

Vitamin D Levels in Pregnancy with Preeclampsia: A Cross-Sectional Study in The Tropics

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ABSTRACT

Biological effect of vitamin D sufficiency has an effect on blood pressure regulation of the renin-angiotensin system which help reducing elevated blood pressure. There is a meaningful difference of vitamin D levels between preeclampsia incidences and normal pregnant women. The purpose of the research is to find out the correlation between vitamin D levels and preeclampsia. Research method used is analytic cross-sectional study with the pregnant women diagnosed with preeclampsia as a population. The sample is 76 people consisting of 38 people of case group and 38 people of control group. The Point-Biserial correlation test is used for result analysis. The result of the research shows that there is no correlation between vitamin D levels and preeclampsia incidences with the p value 0.052. It indicates that vitamin D levels does not correlate with preeclampsia incidence in pregnant women. The finding of the research supports the theory that preeclampsia is influenced by complex etiopathogenesis.

Keywords: Vitamin D, Pregnancy, Preeclampsia.

INTRODUCTION

Preeclampsia is a multifactorial disorder happened as an accumulation of the factors that may involve maternal, placenta, and fetus factors (Cunningham, Leveno, Bloom, Hauth, Rouse, 2010). Preeclampsia is characterized by elevated blood pressure ($\geq 140 / \geq 90$ mmHg) accompanied with proteinuria ($\geq 0,3$ gr/24 hours) in pregnant women who have not previously experienced hypertension happened after 20 weeks pregnancy (Hod et al., 2015). Some theories of the causes of preeclampsia are: the placental vascular disorders theory; the placental ischemia, free radicals, and endothelial dysfunction theory; the immunologic theory, the genetic theory, the nutritional deficiency theory, and the inflammatory theory (Cunningham, Leveno, Bloom, Hauth, Rouse, 2010), (Suparman, 2012). However, the thing that becomes the initial basis for pathogenesis of preeclampsia is a damage related to placenta. Most of the experts are agreed that vasospasm is the early preeclampsia. Vasospasm is a result of the failure of trophoblast invasion which will cause

damage/endothelial injury and subsequently an imbalance between vasoconstrictor and vasodilator levels (Martaadisoebrata, Djamhoer, Firman F. Wirakusuma, 2013).

Immunologic factor is presumed to have a role in hypertension incidence of pregnancy. Placenta preeclampsia shows strong inflammation response, and there is an increase of immunology system activity. It indicates that immunomodulation system of vitamin D potentially provides benefits to placenta implantation during pregnancy (D. Damayanti, 2013)(P. D. Damayanti, 2019).

Sufficiency of fulfilling vitamin D needs gives immunomodulation biological effect and blood pressure regulation. Immunomodulation is involved in T cell activity which is T helper 1 (Th1)/T helper 2 (Th2). In the Th 1 pathway, the production of Tumor Necrosis Factor (TNF α) and interferon (IFN-gamma) is hindered. Meanwhile, in the Th 2 pathway, it is involved in humoral immunity which suppresses the inflammation activity of IL-6 and increases Transforming Growth Factor β 1 (TGF β 1) formation. Furthermore, the biological effect of vitamin D efficiency has an effect on blood pressure regulation in the renin-angiotensin system as well which can help reducing elevated blood pressure (Kiely et al., 2017), (Hyppönen, 2005), (Joong Sik Shin, Mee Yun Choi, Mark S. Longtine, 2012), (Rana et al., 2019).

Vitamin D levels have a role in the beginning of pregnancy in managing risk factors of pregnancy complications; supporting fetal growth, bone development, and immune maturation (Dror et al., 2012). There is a meaningful difference in vitamin D levels between preeclampsia incidence (the levels of 6 vitamin D serums average $18,2 \pm 20$ ng/ml) and normal pregnant women (the serum level of vitamin D averages $33,3 \pm 27,3$ ng/dl) (Bodnar et al., 2014).

The average vitamin D serum level in preeclampsia group is 18 ng/ml, while the serum level in normal pregnant women group is 32 ng/ml (Robinson et al., 2010). The finding is interestingly found in this research is that there is a difference of average vitamin D levels between pregnant women with preeclampsia and normal pregnant women when winter is coming. It is because the pregnant women lack of ultraviolet light from the sun. It is a well-known fact that ultraviolet light can convert pre-vitamin D 3 to pro-vitamin D 3.

Hypertension incidences in pregnancy and preeclampsia in Indonesia as a tropical country with a year-round sunlight exposure are still quite high. The prevalence of preeclampsia incidences with complication in Western Indonesia the period from 1 January 2015 to 31 December 2017 is 14.45% (Martadiansyah et al., 2019)(Sari et al., 2018). Based on the background of the research, this research aims at finding out whether vitamin D levels have or does not have a correlation with preeclampsia incidences in Indonesia.

METHOD

This is an analytic cross-sectional study. The subject of the research is preeclampsia and normal pregnant women who have pregnancy check-ups in the hospitals in Western Indonesia. The locations are selected because the hospitals are recorded as hospitals with a high preeclampsia rate. Sample size is determined through the degree of trust selected

which is 95% and the power test is 90%. Thus, the total sample obtained is up to 78 respondents consisting of 38 case group and 38 control group.

The inclusion criteria for the case group are: a pregnant woman with single live fetus and the gestational age is 20-34 weeks with preeclampsia without any other disease, having a complete medical record since the first trimester, and willing to be a respondent. Furthermore, the inclusion criteria for the control group are a pregnant woman with single live fetus and the gestational age is 20-34 weeks without pregnancy complications, having a complete medical record since the first trimester, and willing to be a respondent. Meanwhile, the exclusion criteria for both case and control groups are: As the researchers collected the data of pregnant women with preeclampsia and absent normal pregnant women from the hospitals/public health centers.

This research examines vitamin D levels as an independent variable; preeclampsia incidence as a dependent variable; and woman's age, parity, body mass index before pregnancy as confounding variables. Univariate statistical data analysis is used for examining the characteristics of respondents, while multifarious point biserial test with SPSS is used for examining the correlation between vitamin D levels and preeclampsia incidences.

FINDING AND DISCUSSION

1. Characteristics of the Study Subject

All pregnant women who have pregnancy check-ups in public health centers should be requested to fill in self-identity, parity, the first day of the last menstrual period (LMP), height, weight before pregnancy, history of illness before and during pregnancy, family history of preeclampsia; and record of the results of blood pressure and proteinuria check-ups through medical records. Both preeclampsia and normal pregnant women who fulfill inclusion criteria are given explanations regarding the background of the research, its purposes, and its procedure as well.

After having been explained, the pregnant women who willingly participate in the research will be requested to sign the approval sheet of informed consent provided. In the next schedule, they will be subsequently invited to take blood sample for vitamin D levels analysis.

The characteristics identification of study respondent shown in the table below:

Characteristics	Groups						p value*	
	Preeclampsia		Normal		Total			
	n	%	n	%	n	%		
Age of Mother (year)	20 - 35 years	24	43,6	31	56,4	55	100,0	0,073
	<20>35 years	14	66,7	7	33,3	21	100,0	
Parity	0	10	55,6	8	44,4	18	100,0	0,589
	>1	28	48,3	30	51,7	58	100,0	
BMI before pregnancy	Not obese	25	45,5	30	54,5	55	100,0	0,200
	Obesity	13	61,9	8	38,1	21	100,0	
Total		38	50,0	38	50,0	76	100,0	

Table 1 shows that both study groups is included in homogenous category. P value of the characteristic of age is 0,073, parity is 0,589, and BMI before pregnancy is 0,200. It indicates that there is no significant difference between normal pregnant women group and pregnant women with preeclampsia group.

2. Vitamin D Levels

Vitamin D levels in this research are the test result of vitamin D levels sample from the pregnant women which is obtained from standard laboratory. Blood sampling for the case group with the control group is conducted through the same step-by-step procedures starting from identification and action informed consent, check-ups preparation, sampling conducted by laboratory staffs, sample analysis conducted by laboratory analysts—to getting the sample test results. The following table is the test result of blood sample of vitamin D levels in the pregnant women of case and control groups:

	Group	
	Preeclampsia	Normal
Average	18,04	20,85
Standard Deviation	6,34	6,04

Table 2 shows the average vitamin D levels in pregnant women with preeclampsia are 18.04 ng/ml, while in normal pregnant women are 20.85 ng/ml. There is no significant difference of vitamin D levels between both study groups. The difference of the average vitamin D levels of both groups is 2.81 ng/ml (15.5%). It indicates that the average vitamin D levels of both groups in this research is low (<30 ng/ml).

Even though the average vitamin D levels between these two study groups is not different, it has a difference in its level of the classification of vitamin D status. The normal pregnant women group with the average vitamin D levels 20.85 ng/ml is included in the mild category (mild deficiency), while the preeclampsia women group with the average vitamin D levels are 18.04 ng/ml is included in the moderate category (moderate deficiency).

In the winter, the average vitamin D levels of preeclampsia pregnant women are 17.6 ng/ml, and normal pregnant women are 19.5 ng/ml. The difference of both of the results in the winter is 1.9 ng/ml (10.7%). There is a difference of average vitamin D levels between pregnant women with preeclampsia and normal pregnant women. This difference can be seen in seasonal changes as well (Bodnar et al., 2014).

Sunlight exposure in certain countries determines the concentration of vitamin D levels in pregnant women. However, this is not applied to Indonesian people who live in the tropics where are rich in sunlight. Although the tropics are rich in sunlight, it does not guarantee the sufficiency of vitamin D levels if it is not accompanied with sufficient sunlight exposure. It is indicated by the low vitamin D levels in normal pregnant women and pregnant women with preeclampsia.

Sunlight is the best main source of vitamin D. UVB light which comes from the sun will be absorbed by skin, and subsequently converts 7-dehydrocholesterol in the skin to pre-vitamin D₃ which is subsequently and spontaneously converted to vitamin D₃ (cholecalciferol). This vitamin D undergoes hydrolysis. The first hydrolysis occurs in the liver in the form of 25 (OH)D, while the second hydrolysis occurs in and out of the liver in the form of 1,25 (OH)₂D (Dawodu & Akinbi, 2013).

UVB light intensity in the time between 1 hour before and 1 hour after midday reaches the highest value in a day. This intensity will be low at 7 a.m., and then increase to the next hours until at 2 p.m., and subsequently decrease at 4 p.m. which is the same intensity as 7 a.m. with the exposure time required is 15 minutes (Holick, 2004), (Kaushal & Magon, 2013).

In tropical countries, people do not feel comfortable being outside the house at 8 a.m.-2 p.m. They would like to spend their times more in these hours at home or office. Beside they do not feel comfortable with it, they usually apply sun protection when they go out. Sunlight exposure is considered as an exposure that can damage the structural integrity of the skin, the changes in the skin tone, and even increase the risk of skin cancer. These two behaviors impact on the inhibition of the benefits of sunlight in the synthesis of vitamin D metabolism.

Furthermore, the other risk factor in decreasing vitamin D levels is obesity. Obesity gives an effect on vitamin D metabolism due to the decreased vitamin D₃ bioavailability from the skin and the deposition occurs in fat which make vitamin D trapped in fat and it cannot be easily excreted, so as to inhibit of converting pre-vitamin D₃ to pro-vitamin D₃ (Yosephin et al., 2014).

3. Correlation between Vitamin D Levels in Pregnant Women and Preeclampsia Incidences
 Table of point biserial correlation test of vitamin D levels with preeclampsia incidences:

		Group
Vitamin D Levels	R	0,224
	P	0,052
	N	76

The statistical test result using Point Biserial Correlation test shows that the p value > 0,05 (p = 0,052). It indicates Ho is accepted, which means there is no correlation between vitamin D levels and preeclampsia incidences. The correlation coefficient with value 0.224 indicates that the closeness of correlation between vitamin D levels and preeclampsia incidences is weak.

The preeclampsia onset is divided into two stages, which are early onset preeclampsia and late onset preeclampsia (Martaadisoebrata, Djamhoer, Firman F. Wirakusuma, 2013). Early onset preeclampsia is characterized by the occurrence of clinical symptoms of preeclampsia before 34 weeks' gestation, while late onset preeclampsia is characterized by the occurrence of clinical symptoms of preeclampsia after 34 weeks' gestation (Martaadisoebrata, Djamhoer, Firman F. Wirakusuma, 2013), (Huppertz, 2008). Early onset preeclampsia is related to the inadequate trophoblast invasion of maternal spiral arteries, the changes in blood flow into the spiral arteries of the placental bed, the increased peripheral resistance of the placental blood vessels, so that it is one of the causes of abnormal blood flow from the umbilical artery. Therefore, early onset preeclampsia is related to the placental factor, while late onset preeclampsia is related to the maternal factor of body system disorders (Huppertz, 2008), (Sylwia Kuc, Maria P.H. Koster, Arie Franx, Peter C.J.I. Schielen, 2013), (Bounds et al., 2015).

Vitamin D levels measurement is a measurement of maternal factors related to the late onset preeclampsia of preeclampsia incidence. Placental factor is related to early onset preeclampsia. This research carries out the measurement to the pregnant women with gestational age < 34 weeks, so that it cannot measure maternal factors. It is indicated from the statistical test result and affirmed with etiopathogenesis that there is no correlation between vitamin D levels and preeclampsia incidences.

CONCLUSION

This research shows that, in tropical countries, there is no correlation between vitamin D levels and early onset preeclampsia incidences. The average value of vitamin D levels in normal pregnant women is included in low category.

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