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High Level of Maternal Low Density Lypoprotein and Insulin-Like Growth Factor Binding Protein 5 as a Risk Factor for Preeclampsia

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Abstract: ***Preeclampsia was a specific syndrome in pregnancy that affects almost every organ.The main outcome of this study was the correlation of Insulin-Like Growth Factor Binding Protein 5 (IGFBP5) level and Low Density Lipoprotein (LDL) level with preeclampsia incidence. Our study is an observational case control study with36 subjects are pregnant mother gestational age of 20 weeks until 40 weeks, pregnancy with single and life fetus, and consented to undergo the research. They were recruited from the Obstetric and Gynecology Department of Sanglah Hospital Denpasarfrom May 2019 to October 2019. Our analysis found that high IGFBP5 levels were risk factor for preeclampsia 13 times compared to low IGFBP5 levels (OR = 13.0; 95% CI = 2.6-65.2; p <0.001). High LDL cholesterol levels were a risk factor for preeclampsia of 9.1 times compared to low LDL cholesterol levels (OR = 9.1; 95% CI = 1.9-41.4; p = 0.003).This study shown that high levels of serum IGFBP5 and LDL cholesterol in pregnant women are risk factors for preeclampsia.***

Keywords: Preeclampsia, Insulin-Like Growth Factor Binding Protein 5, Low Density Lipoprotein

1. Introduction

Preeclampsia was a specific syndrome in pregnancy that affects almost every organ, and it was defined as hypertension (BP > 140/90 mmHg) that appears after 20 weeks of gestational age in previously normotensive patient, accompanied with proteinuria, thrombocytopenia, impaired renal function, impaired liver function, cerebral symptoms, or lung oedema.[1] Preeclampsia still become a problem, aside from its high prevalence, maternal and perinatal deaths contributed by preeclampsia was still high. And also, the risks of preterm labor also exists in patients with preeclampsia. In Indonesia, preeclampsia incidence was 3-10%, where the mortality rate was 26.9% at 2012 and 27.1% at 2013. Based on research done at Sanglah General Hospital in 2009-2010, the prevalence of preeclampsia was 1.36%, 4.79%, 0.43%, and 0.82% for mild preeclampsia, severe preeclampsia, superimposed preeclampsia and eclampsia respectively. Considering the major negative impact of preeclampsia on maternal and perinatal health, an effective and efficient preventive method was necessary. And part of that was early detection of preeclampsia.

Preeclampsia pathogenesis was started with placenta hypoxia that causes the release of anti-angiogenic substance and other biological substance from placenta to maternal circulation. These substances can become natural biomarker for the early detection of preeclampsia. Research about preeclampsia biomarker this far focused on molecules that was involved in placental angiogenesis like soluble fms-like tyrosine kinase-1(sFlt-1)/placental growth factor (PlGF), vascular endothelial growth factor (VEGF), soluble endoglin (sENG), and Pregnancy-Associated Plasma Protein-A (PAPP-A). In a meta-analysis that tested the accuracy ratio of sFlt-1/PlGF to predict preeclampsia, it was concluded that the accuracy ratio was moderate.[2]

Insulin-like growth factor binding protein 5 (IGFBP5) was localized in the syncytiotrophoblast layer at the chorionic villous in the first trimester. It decreased the effects of IGF-1 and IGF-2 at trophoblast cells migration.[3] IGFBP5 was a candidate for preeclampsia biomarker. The expression of IGFBP5 in trophoblast cells was upregulated by promotor of hypomethylation that was triggered by the decrease of DNA methyltransferase 3A (DNMT3A).[4] This hypomethylation and increased expression of IGFBP5, which was observed in preeclampsia caused a resistance on trophoblast migration and invasion. Preeclampsia pathogenesis was strongly correlate with a failure of invasion and trophoblast remodelling in decidua tissue. Because of that, DNMT3A and IGFBP5 also played a role in preeclampsia pathogenesis. Unfortunately, there were no clinical research that compare circulating IGFBP5 serum in preeclampsia and normotensive patient.

Dyslipidemia in pregnancy seems to be correlated with preeclampsia. Moe, et alreported that placental tissue showed acute atherosis characteristics which are subendothelial foam cells, fibrinoid necrosis of artery, infiltration of perivascular lymphocyte, and also early atherosclerotic lesions. [5] Further research concludes that increased serum lipid levels resulted in lipid accumulation in endothel tissue that could decrease prostacycline release and this will finally contributes to preeclampsia clinical manifestations.[6] A systematic review and meta-analysis done by Spracklen, et al concluded that preeclampsia also

correlated with an increase of total cholesterol, non-HDL cholesterol and triglyceride level.[7] The correlations between preeclampsia and LDL cholesterol level also tends to be marginal or not significant.[7] There was a controversy about the correlation between LDL level and preeclampsia. In a longitudinal study done by,it was reported that increase of LDL level in first trimester of pregnancy correlated with increase risk of hypertension in pregnancy.[8] But, Ghodke, et al reported that preeclampsia cannot be predicted with LDL level. It was concluded that further research was needed to evaluate the correlation between LDL level and preeclampsia incidence.[9]

Considering the high correlation between high LDL level and preeclampsia and also the potency of IGFBP5 as a novel biomarker of preeclampsia, the research to find out the correlation of high IGFBP5 and LDL level as a risk factor of preeclampsia was very interesting and important to be done.

2. Methods

This is an observational case control study done in Sanglah Hospital, Denpasar, Indonesia. The inclusion criteria of this study was pregnant mother with gestational age of 20 weeks until 40 weeks, pregnancy with single and life fetus, and consented to undergo the research. While the exclusion criteria of this pregnancy was pregnancy with chronic hypertension disease, obesity, congestive heart failure, diabetes mellitus, renal disease, hyperthyroidism. This study consists of 36 subjects with 18 subjects of case and control group.

As much as 3 cc of blood was taken from peripheral venous and then put in vacutainer tube, the blood was then sent to the laboratory for ELISA examinations. The main outcome of this study was the correlation of IGFBP5 level and LDL level with preeclampsia incidence. The secondary outcome of this study was age, gestational age, parity, and also comorbidities in pregnancy (chronic hypertension, diabetes mellitus, renal disease, congestive heart disease, hyperthyroidism). Statistical analysis done was Kolmogorov Smirnoff and Levene T test for data normality test, t-test, and chi square test. Data analysis was done using SPSS for windows version 22.0.

This study was approved by Research and Development Department of Udayana University Ethical Committee (424/UN14.2.2.VII.14/LP/2019). Patient's identity was concealed and informed consent was taken from every subjects in this study.

3. Result

This is a case control studies on 18 cases of preeclampsia as a case group and 18 cases of normotensive pregnancy as a control group which was carried out in the Obstetrics and Gynecology Department of Sanglah Hospital Denpasar from May 2019 to October 2019.

Distribution of Age, Parity, Pregnancy Age Characteristics in Both Groups

The characteristics of the study groups such as age, parity and gestational age are shown in Table 1. T-independent test was done for age variable and Mann-Whitney test for parity and gestational age variables. P values for each risk factor were found> 0.05, which states that there were no significant differences between the two groups.

Table 1: Characteristics of Subjects by case and control group

Variable	Groups		P Value
	Case (n=18)	Control (n=18)	
Age (years), mean±SD	29,4 ± 5,6	28,6 ± 5,9	0,668[a]
Parity (child), median (IQR)	2,5 (2,0)	2,0 (1,2)	0,521[b]
Gestational age(weeks), median (IQR)	37,0 (1,50)	37,50 (2,0)	0,308[b]

Note: a= *Independent T-test*, b= *Mann-Whitney test*

Risk of Preeclampsia on IGFBP5 Expression

A comparison of IGFBP5 levels between the case and control groups is presented in Table 2. The mean IGFBP5 level was significantly higher in the case group than in the control group.

Table 2: Comparison of IGFBP5 levels between case and control groups

Variable	Groups		P Value
	Case (n=18)	Control (n=18)	
IGFBP5 levels (ng/ml), mean±SD	0,69±0,16	0,54±0,12	0,003

Note: *independent t-test*

Table 3 shows the results of the Chi-Square test that high IGFBP5 levels are a risk factor for preeclampsia 13 times (OR = 13.0; 95% CI = 2.6-65.2; p =0.001) compared to low IGFBP5 levels, with a cut of point value of 0.63 ng / mL based on the ROC curve.

Table 3: Distribution of IGFBP5 levels by Case and Control Group

Variable	Groups		OR (95% IK)	P Value
	Case (n=18)	Control (n=18)		
IGFBP5 level High, n (%) Low, n (%)	 13 5	 3 15	13,0 (2,6-65,2)	0,001

Risk of Preeclampsia on LDL Cholesterol Expression

Comparison of LDL cholesterol levels between the case and control groups was presented in Table 4. The mean LDL cholesterol level was significantly higher in the case group than the control group.

Table 4: Comparison of mean LDL cholesterol levels between case and control groups

Variable	Groups		P Value
	Case (n=18)	Control (n=18)	
LDL Cholesterol level (ng/ml), mean±SD	192,3±19,3	136,2±44,0	<0,001

Note: *independent t-test*

Table 5 shows that high LDL cholesterol levels are a risk factor for preeclampsia 9.1 times (OR = 9.1; 95% CI = 1.9-41.4; p = 0.003) compared to low LDL cholesterol levels, with cut of point value of 182 mg / dl based on the ROC curve.

Table 5: Distribution of LDL cholesterol levels by Case and Control Group

Variable	Groups		OR (95% IK)	P Value
	Case (n=18)	Control (n=18)		
LDL Cholesterol level				
High, n (%)	13	4	9,1 (1,9-41,4)	0,003
Low, n (%)	5	14		

4. Discussion

This study involved 36 samples that met the inclusion and exclusion criteria, which consisted of 18 people as cases and 18 others as controls. The results showed that the mean age of the case group mothers was 29.4 ± 5.6 years and the mean of the control group was 28.6 ± 5.9 years, with p = 0.668. This means that there is no significant age difference between the case group and the control group. In addition, there were no significant differences in parity and gestational age between the case and control groups.

From the Chi-Square test it was found that high IGFBP5 levels were a risk factor for the occurrence of preeclampsia 13 times (OR = 13.0; 95% CI = 2.6-65.2; p =0.001) compared to low IGFBP5 levels, with low values cut of point of 0.63 ng / mL based on the ROC curve.This is the first study on maternal serum to examine IGFBP5 levels. Jia, et alconducted a study on the role of IGFBP5 and DNMT3A expression in the pathogenesis of preeclampsia in the placenta of patients with preeclampsia, hypometylation of the IGFBP5 gene promoter and an increase in IGFBP5 protein expression.[4]

From the Chi-Square test it was found that high LDL cholesterol levels were a risk factor for preeclampsia of 9.1 times (OR = 9.1; 95% CI = 1.9-41.4; p = 0.003) compared to low LDL cholesterol levels, with a cut of point value of 182 mg / dl based on the ROC curve.The same study was carried out by Aziz, et alwith 32 samples, examining serum lipid profiles (total lipids, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol). The results serum triglyceride concentrations significantly increased (232.18 ± 106.41 vs 113.12 ± 21.3, P <001) while serum HDL cholesterol concentrations decreased significantly (39.75 ± 11.99 vs 51, 18 ± 06.09, P <0.01) in the group of preeclamptic pregnant women compared with normal pregnant women. This study concludes that lipid metabolism plays an important role in the pathophysiology of preeclampsia.[10]

Spracklen et al, conducted a study of lipoprotein (a) and the relationship with placental histopathology in preeclampsia with normotensive pregnancy. The results showed a significant difference in the value of lipoprotein (a) between the preeclampsia pregnancy groups (22.70 ± 5.966) and normotensive pregnancies (9.20 ± 5.248). The results were tested by independent t-test with p = 0.0001 (p <0.05), statistically these results indicate that the value of lipopretein (a) between the preeclampsia and normotensive pregnancy groups shows a significant difference, the value of lipoprotein (a) in preeclamptic pregnancy is higher than in normotensive pregnancy. In the study of the relationship of microscopic placental images with lipoprotein values (a), the results of the t independent test showed that there were differences in the mean lipoprotein (a) on the microscopic picture of the placenta, namely stromal fibrosis (p = 0.032), atherosis (p = 0.041), infarction (p = 0.041) 0.038) and thrombosis (p = 0.04).[7]

Oya et al in his study that assessed the relationship between plasma lipid concentrations in early pregnancy and the risk of developing preeclampsia, found that preeclampsia pregnant women had higher total cholesterol and triglyceride concentrations from fasting plasma compared to the normotensive group. From his research he concluded that dyslipidemia in early pregnancy, especially hypergliseridemia, is associated with an increased risk of preeclampsia.[11]

In a prospective cohot study, Enquobahrie et al,assessed plasma lipid concentrations in early pregnancy and the risk of preeclampsia. The results found that pregnancy with preeclampsia had LDL, triglyceride, and LDL / HDL levels higher than normal normotensive pregnancies (10.4%, 13.6% and 15.5%; p <0.05). Triglyceride levels was increased 4.14-fold in pregnancy with preeclampsia compared to normotensive pregnancy. So it was concluded that dyslipidemia in early pregnancy is associated with an increased risk of preeclampsia and very important in the prevention and early treatment of dyslipidemia.[12]

Islam et al, in their study of serum lipid profiles in preeclampsia and eclampsia found a significant increase in triglyceride levels (225.6 ± 28.93 vs 165.6 ± 17.22) and decreased HDL levels (41.8 ± 8.79 vs. 55 , 7 ± 7.11), while LDL levels increased (133.4 ± 11.75 vs. 115.2 ± 10.72) compared to normal pregnant women. In his research he concluded that fat metabolism plays an important role in the pathophysiology of preeclampsia/eclampsia.[13]

Thura et al, conducted a study to assess whether lipid profiles can be used as a screening test to predict the onset of preeclampsia and to determine the relationship of lipid profiles with the severity of preeclampsia. The results of the study showed a significant difference in VLDL cholesterol and triglyceride levels in pregnant women with severe preeclampsia compared to normotensive normal pregnant women as controls, in the case of pregnant women with mild preeclampsia there was no significant difference with normotensive normal pregnant women.[14]

In her research, Sharami et al aims to determine the role of hypertriglyseride in relation to body mass index (BMI) before pregnancy and high risk of preeclampsia. The results of his study in pregnant women with preeclampsia total cholesterol and serum triglyceride levels increased significantly and HDL plasma cholesterol decreased compared with controls (p <0.05), average triglycerides: 375.16 vs 202.85, p <0.01, average cholesterol values 245.64 vs 214.32, p <0.04, mean HDL 40.80 vs 48.95, p <0.03). It can be concluded that dyslipidemia especially hypertriglyceridemia is highly correlated with high BMI before pregnancy in preeclampsia pregnant women and supports the role of dyslipidemia in BMI related to preeclampsia.[15]

From the Chi-Square test it was found that the combination of high IGFBP5 levels and high LDL cholesterol was a risk factor for preeclampsia of 3.2 times (OR = 3.2; 95% CI = 1.83-5.78; p = 0.000). Until now there has been no previous research that conducted a combination of IGFBP5 and LDL cholesterol as risk factors for preeclampsia.

5. Conclusion

It can be concluded that high levels of serum IGFBP5 and LDL cholesterol in pregnant women are risk factors for preeclampsia. High IGFBP5 levels are a risk factor for preeclampsia by 13 times compared to low IGFBP5 levels. Other than that, high LDL cholesterol levels also a risk factor for preeclampsia by 9.1 times compared to low LDL cholesterol levels.

6. Conflict of Interest

The authors declared that there was no conflict of interest.

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