Differences of Cardiovascular Risk-based on Atherogenic Index Plasma Dan Framingham Risk Score in Postpartum with Preeclampsia and Normotensive

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Abstract

BACKGROUND: Cardiovascular disease is the number one cause of death in women worldwide. Preeclampsia may be more than just risk factor for the development of cardiovascular disease later in life. Systematic reviews suggested approximately double the risk of ischemic heart disease, cerebrovascular incidents, and mortality of cardiovascular disease after preeclampsia.

AIM: The aim of the study was to analyze the differences of cardiovascular risk later in life-based on atherogenic index plasma and Framingham risk score (FRS) in postpartum women with preeclampsia compared with normotensive women.

METHODS: This is a study a comparative analytic study with case–control design on 46 subjects, divided by 23 postpartum preeclampsia patients as a case sample subject and 23 postpartum with no history of hypertension as control group. Subjects were examined for blood pressure, height, weight, and asked to fast for at least 8 h before blood lipid profile and glucose were examined with laboratory methods. Atherogenic index plasma and FRS were measured. Data were analyzed using SPSS version 25. p < 0.05 was considered significant.

RESULTS: Based on the results, the study found significant differences between systolic and diastolic blood pressure in preeclampsia compared to the control group. Median systolic and diastolic blood pressure in the preeclampsia group compared to control group were 180 versus 110 in systolic blood pressure; 100 versus 80 in diastolic blood pressure with p < 0.000. Total cholesterol, low-density lipid, high-density lipoprotein, and triglycerides levels in preeclampsia were 218.38 ± 23.26 mg/dL, 128.60 ± 22.74 mg/dL, 38.60 ± 5.99 mg/dL, and 252.73 ± 47.16 mg/dL, respectively, with p < 0.05 and non-preeclampsia group were 143.0 ± 16.82 mg/dL, 69.17 ± 23.03 mg/dL, 51.73 ± 8.65 mg/dL, and 121.30 ± 14.65 mg/dL, respectively, with p < 0.05. Differences in plasma atherogenic index values can clearly be observed in the preeclampsia and control groups (p < 0.05). A similar interpretation was found in the FRS (p < 0.05). There was a significant positive correlation between age and body mass index with atherogenic index plasma and FRS in preeclampsic group.

CONCLUSION: There was a significant difference in atherogenic index plasma and Framingham risk score of postpartum preeclampsia and normotensive women.

Introduction

According to the World Health Organization (WHO), cardiovascular disease is the number one cause of death in the world [1]. Statistical data in Europe show higher mortality from cardiovascular disease in women than in men (49% vs. 41%) [2], and the same prevalence was found in Indonesia [3]. In addition to dyslipidemia, hypertension, smoking, obesity, diabetes mellitus, genetics, and physical inactivity, women have special risk factor, “diseases related to reproduction and pregnancy [4], [5]”. One of those is preeclampsia. Preeclampsia is a vascular disorder, in which women with hypertension at 20 weeks of gestation accompanied by signs of other organ dysfunction [6]. Observational studies revealed an increased risk of long-term cardiovascular disease in women who experience various types of gestational hypertension disorders and preeclampsia. In 2011, the American Heart Association (AHA) added a history of preeclampsia as an independent risk factor for cardiovascular disease 10–15 years after pregnancy [7]. A history of preeclampsia needs special attention, because based on epidemiological studies; it may trigger premature cardiovascular disease [8].

Association between preeclampsia with the risk of cardiovascular disease in the future is incompletely understood [8]. Bellamy et al. suggested that hypertension in pregnancy does not cause cardiovascular changes, instead maternal risk factors before pregnancy determine cardiovascular risk later in life [9]. In contrast to that study, Hromadnikova et al. suggested that the risk of heart disease later develops due to epigenetic changes related to pregnancy complications. The hypothesis suggests that acute atherosclerosis of the spiral arteries by obliteration of the endothelial lumen results in reduced placental...
perfusion, local ischemia, and the onset of oxidative stress. This is caused by the production of excessive reactive oxygen species that induce lipid peroxidation production. Both of these species are known to be the main mediators of systemic and inflammatory vascular dysfunction. Some studies show a decrease in vascular endothelial function for months or even years after preeclampsia. Preeclampsia and atherosclerosis have certain similarities; both are associated with dyslipidemia, endothelial dysfunction, and elevated levels of pro-inflammatory cytokines. Abnormal lipid profiles are strongly associated with atherosclerotic cardiovascular disease and have a direct effect on endothelial dysfunction [10], [11], [12].

AHA and National Institute for Health and Clinical Excellence recommend preventative strategies for cardiovascular events in women with a history of preeclampsia [13]. The predictive capacity of several lipoprotein ratios has been shown to be better for screening purposes. One of them is atherogenic index of plasma (AIP) which most sensitive marker than a single lipid marker and recently as a marker of atherogenicity because it is increased in people with a higher risk for coronary heart disease. Another cardiovascular risk assessment is the Framingham risk score (FRS). This scoring system has been used extensively, even recommended by the national cholesterol education adult treatment program because it can estimate the risk of heart disease in the next 10 years and is proven to be close to the observed risk. This scoring system not only assesses lipid profiles but also includes other cardiovascular risk factors [12], [14], [15], [16].

In general, in Indonesia, postpartum preeclampsia patients would only get short-term care and have lower tendency for complete postpartum care, in that case, health care providers cannot provide management for the long-term effects after preeclampsia. The aim of this study is to assess the differences in risk of cardiovascular disease 1 day postpartum in preeclampsia and normotensive patients. Cardiovascular risk assessment is based on an AIP and FRS to assess the risk for the next 10 years. If differences are found, it can be used as one of the means for postpartum risk screening for cardiovascular disease in the future.

### Materials and Methods

This study is a comparative analytic study with case–control design on 46 subject divided by 23 postpartum preeclampsia patients as a case group and 23 postpartum with no history of hypertension as a control group. Subjects were patients who delivered at Haji Adam Malik Hospital Medan and Universitas Sumatera Utara affiliate hospitals between January 2019 and June 2019. Subjects were selected according to inclusion and exclusion criteria. Preeclampsia patients who met the criteria for diagnosis preeclampsia with severe feature according to Indonesian National Clinical Guideline 2016 and control group who were normotensive during pregnancy were included in this study. All the subjects were ≥30 years old. A thorough history and physical examination were done and patient with a history of hypertension, diabetes mellitus, cardiovascular disease, autoimmune disease, cerebrovascular disease, hepatic disease, thyroid gland, and kidney disease and with history of long-term drugs usage except for vitamins before and during pregnancy were excluded from this study. Informed consents were taken from all the patients included in the study. The study was approved by the Health Research Ethical Committee No 56/TGL/KEPK FK USU-RSUP HAM/2019, Faculty of Medicine, University of North Sumatera, Indonesia.

Blood pressure was measured using a mercury sphygmomanometer. Subjects were asked to fast for at least 8 h. Blood specimen was collected by venipuncture. 2 mL EDTA blood was examined for blood lipid profile and blood glucose by clinical chemical methods. Atherogenic index plasma was calculated using the values of lipid parameter in the following way:

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\text{Atherogenic index plasma} = \log \frac{\text{Triglyceride}}{\text{HDL} - c}
\]

FRS was calculated using Canadian Cardiovascular Society FRS, Table 1.

| Characteristic subject | Case n | % | Control n | % | p-value |
|------------------------|--------|---|-----------|---|---------|
| Age (years)            |        |   |           |   |         |
| 30–34                  | 13     | 56.5 | 11        | 47.8 | 0.659   |
| 35–39                  | 8      | 34.8 | 8         | 34.8 |         |
| 40–44                  | 2      | 8.7  | 4         | 17.4 |         |
| >45                    | 0      | 0    | 0         | 0    |         |
| Parities               |        |     |           |     | 0.039   |
| Primiparity            | 9      | 39.1 | 2         | 8.7  |         |
| Secundi-multiparity    | 14     | 60.9 | 20        | 87.0 |         |
| Grands-multiparity     | 0      | 0    | 1         | 4.3  | 0.007   |
| BMI                    |        |     |           |     |         |
| Underweight            | 0      | 0    | 0         | 0    |         |
| Normoweight            | 9      | 39.1 | 16        | 69.6 |         |
| Overweight             | 6      | 26.1 | 7         | 30.4 |         |
| Obesity                | 8      | 34.8 | 0         | 0    |         |
| Activity               |        |     |           |     | 0.459   |
| Housewife              | 20     | 87.0 | 17        | 73.9 |         |
| Active worker          | 3      | 13   | 6         | 26.1 |         |

p-value assessed using Chi-square.

### Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 25 IBM corp.). Statistical tests performed were Mann-Whitney U-test (for blood pressure and cardiovascular risk assessment because of non-normal distributed data) and independent t-test (for lipid profile because normal distribution data). Correlation between the variables in preeclampsia group was estimated by spearman’s Rho. p < 0.05 was applied to each statistical test and was declared significant.
Table 2: Blood pressure of patients with postpartum preeclampsia and normotensive

| Blood pressure | Case    | Control | p-value |
|----------------|---------|---------|---------|
| Systolic       | 180 (150–200) | 110 (100–130) | 0.000   |
| Diastolic      | 100 (80–120)  | 80 (60–90)   | 0.000   |

Values are median (min-max). p-value assessed using Mann–Whitney U-test.

Results

Characteristics of case and control group

Most of the subject in both groups were aged between 30 and 34 years old, the case group 56.5% and controls 47.8%. Both groups have found the same percentage (34.8%) of subjects aged 35–39 years old. In the case group, there were fewer (8.7%), patients aged 40–44 years compared to the control group (17.5 %) with p > 0.05. Nine women (39.1%) were primiparas and 14 women were secundiparas (60.9%) in the case group, whereas in the control group, 2 women (8.7%) were primipara, 20 women (87%) were secundipara, and just 1 woman was grand-multiparity (4.3%) with p < 0.05. Underweight patients was not found in both groups, normoweight in 9 cases (39.1%)

Table 3: Lipid Profile of patients with postpartum preeclampsia and normotensive

| Lipid profile | Case | Control | p-value |
|---------------|------|---------|---------|
| Total cholesterol | 218.39 ± 23.38 | 143.0 ± 18.82 | 0.000   |
| LDL           | 128.60 ± 22.74  | 69.17 ± 23.03  | 0.000   |
| HDL           | 38.60 ± 5.99    | 51.73 ± 8.65   | 0.000   |
| Triglycerides | 202.73 ± 47.16  | 121.30 ± 14.65 | 0.000   |

p-value assessed using T-independent test.

Lipid parameters were significantly different between the preeclampsia and control group (p < 0.05). The average total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglyceride (TG) levels, respectively, in the preeclampsia group were 218.39 ± 23.36 mg/dL, 128.6 ± 22.74 mg/dL, 38.6 ± 5.99 mg/dL, and 252.73 ± 47.16 mg/dL, whereas in the control group was 143 ± 16.8 mg/dL, 69.17 ± 15.77 mg/dL, 51.73 ± 8.65 mg/dL, and 121.3 ± 14.64 mg/dL, Table 3.

Median atherogenic index plasma was 0.43 (0.31–0.95) in the preeclampsia group and 0.20 (0.16–0.23) in the control group (p < 0.05). A similar interpretation was found in the Framingham, which was 6.30 (5.30–11.7%) in the preeclampsia group and 1.70 (1.8–3.90%) in the control group (p < 0.05). Further, the average interpretation of plasma atherogenic index values in the preeclampsia group is classified as high risk while in the low-risk control group, whereas according to Framingham the score is >5% in all cases group and <4% in the control group, although all are classified as low risk, Table 4.

Atherogenic plasma index and FRS had a significant correlation with age and body mass index (BMI), but the atherogenic plasma index does not have a significant correlation with parity in the preeclampsia group.

Discussion

Atherogenic index plasma and FRS are significantly different in postpartum preeclampsia and normotensive groups (p < 0.05), respectively. The AIP parameter was significantly correlated with BMI and age but did not correlate significantly with parity. FRS parameter correlates with all of them. Similar with Aragon-Charris et al. which assessed the atherogenic plasma index in preeclamptic women, their results indicate that patients with severe preeclampsia and mild preeclampsia have significantly higher AIP, TG, and LDL cholesterol values than pregnant controls and the group of patients with preeclampsia shows significantly lower HDL values when compared to normotensive pregnant women [17].

Singh demonstrated that there was an extremely significant increase in the plasma atherogenic index (p < 0.0001) in the case group compared to the control group, 0.3776 ± 0.6592 and 0.2944 ± 0.01178, respectively; the average AIP value was higher in preeclampsia women and 36% were overweight in 6 case group (26.1%) and 7 control group (30.4%), obesity was found in 8 women in case group (34.8%) with p < 0.05. Based on activity, housewife was found in 20 case (87%) and 17 control group (74%), while active workers in 3 case (13%) and 6 control group (26%) with p > 0.05. All women in the study subjects (100%) did not have a history of smoking either before pregnancy or during pregnancy. It is found that late-onset preeclampsia has a greater frequency of 56.5% compared to 43.5% early-onset preeclampsia in this study.

Table 5: Correlation between age, parity, and body mass index with cardiovascular risk assessment of patients with postpartum preeclampsia (case) subjects

| Cardiovascular risk assessment | Age r-value | p-value | Parity r-value | p-value | Body mass index r-value | p-value |
|-------------------------------|-------------|---------|---------------|---------|------------------------|---------|
| AIP                           | 0.585       | 0.003   | 0.242         | 0.266   | 0.610                  | 0.002   |
| FRS                           | 0.506       | 0.000   | 0.255         | 0.011   | 0.520                  | 0.011   |

AIP: Atherogenic index of plasma, FRS: Framingham risk score. r-value and p-value assessed using spearman Rho correlation test.

Median systolic and diastolic blood pressure were 180 (150–200); 100 (90–120) in the preeclampsia group and 110 (100–130); 80 (60–90) in the non-preeclampsia group (p < 0.05), Table 2.
norotensive women. This indicates that women with AIP values >0.24 9.33 times more risk of experiencing cardiovascular risk later in life [12].

For FRS, in this study, both the case and control groups were classified as low risk (<10%), but Framingham scores in preeclampsia patients had a higher risk value than in the control group of 5.5% and a maximum of 11.7% while in the control group a minimum value of 1.0% and a maximum of 3.9%. The same research results obtained from Christensen et al. This study used the FRS (more focused on lipid parameters and BMI) to evaluate the risk of cardiovascular disease in the next 10- and 30-year in women with preeclampsia and normotension. Outcomes were found to be higher in preeclampsia women, although significant results were found in the 10-year FRS with focal point BMI (3.9 vs. 3.0, p = 0.03). This study concludes that this FRS is best used for primary preventive purposes [8], [18].

Average 10- and 30-year cardiovascular risk according to the FRS that has been traced by Breetvald et al. gave comparable results between the preeclampsia and control groups, 1.6% versus 1.5% (p = 0.22) and 9.0% versus 9.0% (p = 0.49). However, women with hypertension after preeclampsia are more likely to develop cardiovascular disease as those who normalize to return after preeclampsia; average 10- and 30-year cardiovascular risk according to the FRS was 3.1% versus 1.5% (p < 0.01) and 19.0% versus 8.0% (p < 0.01), respectively. When explored further, early-onset preeclampsia was more frequent in women who continued hypertension after preeclampsia and showed a higher risk of cardiovascular disease compared to advanced onset preeclampsia: 1.7% versus 1.3% (p < 0.05) and 10.0% versus 7.0% (p < 0.05), respectively [19].

Smith et al. also calculated the risk of cardiovascular disease in women after pregnancy with both preeclampsia (99 people) and not (118 people). The results showed that 18.2% of preeclampsia women and 1.7% of normotensive women suffering from cardiovascular disease in the next 10 years were 13 times (odds ratio [OR] 13.08; 95% confidence interval CI 3.38–85.5), 31.3% of preeclampsia women and 5.1% of normotensive women suffering from the next 30 years were 8 times (OR 8.43; 95% CI 3.48–23.23), and the lifetime risk was 3 times higher (OR 3.25; 95% CI 1.76–6.11) in 41.4% of preeclampsia women and 17.8% of normotensive women [20].

In addition to studies assessing future cardiovascular risk, several studies have been carried out to prove the real cardiovascular damage after preeclampsia. One of them was carried out by Melchiorre et al., this study evaluating left ventricular disorders in patients with preeclampsia 1–2 years postpartum. The result is that patients with a history of preeclampsia have 2 years postpartum essential hypertension that is statistically significant with moderate to severe impairment of function and shape in the left ventricle. Therefore, it is recommended to assess the risk of heart disease 1–2 years of postpartum to provide benefits and therapeutic intervention [21].

Lipid metabolism is an important key pathophysiology of preeclampsia. In normal pregnancy, TG and plasma cholesterol levels increase and over time, the levels return to normal after delivery. Hormonal variations during pregnancy affect lipid metabolism. Female endogenous sex hormones significantly influence serum lipids. During pregnancy, hepatic lipase activity increases and lipoprotein lipase activity decreases. Hepatic lipase is responsible for increasing the synthesis of TGs in the liver, whereas decreased lipoprotein lipase activity also reduces the effects of catabolism in adipose tissue, resulting in increased TG in the circulation and the second step of uptake of the remaining chylomicrons by the liver is inhibited. Another hypothesis is that hypertriglyceridemia is thought to be a consequence of competition between chylomicrons and very LDL-c (VLDL-c) at lipoprotein lipase levels. Chylomicron clearance occurs through two important stages: Hydrolysis of TG by lipoprotein lipase and the remaining uptake by liver tissue. The inhibition in the second stage triggers accumulation in plasma and eventually becomes an atherogenic risk triggered by hypertriglyceridemia. Lipoproteins are rich in TG associated with inflammation, one of which is through VLDL particles that carry apoC-III. ApoC-III can increase molecular bonds in endothelial cells, strengthen bonds with monocytoid cells [14], [22], [23].

Gestational hyperlipidemia plays a physiological role to supply both cholesterol and TG rapidly for fetal development. Maternal TG levels are hydrolyzed in maternal lipoprotein receptors by lipoprotein fan lipase transported through the placenta through fatty acid-binding protein. TG play a role as regulators in lipoprotein interactions. This is supported by evidence that an increase in plasma concentration is associated with an increased incidence of coronary artery disease, an increase in the number of VLDL cholesterol particles and an increase in the potential for the transfer of a cholesterol ester mass from HDL cholesterol to a lipoprotein containing apolipoprotein [24], [25].

Normal pregnancy is associated with increased levels of TG, total cholesterol, and HDL-c. In the first trimester, an increase in deposition and hypertrophy of maternal fat stores with increased expression of insulin receptors such as glucose is available to meet the metabolic needs of the developing fetus. Increased maternal insulin and progesterone trigger lipogenesis as lipid production is produced, which is transported across the placenta and is metabolized for infant growth. These changes are generally non atherogenic and return to normal after delivery. Preeclampsia women had abnormal lipid results. Limited data regarding the effects of high blood pressure on lipid levels but new-onset preeclampsia triggers an increase in atherogenic lipid parameters with a decrease in cardioprotective HDL [25].
Barry et al. in his study stating that uncomplicated postpartum women, visceral fat correlated independently with insulin sensitivity, blood pressure, and phenotypes of atherogenic lipoproteins whereas BMI and total body fat were not related. Intra-abdominal fat plays a role in pathophysiology as a source of free fatty acids, tumor necrosis factor-α, and plasminogen activator inhibitor-1 which contribute to the risk of cardiovascular disease through pro-inflammatory effects, oxidative stress, fibrinolysis disorders, and increased angiotensin II production. Women with a history of preeclampsia have an atherogenic lipid profile and endothelial dysfunction compared to the control group despite having the same adiposity and insulin sensitivity. This suggests that there are separate mechanisms of obesity and insulin resistance that lead to cardiovascular risk factors in normal pregnancy and preeclampsia [26], [27].

In the case of preeclampsia, changes in lipid metabolism are triggered and are a major cause of endothelial dysfunction which reduces the effects of vasodilation-anticoagulation, increased expression of adhesion molecules, and release of cytokines-production of reactive oxygen species. Bellamy et al. confirmed that women with a history of preeclampsia showed an increased risk of hypertension (RR = 3.7), venous thromboembolism (RR = 1.79), and stroke (RR = 1.81). These findings confirm a possible relationship between hypertension in pregnancy and future cardiovascular disease. Lipids trigger hypertension through oxidative stress, then vascular endothelial proliferation and hypertrophy and collagen deposition that trigger thickening of the vascular media intima and narrowing of the lumen of blood vessels. Lipid peroxide stimulates thromboxane synthesis and inhibits endothelial-derived relaxing factor leading to vasoconstriction. Usha et al. and Bhardwaj et al. found dyslipidemia in preeclampsia women increases atherogenicity. In fact, Barden et al. found persistent 6-week postpartum lipid peroxidation in preeclampsia women; another important fact is that vascular lesions on the placental bed are similar to atherosclerotic plaques. Premature cardiovascular mortality is found to be higher in Asian-Indian races. The first episode of myocardial infarction under 40 years affects nearly 4.4% of women of this race (2–3.5 times higher than European women) [12].

Women with a history of preeclampsia have a high prevalence of several major cardiovascular risk factors. Although the estimated risk of a 10-year cardiovascular disease is low (<10%) after delivery, the number is still higher compared to normal postpartum. Framingham scores are strongly influenced by age at screening; therefore, even though in this study, FRS in the low-risk group but the risk of cardiovascular disease will increase rapidly with age if other factors are not controlled. The significant positive correlation of BMI with AIP and FRS values illustrates that postpartum preeclampsia patients need to modify lifestyle, maintain ideal body weight, and increase physical activity. National Guidance in the United States and the United Kingdom recommend that after a diagnosis of preeclampsia, women should be counseled and followed up for cardiovascular risk modification. As limitations of this study, the increase in AIP and FRS were influenced by BMI and age. These factors may be in the same causal factors between preeclampsia and cardiovascular disease. More research is needed with a larger number of samples and matching adjustments. It is also important to evaluate the risk factors for the cardiovascular disease before pregnancy to reduce the confounding factor.

Conclusion

There was a significant difference in atherogenic index plasma and framingham risk score of postpartum preeclampsia compared to normotensive women.

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