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# Vitamin D Status in Umbilical Cord Blood Related to Neonatal Birth Weight

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## ABSTRACT

**Introduction:** Birth weight is an important determinant of infant's survival and future development. Insufficient supply of vitamin D during fetal growth can affect birth outcomes.

**Objective:** This study aimed to analyze relation of vitamin D status with neonatal birth weight.

**Method:** This study used a cross-sectional design on 144 pregnant women and their infants that met inclusion criteria. Umbilical cord blood 25-hydroxyvitamin D [25(OH)D] was examined by Electro Chemiluminescence Immuno Assay method. Analysis used multiple linear regression.

**Results:** The mean concentration of 25(OH)D was 27.6 ng/mL and only 37.5% neonates had adequate vitamin D. The average birth weight was 3090.6 gr. After being controlled by maternal weight gain during pregnancy and energy intake, the mean birth weight was significantly 166.5 gr smaller in neonates with vitamin D deficiency ($p<0.05$).

**Conclusion:** Vitamin D status is related to neonatal birth weight. Efforts to increase vitamin D intake in pregnant women are necessary to improve fetal vitamin D status followed by exposure to sunlight.

***Keywords:*** *Birth weight, neonatal, vitamin D*

## Introduction

Birth weight is an important indicator for assessing the infant survival. Low birth weight (LBW) in Indonesia is still a problem because 11.2% have an impact on prenatal death [(1)]. LBW is a significant predictor of prenatal mortality and morbidity. Barker's theory explains that LBW also increases the risk of poor cognitive development and non-communicable diseases in the future, such as diabetes and cardiovascular disease[(2,3)].

Based on the 2013 National Basic Health Research, the LBW prevalence at 10.2%, Bengkulu Province at 9.7%, the highest in Sumatra [(1)]. In Asian countries, LBW is mostly associated with intrauterine growth retardation [(4)]. Maternal malnutrition is the main factor contributing to poor pregnancy outcomes [(5)].

Vitamin D 25(OH)D is one of the essential minerals that have various functions of the body's physiological processes. Primary functions was to maintain calcium levels in a healthy physiological range to support multiple metabolic functions, regulation of bone transcription, and metabolism [(6)]. Another role is to modify the immune system and regulate cell proliferation and differentiation [(7)]. An adequate vitamin D concentration during pregnancy is needed for growth and mineralization of the developing fetal bone [(6)]. Vitamin D deficiency in pregnant women results in neonatal insufficiency [(8)] and is often associated with adverse birth outcomes [(9)].

The study on vitamin D in Indonesia is very limited. Study on the first-trimester pregnant women in Jakarta shows the vitamin D deficiency by around 90% [(10)]. Studies examining correlation of vitamin D with neonatal birth weight have never been carried out. Therefore, this study aimed to assess relationship of vitamin D serum with birth weight.

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## Materials and Method

This study used a cross-sectional design conducted in Bengkulu, Indonesia. Samples of the study were 144 pregnant women and neonates' mothers who met the criteria, including single pregnancy, gestational age ≥ 32 weeks, infants born at term. The exclusion criteria were mothers suffering from chronic diseases, namely diabetes, hypertension, parathyroid disorders, liver, heart or kidney disease; infectious diseases (tuberculosis, malaria, HIV-AIDS); taking medicines that affect vitamin D metabolism (including glucocorticoids and anti-seizures), neonatal births with congenital malformations.

Data collection on maternal characteristics include age, education level, occupation, family income, and obstetric history through interviews. Addition of maternal weight during pregnancy is known by comparing differences in body weight at the end of the third trimester with pre-pregnancy weight written in the "maternal and child health book". Maternal nutritional intake macronutrients (energy, protein and fat) were obtained using 2x24 hour recall technique.

Serum vitamin D samples are taken from cord blood on the placental side of the mother. Blood samples were centrifuged at 1500 rpm for 15 minutes and stored in a freezer at -20 °C, for further analysis using the Electro Chemiluminescence Immuno Assay (ECLIA). Analysis was carried out at "Kimia Farma Laboratory" that is accredited and has ISO 9001:2015. The reference values used by the laboratory are also values recommended by the Clinical Guidelines Subcommittee of the Endocrine Society. Vitamin D deficiency if 25(OH)D ≤ 20 ng/mL, insufficiency if 25(OH)D 21-29 ng/mL and sufficiency if 25(OH)D ≥ 30 ng/mL [11]. Specifically, the cut off vitamin D in neonates is absent [12]. Calcium examination was measured by a photometer using the Ion Selective Electrode (ISE) method. The birth weight of infants was measured during the first hour of birth with the Seca brand portable scales (type 231/231 Corp Hamburg, Germany) with an accuracy of 0.01 gr.

Analysis of two mean independent tests (independent t-test) was applied to determine differences in vitamin D serum with average birth weight. The multivariate analysis used multiple linear regression. Significant if p value < 0.05.

## Findings

Based on maternal characteristics, the average age was 27.8 years. They were mostly senior high school graduates (41.7%) andhousewives (81%). The average family income was IDR 2,307,638. The average weight gain was 12.7 kg, the average nutritional intake per day, energy of 1682.1 kcal, protein of 59.5 gr, fat of 53.2 gr.

The average birth weight was 3090.6 gr. The average concentration of vitamin D 25(OH)D was 27.6 ± 9.5 ng/mL and concentration of calcium was 10.1 ± 1.8 mg/dL (table 1).

**Table 1: Characteristics of neonatal**

| Variable | Mean ± SD | Min-Max |
|---|---|---|
| Birth weight (gr) | 3090.6 ± 397.2 | 2200-4200 |
| Vitamin D [25(OH)D] (ng/mL) | 27.6 ± 9.5 | 6.5 - 49.2 |
| Calcium serum (mg/dL) | 10.1 ± 1.8 | 5.5 - 14.5 |

In bivariate analysis, vitamin D status was divided into 2 groups, deficiency of 25(OH)D (< 30 ng/mL) and sufficiency of 25(OH)D (≥ 30 ng/mL). The average birth weight differed significantly between vitamin D deficiency and sufficiency (table 2).

**Table 2: The mean of birth weight neonates based on vitamin D**

| Vitamin D Status | Birth weight | | | p |
|---|---|---|---|---|
| | Mean ± SD | n | % | |
| Deficiency (< 30 ng/mL) | 3018.5 ± 372.7 | 90 | 62.5 | 0.002* |
| Sufficiency (≥ 30 ng/mL) | 3211.4 ± 410.2 | 54 | 37.5 | |

*p = < 0.05

Concentration of calcium, maternal weight gain during pregnancy and energy intake were correlated with neonatal birth weight (p-value < 0.05) (table 3).

**Table 3: Corelation maternal characteristics to birth weight**

| Variable | P value | r |
|---|---|---|
| Calcium | <0.001* | 0.327 |
| Maternal age | 0.135 | 0.125 |
| Maternal weight gain | 0.023* | 0.190 |
| Energy intake | <0.001* | 0.317 |
| Protein intake | 0.254 | 0.096 |
| Fat intake | 0.218 | 0.103 |

*p = < 0.05

In multivariate analysis, the regression model showed that, after being controlled for maternal weight gain and maternal energy intake, the average birth weight was significantly 166.5 gr smaller in neonates with vitamin D deficiency, p value = 0.008 (table 4).

**Table 4: Regression linier model of birth weight**

| | | | 95.0% CI for β | |
|---|---|---|---|---|
| **Variable** | **β** | **p** | **Lower bound** | **Upper bound** |
| Vitamin D deficiency | -166.5 | 0.008 | - 44.1 | - 288.9 |
| Maternal weight gain | 43.8 | <0.001 | 21.2 | 66.4 |
| Energy intake | 0.35 | 0.001 | 0.1 | 0.5 |

## Discussion

The results of this study noted the average 25(OH)D was 27.6 ng/mL. By using the cut off the US Endocrine Society, the recommended vitamin D concentration ≥ 30 ng/mL. The study indicated the deficiency 62.5% (deficiency at 25.7% and insufficiency at 36.8%). Not much different from the Hawaii by 68% (deficiency at 19% and insufficiency at 49%) [13]. In India, deficiency is much higher at 83% (deficiency 63% and insufficiency 20%) [14]. If comparing the average of vitamin D in three countries, there is almost no significant difference.

Umbilical cord vitamin D status describes maternal vitamin D status [15–17] because maternal vitamin D is the only source of fetal vitamin D that easily enters the fetus through the placenta [18]. Therefore, low maternal vitamin D levels have implications for low fetal vitamin D status. Although the Bengkulu City is a tropical region located at 30045'- 30059 'South Latitude - 102014'-102022' East Longitude in which the sun shines throughout the year, only a small portion of mothers (37.5%) have a sufficient level of vitamin D. This study supports a previous research through a systematic review that vitamin D deficiency is common and has become an epidemic of public health problems around the world, especially women and children [19,20], including in countries with sun-rich exposures throughout the year such as the Middle East [16].

Low concentrations of vitamin D can be affected by limited exposure to sunlight as the primary source of vitamin D and and food intake of source of vitamin D [21]. In this study, the factors that might cause vitamin D deficiency was not examined. However, the phenomenon of female in Bengkulu showing a tendency to avoid themselves from the sun exposure, using sunscreen to make the skin white and wearing clothes that cover almost full body when going outside home can limit vitamin D synthesis through the maternal skin. For further studies, these factors need to be considered.

This study proves a significant association between vitamin D status and birth weight. The average birth weight was 166.5 gr in neonatals with vitamin D status < 30ng/ml compared vitamin D status ≥ 30 ng/mL. These results can be attributed to the important role of vitamin D status in determining the transfer of vitamin D and calcium from the mother to the fetus through the placenta. An adequate amount of vitamin D increases the transfer efficiency and calcium absorption to the fetus. Without vitamin D, only 10% to 15% of the diet calcium can be absorbed. In women on which 25-hydroxyvitamin D levels increases from an average of 20 to 32 ng/mL, the interaction of 1,25-dihydroxy vitamin D (an active form of vitamin D) with vitamin D receptor (VDR) increases the efficiency of calcium transport to the intestine by 45 up to 65% and absorption of calcium 30 to 40% [6]. By these data, 25-hydroxyvitamin D levels from 21 to 29 ng/mL (52-72 nmol/L) can be considered to indicate relative deficiencies of vitamin D, and levels of 30 ng/mL or higher indicate the recommended vitamin D limit[11].

Growing evidence suggests that vitamin D deficiency during pregnancy can interfere with fetal growth and adverse pregnancy outcomes. This evidence shows the same results with this study. Studies in South India showed a significant difference in the average birth weight of infants based on the concentration of vitamin D in cord blood. The lower levels of vitamin D, the lower the average birth weight of the infant [14]. Studies in Iran proved a significant relationship of vitamin D deficiency in pregnant women with LBW [22]. Several studies in China found that both mother and neonate at Beijing had normal levels of 25(OH)D (> 30 ng/mL) and severe vitamin D deficiency in mothers and neonates had a higher risk of LBW with an average baby weight birth 3354.8 gr at birth was among neonates with < 25 nmol/L and 3640 gr among neonates with vitamin D ≥ 25 nmol [15]. Maternal vitamin D status was positively associated with infant birth weight, after adjusting for confounders, birth weight increased by 69 gr/mL by an increase of 25(OH)D less than 20 ng/mL [23]. Maternal vitamin D deficiency significantly increases the risk of neonatal low birth weight by 2.8 times[17].

The case is slightly different from the results of a study in Anhui, China, which showed an inverse U-shape relationship between birth weight on cord D vitamin status. There was an increase in birth weight of 61 gr at a concentration of < 40 nmol/L, but decreased by 68.5 gr at a concentration of 40-70 nmol/L [24]. Even though the results are diverse, but many other shreds of evidence support the positive relationship of vitamin D and birth weight. Results of Randomized Clinical Trial (RCT), by providing vitamin D supplementation to pregnant women (gestational age of 24-26 weeks) with deficient and insufficient vitamin D < 30 ng/mL of 25(OH)D, showed that vitamin D supplements increased maternal blood vitamin D levels and fetal growth such as length of body weight and neonatal head circumference [25]. A meta-analysis conducted on 13 RCTs also showed the benefits of vitamin D supplementation during pregnancy which increased circulating levels of 25(OH)D during labor by 66.5 nmol/L, body weight by 107.6 gr and birth length by 0.3 cm [26]. These results are strengthened by other meta-analysis reported from three experimental studies (Brooke 1980; Marya 1988 and Sablok 2015) involving 493 pregnant women who received vitamin D supplements during pregnancy that had fewer babies with birth weight below 2500 gr compared with pregnant women who did not receive the intervention [27].

## Conclusion

Maternal vitamin D status measured through neonatal umbilical cord is correlated with birth weight. The average of neonatal birth weight is lower on the vitamin D deficiency status. Efforts to increase vitamin D intake in pregnant women to improve fetal vitamin D status, which has implications for neonatal birth weight, need to be made. In addition, it is necessary to be followed by an increased exposure to sunlight.

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**Ethical Clearence:** The Ethical clearance has been endorsed by the Health Research Ethics Committee Faculty of Public Health, Indonesia University.

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