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CORRELATION STATUS OF VITAMIN D WITH EARLY ONSET PREECLAMPSIA

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ABSTRACT

Background: Preeclampsia is one of the contributors to the causes of maternal and child mortality in the world, WHO notes preeclampsia occurs with an incidence of 3-10% of all pregnancies, whereas early onset preeclampsia affects about 7% of all cases of preeclampsia. Vitamin D status is often associated with poor pregnancy outcomes, especially in preeclampsia.

Objective: To determine the relationship between Vitamin D status reflected by serum 25-hydroxyvitamin D levels and the incidence of early onset preeclampsia.

Method: This study is a case control analytic that compares the total plasma levels of 25-hydroxyvitamin D serum in normal pregnancies <34 weeks and cases of early onset preeclampsia. Characteristics of the study subjects and vitamin D levels were collected on each subject. Levels of plasma 25-hydroxyvitamin D are reported in nanograms per milliliter. To analyze the relationship between Vitamin D levels, an independent T test was performed and Chi Square test at a significance level of 5% ($p < 0.05$).

Results: This study is a case control analytic that compares the total plasma levels of 25-hydroxyvitamin D serum in normal pregnancies <34 weeks and cases of early onset preeclampsia. Characteristics of the study subjects and vitamin D levels were collected on each subject. Levels of plasma 25-hydroxyvitamin D are reported in nanograms per milliliter. To analyze the relationship between Vitamin D levels, an independent T test was performed and Chi Square test at a significance level of 5% ($p < 0.05$).

Conclusion: Vitamin D deficiency is associated with an increased risk of early onset preeclampsia

KEYWORDS : 25-hydroxyvitamin D, preeclampsia, vitamin

INTRODUCTION

WHO noted that preeclampsia occurred with an incidence 3-10% of all pregnancies.[4] For Indonesia, high blood pressure (preeclampsia and eclampsia) was found to contribute 21.5% to maternal deaths in 2010. However, this figure increased to 27.1% in 2013 .

Vitamin D (calciferol) is one member of the group of fat-soluble vitamins (seco-sterol) and is found only in certain types of food. The form of physiological or active vitamin D is D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D3 is synthesized on the skin with the help of ultraviolet (UVB) to 7-dehydrocholesterol while D_2 is synthesized with UV light against ergosterol in other fungi and plants. Height, season, age, use of sunscreen, and skin pigmentation affect the production of D_3 on the skin.

Preeclampsia is hypertension that arises after 20 weeks' gestation and is accompanied by proteinuria. Based on its onset, preeclampsia is divided into early onset and late onset preeclampsia. Early onset Preeclampsia is preeclampsia that occurs before 32-34 weeks of gestation. Preeclampsia early onset affects about 7% of all cases of preeclampsia.

In a study conducted by Gernand et al, it was found that the risk of early onset preeclampsia in women with 25 (OH) D <30 nmol/ l2,4 times higher among women with 25 (OH) D levels ≥75 nmol/l . The study uses multiple cut off points of 30, 50, and 75 nmol/l. This cut number corresponds to the Institute of Medicine, which is the definition of risk for deficiency (<30nmol/l) and inadequate risk (30 to <50 nmol/l) related to bone health, and deficiency of the Endocrine Society (<50nmol/l) and insufficiency (50 to <75nmol/l). Research suggests early onset preeclampsia is caused by imperfect implantation, spiral artery remodeling and placental development. In a study conducted by Shiaoyng et al., It was said that human hemocytic placenta is extra renal tissue with high expression of activating vitamin D (1 -hydroxylase / CYP27B1) enzyme. These enzymes and 1,25-D3 receptors are expressed in human decidua and placental villi and the

highest expression is seen in the first and second trimesters. This could explain the role of vitamin D in the process of uteroplacental desidualization and remodeling where if this process is disrupted it is likely the pathogenesis of the occurrence of preeclampsia.

The working relationship of vitamin D and the occurrence of preeclampsia caused the authors to be interested in examining the relationship between serum vitamin D concentration and the occurrence of early onset preeclampsia.

METHOD
This research is an analytic case control study with a population of all patients with early onset preeclampsia who are treated and terminated and patients with normal pregnancies who come to the Haji Adam Malik Central General Hospital Medan, Dr. Pirngadi General Hospital Medan, and Sundari Hospital and examining vitamin D levels were carried out at the Prodia Laboratory in Medan from October 2017 to February 2018. In this study, 22 samples were taken with PE early onset pregnancies and 22 samples with normal pregnancies

RESULT
The following are the results of the characteristics of the research subjects based on age, childbirth, and education.

Table 1. Characteristics of Subject Research

	Preeklamsia (n=22)	Normal Pregnancy (n=22)
Age, n (%)		
> 35 Year	5 (22,7)	3 (13,6)
≤ 35 Year	17 (77,3)	19 (86,4)
Parity, n (%)		
Primigravida	7 (31,8)	9 (40,9)
Multigravida	11 (50,0)	7 (31,8)
Sekundigravida	4 (18,2)	6 (27,3)
Education, n (%)		
Elementary School	4 (18,2)	2 (9,1)
Junior High School	4 (18,2)	3 (13,6)
Senior High School	12 (54,5)	14 (63,6)
College	2 (9,1)	3 (13,6)

Table 1. above explains that subjects aged ≤ 35 years are dominant in two groups, as many as 17 people in the group of women who are preeclampsia and 19 people (86.4%) in the group of normal pregnant women. Subjects with multigravida parity were 11 people (50%) in the preeclampsia group and 9 primigravida subjects (40.9%) in the group of women with normal pregnancy. Most of the subjects with high school education in the preeclampsia group were as many as 12 people (54.5%) and as many as 14 people (63.6%) in the group of normal pregnant subjects.

Table 2. Description of Vitamin D Level in Groups of Subjects with Preeclampsia and Normal Pregnancy

Vitamin D Level	Preeklamsia (n=22)	Normal Pregnancy (n=22)
Deficiency (<20ng/mL)	15 (68,2)	1 (4,5)
Insufficiency(20-30ng/mL)	5 (22,5)	0
Optimal (30-80ng/mL)	2 (9,1)	21 (95,5)
Mean	16,79	44,42
SD	8,98	9,79
Minimum	4	16,40
Maximum	32,6	64,20
95% IK	12,8 – 20,77	40,08 – 48,76

Based on table 2, it was explained that most subjects with preeclampsia had vitamin D deficiency as many as 15 people (68.2%). The average vitamin D level was 16.79 ng / mL with

the lowest levels of 4 ng / mL and the highest was 32.6 ng/mL. Meanwhile, most subjects had optimal vitamin D of 21 people (95.5%). Only 1 person (4.5%) with vitamin D deficiency. The average vitamin D level in the normal pregnant subject group was 44.42 ng mL with the lowest average of 16.40 and the highest 64.20 ng/mL.

Table 3. Differences in mean vitamin D between preeclampsia and normal pregnant subjects

	Preeklamsia (n=22)	Normal Pregnancy (n=22)	p
Vitamin D, rerata (SD), ng/mL	16,79 (8,98)	44,42 (9,79)	<0,001

Based on table 3. Using the independent T test showed that there were significant differences in the mean vitamin D levels between groups of subjects with preeclampsia and groups of subjects with normal pregnancy ($p < 0.001$).

Table 4. Correlation of MCP-1 levels in menopausal women with OAB with OAB Score

Vitamin D Level	Preeklamsia (n=22)	Normal Pregnancy (n=22)	p
< 30 ng/mL	20 (90,9)	1 (4,5)	<0,001
≥ 30 ng/mL	2 (9,1)	21 (95,5)	

Based on table 4, using the Chi Square test showed that there were significant differences in the levels of vitamin D between groups of subjects with preeclampsia and groups of subjects with normal pregnancy ($p < 0.001$). Of the 22 subjects in preeclampsia there were 20 people (90.9%) subjects had vitamin D levels <30 ng/mL, while in the normal pregnant subjects group only 1 person (4.5%) subjects with vitamin D levels <30 ng/mL .

DISCUSSION
This study included 22 subjects who had preeclampsia and 22 normal pregnant subjects who were in accordance with the inclusion and exclusion criteria. Subjects aged ≤ 35 years were dominant in two groups, as many as 17 people in the group of women who had preeclampsia and 19 people (86.4%) in the group of normal pregnant women. Subjects with multigravida parity were 11 people (50%) in the preeclampsia group and 9 primigravida subjects (40.9%) in the group of women with normal pregnancy. Most of the subjects with high school education in the preeclampsia group were as many as 12 people (54.5%) and as many as 14 people (63.6%) in the group of normal pregnant subjects. Xin Zhao and Rui Fang, 2017, reported that there were significant differences in serum concentrations of 25 (OH) 2 D in pregnancies of various ages ($p < 0.001$), and serum concentrations of 25 (OH) 2D significantly lower in women over 35 years and women multiparas have a higher serum 25 (OH) 2D concentration compared to nullipara women ($p < 0.001$).

Most subjects with preeclampsia had vitamin D deficiency as many as 15 people (68.2%). The average vitamin D level was 16.79 ng/mL with the lowest levels of 4 ng / mL and the highest was 32.6 ng / mL. Meanwhile, most subjects had optimal vitamin D levels of 21 people (95.5%). Only 1 person (4.5%) with vitamin D deficiency. The average vitamin D level in the normal pregnant subject group was 44.42 ng / mL with the lowest average of 16.40 and the highest 64.20 ng/mL.

Christopher J. R, 2010, reported that plasma 25 (OH) 2D levels were significantly lower in patients with Early onset Preeclampsia than normal patients 18 vs 32ng / mL (P <.001). Using the independent T test showed that there were significant differences in the levels of vitamin D between groups of subjects with preeclampsia and groups of subjects with normal pregnancy ($p < 0.001$). Using the Chi Square test showed that there were significant differences in the levels of

vitamin D between groups of subjects with preeclampsia and groups of subjects with normal pregnancy (p <0.001). Of the 22 subjects in preeclampsia there were 20 people (90.9%) subjects had vitamin D levels <30 ng/mL, while in the normal pregnant subjects group only 1 person (4.5%) subjects with vitamin D levels <30 ng/mL .

Xin Zhao and Rui Fang, 2017, reported that serum 25 (OH) D midgestation concentrations were found to be lower in women with severe preeclampsia compared with those without preeclampsia (p <0.001). Where there were significant differences in the incidence of severe preeclampsia in pregnant women with differences in vitamin D status (<50 versus 50 nmol/L, p_0,002). A total of 1.4% of pregnant women with vitamin D deficiency (<50 nmol / L) subsequently developed severe preeclampsia, of which only 0.6% in pregnant women with vitamin D sufficient (50 nmol / L) developed severe preeclampsia.

In the 2014 Royal Collage of Obstetricians & Gynecologists (RCOG), there is evidence of conflict whether hypovitaminosis vitamin D in pregnancy is associated with hypertension and preeclampsia. In three studies, preeclamptic women had lower vitamin D levels than women without preeclampsia. Decreased vitamin D levels in half of pregnancy are associated with an increased risk of preeclampsia and in neonates in preeclampsia women have a 2 times higher risk of having vitamin D levels <37.5 nmol/L (vitamin D deficiency). In the case control study, women with severe preeclampsia before 34 weeks' gestation had low vitamin D levels compared to normal pregnant women. Furthermore, women with early onset preeclampsia and small pregnancies (KMK) have lower vitamin D levels than women with early onset preeclampsia but not with small babies during pregnancy. However, two meta-analyzes, including a meta-analysis of 31 studies, showed that vitamin D insufficiency was associated with preeclampsia and gestation.

CONCLUSION

1. Subjects with preeclampsia had vitamin D deficiency as many as 15 people (68.2%). With an average vitamin D level it is 16.79 ng / mL. Meanwhile, subjects with normal pregnancy had optimal vitamin D levels of 21 people (95.5%). With an average vitamin D of 44.42 ng/mL.
2. From the results of this study, it can be concluded that there is a relationship between vitamin D status and the incidence of Preeclampsia Early onset.

REFERENCES

1. Anne Cather Staff, Christopher W.G Redman. (2018). Chapter 10. The Differences Between Early- and Late-Onset Pre-eclampsia. In S. Saito, Preeclampsia (pp. 157-169). Japan, Kumamoto, Japan: Springer.
2. Anupama, Sunanda, Jyothirmayee. Role of Vitamin D Supplementation in Prevention of Preeclampsia. Journal of Dental and Medical Sciences 2016;15(9):51-55
3. Bakacak, M, et al. Comparison of Vitamin D Levels in Cases with Preeclampsia, Eclampsia, and Healthy Pregnant Women. Int J Clin Exp Med 2015;8(9):16280-16286
4. Barebring, L. Longitudinal Vitamin D Status During Pregnancy in Sweden. University of Gothenburg 2017
5. Bikle, Adams, Christakos. Chapter 28 Vitamin D: Production, Metabolism, Mechanism of Action, and Clinical Requirements. American Society for Bone and Mineral Research 2008
6. Gernand AD, Sinham HN, Baca KM, et al. Vitamin D, pre-eclampsia, and preterm birth among pregnancies at high risk for pre-eclampsia: an analysis of data from a low-dose aspirin trial. BJOG October 2016
7. Hypponen, E, et al. Vitamin D and Pre-Eclampsia: Original Data, Systematic Review, and Meta-Analysis. Ann Nutr Metab 2013;63:331-340
8. Kareem Washington1, 2. S. (2018). A Review: Molecular Concepts and Common Pathways Involving Vitamin D in the Pathophysiology of Preeclampsia. Scientific Research Publishing, 198-217.
9. Jeyabalan A. Epidemiology of preeclampsia: Impact of obesity. Nutr Rev. Oct 2013;71(01).
10. Manasova, GS, et al. Vitamin D Deficiency States: Some Aspects of Influence to the Course and Outcome of Pregnancy. Journal of Education Health and Sport 2015;5(7):507-520
11. Nejadi, N, et al. Vitamin D Binding Protein As Screening Biomarker Candidate for Late Onset Preeclampsia without Intrauterine Growth Restriction During 16 Week of Gestation. Journal of Paramedical Sciences 2015;6(1)
12. O'Mahony, et al. The Potential Role of Vitamin D Enhanced Foods in Improving Vitamin D Status. Nutrients 2011;3:1023-1041
13. Purswani, et al. The Role of Vitamin D in Preeclampsia: A Systematic Review. BMC Pregnancy and Childbirth 2017;17:231
14. Pusat Data dan Informasi Kementerian Kesehatan RI.Situasi Kesehatan Ibu. InfoDATIN. Kementerian Kesehatan RI. 2014.
15. Robinson CJ, Alanis MC, Wagner CL, et al. Plasma 25-hydroxyvitamin D Levels in Early-Onset Severe Preeclampsia. Am J Obstet Gynecology 2010;203(366):e1-6
16. Scholl, Chen, Stein. Vitamin D, Secondary Hyperparathyroidism, and Preeclampsia. Am J Clin Nutr 2013
17. Shiaoyng, C, et al. Vitamin D Promotes Human Extravillous Trophoblast Invasion In Vitro. Placenta 2014;36(4):403-9
18. Sowell, Keen, Uriu-Adams. Vitamin D and Reproduction: From Gametes ti Childhood. Healthcare 2015;3:1097-1120
19. Tabesh, et al. Maternal Vitamin D Status and Risk of Pre-Eclampsia: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2013;98(8):3165-3173
20. The American College of Obstetricians and Gynecologists. Hypertension in Pregnancy. 2013
21. Tranquilli, et al. The Definition of Severe and Early onset Preeclampsia: Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 2013;3:44-47
22. Viswanathan, Viswanathan, Daniel. Perinatal Outcome During Expectant Management of Early Onset Severe Preeclampsia. Sch J App Med Sci 2015;3(2C):751-755
23. Wagner, CL, et al. The Role of Vitamin D in Pregnancy and Lactation: Emerging Concepts. Women's Health 2012;8(3):323-340
24. World Health Organization. Dibalik Angka: Pengkajian Kematian Maternal dan Komplikasi untuk Mendapatkan Kehamilan yang Lebih Aman. Indonesia. 2007.
25. Yu, C, et al. Maternal Serum Vitamin D Levels at 11-13 Weeks of Gestation in Preeclampsia. Journal of Human Hypertension 2013;27:115-118
26. Zhao, et al. Maternal Vitamin D Status in the Late Second Trimester and the Risk of Severe Preeclampsia in Southeastern China. Nutrients 2017;9(138)