g) was measured using a calibrated electronic digital scale (Seca 727, Hamburg, Germany) to the nearest 0.1 g. The length was measured using a standard length-measuring board (Seca GmbH & Co. Hamburg, Germany) to the nearest 0.1 centimeters (cm). Head circumference was measured with a non-stretch measuring tape to the nearest 0.1 cm. Infants were classified as small for gestational age (SGA) if

their birth weight were 10th percentile for gestational age, appropriate for gestational age (AGA) if their birth weight were 10th and < 90th percentile for gestational age, and large for gestational age (LGA) if their birth weight were ≥ 90th percentile for gestational age, using PediTools Fenton 2013 [13].

According to the guideline, all babies born at Dr. Sardjito General Hospital with a birth weight <1500g received total parenteral nutrition (TPN) within the first 24 hours after birth. The contents of TPN were glucose, amino acids, electrolytes and vitamins. TPN provided vitamin D intake of 40-60 IU. Enteral feeding started within 24 hours after birth. Vitamins supplementation was given after full feeding achieved. Oral vitamins would provide 120-160 IU of vitamin D. For newborns referred to RSUP Dr. Sardjito, nutritional and feeding history including TPN was assessed through anamnesis from the nurses or midwives who transports the patients and from referral records.

*Vitamin D status*. Serum 25-OHD examination using the electro-chemiluminescent immune-assay (ECLIA) method using Cobas E411 (fully automated) hormone-immunoassay analyzer was carried out at around 4 weeks of life at the Clinical Pathology Laboratory of Dr. Sardjito General Hospital. The result of serum 25-OHD by ECLIA had a good correlation (r=0.980) compared to reference standard, i.e. isotope dilution liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) [14]. The results of serum 25-OHD levels stratified with respect to the American Academy of Pediatrics (AAP)'s definition of vitamin D status as severe (<5 ng/mL) or mild/moderate deficient (5–15 ng/mL), insufficient (16–20 ng/mL), and sufficient (21–100 ng/mL) [15].

**Data analysis**

The results of serum 25-OHD levels were analysed as a continuous variable. Data were analysed using the SPSS program for macOS version 26 (IBM Corp., Chicago, IL, USA). Data were expressed as means ± standard deviation (SD) or ratio. The associations between serum 25-OHD levels and the maternal determinants (age (years), parity, education level, and socioeconomic status) or neonatal determinants (sex, birth weight, birth length, and head circumference, gestational age, gestational age appropriateness, feeding, vitamin D supplementation, and postnatal steroid) were analysed using linear regression. Significance was set at $p < 0.05$. Multiple linear regression analysis was also performed to assess which variables were independently associated with serum 25-OHD levels. Variables with $p < 0.25$ in the simple regression analysis were included in the multiple regression model.

**Table 1. Maternal and neonatal characteristics**

| Characteristics | Mean ± SD or n (%) |
|---|---|
| Maternal | |
| Maternal age (years) | 29.76 ± 6.29 |
| Parity, n (%) | |
| Primiparous | 67 (40.6) |
| Multiparous | 98 (59.4) |
| Education[1], n (%) | |
| Lower education | 47 (28.5) |
| Higher education | 118 (71.5) |
| Socioeconomics, n (%) | |
| Poor | 73 (44.2) |
| Wealthy | 92 (55.8) |
| Neonatal | |
| Birth weight (g) | 1290.9 ± 166.2 |
| Birth length (cm) | 39.4 ± 3.1 |
| Head circumference (cm) | 27.9 ± 2.1 |
| Gestational age (weeks) | 31.4 ± 2.7 |
| Age of Serum 25-OHD measurement (days) | 27.62 ± 16.74 |
| Gender, n (%) | |
| Male | 88 (53.3) |
| Female | 77 (46.7) |
| Nutrition, n (%) | |
| Exclusive | 134 (81.2) |
| Not exclusive | 31 (18.8) |
| TPN[2], n (%) | |
| Yes | 146 (88.5) |
| No | 19 (11.5) |
| Duration of TPN (days) | 12.2 ± 10.5 |
| Serum 25-OHD level (ng/ml) | 11.5 ± 7.6 |
| Vitamin D status, n (%) | |
| Normal | 16 (9.7) |
| Insufficiency | 20 (12.1) |
| Deficiency | 91 (55.2) |
| Severe deficiency | 38 (23) |
| Gestational appropriateness, n (%) | |
| SGA[3] | 52 (31.5) |
| AGA[4] | 110 (66.7) |
| LGA[5] | 3 (1.8) |

[1]Lower education = elementary school - junior high school, Higher education = senior high school - senior high school; [2]TPN = total parenteral nutrition; [3]SGA = small for gestational age; [4]AGA = appropiate for gestational age; [5]LGA = large for gestational age

**Table 2. Linear regression of predictor factors and serum 25-OHD level**

| Predictors | Simple linear | | | | Multiple linear | | |
|---|---|---|---|---|---|---|---|
| | **B** | **CI 95%** | **p** | **$R^2$** | **B** | **CI 95%** | **p** |
| Birth length (cm) | 0.52 | 0.15-0.90 | 0.006 | 0.05 | 0.23 | -0.20-0.65 | 0.293 |
| Head circumference (cm) | 0.18 | -0.36-0.73 | 0.509 | 0.00 | | | |
| Birth weight (g) | 0.01 | 0.00-0.02 | 0.004 | 0.05 | 0.01 | 0.00-0.14 | 0.249 |
| Gestational age (weeks) | -0.07 | -0.51-0.37 | 0.763 | 0.00 | | | |
| Sex (0=female; 1=male) | 1.03 | -1.30-3.36 | 0.384 | 0.01 | | | |
| Parity | 2.20 | -0.15-4.55 | 0.066 | 0.02 | 0.34 | -0.80-1.48 | 0.557 |
| Maternal age (years) | 0.03 | -0.06-0.31 | 0.187 | 0.01 | 0.04 | -0.18-0.24 | 0.792 |
| Nutrition (0=not exclusive; 1=exclusive breastmilk) | -0.82 | -3.80-2.16 | 0.589 | 0.00 | | | |
| Receiving TPN[1] (0=yes; 1=no) | 5.51 | 2.15-8.88 | 0.001 | 0.06 | 3.88 | 0.06-7.70 | 0.047 |
| Duration of TPN[1] (days) | 0.08 | -0.02-0.18 | 0.132 | 0.01 | 0.08 | -0.04 - 0.20 | 0.196 |
| Socioeconomics (0=wealthy; 1=poor) | -1.27 | -3.60-1.07 | 0.287 | 0.01 | | | |
| Age of 25-OHD measurement (days) | -0.05 | -0.16-(-0.02) | 0.009 | 0.04 | -0.02 | -0.14-0.04 | 0.25 |
| Gestation appropriateness[2] (0=AGA, 1=SGA, 2=LGA) | -0.94 | -3.20-1.32 | 0.412 | 0.00 | | | |
| Parental education[3] (0=higher education, 1=lower education) | 0.91 | -1.67-3.49 | 0.488 | 0.00 | | | |
| Adjusted $R^2$ | | | | | | 10.3% | |

[1]TPN: total parenteral nutrition containing vitamin D; [2]SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age[3]; Higher education: senior high school - senior high school, Lower education: elementary school - junior high school

## RESULTS

A total of 165 very low birth weight infants consisting of 88 male and 77 female newborns were included in this study. Most mothers had multiparous pregnancy (59.4%), higher education status (71.5%), and high/wealth socioeconomic status (55.8%). **Table 1** showed that most of the infants had vitamin D deficiency (78.2%). The mean ± SD of the serum 25-OHD level was 11.5 ± 7.6 ng/ml (range 2.9 - 45.5 ng/ml). The mean ± SD of the gestational age was 31.4 ± 2.7 weeks (range of 25.0 – 39.0 weeks), while the mean ± SD of birth weight was 1290.9 ± 166.2 g (range 678 – 1496 g). Most of the infants were appropriate for gestational age (AGA) (66.7%).

Linear regression analysis found that birth weight, birth length, parity, maternal age, and receiving TPN containing vitamin D had positive association with serum 25-OHD level and statistically significantly (**Table 2**). However, serum 25-OHD measurement was negatively associated with serum 25-OHD level. We performed multiple linear regression analysis to assess which of those variables were independently associated with serum 25-OHD levels. The results of multiple linear regression analysis showed that only receiving TPN containing vitamin D was positively and independently associated with serum 25-OHD levels ($p$ = 0.047). Newborns who received TPN containing vitamin D had higher serum 25-OHD levels than those who never got it (12.2 ± 7.7 vs 6.9 ± 4.2 ng/ml). These determinants contributed to 10,3% of the variability of serum 25-OHD levels.

## DISCUSSION

The present study was conducted to investigate the prevalence and risk factors of vitamin D deficiency in very low birth weight infants during hospitalization in the NICU. The results of our study showed that newborns receiving TPN had a higher serum 25-OHD level compared to those who did not. During pregnancy the placenta is the conduit for all nutrient delivery from the mother to fetus. Following birth, breast milk is the natural source of nutrition for a healthy infant born at term. However, human milk may not provide enough vitamins for preterm babies. Furthermore, parenteral nutrition may be the first method of vitamin delivery in premature newborns since they may be too ill or unstable to begin enteral feeding [16]. Other evidence in pediatric patients suggests vitamin D deficiency and reduced bone mineral density, both during and after cessation of parenteral nutrition [17].

In most newborns, a total daily intake of 400 IU will result in blood 25(OH)D levels above 20 ng/mL, with the average being well above 30 ng/mL. In premature babies (1-2.5 kg) who depend on parenteral nutrition, adding a multivitamin of 2 mL/kg 400 IU per 5 mL will provide an intake of 160-400 IU/day [6]. A randomized clinical trial in infants aged between 23 and 27 completed weeks of gestation supplemented with 1) placebo (intake of approximately 200 IU/d in parenteral nutrition or feeds); 2) 200 IU supplement (daily intake of approximately 400 IU attributable to 200 IU supplement + 200 IU in parenteral nutrition or feeds); or 3) 800 IU supplement (daily intake of approximately 1000 IU attributable to 800 IU supplement +200 IU in parenteral nutrition or feeds). On day 28, the percentage of infants with blood serum 25-OHD <20 ng/mL was 41% with placebo, 16% with 200 IU, and 0% with 800 IU, but some of the highly supplemented groups had relatively high serum levels 25-OHD levels without any sign of toxicity [11]. In our unit, TPN provide vitamin D intake of 40-60 IU and 120-160 IU from the oral supplement. These amount is still lower compare to recommended dose by AAP (400 IU/day) [6].

Another interesting results of this study was that 78.2% of VLBW had a vitamin D deficiency and the average level of serum 25-OHD was 11.5 ng/dL. A study in Tanzania found that 81% of low birth weight infants (<2500g) had vitamin D deficiency [2]. In contrast, data from developed country showed that at birth, 18% of VLBW had vitamin D deficiency, and the mean serum 25-OHD level was 31.4 ng/ml [10]. Maternal status of vitamin D affects the neonatal vitamin D status because, vitamin D is primarily transferred to the fetus across the placenta. Consequently, prevalence of vitamin D deficiency at birth reflect the rates of maternal deficiency [18]. Furthermore, it is known that vitamin D is transferred to the fetus in the third trimester of pregnancy. Consequently, preterm infants are born with lower vitamin D levels compare to the term infants [10].

Premature infants have a higher risk of lower serum 25-OHD levels, compared with more mature infants. In addition to bone morbidity, reduced vitamin D 25-OHD also increases the risk of acute respiratory morbidity and bronchopulmonary dysplasia in premature infants. Lower serum vitamin D concentrations in preterm infants are not only due to the loss of vitamin D transfer time that usually occurs late in gestation, but may also be due to maternal deficiency [11].

The main source of vitamin D (90%) is from the activation of provitamin D 3 in the skin by ultraviolet B to form cholecalciferol (vitamin D3), which is converted in the liver into 25-OHD [18]. Indonesia is located at the Southeast Asia area which has tropical climate. Countries with tropical climates get abundant sun exposure throughout the year. vitamin D deficiency was thought to be unusual. In fact, a meta-analysis included 6 studies involving 830 pregnant women reveal that 63% of pregnant women in Indonesia had vitamin D deficiency [19]. Another study among Southeast Asian countries reported that the prevalence of vitamin D deficiency ranges from 6-70%. It suggests that people behavior also affects the effectiveness of sun exposure, such as the use of sunscreen, the use of clothing that covers the body surface, and the duration of sun exposure [20].

It is known that maternal vitamin D deficiency is associated with several problems in the neonatal period and childhood including hypocalcemia, with or without seizures, rickets, and tooth enamel decay. Reduced fetal growth has also been linked to vitamin D deficiency in the mother, though the results of other studies show that vitamin D supplementation in pregnant women failed to show any impact on the baby's birth weight [18].

Several limitations in this study should be noted. In this study we were unable to record in detail the baby's feeding, including the time when vitamin supplementation was started and the vitamin dose given in TPN. This may be an important predictor factor. Data on maternal serum 25-OHD levels was also not available. Data on the history of administering TPN to referred patients is only obtained from anamnesis from the health worker who accompanied the patient.

## CONCLUSIONS

The results of this study showed that giving TPN containing vitamin D to VLBW infants may increase serum 25-OHD level. However, the prevalence of vitamin D deficiency was still high, meaning that the dose of vitamin D given in our TPN formula was still too low. Since most of newborn suffer from vitamin D deficiency,

supplement vitamin D as early as after fullfeed was achieved and increasing the dose of vitamin D of TPN formula was recommended.

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*Declaration of conflicting interests*

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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