

# Correlation of Maternal Prenatal Vitamin D Level with Postnatal Infant Growth in Length and Head Circumference: A Cohort Study on Vitamin D Status and Its Impact During Pregnancy and Childhood in Indonesia

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**Objective:** To determine the correlation of first trimester maternal 25-(OH)-D level with postnatal infant growth in Indonesia.

**Materials and Methods:** A cohort of 116 mother–infant pairs from Indonesia was prospectively studied. 25-(OH)-D level was measured in maternal serum at 10–14 weeks of gestation and in umbilical cord blood shortly after birth. The newborns were observed longitudinally for 24 months. Length and head circumference were measured at birth and at ages 3, 6, 12, and 24 months. Spearman correlation and multiple linear regression analyses were performed.

**Results:** Mean 25-(OH)-D levels in the prenatal maternal serum and umbilical cord blood were  $17.55 \pm 7.33$  ng/mL and  $16.27 \pm 6.14$  ng/mL, respectively. Prenatal maternal 25-(OH)-D level weakly correlated with infant length ( $r = -0.35$ ) and head circumference ( $r = -0.21$ ) z-scores at age 3 months. Umbilical cord blood 25-(OH)-D level did not correlate with infant length or head circumference at any time point. Multiple linear regression showed an independent association between prenatal maternal 25-(OH)-D level and infant length z-score at age 3 months ( $p = 0.01$ ,  $SE \beta = 0.02$ , and coefficient  $\beta = -0.06$ ).

**Conclusion:** First trimester maternal serum 25(OH)D level correlated with infant length and head circumference at age 3 months.

**Keywords:** umbilical cord blood, first trimester, infant, growth, pregnancy, vitamin D

## Introduction

Vitamin D is a secosteroid prohormone with two active metabolites, calcidiol (25-(OH)-D) and calcitriol (1,25-OH<sub>2</sub>-D); each has roles in various metabolic processes.<sup>1</sup> Several randomized clinical trials have shown the importance of vitamin D supplementation during the first 6 months of life in promoting growth in low birth weight babies.<sup>2</sup> Vitamin D status during pregnancy and the first two years of life have a long-term effects on bone structure.<sup>3,4</sup>

Vitamin D deficiency during pregnancy has become a significant global health problem. Reported prevalence rates of vitamin D deficiency in pregnant women range from 20% to 90%.<sup>5,6</sup> One study of 160 pregnant women in West Java reported a normal vitamin D level ( $>30$  ng/mL) in only 3.5% of subjects in the first trimester of pregnancy; 21% were diagnosed with vitamin D insufficiency (25-(OH)-D level 25–29.6 ng/mL) and 75.5% with vitamin D deficiency (25-(OH)-D level  $<20$  ng/mL).<sup>7,8</sup> Vitamin D deficiency occurs in 40% to 50% of children worldwide. In Indonesia and Vietnam, the percentage of children with adequate 25-(OH)-D status is approximately 5% and 20%, respectively.<sup>9</sup>

Vitamin D deficiency has detrimental skeletal and extraskeletal consequences, especially in children. Up to 50% of children in countries with different economic status that receive a sufficient amount of sunshine across Africa, Asia, Europe, and North America are predicted to be vitamin D deficient.<sup>6</sup> The American Academy of Pediatrics and Institute

of Medicine both define vitamin D deficiency and insufficiency in children as 25-(OH)-D levels of  $\leq 15$  ng/mL and  $\leq 20$  ng/mL, respectively. The Endocrine Society Task Force on Vitamin D defines deficiency in children as 25-(OH)-D level  $\leq 20$  ng/mL, which is the same definition for adults.<sup>10,11</sup>

Although previous studies of the association of maternal vitamin D level during pregnancy with intrauterine or postnatal child growth are abundant, their findings are inconsistent and their recommendations vary.<sup>12–20</sup> Moreover, few studies have examined vitamin D status in tropical countries.<sup>13</sup> This study aimed to analyze the correlation of prenatal maternal vitamin D level in the first trimester with postnatal infant growth in Indonesian mothers and infants.

## Materials and Methods

This study was part of a more extensive prospective cohort study conducted in Sukabumi city and Waled district, West Java, Indonesia from July 2016 to April 2018. The study was approved by the Research Ethics Committee of Universitas Padjadjaran.

The study subjects were women in early pregnancy with gestational age 10 to 14 weeks. All were singleton pregnancies. Women with associated comorbidities such as diabetes mellitus or pre-eclampsia were excluded. Midwives at primary health centers informed prospective participants of the study and then referred them to Al Mulk Hospital Sukabumi or Waled District Hospital to obtain more comprehensive information. Mothers who agreed to participate provided written informed consent. The subjects were observed during pregnancy until the time of labor. 25-(OH)-D level was measured in maternal serum at 10–14 weeks of gestation and in umbilical cord blood shortly after birth. The newborns were observed longitudinally for 24 months. Length and head circumference were measured at birth and at age 3, 6, 12, and 24 months.

25-(OH)-D blood level was measured using the enzyme-linked fluorescent assay technique with the VIDAS<sup>®</sup> 25 OH Vitamin D TOTAL (Biomerieux, Marcy-l'Étoile, France), an automated system that combines enzyme immunoassay and final fluorescence detection. This technique can measure 25-(OH)-D over a wide range of levels and correlates well with liquid chromatography-tandem mass spectroscopy results, the gold standard method of vitamin D level measurement.<sup>21</sup> Anthropometric measurements were performed by trained staff according to World Health Organization standards.<sup>22</sup> Growth measurements were converted to *z* scores using the World Health Organization Anthro Calculator.<sup>23</sup>

Categorical data are presented as numbers with percentage. Continuous data are presented as means with standard deviation. Maternal and umbilical cord blood 25-(OH)-D levels were compared between various patient characteristic groups using the Mann–Whitney *U*-test or Kruskal–Wallis test as appropriate. Spearman's rank correlation was used to determine the correlations between maternal and umbilical cord blood 25-(OH)-D levels and *z* scores of infant length and head circumference. The correlation of other covariates with length and head circumference *z* scores was analyzed using multiple linear regression. Statistical analyses were conducted using SPSS software version 20 (IBM Corp., Armonk, NY, USA).  $P < 0.05$  was considered significant.

## Results

One hundred forty-two pregnant women in public health centers across Sukabumi and Waled district were eligible for study inclusion. After exclusions, including one newborn with anencephaly, 116 mother–infant pairs were analyzed. Mother and infant characteristics, maternal serum and umbilical cord blood 25-(OH)-D levels are shown in Table 1. Maternal serum and umbilical cord blood 25-(OH)-D levels did not differ between subjects when grouped according to various characteristics, except for maternal educational level.

Distribution of patients grouped according to 25-(OH)-D level status (insufficiency, deficiency, normal) in maternal serum and umbilical cord blood is shown in Figure 1. Overall, the normal status of vitamin D (25-(OH)-D  $\geq 20$  ng/mL) about 22%, meanwhile the mean 25-(OH)-D levels in maternal and umbilical cord blood were  $17.55 \pm 7.33$  ng/mL and  $16.27 \pm 6.14$  ng/mL, respectively.

Infant length and head circumference *z* scores at birth and ages 3, 6, 12, and 24 months are depicted in Table 2. Correlation of prenatal maternal serum and umbilical cord blood 25-(OH)-D levels with infant length and head circumference *z* scores over time is shown in Table 3.

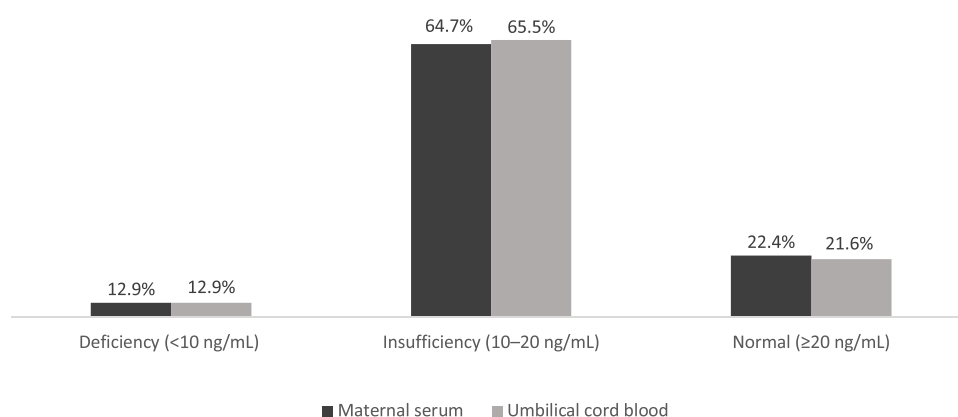
**Table I** Characteristics of Mother, Infant and Mean 25-(OH)-D Level

| Characteristics       | N (116) | %    | Mean 25-(OH)-D Level (ng/mL) |                |
|-----------------------|---------|------|------------------------------|----------------|
|                       |         |      | Maternal Serum               | Umbilical Cord |
| <b>Infant</b>         |         |      |                              |                |
| Sex:                  |         |      |                              |                |
| Male                  | 55      | 47.4 | 16.5                         | 15.3           |
| Female                | 61      | 52.8 | 17.1                         | 15.1           |
| Gestational age:      |         |      |                              |                |
| Term                  | 112     | 96.6 | 17.1                         | 15.2           |
| Preterm               | 4       | 3.4  | 18.85                        | 15.1           |
| Exclusive breastfeed: |         |      |                              |                |
| Yes                   | 105     | 90.5 | 18.1                         | 15.3           |
| No                    | 11      | 9.5  | 17.1                         | 14.85          |
| <b>Maternal</b>       |         |      |                              |                |
| Age (years):          |         |      |                              |                |
| < 20                  | 6       | 5.2  | 16.8                         | 15.9           |
| 20–29                 | 58      | 50   | 16.1                         | 15.2           |
| ≥ 30                  | 52      | 44.8 | 16.1                         | 15.2           |
| Education*:           |         |      |                              |                |
| Average               | 32      | 72.4 | 18.4                         | 22.44          |
| Low                   | 84      | 27.5 | 18.1                         | 15.4           |
| Occupation:           |         |      |                              |                |
| Housewife             | 100     | 86.2 | 17.2                         | 15.3           |
| Manual labor          | 16      | 13.8 | 15.6                         | 14.3           |
| Pre-pregnancy BMI:    |         |      |                              |                |
| <18.5                 | 11      | 9.5  | 14.2                         | 15.5           |
| 18.5–24.9             | 73      | 63   | 16.9                         | 15.35          |
| 25.0–29.9             | 32      | 27.5 | 23.8                         | 14.95          |
| Parity:               |         |      |                              |                |
| Nulliparous           | 84      | 72.4 | 16.5                         | 15.2           |
| Multiparous           | 33      | 27.5 | 17.9                         | 15.2           |

**Note:** \*Significant difference ( $p < 0.05$ ).

**Abbreviation:** BMI, body mass index.

Prenatal maternal serum 25-(OH)-D level significantly correlated with both length and head circumference  $z$  scores at age 3 months. In contrast, umbilical cord blood level did not significantly correlate with either at any time point. Multiple regression analysis of factors associated with infant length and head circumference  $z$  scores at age 3 months is shown in Table 4. Prenatal maternal 25-(OH)-D level was independently associated with infant length  $z$  score ( $p = 0.01$ ).



**Figure I** Distribution of patients grouped according to 25-(OH)-D status in prenatal maternal serum and umbilical cord blood.

**Table 2** Infant Length and Head Circumference z Scores Over Time

| Variable                     | Statistics     |        |              | p-value |
|------------------------------|----------------|--------|--------------|---------|
|                              | Mean (SD)      | Median | Range        |         |
| 1. Infant length             |                |        |              | <0.001  |
| 0 months                     | -0.15 (1.09)   | -0.08  | -3.11; 3.14  |         |
| 3 months                     | -0.26 (1.58)   | 0.01   | -3.28; 2.72  |         |
| 6 months                     | 0.38 (1.40)    | 0.44   | -3.40; 3.00  |         |
| 12 months                    | -1.27 (0.86)   | -1.36  | -3.62; 1.25  |         |
| 24 months                    | -1.00 (0.91)   | -1.12  | -3.35; 1.0   |         |
| 2. Infant head circumference |                |        |              | <0.001  |
| 0 months                     | -1.434 (1.177) | -1.4   | -4.3; 1.8    |         |
| 3 months                     | -0.614 (1.373) | -0.44  | -3.86; 2.12  |         |
| 6 months                     | -0.720 (1.039) | -0.57  | -2.72; 2.20  |         |
| 12 months                    | -0.876 (0.905) | -0.79  | -3.32; 1.32  |         |
| 24 months                    | -0.975 (1.063) | -0.95  | -3.36; 01.67 |         |

**Note:** Comparisons were performed using the Friedman test.

**Abbreviation:** SD, standard deviation.

**Table 3** Spearman Correlation Analysis of Prenatal Maternal Serum and Umbilical Cord Blood 25-(OH)-D Level with Infant Length and Head Circumference z Scores

| Time of Measurement | Prenatal Maternal Serum Level |                  |                    |             | Umbilical Cord Blood Level |      |                    |      |
|---------------------|-------------------------------|------------------|--------------------|-------------|----------------------------|------|--------------------|------|
|                     | Length                        |                  | Head Circumference |             | Length                     |      | Head Circumference |      |
|                     | r                             | p                | r                  | P           | r                          | p    | r                  | p    |
| 0 month             | -0.02                         | 0.80             | -0.02              | 0.85        | -0.09                      | 0.48 | -0.07              | 0.45 |
| 3 months            | <b>-0.35</b>                  | <b>&lt;0.001</b> | <b>-0.21</b>       | <b>0.02</b> | -0.22                      | 0.11 | -0.15              | 0.11 |
| 6 months            | -0.18                         | 0.05             | 0.03               | 0.74        | -0.09                      | 0.31 | 0.04               | 0.63 |
| 12 months           | -0.176                        | 0.06             | -0.08              | 0.41        | -0.00                      | 0.98 | -0.09              | 0.33 |
| 24 months           | 0.181                         | 0.071            | -0.16              | 0.11        | 0.05                       | 0.64 | 0.04               | 0.70 |

**Note:** Significant p values <0.05 are shown in bold.

**Table 4** Multiple Regression Analysis of Factors Associated with Infant Length and Head Circumference at Age 3 Months

| Variable                                  | Length* |        |             | Head Circumference** |        |             |
|-------------------------------------------|---------|--------|-------------|----------------------|--------|-------------|
|                                           | Coeff B | SE (B) | p-value     | Coeff B              | SE (B) | p-value     |
| Prenatal maternal 25-(OH)-D level (ng/mL) | -0.06   | 0.02   | <b>0.01</b> | -0.03                | 0.01   | 0.12        |
| Parity                                    | 0.48    | 0.32   | 0.14        | 0.59                 | 0.28   | <b>0.04</b> |
| Mother occupation                         | 0.40    | 0.42   | 0.34        | -0.43                | 0.37   | 0.26        |
| Mother education                          | 0.28    | 0.30   | 0.34        | 0.37                 | 0.27   | 0.17        |
| Gestation age                             | 0.21    | 0.10   | <b>0.03</b> | 0.07                 | 0.08   | 0.43        |
| Exclusive breastfeeding (0 = No; 1 = Yes) | -0.18   | 0.49   | 0.71        | 0.36                 | 0.44   | 0.42        |
| Sex (M = 1; F = 2)                        | 0.11    | 0.28   | 0.70        | -0.03                | 0.25   | 0.91        |
| Constant                                  | -8.82   | -      | -           | -3.70                | -      | -           |

**Notes:** \*R<sup>2</sup> = 19.2%. \*\*R<sup>2</sup> = 10.7%. Significant p values <0.05 are shown in bold.

## Discussion

Approximately one billion people around the world have vitamin D insufficiency or deficiency despite residing in countries with year-round exposure to sunshine.<sup>11</sup> In this study of 25-(OH)-D level measured in pregnant women at 10 to

14 weeks of gestational age and in the umbilical cord at the time of birth, the level was insufficient or deficient at both time points. Totally about 78% pregnant women had hypovitaminosis, which is higher than the study in Brazil.<sup>24</sup> Low vitamin D level in pregnancy is associated with lower birth weight and increased risk of small for gestational age.<sup>12,16,19,24</sup> Low maternal vitamin D level is also associated with poor intrauterine fetal growth.<sup>16</sup> Vitamin D deficiency may result in reduced linear growth and skeletal development. A recent study in West Java, Indonesia, reported that maternal serum vitamin D level was significantly associated with fetal biparietal diameter ( $\beta = 0.172$ ,  $p = 0.028$ ) and abdominal circumference ( $\beta = 0.819$ ,  $p = 0.001$ ).<sup>25</sup> The impact of maternal vitamin D status on infant growth may continue beyond birth.<sup>16,18,20</sup>

To our knowledge, this is the first study in Indonesia to examine the association of prenatal maternal and umbilical cord vitamin D levels with infant measurements in the first 2 years of life. Other cohort studies in Singapore,<sup>13</sup> Vietnam,<sup>14</sup> and Sri Lanka<sup>15</sup> found no correlation between maternal vitamin D deficiency and anthropometric measurements at birth and postnatal growth in the first two years of life. In a recent systematic review,<sup>20</sup> infant weight was not correlated with maternal or umbilical cord blood vitamin D levels. Studies conducted in a multi-ethnic Asian population and an Australian population have reported similar findings.<sup>13,18</sup>

Previous studies have shown that maternal vitamin D level is significantly associated with infant linear growth at age 9 months and that a low level may increase the risk of stunted growth by four times<sup>12,26</sup> Meanwhile, our study demonstrated an inverse correlation between prenatal maternal 25-(OH)-D level and infant length at age 3 months. This conforms to similar studies, which have shown an inverse association of maternal 25-(OH)-D level and infant length at age 6 months.<sup>14,16</sup> By age 12 months, infant vitamin D levels increase, which may result in a growth spurt in length.<sup>12</sup> On the other hand, the vitamin D level in pregnancy and obstetric results was associated with maternal polymorphisms in VDR. Hence, the VDR polymorphism may be a protective or risk factor for adverse events, according to the genetic profile of the woman.<sup>27</sup> Our head circumference findings were similar to those of several other studies conducted in subtropical or tropical countries that demonstrated no correlation with umbilical cord blood vitamin D level.<sup>13,18–20</sup>

This study had several limitations. Confounding may have occurred because of interrelations among growth, eating patterns, comorbidities, and macro- and micro-nutritional intake. Since genetic variation may influence serum concentration of vitamin D, future longitudinal prospective and bigger studies are warranted.

## Conclusion

Maternal serum 25-(OH)-D level in the first trimester of pregnancy had a significant inverse correlation with infant length and head circumference measured at age 3 months. Future studies should examine other infant growth parameters, such as muscle mass and adiposity, and consider more comprehensive maternal data regarding socioeconomic status, daily food intake, and nutrition.

## Data Sharing Statement

The datasets from this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

The study was approved by the Ethics Research Committee of Universitas Padjadjaran (No. 133/UN6.KEP/EC/2018) and performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

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## Author Contributions

All authors made a significant contribution to the study, whether in conception, study design, execution, data acquisition, analysis, or interpretation. The authors also took part in drafting, revising, and critically reviewing the article and approved the final version for publication by this journal. The authors agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no conflicts of interest to declare.

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