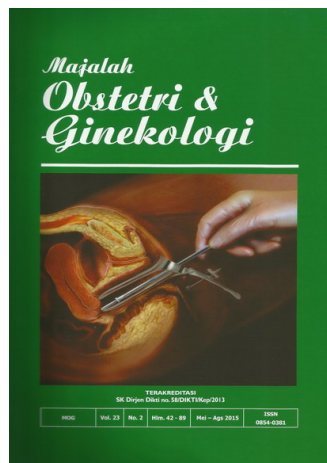




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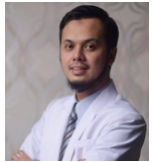
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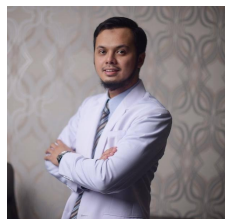


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25(OH)D Inadequacy Has Different Pathway with VEGF in Increases the Risk of Severe Preeclampsia

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ABSTRAK

Tujuan: Mengidentifikasi hubungan secara in vivo antara 25(OH)D dengan VEGF dalam kejadian preeklampsia berat.

Bahan dan Metode: Penelitian ini merupakan sebuah penelitian analitik cross-sectional terhadap 36 wanita hamil, yang terdiri dari 18 pasien preeklampsia berat dan 18 pasien kontrol dengan usia kehamilan yang sesuai. Pemeriksaan kadar 25(OH)D serum dilakukan dengan chemiluminescent immunoassay (CLIA) dan pemeriksaan VEGF serum dengan sandwich ELISA terhadap semua pasien.

Hasil: Semua pasien sampel memiliki kadar 25(OH)D yang termasuk dalam kelompok insufisiensi dan defisiensi. Baik 25(OH)D dan VEGF serum berhubungan secara signifikan dengan kejadian preeklampsia berat dengan P masing-masing 0,012 dan 0,010. Tidak didapatkan hubungan bermakna antara kadar 25(OH)D serum dengan VEGF serum (P=0,629).

Simpulan: Kadar 25(OH)D yang rendah berhubungan dengan peningkatan resiko terjadinya preeklampsia berat. Data yang ada tidak mendukung hipotesis mengenai VEGF mediator hubungan antara rendahnya kadar 25(OH)D serum dengan kejadian preeklampsia berat.

Kata kunci: Vitamin D, 25-hydroxyvitamin D, vascular endothelial growth factor, VEGF, preeklampsia berat

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INTRODUCTION

Preeclampsia is still a major cause of maternal morbidity and mortality in the world. Data from WHO on 2012 mention as many as 10% of all pregnancy are complicated with preeclampsia, with 5% of them need intensive care for eclampsia and severe preeclampsia complication. Almost 25% of babies born to preeclamptic mother are IUGR.¹

Vitamin D has been known to have a major role in calcium metabolism, immune system, proliferation, differentiation of cells, infection, and cancer.² In the last 10 years, vitamin D has been studied to determine its effect on conception, pregnancy and neonatal health.³ The maternal serum and umbilical cord level of 25(OH)D has been proven to penetrate the placenta and fully meet the fetal needs of vitamin D.⁴ Levels of 25(OH)D in the serum is directly related to the intake of vitamin D and sun exposure.⁵ Low level of 25(OH)D in

ABSTRACT

Objectives: To identify in vivo correlation between 25(OH)D and VEGF in severe preeclampsia.

Materials and Methods: A case control, cross sectional study of 36 pregnant women which consist of 18 patients with preeclampsia and 18 patients as control with gestational age-matched. We perform 25(OH)D serum examination by chemiluminescent immunoassay (CLIA) and VEGF serum examination by sandwich ELISA to all patients.

Results: All patients are in 25(OH)D insufficiency and deficiency state. Both maternal 25(OH)D and VEGF levels were inversely associated with the risk of preeclampsia (both P<0.05). There is no correlation between 25(OH)D serum level and VEGF serum level (P=0,629).

Conclusion: Maternal vitamin D deficiency is associated with increased preeclampsia risk. However, our data do not support the hypothesis that the association between vitamin D deficiency and preeclampsia is mediated by impaired level of VEGF.

Keywords: 25-hydroxyvitamin D, vascular endothelial growth factor, preeclampsia

the first trimester of pregnancy is associated with the incidence of preeclampsia.⁶ Furthermore, vitamin D supplementation during the first year of life may reduce the risk of preeclampsia by 50% in the first pregnancy.⁷ Magnus (2001) examined the incidence of preeclampsia is associated with season. It was significantly lower in the summer with high sun exposure and calcidiol levels reached its peak.⁷

Vitamin D deficiency (levels of 25(OH)D<17.5 nmol/L) and insufficiency (levels of 25(OH)D<50nmol/L) apparently were found in tropical countries with abundant sun exposure such as India and Bangladesh. Green (2008) examined the levels of 25(OH)D in women of reproductive age in Jakarta and Kuala Lumpur, showed 60% of them having insufficient levels of 25(OH)D. Many studies tried to unravel the pathogenesis of preeclampsia associated with vitamin D deficiency, for example in the inflammatory response pathways, oxidative stress and angiogenesis. However,

so far they have not obtained satisfactory results. One of the factors of angiogenesis is vascular endothelial growth factor (VEGF), considered able to be a predictor factor for preeclampsia and even a therapeutic agent for preeclampsia. Vitamin D is proven invitro to increase the activity of VEGF as specific mitogen and proliferation of blood vessels. Our study aims to investigate the relationship between 25(OH)D levels and serum VEGF in pregnancy with preeclampsia, by comparing it with low risk pregnancies. The results of this study are expected to provide an overview of how the role of 25(OH)D in the pathogenesis of preeclampsia, and how this relates to angiogenesis pathway.

MATERIALS AND METHODS

Subjects

Participating in this study were 36 pregnant women which consist of 18 patients with preeclampsia and 18 patients as control with gestational age-matched. Pregnant women were recruited consecutively into the study during their visit at the antenatal clinics and delivery room of Soetomo general hospital and Soewandhi general hospital between November 2014 and February 2015. Women with a history of any disease including chronic hypertension, obesity, diabetes, liver disease, kidney failure, autoimmune, twin pregnancy, and granulomatous diseases were excluded. Participants were interviewed and a data form was used to collect information about personal details, age, gestational age, prepregnancy weight, parity, educational status, sun exposure duration, intake of food contains vitamin D, and sunblock usage. Informed consent was obtained and ethical approval was obtained from Ethical board.

Serum 25(OH)D and VEGF measurement

We perform 25(OH)D serum examination by chemiluminescent immunoassay (CLIA) and VEGF serum examination by sandwich ELISA to all patients. Cut-off values for 25(OH)D were as follows: deficiency (less than 10 ng/mL), insufficiency (10 to 30 ng/mL), and normal (more than 30 ng/mL). Cut-off for VEGF values were not available. Statistical analysis was carried out using the IBM SPSS (Statistical Package for the Social Sciences) statistical software package version 20.0. Data were expressed as mean \pm standard deviation (SD) or number and percentage of subjects. Correlations were performed using Spearman's test. Comparisons were

conducted using unpaired Student's two-tailed t-test (Mann-Whitney as alternative). Chisquare tests (Fisher's test as alternative) were used to compare categorical variables. In all tests, the level of significance was $P < 0.05$.

RESULTS AND DISCUSSION

In total, 36 subjects enrolled with 18 subjects each in severe preeclampsia and control group (Table 1). The mean age of these subjects was 28.1 (SD 6.57) years. There were one subject aged less than 18 years old and six subjects aged more than 35 years old. Prepregnancy BMI in severe preeclampsia and control group were 23.3 (SD 2.4) and 23.2 (SD 3.5), respectively. Most of the subjects are having their first pregnancy. The educational status were middle to high which means most of the subjects at least have finished their high school. We found no variables significantly influenced the incidence of preeclampsia. The 25(OH)D levels in severe preeclampsia and control group were 11.7 (SD 4.8) and 15.9 (SD 4.5) ng/mL, respectively. The VEGF levels in preeclampsia and control group were 13.3 (SD 3.1) and 17.5 (SD 5.5) pg/mL, respectively. Both maternal 25(OH)D and VEGF levels were inversely associated with the risk of preeclampsia (both $P < 0.05$).

Most of the subjects have 25(OH)D levels between 10 to 30 ng/mL (Table 2). Around 75% have insufficient levels of 25(OH)D. There were no variables with the P values less than 0.005. There were 20 out of 27 subjects (74.1%) are at 28 weeks or more of gestational age having insufficient levels of 25(OH)D compared to 66.6% subjects in the deficiency levels of 25(OH)D. Most of the subjects are exposed to sunlight more than 90 minutes per day. More than 75% subjects in each group taken at least twice per week of food that may contains high level of vitamin D.

The overall mean of 25(OH)D levels was 13.9 (SD 5.06) ng/mL. There were a significant association as shown (Table 3) between 25(OH)D levels and the incidence of preeclampsia with OR 13.6 ($P = 0.012$, 95% CI 1.47 to 125.31).

Overall mean of VEGF levels was 15,4 (SD 4,89) pg/mL. We also found a significant association between VEGF levels and the incidence of preeclampsia ($P = 0.010$). But correlation analysis found out that there is no correlation between 25(OH)D serum level and VEGF serum level ($P = 0,629$).

Table 1. Subjects' characteristics based on severe preeclampsia incidence

Variables n(%)	Group		P
	Severe preeclampsia	Control	
Age, mean(SD) [year]	29.2(6.9)	26.9(6.3)	0.305
Gestational age (n,%)			
24-33 weeks	9 (50.0)	9(50.0)	1.000
≥34 weeks	9 (50.0)	9(50.0)	
Prepregnancy BMI, mean(SD)	23.3(2.4)	23.2(3.5)	0.957
Parity (n,%)			
Primigravida	11 (61.1)	10 (55.6)	0.735
Multigravida	7 (38.9)	8 (44.4)	
Educational status (n,%)			
Low	9 (50.0)	1 (5.6)	0.057
Middle	5 (27.8)	14(77.8)	
High	4 (22.2)	3 (16.7)	
Working (n,%)			
Yes	8 (44.4)	12 (66.7)	0.180
No	10 (55.6)	6 (33.3)	
Hypertension history (n,%)			
Yes	6(33.3)	5(27.8)	0.717
No	11(66.7)	13(72.2)	
Diabetes history (n,%)			
Yes	1(5.6)	5(27.8)	0.177
No	17(94.4)	13(72.2)	
25(OH)D, mean(SD) [ng/mL]	11.7(4.8)	15.9(4.5)	0.012*
VEGF, mean(SD)[pg/mL]	13.3(3.1)	17.5(5.5)	0.010*

*significant at P<0.05

Table 2. Subjects' characteristics based on levels of 25(OH)D serum

Variables n(%)	Levels of 25(OH)D serum		P
	Deficiency	Insufficiency	
	N = 9	N = 27	
Age, mean(SD)	27.2(5.7)	28,3(6.9)	0.657
Gestational age (n,%)			
24-28 weeks	3(33.3)	7(25.9)	0.686
>28 weeks	6(66.6)	20(74.1)	
Prepregnancy BMI, mean(SD)	23,9(3.1)	23,1(2.9)	0.391
Parity (n,%)			
Primigravida	5(55.6)	16(59.3)	1.000
Multigravida	4(44.4)	11(40.7)	
Educational status (n,%)			
Low	4(44.4)	6(22.2)	0.893
Middle	3(33.3)	16(59.3)	
High	2(22.3)	5(18.5)	
Working (n,%)			
Yes	5(55.6)	15(55.6)	1.000
No	4(44.4)	12(44.4)	
Hypertension hist. (n,%)			
Yes	4(44.4)	7(25.9)	0.409
No	5(55.6)	20(74.1)	
Diabetes history (n,%)			
Yes	1(11.1)	5(18.5)	1.000
No	8(88.9)	22(81.5)	
Sun exposure(n,%)			

<90 min/day	2(22.2)	4(14.8)	0.627
90 min/day	7(77.8)	23(85.2)	
Vit D food intake (n,%)			
Often	5(55.6)	15(55.6)	0.893
Seldom	2(22.2)	12(44.4)	
Never	2(22.2)	0(0.0)	
Long sleeves (n,%)			
Yes	3(33.3)	9(33.3)	1.000
No	6(66.7)	18(66.7)	
Sunblock usage			
Yes	2(22.2)	3(11.1)	0.581
No	7(77.8)	24(88.9)	

Table 3. Association between incidence of severe preeclampsia and 25(OH)D levels

25(OH)D levels	Group, n(%)		OR	P	CI	
	Severe preeclampsia	Control			Lower	Upper
Deficiency	8(44.4)	1(5.6)	13.6	0.012	1.47	125.31
Insufficiency	10(55.6)	17(94.4)				

Our study did not found any variables that related to the incidence of severe preeclampsia. Lechterman (2014) reported the same results which mentioned that mother’s age, prepregnancy BMI, gestational age, and parity did not influenced the incidence of severe preeclampsia. Most of our subjects having severe preeclampsia are primigravida and low educational status. Opitasari (2014) reported similar findings that parity and educational status are factors influencing the incidence of severe preeclampsia.⁸

Vitamin D deficiency and insufficiency

The present study showed a high prevalence of vitamin D deficiency and insufficiency among pregnant women in Surabaya. About 25% have 25(OH)D levels lower than 10 ng/mL and 75% have 25(OH)D levels between 10 to 30 ng/mL. None of them have normal 25(OH)D levels. There were no variables found out to be significantly influenced the incidence of deficiency or insufficiency of 25(OH)D levels. Other study reported by Lechterman at 2014 reported similiar results.

Vitamin D levels is influenced by adipose tissues. In obese, vitamin D was stored in the fat cells that causing a low 25(OH)D levels in serum.⁹ Therefore, in subjects with obese or overweight, the 25(OH)D levels are expected to dropped.¹⁰ In our study, there were no obese women since its already excluded in the recruit-ment, and 25% subjects are overweight. But there were no significant association between BMI and 25(OH)D levels in our study. This could be due to our small sample and no subject have normal 25(OH)D levels. Same results reported by Li (2011), who reported that

BMI was not associated with the levels of 25(OH)D serum in pregnancy.

Skin colour was not included in our study since most of our subject are Asians. De-Regil (2012) and Tsiaras (2011) reported that skin colour influenced the levels of vitamin D. They categorized the skin colour to African-American, Caucasian, and Asian.^{10,11}

Intake containing vitamin D especially in Asian, contributed to 25(OH)D serum levels. Even though it is not the main cause for vitamin D deficiency, some study reported it influced the vitamin D status.¹² In our study, food intake was not significantly differs between vitamin D deficiency and insufficiency. This could be due to our data collection about the food intake did not considered food with vitamin D fortification or the concentration of vitamin D in those food. We only collected the information about how many times subject consumes food enriched with vitamin D.

Levels of 25(OH)D serum and severe preeclampsia

Our study revealed the 25(OH)D serum was between 4.5 to 26.8 ng/mL. This findings are similar with other studies especially in Asian. Sachan (2005) reported in India 84% women with 25(OH)D serum levels lower than 22.5 ng/mL. Cut-off values for 25(OH)D serum is different among studies. Sachan used the cut-off level for normal 25(OH)D is between 30 to 80 ng/mL. While in Australia, the cut-off levels used are around 20 ng/mL. The low 25(OH)D levels in Asian women are

suspected due to pigmentation and low intake of food containing vitamin D.^{12,13}

Levels of 25(OH)D is the gold standard for evaluating vitamin D status. But since vitamin D metabolism is complicated, the levels of 25(OH)D will give different implication in every person. Therefore, it is suggested that to know the vitamin D status, other parameters such as parathyroid hormones are needed to be checked also. Parathyroid hormones usually will be lower when 25(OH)D lower than 20 ng/mL.¹⁴

There were a significant difference between preeclamptic mother and control regarding the 25(OH)D levels with P values lower than 0.05. This findings are also supported by Xu (2014) with similar findings. Our study reported that the 25(OH)D levels in preeclampsia was 26% lower than in control group. This is greater than previous studies reported by Xu (2014) around 14% and Bodnar (2007) around 15%. However, the mean levels of vitamin D in this study is lower than those studies. Mean of 21.76 ng/mL vs. 19.08 ng/mL at study Xu (2014) and mean of 22.8 ng/mL vs. 19.6 ng/mL at study Bodnar (2007). This is probably due to the sample of this study was obtained from a variety of gestational age with many different characteristics. Furthermore, our research sampling conducted from November 2014 to February 2015 in Surabaya, where rainfalls is very high every day. It is said that differences in levels of 25(OH)D between preeclampsia patients and controls obtained more significantly in the summer, when the levels of 25(OH)D in normal pregnancy increased, but remained lower in patients with preeclampsia.⁸

Recent studies have found that levels of 25(OH)D in early pregnancy is lower in women who eventually experienced preeclampsia. Decreased levels of 25(OH)D to 20 ng/mL, gives a 2-fold increased risk of the occurrence of preeclampsia.⁶ Research in Norway for 23,423 nulliparous women, found that vitamin D supplementation as 10-15 µg/day is associated with a 27% reduction in the risk of preeclampsia compared with no supplementation (OR=0.73, CI 0.58-0.92).¹⁵ In this study, the odds ratio (OR) is 13.6. Since our study did not have any subjects with normal value of 25(OH)D, we assumed that insufficiency were better than deficiency. With this OR, it means that the conditions of deficiency of 25(OH)D increase the risk of severe preeclampsia at 13.6 times compared insufficiency of 25(OH)D.

Levels of VEGF and severe preeclampsia

In this study, serum VEGF levels associated with the incidence of severe preeclampsia (P = 0.010). These results are similar to results of a study by Wang (2009)

which found a significant decrease in the levels of free VEGF and PIGF serum preeclamptic patients compared to normotensive patients and nonproteinuria using sandwich ELISA examination technique. VEGF is necessary to regulate blood pressure and maintain the integrity of the glomerular filtration barrier. The interaction of VEGF with its receptors is essential for the growth and function of the placenta, as well as stabilization of the maternal blood vessels. Decrease in the concentration of free VEGF in the serum of patients preeclampsia causes endothelial cell dysfunction maternal circulation. Polliotti et.al. showed that low VEGF levels are predictors of preeclampsia in the future. Levine et.al. found that levels of free VEGF in patients with preeclampsia found to be lower than normotensive women since 5 weeks prior to the occurrence of preeclampsia.¹⁶

In contrast, several studies such as Lyall (1997) and Oh (2001) found an increase in total circulating VEGF in serum of women with preeclampsia compared with normotensive women, as well as research by McKeeman (2004) and Shaarawy (2005).¹⁶ The discrepancy may occur due to the type of sandwich ELISA cannot detect the levels of VEGF total (bound and free) in serum. The study that found elevated levels of serum VEGF preeclampsia are using radioimmunoassay or ELISA system techniques that examine VEGF levels in total, unlike our study.

Levels of 25(OH)D and levels of VEGF serum

Our study found that levels of 25(OH)D serum in patients with preeclampsia and control is not associated with serum VEGF levels (P = 0.629), although both have a significant relationship with the occurrence of preeclampsia. This may be due to the number of samples is small (18 people for each group). Another possibility is that each of the 25(OH)D and VEGF have another pathophysiology in relation to the incidence of severe preeclampsia.

It has been known that there are several biological pathways for 25(OH)D in affecting the placenta, fetal, maternal health and pregnancy growth. Vitamin D has a role as an immunomodulator that is able to regulate the immune response to the mother's placenta, and is able to prevent infection during pregnancy.¹⁷ While in relation to preeclampsia, vitamin D deficiency predisposes pro-inflammatory response and increased oxidative stress which ended with endothelial dysfunction. Increased proinflammatory factors and oxidative stress may be an important factor in the pathophysiology of preeclampsia. Low levels of 25(OH)D are related to inflammatory vascular endothelial cells, increased NF B signaling in suppressing vascular endothelial function, and reduced

VDR on vascular endothelium and decreased expression of 1- hydroxylase. In addition, cells expressing placental trophoblast 1 α -hydroxylase (CYP27B1) and VDR in large numbers, so there is the hypothesis that vitamin D has an important anti-inflammatory role of the placenta.

Some studies also showed an increase in oxidative stress in subjects with deficiency of vitamin D. This increase can be reversed by vitamin D supplementation.¹⁸ In 2014, Wei conducted a study on the relationship of the levels of 25(OH)D with increased oxidative stress biomarkers and found that levels of 25(OH)D serum biomarkers associated with increased levels of F2-isoprostanes (5-iPF2 α -VI) on gestational age 12 to 18 weeks ($r = -0.261$, $P=0.01$) and 24 to 26 weeks ($r = -0.246$, $P=0.02$). After getting rid of confounding factors, it was found that levels of 25(OH)D less than 50 nmol/L at 24 to 26 weeks of gestation increased risk of preeclampsia (OR 4.20, 95% CI 1.4 to 12.6).¹⁹

In this study, no relationship was found between decreased levels of 25(OH)D serum with decreased serum levels of VEGF. In this study, no assessment levels of pro-inflammatory factors and biomarkers of oxidative stress on the entire subject of research, so we can not evaluate whether inflammatory or oxidative stress factors that are more affected by reduced levels of 25(OH)D serum in the pathophysiology of preeclampsia.

Studies on the role of VEGF in preeclampsia find some mechanism reduction of VEGF. Several studies have reported increased levels of antiangiogenesis factors such as soluble fms-like tyrosine kinase (sFlt-1) is able to reduce levels of free VEGF to below the critical point needed for vasculogenesis and maintain vascularity which has been formed during pregnancy.¹⁶ sFlt-1 is expressed and secreted by several human tissues including endometrial, endothelial cells, and placental villus tissue. Several studies using primary cultures of isolation of human cytotrophoblast cells showed that low oxygen levels increased the expression of sFlt-1. sFlt-1 binds to VEGF with high affinity, resulting in lower levels of free VEGF. In normal pregnancy, levels of sFlt-1 will increase with gestational age, but the increase occurred more rapidly in serum and placental tissue of preeclampsia patients. Increased expression of sFlt-1 obtained in vitro and in vivo models with sFlt-1 by hypoxia conditions still can not be explained by either. In this study, we did not examine antiangiogenesis factors such as sFlt-1, which may explain the decrease in VEGF in our study.

CONCLUSION

Maternal vitamin D deficiency is associated with increased preeclampsia risk. However, our data do not support the hypothesis that the association between vitamin D deficiency and preeclampsia is mediated by impaired level of VEGF, although there were significant differences of VEGF levels in preeclamptic mother to normotensive mother. Further research are needed to evaluate this phenomenon.

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