Cord blood vitamin D is correlated with problem solving domain in early childhood neurodevelopment: A Cohort Study on Vitamin D Status and Its Impact during Pregnancy and Childhood in Indonesia

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Abstract

Fetal vitamin D level is known to influence brain development and subsequent postnatal neurodevelopment, although several studies stated that this correlation remains controversial. We aimed to determine the correlation between cord blood vitamin D level and neurodevelopmental status in the first 1000 days of life. This was a cohort study, located in Sukabumi and Waled districts of West Java, Indonesia, from 2016–2019. Subjects were term infants with no congenital abnormalities, born from pregnant women involved in a previously conducted cohort study. The cord blood sample collected at delivery was used to measure 25 (OH)-vitamin D level. Neurodevelopmental status was examined after the infants reached 6, 12, and 24 months of age using Ages and Stages Questionnaire-3 (ASQ-3). Statistical analysis was performed using rank Spearman's correlation. Blood samples were collected from 116 subjects. The mean value of vitamin D levels was 16.2 ng/mL (8.0–35.4 ng/mL). As many as 12.9%, 65.5% and 21.6% of newborns had vitamin D deficiency, insufficiency and normal vitamin D levels. The correlation was found between cordblood vitamin D levels and the problem-solving domain at the age of 12 and 24 months old; r = 0.217, and r = 0.414 respectively. Multiple linier regression analysis result showed a decrease problem solving domain score of 0.641 was associated with decreased of vitamin D. Cordblood vitamin D level correlates with infant neurodevelopmental status. Screening of vitamin D level is crucial during pregnancy and early childhood to improve neurodevelopmental outcome.

Background

Vitamin D is a pro-hormone secosteroid with active metabolites of calcidiol/25(OH)D and calcitriol/1,25-(OH)2-D.[1,2] Vitamin D classically participates in calcium and phosphorus metabolism, thus contributes to bone growth and reorganization. The non-classical role of vitamin D found significantly on extra skeletal sites, including in reducing oxidative stress, antimicrobial defense, immunoregulation, anti-inflammatory, anticancer, neuroprotective, and child neurodevelopment roles.[1,3,4]

The emerging awareness of hypovitaminosis D, including both deficiency and insufficiency conditions, is a major health problem across countries and regions among all age groups.[5] According to the South East Asian Nutrition Survey (SEANUT), as serum 25-hydroxy-vitamin D (25 (OH) D) < 25 nmol / L (< 10 ng / mL), and 25 nmol / L to < 50 nmol / L (< 20 ng / mL) are defined as vitamin D deficiency and insufficiency, respectively.[5]

There are numerous study investigating the correlation between maternal vitamin D levels in various gestational ages and cord blood / or newborn vitamin D levels. A previous study stated that a positive correlation was observed, while this positive correlation was absent in another study.[6,7] The presence of this correlation was assumed to be a result of vitamin D diffusing across the placenta from mother to fetus, therefore, fetuses are utterly dependent on their mother's vitamin D status.[6]

Some observational studies had been conducted to analyze the relationship between newborn vitamin D levels taken from cord blood and neurodevelopmental status, with various results. Two previous studies conducted in the United State[8] and Australia[9] discovered a positive relationship between cord blood vitamin D levels and early childhood development, including neurocognitive and language aspects. However, another study in Shanghai observed there was no association between cord blood vitamin D levels and all developmental aspects in children aged 2 years old.[10]

The first 1000 days of life was considered as a critical period, in which rapid central nervous system (CNS) development occurred. Disturbance in that period, one of which is hypovitaminosis D, could create a huge impact on the neurodevelopmental process. Therefore, researchers were interested in investigating the correlation of vitamin D levels with the developmental status of children at this critical period.[11]

Methods

Design and study population

This was a cohort study and a part of larger study on 'Vitamin D status and its impact on pregnancy and childhood in Indonesia'. The study was conducted at Sukabumi and Waled district, West Java, Indonesia, from 2016 to 2019. The ethical approval had been obtained by the Research Ethics Committee, Universitas Padjadjaran.

The study subjects included infants born from pregnant women in the previously mentioned study. The pregnant women were informed about the research by our team in respective locations. Written consent was obtained from women who had agreed to all research procedures. Cord blood samples were taken immediately after the delivery process, then stored and examined for 25-(OH) vitamin D levels. The development status of their child was assessed in the 6^{th}, 12^{th} and 24^{th} month.

The inclusion criteria in this study were babies born at term (37–42 weeks gestation) and appropriate for gestational age. Exclusion criteria were infants with congenital abnormalities, history of bilirubin encephalopathy, seizures, and asphyxia.

Laboratory examination

Vitamin D samples were taken from biological material withdrawn from cord blood and stored in the temperature of -70 to - 80˚C. Measurement of vitamin D levels was done using the Enzyme Linked Fluorescent Assay (ELFA) technique, with the VIDAS® 25 OH Vitamin D TOTAL (VITD) measuring device.[12] This method was chosen because it has a wide measurement range and has a good correlation with the standard vitamin D test using liquid chromatography-tandem mass spectroscopy (LC–MS/MS). This method had the ability to detect 25(OH) vitamin D levels as low as 8.1 ng/mL.[12] Vitamin D levels are categorized as being deficient if serum levels were less than 10 ng/mL or 25 nmol/L.[5]

Child developmental tools

Child developmental assessments were carried out in the study site at Sukabumi and Waled regional health centres. Mothers recruited to the study were contacted by the research team to schedule follow-up of the infants at the ages of 6 (V1), 12 (V2) and 24 (V3) months at the regional primary health centres for assessment of their neurodevelopment status using the Ages and Stages Questionnaire-3(ASQ-3). The ASQ-3 was translated into Bahasa Indonesia and it had been validated. This tool consisted of 30 questions assessing five development domains: gross motor, fine motor, communication, problem-solving and personal-social domains. The answers to each question were scored as follows: 'yes' obtained a score of 10, 'sometimes' had a score of 5 and 'no' had a score of 0; each domain was then summed. Higher scores reflected better developmental state. These assessments were conducted by researchers and research assistants who had received standardized training.[13]

Statistical analysis

Mean, median, range, standard deviations, frequencies, and percentages were used to describe numerical or categorical data in descriptive analysis. To determine the differences between the development status of children from various aspects based on subject characteristics, the Mann-Whitney test or the Kruskal-Wallis test was used. The correlation between newborn vitamin D levels and the scores for each development domains was calculated using Spearman's Rank correlation. Categorical differences between vitamin D levels and each developmental domain were tested using the ANOVA test. Multiple linear regression analysis was performed to adjust all variables tightly correlated with vitamin D level and external variables. Result with a *p*-value less than 0.05 was considered significant. Data were managed and analyzed using the Statistical Product and Service Solution (SPSS version 20.0) program.

Covariate

The covariates in this study were mother's age, parity status, mother's education status, and occupation. Characteristics of infants were sex and exclusive breastfeeding.

Results

Of the 141 babies born from previous cohort studies, 4 babies were born premature, 10 babies were intrauterine growth restriction (IUGR), and 11 babies did not come for follow-up until the end of the observation, so they were excluded. (figure 1) Therefore, the total subjects in this study were 116. The minimum sample had been fulfilled, with the power of a test of 95%.

Data on the subject's characteristics were presented in table 1; the majority of mothers were housewives (86.2%), primipara (72.4%) and had a low educational level (72.43%). The majority of infants received exclusive breastfeeding (90.5%).

Table 1. General characteristic of infants and mothers (n = 116)

Characteristics	Total	%
Characteristics of infants		
1. Gender :		
	55	47.4
Male Female		
	61	52.6
1. Exclusive breastfeeding :		
YesNo		
	105	90.5
Characteristics of mothers		
	11	9.5
1. Mother’s age (years) :		
< 20		
	6	5.2
20 – 29		
	58	50.0
≥ 30		
	52	44.8
2. Education :		
Low Average Well		
	84	72.4
1. Occupation :		
	28	24.1
Housewife Employee		
	4	3.4
4. Parity : Primipara Multipara		
	100	86.2
	16	13.8
	84	72.4
	33	27.6

One hundred and sixteen serum newborns were examined for vitamin D levels. The mean value of newborn vitamin D levels in this study was 16.27 ng/mL. As many as 12.9% of infants have vitamin D deficiency, 65.5% have insufficiency condition, and 21.6% have normal vitamin D levels. (table 2)

Table 2. Cord blood vitamin D in newborn

Cord blood vitamin D (ng/mL)	n (%)
Deficiency (<10 ng/mL)	15 (12.9)
Insufficiency (10 - <20 ng/mL)	76 (65.5)
Normal (≥ 20 ng/mL)	25 (21.6)
Mean (SD) : 16.27 (6.14)	
Median (range) : 15.25 (8.0 – 35.4)	

The mean ASQ development score for each domains of 3 different times visit can be seen on table 3. There is a significant difference in the ASQ development score in the five development domains at each different visit (V1, V2, V3).

Table 3. ASQ mean scores on each development domains of three different times visit

Development Domains		Time visit			p-value*)
		6 months (V1)	12 months (V2)	24 months (V3)	
1.	Social personal	52.03 (7.60)	47.52 (8.69)	44.31 (7.58)	<0,001
2.	Problem solving	55.04 (6.06)	47.3 (6.89)	49.46 (9.85)	<0.001
3.	Fine motor	54.14 (7.08)	49.57 (6.23)	33.97 (11.13)	<0.001
4.	Gross motor	43.58 (10.10)	48.3 (9.50)	43.43 (11.34)	<0.001
5.	Communication	54.96 (5.17)	52.61 (5.67)	53.82 (10.00)	0.005

*) Based on Kruskal-Wallis test

The correlation was found between newborn vitamin D levels and the developmental problem-solving domain (table 4) at the age of 12 and 24 months old; r = 0.217, and r = 0.414 respectively; in other words, the higher the newborn vitamin D levels, the higher the problem-solving scores. This showed that the strength of correlation had increased in the 24th month of observation; which according to Guilford correlation criteria, it had a moderate correlation.

Table 4. Correlation between newborn vitamin D levels and infant development

	Development domains	Correlation coefficient (r_s)		
		6 months	12 months	24 months
1.	Social personal	0.046	0,001	0.180
2.	Problem-solving	-0.083	0.217*	0.414*
3.	Fine motor	-0.057	0.105	0.084
4.	Gross motor	0.112	0.183	-0.030
	Communication	-0.006	0.001	0.111

rs = Spearman's Rank correlation coefficient

*p<0.05

Based on the ANOVA test (table 5), the results show that vitamin D levels have a significant relationship to the problem-solving domain at the last two visits (V2, V3). To further prove the relationship between vitamin D levels and the personal-social domain, a multivariate logistic regression analysis was carried out (table 6). The result shows that a decrease in the problem-solving domain score of 0.641 is associated with a decrease in vitamin D levels.

Table 5. Comparison of infant development status in three different time visits based on level of vitamin D levels

Development domains	Cord blood vitamin D (Category)			p-value*)
	Deficiency (n=15)	Insufficiency (n=76)	Normal (n=26)	
1. Visit 6 Months :				
Social personal	52.33 (7.76)	51.38 (8.11)	53.80 (5.64)	0.384
Problem solving	57.00 (5.28)	54.61 (6.36)	55.20 (5.49)	0.375
Fine motor	55.67 (5.88)	53.75 (7.22)	53.80 (7.26)	0.336
Gross motor	46.67 (6.99)	43.62 (10.44)	41.60(10.48)	0.310
Communication	55.33 (4.81)	55.07 (5.13)	54.40 (5.65)	0.820
1. Visit 12 months				
Social personal	46.67 (7.48)	47.93 (9.41)	46.80 (7.20)	0.767
Problem solving	43.33 (7.94)	47.53 (6.49)	49.00 (6.77)	**0.036**
Fine motor	49.33 (4.58)	49.40 (6.47)	50,20 (6.53)	0.849
Gross motor	45.00(11.02)	48.20 (9.36)	50.60 (8.70)	0.195
Communication	52.00 (4.14)	53.20 (5.85)	51.20 (5.82)	0.285
III. Visit 24 months :				
Social personal	39.64(11.68)	44.32 (6.67)	47.27 (5.50)	**0.012**
Problem solving	43.57(10,46)	48.56 (9.80)	55.91 (5.70)	**<0.001**
Fine motor	35.71(13.13)	32.58 (10.31)	37.05(11.91)	0.218
Gross motor	41.07(13.89)	45.00 (10.27)	40.23(12.29)	0.164
Communication	48.21(18.97)	54.24 (8.00)	56.14 (5.76)	0.057

*) Based on One-way ANOVA.

Table 6. Factors affecting of decreased problem-solving domain using regression analysis

Variable	Problem solving*)		
	Coeff B	SE (B)	p-value
New born Vitamin D (ng/mL)	-0.641	0.175	**<0.001**
Parity	-0.217	2.434	0.929
Mother Occupation	-3.102	3.194	0.334
Mother Education	1.446	2.472	0.560
Gestation age	0.725	0.713	0.312
Exclusive breastfeeding (0=no; 1= Yes)	-7.099	3.867	0.070
Sex (M=1; F=2)	6.345	2.206	**0.005**
Constant	-13.159	-	

*) R^2 = 21.4 %’ **) R^2 = 3.5%

Discussion

Hypovitaminosis D in pregnant women and neonates is a current major concern in obstetrics and neonatology field.[6] This study, as a part of the first cohort study in Indonesia about Vitamin D status and its impact on pregnancy and childhood in Indonesia.[7] The first evidence related to vitamin D role on brain function was reported two decades ago through the discovery of vitamin D receptors (VDR) autoradiography in experimental animal brains and the discovery of 1,25-(OH)2-D/calcitriol in cerebrospinal fluid.[14] In addition to that, VDRs are also widely distributed in mammalian brain and first expressed in brain development during the critical period of cell proliferation. These receptors could be found in certain brain regions, such as temporal lobes, cingulate, thalamus, cerebellum, amygdala and hippocampus areas.[14,15] Calcitriol also works by affecting the production of cytokines and affecting neurotransmitters and synaptic plasticity, which play important roles in the learning process and neurocognitive development.[15,16]

Fetal brain development starts during early period of pregnancy. Some parts of the brain will develop rapidly in the last trimester, and the process of differentiation and synaptogenesis will develop up to post-natal period with the critical time in the first 1000 days of life.[16] Thus, disruption in that period such as low maternal vitamin D level during pregnancy could lead to impaired fetal brain structure formation, such as brain ventricular enlargement and neocortex region thinning.[4,17] Another concept suggests that vitamin D deficiency may weaken the integrity of perineuronal nets (PNNs), so that neural-circuit function will be disturbed and cognitive processes such as learning and memory will be impeded.[18]

The mean value of newborn vitamin D level from 116 subjects in this study was 16.2 ng/mL (8.0–35.4 ng/mL). As many as 12.9% of infants have vitamin D deficiency and 65.5% have insufficiency condition.[5] A previous study on vitamin D level in the first trimester of pregnancy, which is a part of this cohort study, showed that the mean value of maternal 25 (OH) vitamin D level was 17.52 ng/mL.[7] This result is similar to other previous studies[6,8] which showed that newborn vitamin D level is lower (75–90%) than maternal vitamin D level. This could happen because the mother had to fulfill her own vitamin D requirement beside her fetal.[19]

Previous studies conducted to determine the correlation of vitamin D levels during early[4], mid[20], and late pregnancy, and/or cord blood at birth[8] with child development had been carried out in several countries with various results.[9] The previous part of this cohort study in Indonesia about associations between maternal vitamin D levels in early pregnancy (10–14 weeks gestation) with child development in the first year ages of life (3 months, 6 months, and 12 months), showed that ASQ scores in gross motor domains were significantly lower at 3 months of age, and did not have a significant difference for all developmental aspects at older ages (6 and 12 months).[7,19]

In this study, we examined cord blood vitamin D samples because maternal vitamin D could pass through the placenta and enter the fetal bloodstream, with the half-life around 2 months. Therefore, it could represent vitamin D level in the newborns.[21,22] This study showed correlations between cord blood vitamin D levels and the developmental problem-solving domain at 12 and 24 months of age ($r = 0.217$ and $r = 0.414$), but no correlation with gross motor, fine motor, communication and personal social domains. Multiple linear regression analysis reinforces the state that a decrease in problem-solving scores is associated with a decrease in vitamin D levels. This could be explained by the extraskeletal effect of vitamin D on neuroplasticity[15,16], which determined neurocognition aspect. Problem-solving domain can be a representative of neurocognition aspect. Adverse effects occuring in early life, such as hypovitaminosis D and inadequate stimulations, could cause neurocognition disturbance that can persist until later life. This was consistent with a recent meta-analysis study, regarding the association of maternal or newborn vitamin D levels with neurodevelopmental outcomes, which found that prenatal vitamin D levels had borderline positive associations with the infant cognitive development but no association with infant motor development.[23]

A cohort study in the United States assessing the relationship between cord blood vitamin D and developmental and cognitive achievement scores, showed that an increase in 5 nmol/L of vitamin D levels in the cord blood was associated with a very small increase in the Wechsler Intelligence Scale for Children (WISC) score at the age of seven years old.[8,24] Other study in Australia stated that cord blood vitamin D level had a positive association with language development in children aged 18 months and 4 years old, although the association was weak.[9] Thus, it could be concluded that vitamin D has an effect on child development, despite the weak association found on the currently available evidence.

The effort to increase infant vitamin D levels can be done in several ways. The provision of vitamin D supplementation in Indonesia is still difficult as a standard due to the high price. As an alternative, exposing 18.59% of body surface area to sunlight for 37.5 minutes per day especially between 10.00–13.00 is proven to be an effective method to meet daily vitamin D requirements, as reported by Judistiani et al.[25]

The limitation of this study was not report, several factors that could have affected vitamin D levels and neurodevelopmental status at the age of two year old, such as parenting style and complementary food given after the age of 6 months old. Future long-term cohort studies taking these factors into consideration or randomized clinical trial giving vitamin D supplementation is required.

Conclusion

Vitamin D level correlates with infant neurodevelopmental status. Screening of vitamin D level is crucial to be done during early infancy, for early detection and intervention, as well.

Declarations

Ethics approval and consent to participate

An ethical approval was issued by the Health Research Ethics Committee Faculty of Medicine, Universitas Padjadjaran 335/UN6.KEP/EC/2018. Written informed consent was obtained from the parents

Consent for publication

Not applicable.

Availability of data and materials

All data and materials of this study are available at Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia, by contacting the corresponding author Meita Dhamayanti, email meita.dhamayanti@unpad.ac.id

Competing interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article

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Author Contribution

SS, MD contributed equally to this work, MD, DS, SS designed the research with contributions from all authors, SS, LG searched the literature and extracted the data, RTD, BS contributed to the critical revision of the manuscript before publication

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Figures

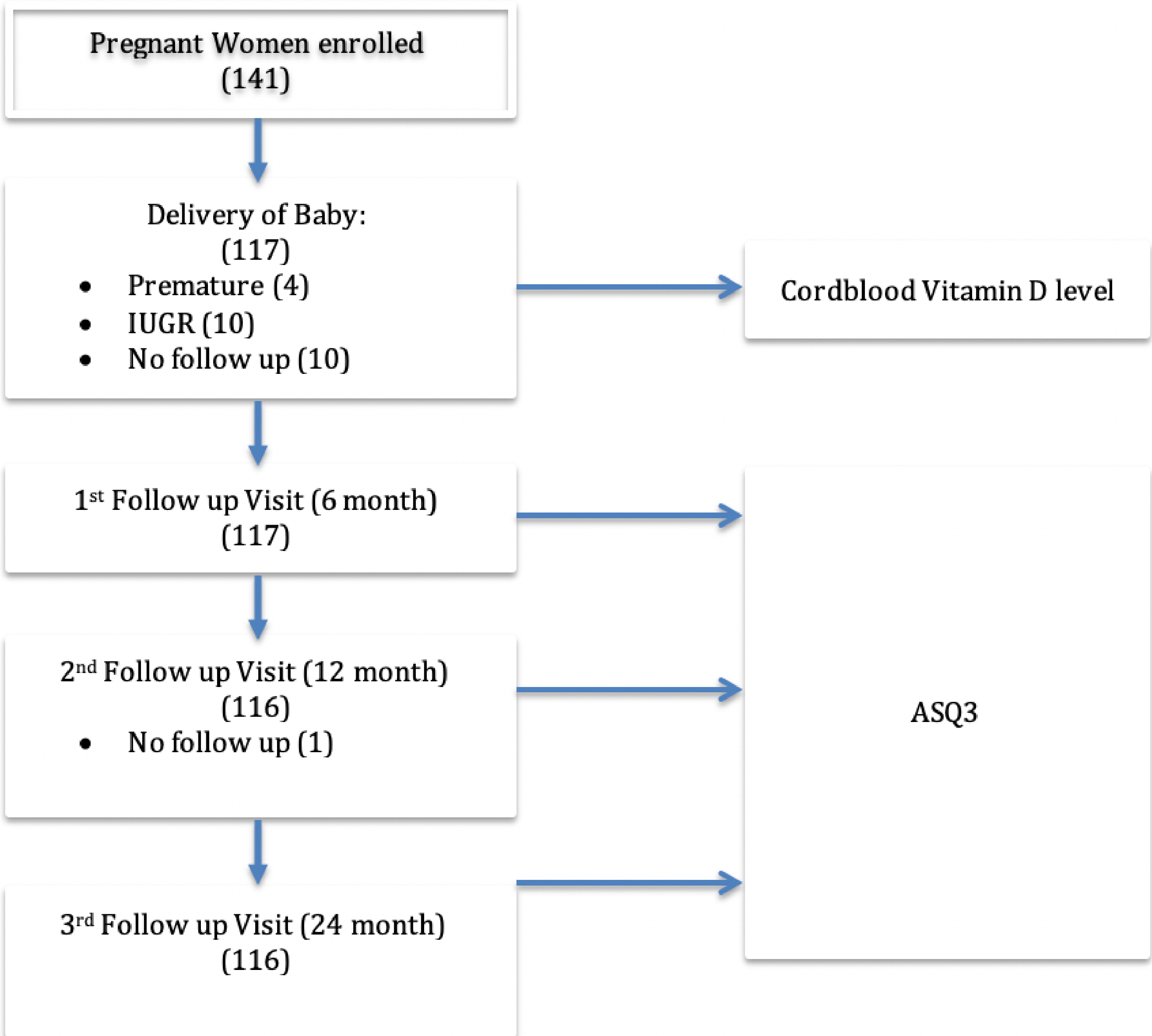

Figure 1

Flow chart of subject participation

Supplementary Files

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