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Vitamin D Levels and Incidence of Preterm Labor

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Abstract

One pathophysiology of preterm delivery is maternal or fetal hypothalamus-pituitary-adrenal (HPA) axis activation. The HPA axis can be affected by vitamin D, which increases uterine contractions and affects the body's immune mechanism against bacterial infections. A lower level of vitamin D in pregnant women is suspected to contribute to the incidence of premature conditions. This study aimed to compare the 25-hydroxy-vitamin D3 concentration in preterm parturient with non-preterm parturient, and the correlation between vitamin D level and the incidence of preterm labor. This comparative analytic study used a cross-sectional approach and involved 46 subjects who were divided into case and control groups. This study was conducted in August–September 2017 at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The Electro-chemiluminescence Immunoassay (ECLIA) method was used to examine the serum 25-hydroxy-vitamin D3 concentration in case and control groups, demonstrating that 25-hydroxy-vitamin D3 concentration in case group (17.26 ng/mL) was significantly ($p<0.0001$) lower than in control group (24.30 ng/mL). The correlation coefficient between the 25-hydroxy-vitamin D3 and the incidence of preterm labor was -0.837 ($p<0.001$). Thus, there was a correlation between the 25-hydroxy-Vitamin D3 level and the incidence of preterm labor that vitamin D supplementation in pregnant women must be considered.

Keywords: 25-hydroxy-vitamin D3, preterm delivery, vitamin D

Introduction

Vitamin D has roles in different organ systems.[1] Vitamin D is one of the nutrients needed during pregnancy that has a role in maternal and fetal calcium metabolism and bone health.[2] In many studies, vitamin D was suggested to have a role in various body systems, such as the nervous system, immune system, circulation system, and regulation of expression of specific genes.[3-6]

In the past several years, the prevalence of vitamin D deficiency and the incidence of low vitamin D status have increased in developing and some developed countries.[7] Several reports indicate that vitamin D deficiency has a role in the pathophysiology of cancer, cardiovascular disease, diabetes, and morbidity in pregnancy.[2] Vitamin D statuses got special attention related to exposure to ultraviolet rays in Southeast Asian countries. Singapore is one of the countries where the population matches the research on the association between vitamin D status and UV exposure. Singapore has a slightly lower prevalence of vitamin D deficiency than Thailand, possibly related to the geographical site closer to the equator.[1] Previous cohort study by Jusdistiani et al.,[8] at four cities in West Java, showed that around 195 pregnant women (96.06%) had hypovitaminosis D (< 30 ng/mL), which approximately 152 (75%) had vitamin D deficiency, and 43 (21%) had vitamin D insufficiency. Most who had insufficiency also had anemia.

Vitamin D deficiency, the level in serum < 20 ng/mL, is known as the cause of osteoporosis, muscle impairment, pain, and fractures. That was a significant public health problem.[1] Maternal vitamin D deficiency during pregnancy occurs commonly in developed countries.[9] However, vitamin D deficiency in pregnancy

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cause disorders in pregnancy, including preterm labor and adverse neonatal outcomes.[10]

Vitamin D was known to have a role in preterm delivery.[11] It can affect the hypothalamus-pituitary-adrenal (HPA) axis by increasing uterine contractions and affecting the body's immune mechanism against bacterial infections. This study will prove that the incidence of preterm birth has occurred due to vitamin D deficiency. So, this study aims to analyze and compare the relationship of vitamin D levels between the incidence of preterm labor in preterm and non-preterm parturient patients.

Methods

The research method used was a cross-sectional comparison analysis. The research materials were obtained from the medical records of Dr. Hasan Sadikin General Hospital from August–September 2017. This study took blood samples from preterm labor patients with 2834 weeks gestation age ranges and the results were 46 subjects consisting of 23 subjects of preterm parturient patients (cases) and 23 subjects of non-parturient preterm (controls). This study analyzes the correlation between research variables. Descriptive analysis is used to see the frequency distribution and percentage of various independent or dependent research variables. Statistical analysis used to analyze patient category characteristic data was tested by chi-square test and unpaired T. The relationship between preterm labor and vitamin D levels was tested with the Mann-Whitney test. The significance criteria used is p-value ≤0.05 as significant or statistically significant, and p-value >0.05 as not significant or not statistically significant. The Biserial Point test tested the 25-hydroxy-Vitamin D3 levels and the incidence of preterm labor correlation. The SPSS Program version 23.0 for Windows was used to conduct the statistical tests. All subjects provided written informed consent for participating the study. This study was approved by the Research Ethics Committee RSUP Dr. Hasan Sadikin Hospital Bandung with registered number LB.04.01/A05/EC/228/VIII/2017.

Results

During this study period, 46 subjects consisting of 23 subjects of preterm parturient patients (cases) and 23 subjects of non-parturient preterm (controls) occupied the inclusion and exclusion criteria. The 23 subjects of preterm

Table 1 Subject Characteristics

Variable	Group		p-value
	Case	Control	
	n=23	n=23	
Age (year)			
Mean±STD	28.35±2.85	27.96±4.40	0.722*
Median	28.00	28.00	
Range (min-max)	22.00–34.00	18.00–35.00	
BMI (kg/m^2)			
Mean±STD	22.64±1.45	22.71±1.72	0.884*
Median	22.97	23.11	
Range (min-max)	19.72–25.39	19.14–25.39	
Parity			
Nulliparous	8 (34.80%)	11 (47.80%)	0.869**
Multiparous	15 (65.20%)	12 (52.20%)	
Occupation			
Civil servant/private (working)	11 (47.80%)	10 (43.50%)	0.913**
Housewives (not working)	12 (52.20%)	13 (56.50%)	

Description: * based on unpaired T test; ** based on chi square test

Table 2 Correlation between 25-hydroxy-vitamin D_3 Levels in Preterm Parturient and Non-Preterm Parturient Groups

Variable	Group		p-value
	Case	Control	
	n= 23	n= 23	
Vitamin D (ng/mL)			
Median	17.26 (1.6)	24.30 (3.0)	<0.0001*
Range (min-max)	15–21	18–31	

Description: * based on unpaired T test

parturient patients were hospitalized at Dr. Hasan Sadikin General Hospital, and the 23 subjects of non-preterm parturient patients (control) were treated at Obstetrics Clinic Dr. Hasan Sadikin General Hospital who had homogeneous characteristics with preterm pregnancy subjects. The blood sample from every subject in this study has been taken to analyze the levels of 25-hydroxy-vitamin D3.

Table 1 shows the case and control subjects characteristics based on age, parity, body mass index (BMI), and occupation. The mean age was 28.15±3.67 years, and the mean BMI was 22.68 ±1.58 kg/m^2. It can be seen that nulliparous parity was 19 (41.30%), and multiparous parity was 27 (58.70%). The 21 people (45.70%) were civil servants/private employees (working), and 25 people (54.30%) were housewives (not working).

Table 1 compares the age, BMI, and occupation of preterm parturients (case group) and non-preterm parturients (control group). The patients' mean age in the case group was 28.35±2.85 years, and the control group was 27.96±4.40 years. The mean BMI in the case group was 22.64±1.45 kg/m^2, and in the control group was 22.71±1.72 kg/m^2. The number of civil servants/private employees in the case group was 11 people (47.80%), and the number of housewives was 12 people (52.20%), while in the control group, only 10 people (43.40%) were working people and 13 people (56.50%) were not working people. Nulliparous parity in the case group was eight people (34.80%), and multiparous was 15 people (65.20%), while in the control group, nulliparous was 11 people (47.80%), and multiparous was 12 people (52.20%).

Numerical data, such as age and BMI, normally distributed data, have been tested using an unpaired T-test. The result showed that all of this study's variables were insignificant (p>0.05). It can be explained that there was no significant difference in age and BMI variables between the case and control groups.

Categorical data, such as parity and occupation, were analyzed using Chi-Square. However, only occupation data can be tested by the Chi-Square test. In contrast, the parity data was tested by an alternative test, the Exact Fisher test, because the Chi-Square test's requirement was not fulfilled. The result showed no significant or statistically significant difference (p>0.05) between the parity and occupation variables in the two study groups: the preterm parturient and the non-preterm parturient.

Based on the analysis of the patient characteristics, all p-value >0.05 showed that at the beginning of the examination, both groups were equal or had no characteristic difference. This indicates that both groups are homogeneous, which means all of the characteristics fulfilled the requirements to compare and test for further statistical hypotheses.

The 25-hydroxy-Vitamin D3 levels in the serum of both groups were described in Table 2. It was shown that the serum 25-hydroxy-Vitamin D3 concentration in the control and case groups was 17.26 ng/mL and 24.30 ng/mL, respectively. The result showed a statistically significant difference (p<0.0001, using the Mann-Whitney test) between the mean value of variables 25-hydroxy-vitamin D3 in the case and control groups.

Correlation coefficient (r) analysis between 25-hydroxy-vitamin D_3 levels and the incidence of preterm labor value was -0.837 with p-value >0.001 (based on Biserial Point Correlation Coefficient). It showed that significant correlation or statistically significant. Thus, it can be concluded that there was a correlation between 25-hydroxy-Vitamin D3 levels and the incidence of preterm labor.

Discussion

In this study, the characteristics of the research subjects compared were age, BMI, parity, and occupation because these four factors are suspected to be confounding factors in the results of this study. The characteristics of the subjects between the two groups must be homogeneous. Thus, the two groups could be compared to each other. The results showed that there was no significant difference in all of the characteristics of this study subjects, which are age (p-value= 0.201), BMI (p-value=0.884), parity (p-value =0.369) and occupation (p-value=0.913). It means that both groups are homogenous. Therefore, the bias between age, BMI, parity, and occupation in both groups could be diminished so that both groups could be compared.

This study showed that the 25-hydroxy-vitamin D3 level in preterm parturient patients was significantly lower than in non-preterm parturient patients. Around 47.82% of subjects had 25-hydroxy-vitamin D3 levels lower than 20 ng/mL, which means the subjects sustained deficiency. About 52.18% of subjects had been included in normal groups (≥ 20 ng/mL). Vitamin D deficiency is a global health problem. At least 20 ng/mL of 25-hydroxy-vitamin D3 levels are needed for bone health.[12] In this study, nearly 91.30% of preterm parturient subjects sustained vitamin D deficiency, and the rest were normal. In the preterm non-preterm parturient subjects, 4.35% of it had been included in the deficiency group and 95.65% in the normal group.

Vitamin D is essential in maintaining calcium homeostasis, bone development, and mineralization. The primary source of vitamin D was exposure to ultraviolet B waves (290–320 nm).[13] The previous observational study described that vitamin D deficiency became one of the factors in the pathophysiology of some cancer, cardiovascular disease, hypertension, diabetes, and obstetrical morbidity. In 2005–2006, 69% of Indonesian pregnant women and 78% of non-pregnant women had 25-hydroxy-vitamin D3 levels lower than 30 nmol/L based on National Health and Nutrition Examination Survey (NHANES).[14]

In both groups, the distribution results of 25-hydroxy-vitamin D3 level and age showed that the control group was spread over the age range 18 to 35 years old, have the mean value of 25-hydroxy-vitamin D3 level being 24.30 ng/mL, whereas in the case group was spread over the age range 22 to 34 years old have the mean of 17.26 ng/mL. Preterm pregnancy, which was previously unknown, is now being discovered through several studies. The NHANES study found that preterm pregnancy occurred at various ages. Approximately 82% of pregnant women had vitamin D deficiency, which is 34% of them happened at age above 35 years old, 14% occurred above 40 years old, and the rest happened at 45 years old. Women who have a BMI above the normal range are found that they have vitamin D deficiency.[15]

Based on the results that have been presented, it can be concluded that there was a correlation between the 25-hydroxy-vitamin D3 level and the incidence of preterm labor. Statistical analysis results of the correlation of the 25-hydroxy-vitamin D3 and the incidence of preterm labor, which was tested by the biserial point correlation, showed that r=-0.837 with p-value <0.001. This result is accorded with the study which had done by Holick et al.,[10] which stated an inverse correlation between the 25-hydroxy-vitamin D3 and the incidence of preterm labor. Liu et al.[11] conducted a cohort of 39 pregnant women with preterm labor, which explained a statistically significant result (p = 0.002) that the lower the vitamin D level, the higher the incidence of preterm labor.

Vitamin D supplementation is known to decrease the body's response to pathogens by reducing the production of interleukin-6, interleukin-1, and tumor necrosis factor compounds by macrophages, thus playing a direct role in regulating myometrial contractility.[16,17] Vitamin D is also known to directly affect myometrial contractility by regulating Connexin-43 gene expression (gap junction association protein) at the transcriptional level of mRNA through nuclear VDR.[18] Study also suggested that vitamin D was able to reduce cytokines and Contractile-Associated Protein (CAP) due to the induction of inflammation in human myometrial smooth muscle cells and could prevent preterm birth through inhibition of infection/inflammatory pathways.[19,20]

The correlation between vitamin D and the incidence of preterm birth in the Indonesian population still needs further research. However, this has proven that preterm birth is associated with maternal vitamin D deficiency status. Thus, it can be concluded that the effectiveness of vitamin D as an alternative non-surgical and non-invasive therapy in cases of preterm labor requires further research. Vitamin D supplementation during pregnancy must be considered.

The limitation of this study is that it does not

exclude confounding factors such as age, BMI, parity, and occupation. Further research can be done on more homogeneous subjects.

Based on the result of this study, it is concluded that there was a significant difference between 25-hydroxy-vitamin D3 levels in preterm parturient patients and non-preterm parturient patients. There was also a correlation between the 25-hydroxy-vitamin D3 and the incidence of preterm labor. Dietary recall of meals containing vitamin D and sun ray exposure must be further assessed in the following study. Vitamin D supplementation in pregnant women must be considered.

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