Dyslipidemia as a Risk Factor for Preeclampsia in Pregnant Women: A Case - Control Study in Bali, Indonesia

Sawitri Ellena Juniarti, Ketut Suwiyoga, Ketut Surya Negara

Department of Obstetrics and Gynecology, Sanglah General Hospital, Universitas Udayana, Bali, Indonesia

Abstract: The etiology and pathogenesis of preeclampsia (PE) are still not known with certainty. Dyslipidemia and lipid profiles in pregnant women are still a polemic problem that may lead to the risk of PE in limited resources setting. This study aims to determine the role of dyslipidemia in pregnant women as a risk factor for PE. An observational with a case - control study was conducted in the delivery room of the emergency room from July to November 2020 in Bali. The Odd ratio of total cholesterol, LDL, HDL, and triglyceride levels is 0.688; 2.250; 1.250; and 2.154 respectively. Dyslipidemia may increase the risk of PE by 4 times compared with pregnant women who are not dyslipidemia (OR 4.297; 95% CI 1.413 – 13.068; p = 0.008). Triglyceride levels and dyslipidemia are indeed play role in the risk of PE. Therefore, screening of lipid serum should be used as a fixed protocol in the center of care for pregnant women to detect the risk of PE.

Keywords: dyslipidemia, lipid levels, preeclampsia, pregnant woman

1. Introduction

Preeclampsia (PE) is still a maternal health problem related to maternal and fetal prevalence, pathogenesis, treatment, and prognosis. The prognosis of PE is related to handling, whereas the management of PE is related to its pathogenesis mechanism. The cause of PE is pregnancy itself, while the pathogenesis mechanism is multifactorial so that this disorder is still a disease of theories.

The prevalence of PE is estimated to be seven times higher in developing countries than in developed countries. The prevalence of preeclampsia in developed countries ranges from 1.3 – 6 %, while in developing countries ranges from 1.8 to 18 %. The incidence of preeclampsia in Indonesia alone is 128.273 / year or around 5.3% [1]. The maternal mortality rate (MMR) is 359 per 100, 000 live births [2]. The three main causes of maternal death are bleeding (30%), PE (25%), infection (12%), and non - obstetrics [3]. Preeclampsia can cause cerebrovascular organ damage, kidney failure, liver failure, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and slow fetal growth [4–6]. Various attempts have been made by researchers and services to reduce prevalence that focuses on clinical risk factors, including age too young or old, obesity, short pregnancy distances, malnutrition, anemia, and vitamin D deficiency, and others. Apart from that, a maternal approach through psychological and spiritual approaches has also been carried out; but not satisfactory. Plasma lipid status has received attention concerning dyslipidemia. Dyslipidemia in metabolic syndrome and obesity is characterized by an increase in triglycerides, free fatty acids, and a decrease in High - density lipoprotein (HDL) [7].

2. Literature Survey

The lipid theory in the pathophysiology of PE states that the development of atherosclerosis in the placental spiral arteries in mothers with PE indicates an increase in triglyceride levels that causes these abnormalities to occur [8]. A meta - analysis by Gallos et al. (2013) stated that the triglyceride concentration in pregnant women with PE was significantly higher than that in pregnant women with normal blood pressure [9]. Another meta - analysis study stated that high triglyceride concentrations and low high - density lipoprotein cholesterol (HDLc) are associated with PE [10]. The main modulator of hypertriglyceridemia in pregnancy is estrogen which plays a role in the induction of hepatic endogenous triglyceride biosynthesis in the form of very - low - density lipoprotein (VLDL) [11]. This process is modulated by hyperinsulinemia in pregnancy. Hypertriglyceridemia will be associated with hypercoagulability. Maternal with high blood triglyceride levels during pregnancy had a 2 - fold risk of developing PE, then at age adjustment, Body mass index (BMI) and parity indicated a 4 - 5 fold risk, compared to women with normal triglyceride levels. The examination of blood triglyceride levels at 28 - 32 weeks' gestation is a predictive step for assessing PE. The severity of PE is associated with high levels of serum triglycerides, cholesterol, LDL and VLDL, and low levels of HDL [8]. Serum HDL levels in PE were lower compared to the normotensive control group there was an analytically significant relationship between low HDL levels and the incidence of PE [12].

A meta - analysis by Spracklen et al. (2014) stated that pregnant women with PE had greater lipid profile changes compared to normal pregnant women [13]. Efforts to prevent PE by controlling lipid intake can be carried out in ante - natal care; especially maternal who have clinical risk factors through nutrition intake education. Research on the association of maternal lipid profile in the incidence of PE was less common in Indonesia so that more studies in low - middle income settings are needed. This study aims to determine the role of dyslipidemia in pregnant women as a risk factor for PE.
3. Methods

This is an observational study in which a nested case-control study was conducted in the delivery room of the emergency room of Sanglah General Hospital in Denpasar, Bali from July to November 2020. This study was approved by the Health Research Ethics Committee of Sanglah General Hospital, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, with the number 483/UN14.2.2.VII.14/LP/2020. Informed consent was signed by study participants or from the legal guardians. The inclusion criteria consisted of pregnant women > 20 weeks who came in the Emergency Room to deliver their babies, filled in the informed consent. Pregnant women who experienced diabetes mellitus, kidney disorder, heart defect, chronic hypertension, multiple pregnancy, and fetal death in utero were excluded from the study.

Study participants underwent physical examination when they first came to the emergency room. Participants were checked for blood pressure. The blood pressure was measured in the middle of the left arm using a Mercury Free sphygmomanometer. Systolic blood pressure was determined by the Phase I Korotkoff (when the pulse was first heard) and diastolic pressure by the Phase V Korotkoff (loss of the pulse). Participants were categorized as preeclampsia if the test results showed blood pressure ≥ 140/90 mmHg accompanied by qualitative proteinuria = +1. Afterward, a complete blood count and cholesterol test were conducted on participants. The cholesterol tests include LDL, HDL, total cholesterol, triglycerides, and cholesterol ratio. The cholesterol ratio was calculated by dividing the total cholesterol by the high-density lipoprotein level. We categorized the participants who were diagnosed as dyslipidemia if the value of the cholesterol ratio is ≥ 4 mg/dL, and classified the cholesterol ratio < 4 mg/dL as participants with non-dyslipidemia [14]. The participants were divided into two groups. The first group consisted of participants who classified PE and the second group was participants who tested normal in blood pressure categorized as Non-PE.

Microsoft Excel 2013 and IBM SPSS Statistic Version 23 were used for analyzing the data. The data were analyzed descriptively and analytically. The T-independent test was applied to seek the differentiation of lipid levels and other variables between the two groups. In this study, we looked for the risk factors of lipid levels such as LDL, HDL, total cholesterol, triglycerides, and cholesterol ratio which are related to dyslipidemia in the occurrence of PE during the pregnancy. Therefore, the Odd Ratio (OR) and Confidence Interval (CI) were calculated. To determine the risk factors of dyslipidemia for the incidence of PE, the Chi-Square test was used. A p-value < 0.05 was considered significant statistically.

4. Results

Sixty - seven participants were included during the study period. Out of 67 participants, four of them refused to take part in the study, meanwhile, three of them were excluded due to heart defects. Thus, leaving 60 participants who met the inclusion and exclusion criteria. Sixty pregnant women were grouped into 2 (two) groups, namely 30 pregnant women with PE as the case group and 30 pregnant women without PE as the control group. Based on the results of the participants’ characteristics in Table 1, the mean age of pregnant women was 29.62 ± 7.23 years old. Table 1 also shows the mean BMI of pregnant women classified as obese, which ranges from 26.63 ± 3.94.

![Figure 1: Research Flow](image)
Table 1: The characteristic of study participants (n = 60)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year old)</td>
<td>29.62 ± 7.23 [18 – 45]</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>36.34 ± 3.72 [25.1 – 40.6]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.82 ± 4.91 [145 – 168]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.53 ± 8.88 [43 – 87]</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>26.63 ± 3.94 [19.10 – 38.70]</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>248 ± 67.23 [138 – 492]</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>57.25 ± 16.57 [26 – 100]</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>153.82 ± 56.87 [59 – 335]</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>278.32 ± 91.77 [100 – 536]</td>
</tr>
<tr>
<td>Cholesterol Ratio (mg/dL)</td>
<td>4.56 ± 1.49 [1.90 – 10.10]</td>
</tr>
</tbody>
</table>

Data are presented as Mean ± Standard Deviation [Inter Quartile Range]

Table 2 showed the results of different tests on the variables of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and cholesterol ratio using the T - independent test. In this study, there was no difference between the lipid levels (total cholesterol, HDL, LDL, and cholesterol ratio) and the risk of PE, except that the triglyceride level showed a result of \( p = 0.001 \). Approximately, seventy-six percent of participants of the PE group experienced dyslipidemia (Table 3). We calculated the risk of lipid levels in the occurrence of PE in Table 3. The results showed that the triglyceride and dyslipidemia were significant statistically (\( p = 0.038 \); \( p = 0.008 \)) correlated with preeclampsia. The Odd Ratio of those two variables are 2.154 and 4.297 higher than participants who were not classified as preeclampsia.

5. Discussion

In this study, we found that most of the case group (70%) were under 35 years old, 13.3% were over or equal to 35 years old and those over 40 years old were 16.7%, while in the control group who were over 35 years old was only 20%. Moreover, the average of the participants was classified obese according to their BMI. Based on research conducted in Iowa, United States with a sample size of 556 pregnant women with PE and 449 pregnant women Non-PE reported that BMI had a statistically strong relationship with the incidence of PE (\( p = 0.001 \)) [15].

Cholesterol is required for placental steroid synthesis. Increased cholesterol levels during pregnancy can increase the accumulation of maternal fat stores in the first two-thirds of pregnancy to become a source of calories for the mother and fetus during the late stages of pregnancy and breastfeeding [16, 17]. A meta-analysis study conducted in 2014 which reported the conclusions of the study from 1950 - July 2013, involved at least 61 studies from various countries stating that total cholesterol levels were statistically different, especially in the first, second, and third trimesters [13]. Unfortunately, this study did not calculate the cholesterol levels in the previous trimester. We examined the cholesterol levels of the participants when they first came to our unit. Table 2 reported that there is no difference between PE group and Non-PE group (254.10 ± 80.03 vs. 242.30 ± 52.14 mg/dL; \( p = 0.501 \)). Furthermore, the study found that there is no significant correlation between cholesterol level and the risk of PE with \( p = 0.542 \); OR 0.688; 95% CI 0.206 – 2.297 mg/dL. This finding was supported by the research of Dahlan et al. (2018) and Serrano - Berrones et al. (2019) also reported that cholesterol levels were not associated with the incidence of PE with \( p > 0.75 \) [18, 19].

In the PE group, 20% of participants had HDL cholesterol levels ≤40 mg/dL, while 80% of the participants had HDL cholesterol levels ≥ 40 mg/dL. In the Non-PE group, only about 10% of participants had HDL cholesterol levels < 40 mg/dL, while 90% of them had HDL levels ≥ 40 mg/dL. The results of the study stated that there was no significant correlation between the reduction in HDL levels and the risk of PE in pregnant women who were involved in this study (\( p = 0.278 \); OR 2.250, 95% CI 0.507 - 9.993). However, a decrease in HDL levels may increase the risk of PE by 2.2 times the Non-PE pregnant women. Dahlan et al. (2018) investigated the relationship between the lipid profile of pregnancy in trimester II and the incidence of PE in several Makassar City Health Centers from March 2015 to March 2016. From these results, it was found that the mean HDL levels were lower in the PE group than in the non-PE group, namely 64.75 ± 14.64; 67.86 ± 16.72 mg/dL [19].

A study conducted by Dahlan et al. (2018) was in line with this study because there is no significant relationship between decreased HDL levels and the risk of developing PE [19]. On the other hand, many studies suggested that HDL levels provide a significant correlation with the risk of PE [20, 21]. However, in other studies, greater differences in the third trimester compared with the first or second trimester were also observed for levels of total cholesterol, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol, suggesting that PE women experienced greater changes in lipid levels during pregnancy compared to normotensive women [13, 22]. Despite multiple theories contradicting this study, the potential effect between genetic predisposition on the level of HDL cholesterol and an increased risk of PE, suggests that dyslipidemia may be a sufficient component along the causal pathway to PE [15].

Approximately 16.7% of pregnant women had optimal LDL levels <100 mg/dL, while 83.3% had increased LDL levels ≥100 mg/dL (Table 3). In contrast to the PE group, as many as 20% of Non-PE pregnant women obtained optimal LDL levels <100 mg/dL. On the other hand, 80% of them experienced an increase in LDL levels ≥ 100 mg/dL. In this study, there was no association between increased LDL levels and the risk of PE as evidenced by \( p = 0.739 \); OR 1.250, 95% CI 0.336 - 4.644. This means that an increase in LDL levels can increase the risk of PE by 1.2 times. Spracklen conducted a study involving 164 pregnant women with PE and 110 Non-PE pregnant women in 2015 (15). The study assessed the profile of lipid levels in pregnant women with a mean result of 50.2 ± 6.0 mg/dL for pregnant women with PE and 49.8 ± 5.6 mg/dL for non-PE pregnant women. From this study, it was found that the different test results were \( p = 0.57 \), which means that there was no difference in LDL levels for the two groups [15].

A similar study was conducted at the Teaching Hospital in Lagos Nigeria involving 240 pregnant women consisting of 120 pregnant women without a diagnosis of PE and 120 women with PE (72 moderate PE; 48 severe PE). The results showed a significant difference in results between pregnant

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women with PE and pregnant women without PE (156.5 ± 11.0 mg/dL vs.109.7 ± 6.9 mg/dL). It can be seen that LDL levels for pregnant women with PE were higher than those for non-PE pregnant women and this study also obtained a significant correlation with the severity of PE in the second and third trimesters of pregnancy (r = 0.278; p = 0.001) [21]. The conclusions noted that there is an increase in serum lipids in pregnancy regardless of the development of PE. The positive correlation of maternal serum lipids with PE suggests a causal relationship [21]. Although in this study, LDL levels did not correlate with the risk of PE, there were similarities in the results that in pregnant women, whether they had PE or not, it was certain that they would experience an increase in lipid levels.

A total of 100% of the PE group had triglyceride levels ≥150 mg/dL, whereas in the Non - PE group at 86.7% of them had increased triglyceride levels ≥150 mg / dL. There were differences in triglyceride levels between groups of pregnant women with PE and Non - PE pregnant women with a value of p = 0.001. Also, it was found that an increase in triglyceride levels had a significant relationship with the risk of PE in pregnant women with p = 0.038; OR 2.154, 95% CI 1.162 - 2.854. It can be concluded that pregnant women who have elevated triglyceride levels will experience a risk of PE 2 times greater than pregnant women who have normal triglyceride levels. The meta - analysis carried in 2013 found strong evidence from 24 case - control studies involving 2720 pregnant women that PE was associated with increased serum triglyceride levels, a mean difference of 0.78 mmol/L, 95% CI 0.6 - 0.96, p <0.001. These findings were also supported in five cohort studies that recruited 3147 pregnant women in the second trimester before the onset of preeclampsia, which proved that hypertriglyceridemia accelerated the incidence of PE (mean difference 0.24 mmol/L, 95% CI 0.13 - 0.34, p = 0.001 [9].

Table 2: The lipid levels and dyslipidemia as risk factors of preeclampsia

<table>
<thead>
<tr>
<th>mg/dL</th>
<th>PE n (%)</th>
<th>Non - PE n (%)</th>
<th>Odds Ratio (OR)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>22 (73.3)</td>
<td>24 (80)</td>
<td>0.688</td>
<td>0.206 – 2.297</td>
<td>0.542</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>8 (26.7)</td>
<td>6 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>24 (80)</td>
<td>27 (90)</td>
<td>2.250</td>
<td>0.507 – 9.993</td>
<td>0.278</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>6 (20)</td>
<td>3 (10)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100</td>
<td>25 (83.3)</td>
<td>24 (80)</td>
<td>1.250</td>
<td>0.336 – 4.644</td>
<td>0.739</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>5 (16.7)</td>
<td>6 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 150</td>
<td>30 (100)</td>
<td>26 (86.7)</td>
<td>2.154</td>
<td>1.626 – 2.854</td>
<td>0.038*</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>0 (0)</td>
<td>4 (13.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>23 (76.7)</td>
<td>13 (43.3)</td>
<td>4.297</td>
<td>1.413 – 13.068</td>
<td>0.008*</td>
</tr>
<tr>
<td>Negative</td>
<td>7 (23.3)</td>
<td>17 (56.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number and percentage; The Chi - square test was used. *A p - value < 0.05 was considered significant statistically.

Total cholesterol is higher in PE and postpartum pregnancy, increasing systolic and diastolic blood pressure. LDL and triglycerides were higher in PE and postpartum pregnancy, higher systolic blood pressure [20]. Alahakoon et al. (2020) investigated the serum lipid profiles in maternal and fetal circulation with PE and fetal growth restriction (FGR). The study involved pregnant women in the range of gestational age 24 - 40 weeks. The results of this study, there was a significant difference in the mean triglyceride levels between preeclampsia pregnant women and normal pregnant women, namely 4.21; median 0.35 mmol/L and 2.99; median 0.16 mmol/L. These results suggest that the increase in maternal triglyceride levels in PE is consistent with the increase in serum lipid levels in normal pregnancy [23]. The two studies above are consistent with the results of our study that PE and normal pregnant women alike experienced changes in lipid profiles. In the case of this study, hypertriglyceridemia had a significant relationship to the risk of PE.

Several lipoprotein ratios are used to predict the risk of cardiovascular disease, namely the ratio between total cholesterol/HDL known as the atherogenic index or Castelli index with the target level in women is less than 4.0 mg/dL, the ratio of LDL cholesterol/HDL to the target level less than 2.5 [14]. For this study, only the total cholesterol/HDL ratio as dyslipidemia was investigated concerning the risk of developing PE. Eighty percent of pregnant women with PE had dyslipidemia, while in the control group 40% of non-PE pregnant women had dyslipidemia. There was no difference in dyslipidemia between groups of pregnant women with PE and pregnant women without PE. In the correlation test, it was found that dyslipidemia had a significant relationship with the risk of PE in pregnant women with a value of p = 0.008; OR 4.297; 95% CI 1.413 – 13.068. It can be concluded that pregnant women who have dyslipidemia will experience a risk of PE 4 times greater than pregnant women who do not have dyslipidemia. Although the pathogenesis of preeclampsia has not been fully elucidated, all pathobiological mechanisms may be rooted in abnormal lipid profiles, which in turn can be associated with obesity. Thus, identifying specific lipid profiles in women, who are affected by the disorder, through the use of lipidomic methods, could be the next step in explaining the pathological process of the condition [24]. The weakness of this study is the use of the case - control method because it only observes total cholesterol, HDL, LDL, and triglyceride levels only for a moment without knowing the total cholesterol, HDL, LDL, and triglyceride levels beforehand. It would be better if the blood pressure measurement is done in each trimester of pregnancy.

6. Conclusion

The prediction of preeclampsia in pregnancy is still the focus of research. Medical personnel relies primarily on maternal risk factors to identify women at increased risk of pathological conditions. Therefore, further research needs to be done by assessing serum lipid levels in each trimester of pregnancy. In addition to examining the lipid levels and blood pressure of pregnant women in each trimester, the PE group needs to be divided into several categories such as PE with severe symptoms and PE without severe symptoms. Serum lipid screening can be used as a fixed protocol in the center of care for pregnant women to detect the risk of PE.
7. Future Scopes

Based on the results of this study, there was a significant difference in the mean triglyceride levels between preeclampsia pregnant women and normal pregnant women and identifying specific lipid profiles in women, who are affected by the disorder, through the use of lipidomic methods, could be the next step in explaining the pathological process of the condition. Therefore, further research needs to be done by assessing serum lipid levels in each trimester of pregnancy.

References