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Low Maternal 25(OH)D (Vitamin D) Serum Levels as a Risk Factor for Preterm Labor

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Abstract: Preterm birth is the biggest cause of mortality in children under 5 years old in the world. The main causes of preterm birth are inflammation and intrauterine infection. Vitamin D plays a role in preventing preterm birth by reducing the oxidative stress of tissues that causes an inflammatory reaction. The purpose of this study is to determine that low maternal Vitamin D serum level as a risk factor for preterm delivery. This study is an analytic study with case control design with 54 samples, and divided into two groups, 27 preterm delivery samples as a case group and 27 preterm pregnancy samples as a control group. This research was conducted at the Obstetric and Gynecology Outpatient Clinic and the delivery room at Sanglah Hospital Denpasar during December 2018 to April 2019. The results of this study found a statistically significant difference ($p = 0.028$) between the case and control groups. Low vitamin D levels are a risk factor for preterm labor by 3.45 times compared with patients with high vitamin D levels (OR = 3.45, 95% CI = 1.12-10.67, $p = 0.028$). The conclusion of this study was that low maternal 25(OH)D (Vitamin D) serum levels is a risk factor for preterm deliveries.

Keywords: Preterm Deliveries, Vitamin D, Risk Factor

1. Introduction

Preterm labor is the biggest cause of mortality in children under 5 years in the world. Immaturity of the organ systems of premature infants increases neonatal morbidity and mortality compared to term birth infants. The incidence of preterm birth in the world increased from 7.5% (2 million births) in 2005 to 8.6% (2.2 million births) in 2010, where the incidence rate in various countries varied between 5-25%. [1] In Indonesia the incidence of preterm birth ranged from 10-20% in 2009 and makes Indonesia to be the fifth place in the world. [2] From the medical records of Sanglah General Hospital in 2015 the number of preterm deliveries was 285 cases (23.7%) from 1198 births. [3].

There are four mechanisms of preterm labor, which are infection and inflammation, mechanical stretching, premature activity of the fetal hypothalamic pituitary axis and decidual hemorrhage. [4] As is well known, the most common causes of preterm labor are inflammation and intrauterine infection. Vitamin D plays a role in preventing preterm labor by reducing tissue oxidative stress which causes an inflammatory reaction, preventing excessive apoptosis and modulating infection-preventing factors. [5] Vitamin D plays a role in inhibiting several inflammatory factors such as tumor necrosis factor-α and interleukin 6. Vitamin D also stimulates the formation of anti-inflammatory cytokines and cathelicidin, and activates monocyte cells and macrophages. [6, 7]

Vitamin D plays an important role in modulating and effectively coordinating between anti-inflammatory and antimicrobial factors so that a pregnancy can last into term. Several studies have shown that the function of vitamin D is not only limited to calcium regulation but also plays a role in mitosis and cellular differentiation, expression of nitric oxide synthetase (NOS), regulation of the immune system gluthation synthesis and neurotropic factors. [8, 9]

Some studies revealed that low vitamin D levels have been shown to be significantly associated with an increased risk of preterm labor. [10-12] Apart from some contradictory reports, vitamin D deficiency can be influenced by low vitamin D food intake, limited sun exposure, skin phototype, geographical differences and BMI. [13-15] Therefore, it is important to do a

research that low vitamin D serum levels as a risk factor for preterm labor in Indonesian population especially in Bali to evaluate biomarkers that can be utilized as a risk factor for preterm labor.

2. Materials and Methods

This study used a Case-Control design conducted at the Obstetric and Gynecology Outpatient Clinic of Sanglah Hospital Denpasar and the delivery room of Sanglah Hospital Denpasar, from December 2018 to April 2019. The sample in this study was 27 pregnant women who experienced preterm labor as a case group and 27 pregnant women with a normal preterm pregnancy as a control group. The sample in this study was obtained through consecutive sampling. Inclusion criteria for case were single life pregnancy, gestational age between 20 weeks of gestation until less than 37 week of gestation, minimal uterine contraction was two times within 10 minutes and cervical dilatation ≥ 2 cm. Exclusion criteria were premature rupture of membrane, antepartum bleeding, fetal congenital anomaly, pregnant mother with comorbidities such as asthma, diabetes mellitus, heart disease and another comorbidity, history of cervical operative procedure.

The research material was maternal venous blood samples taken from cubital veins, was examined by *Quantitative Sandwich Enzyme Immunoassay Technique* to determine Vitamin D levels. Risk analysis was used to calculate Odds Ratio values to determine low vitamin D level as a risk factor for preterm labor. Statistical analysis was performed using SPSS version 26.0. Bivariate analysis results with P values of <0.05 were considered to be statistically significant. The results were reported as odds ratio (OR) with 95% confidence interval (CI). The study was approved by the Medical and Health Research Ethics Committee of Universitas Udayana Medical School/Sanglah Hospital, Denpasar.

3. Result

This study used 54 subjects divided into two groups. The case group was 27 people with preterm labor, while the control group was 27 people with normal preterm pregnancies. The mean distribution according to age, parity, BMI (Body Mass Index) and gestational age in both study groups can be seen in table 1.

Table 1. *The mean distribution according to age, parity, BMI (Body Mass Index) and gestational age in both study groups.*

Variable	Preterm Labor Groups (n=27)		Preterm Pregnancy Groups (n=27)		p
	Mean	SD	mean	SD	
Age (year)	27,30	5,93	29,00	7,11	0,425
Parity	1,00	1,24	0,93	0,83	0,762
BMI (kg/m^2)	21,81	3,37	23,97	4,73	0,113
Gestational age (weeks)	34,15	1,49	33,43	1,56	0,091

Based on table 1, the variables of age, parity, BMI, and gestational age obtained p value for each variable is > 0.05 which states that there are no significant differences between the two groups.

Determination of the cut off value of Vitamin D levels in maternal blood serum which is used as a predictor limit value for preterm labor was obtained through a preliminary analysis using the ROC curve calculation. The analysis was carried out on 21 samples taken from the same population and the cut off point value was 3.37 ng/ml, with a sensitivity of 81.5% and a specificity of 98.3%.

The Chi-Square test was conducted to determine the relationship between Vitamin D levels and the risk of preterm labor. Vitamin D levels as a risk factor for preterm labor can be seen in table 2.

Table 2. *Vitamin D levels as a risk factor for preterm labor.*

		Group		OR	CI 95%	p
		Preterm labor	Preterm pregnancy			
Vitamin D [25(OH)D]	Low	19	11	3,45	1,12-10,67	0,028
	High	8	16			

Based on table 2, it showed that low Vitamin D levels as a risk factor for preterm labor by 3.45 times compared with groups of patients with high Vitamin D levels (OR = 3.45, 95% CI = 1.12-10.67, p = 0.028).

4. Discussion

In this study using ROC analysis with a cut-off value of 3.37 ng/ ml (sensitivity of 81.5% and specificity of 98.3%) obtained significantly different results between the preterm labor group and the preterm pregnancy group. Statistical tests showed that low vitamin D levels (<3.37 ng/ ml) at 20 weeks until ≤ 37 weeks gestational age have 3.45 times chance of preterm labor (OR = 3.45, 95% CI = 1.12 -10.67, p value = 0.028). This can be explained by the fact that low vitamin D [25 (OH) D] serum level is a risk factors for preterm labor through an immune system deficiency mechanism that caused an increase in oxidative stress which increased the susceptibility to inflamation and infection.

The result of this study are in accordance with the study conducted in Poland comparing preterm labor with term delivery, it was found that pregnant women experienced a

significantly more frequent preterm delivery in women with vitamin D levels below 10 ng/dl (severe vitamin D deficiency) (34% vs. 14.2%, p = 0.001). Based on these results, it can be concluded that vitamin D levels below 10 ng/ml significantly increase the risk of preterm labor. (OR = 2.62, 95% CI: 1.15–5.98, p = 0.023). [16] Another study conducted by McDonell revealed that the group of pregnant women with vitamin D levels > 40 ng/ml during pregnancy reduced the risk of preterm birth by 62% (p < 0.0001) compared to the group of women with vitamin D levels. Maternal D is below 20 ng/mL [17].

A metaanalysis of 6 Randomized Clinical Trial (RCT) studies and 18 observational studies showed that vitamin D deficiency (<50nmol / L) increased the risk of preterm birth by 1.25 times (95% CI = 1.13-1.38) and vitamin D supplementation during pregnancy can reduce the risk of preterm by 57% (95% CI = 0.36-0.91). [18] Providing vitamin D supplementation to pregnant women at a dose of 2000 IU is known to reduce the risk of preterm birth (p<0.005). [19] Indonesian female population as a non-white population can be influenced by vitamin D levels during pregnancy. Vitamin D levels in early pregnancy also have a significant effect for the risk of preterm birth, where the risk of preterm birth before 37 weeks is significantly decreased in a group of women with vitamin D levels of 90nmol / L (p <0.001). [20].

Based on its pathophysiology, vitamin D can affect preterm birth through inflammatory and immunomodulating processes that are responsible for the adequate functioning of toll-like receptors that initiate immune responses. Inflammatory in the myometrium and cervix due to vitamin D deficiency are thought to cause preterm birth in pregnant women with low vitamin D levels, whereas in a study of the American female population, group with vitamin D levels below 20 ng / ml had a risk of giving birth 6 weeks earlier compared to group with vitamin D levels greater than 40ng / ml. [21] In addition, as many as 50% of cases of spontaneous preterm birth have been associated with infection, because high concentrations of phospholipase A2 which act as prostaglandin precursors can increase uterine activity. Vitamin D is known to target the activity of antimicrobial peptides especially cathhelicidin in urogenital epithelial cells and also increase the macrophage system stimulation in decidual and trophoblastic cells. Vitamin D also increased the production of hydrogen peroxide and its secretion in monocyte cells so that the microorganisms eradication can increase. [18].

The association of vitamin D with inflammation and immunity also revealed in a study conducted by Elhusseini et al. showed an association between low levels of vitamin D and increased expression of steroid receptors in murine myometrium, increased fibrosis and inflammation and the presence of immunosuppression through expansion of Tregs in the myometrium. They showed that vitamin D deficiency can impair the infiltration and expansion of Tregs in the myometrium which is indicated by a significant increase in myometrial CD45+ Foxp3+ cells and an increase in the production of TGF-B and IL-10 as pro-inflammatory cytokines. [22] In addition, vitamin D also known to reduce the incidence of iatrogenic preterm birth by influencing placental function, where based on previous literature vitamin D can reduce oxidative stress which has a relationship with the incidence of preeclampsia which is also related to the occurrence of iatrogenic preterm birth. [18] The role of vitamin D on the placenta is evidenced in study conducted by Bodnar investigated spontaneous preterm birth by looking at placental histology and its relation to vitamin D. They found that vitamin D level > 30 nmol / L had a significant association with lower inflammation in placental histology. [20].

The high prevalence of vitamin D deficiency in Asia including Bali, Indonesia is likely due to skin pigmentation, traditional dress code, religious factors, air pollution, lack of outdoor activities, lifestyle, sunscreen use, nutrition factors, and intake of fish fat and cod liver oil supplementation are important determinants of vitamin D deficiency. [23-25] Skin color, living in a highland in a country, weather, diet, lack of Vitamin D fortification in food are also cited as important factors for vitamin D deficiency. [24].

5. Conclusion

The conclusion of this study was that low maternal 25(OH)D (Vitamin D) serum levels is a risk factors for preterm labor. Low Vitamin D plays an important role for preterm labor through an immune system deficiency mechanism that caused an increase in oxidative stress which increased the susceptibility to inflamation and infection. Further research in another country is needed due to the different of sun exposure and using different research methods to obtain more accurate data on the prevalence of vitamin D deficiency in pregnant women and the role of vitamin D in the prevention of prematurity. Screening for vitamin D [25(OH)D] deficiency may be considered at the time of ANC to reduce the risk of preterm delivery. Giving vitamin D as a form of prevention in pregnant women with vitamin D deficiency can be a consideration in reducing the risk of preterm labor.

Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

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