The Association of C-Reactive Protein Levels in Second Trimester of Pregnancy with Preeclampsia

Hubungan Kadar C-Reactive Protein pada Kehamilan Trimester II dengan Preeklamsia

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INTRODUCTION

The three major causes of maternal mortality in Indonesia are bleeding (30%), eclampsia (25%) and infection (12%). The World Health Organization (WHO) estimated that the rate of preeclampsia were seven times higher in developing countries compared to developed countries. The prevalence of preeclampsia in developed countries ranges from 1.3% to 6%, while in developing countries from 1.8% to 18%. The incidence of preeclampsia in Indonesia is 128 273 per year, or 5.3%.1

During the last 8 years (from 2005 to 2013), the incidence of severe preeclampsia tends to increase at Dr. Wahidin Sudirohusodo Hospital. The incidence of severe preeclampsia in 2005-2007 by 8%, rising to 8.6% in the period 2007-2009, then in 2009-2011 increased by 13.47% and in the period of 2011-2013 the incidence up to 16.51%.2

Preeclampsia is best described as a special-pregnancy syndrome involving multiorgan systems.3,4 In the past, preeclampsia could be diagnosed whenever we found its clinical triad i.e,
blood pressure $\geq 140/90$ mmHg, proteinuria and edema. Currently, edema is no longer be included in the diagnostic criteria for preeclampsia because edema was also observed in normal pregnancy. Proteinuria was defined as urinary protein excretion exceeds 300 mg in 24 hours, the ratio of protein: urinary creatinine $\geq 0.3$ or presence of protein as much as 30 mg / dl (1+) in a random sample of urine is settled.\textsuperscript{1,5}

The risk factors that have been identified can be helpful in assessing the risk of pregnancy in early antenatal visit. There are two parts of risk factors of preeclampsia, included high risk factors (major factors) and additional (minor factors). High risk for preeclampsia is history of preeclampsia in a previous pregnancy, multiple pregnancy, diseases that accompany pregnancy (chronic hypertension, diabetes mellitus, chronic kidney disease and phospholipid syndrome). Additional risk factors are the body mass index $\geq 35$ kg/m$^2$, vascular diseases, maternal age $\geq 40$, nullipara (the first pregnancy with a new partner or a previous pregnancy is $\geq 10$ years), a history of preeclampsia at her mother or sister, pregnancy with donor sperm insemination, oocyte or embryo, diastolic blood pressure $\geq 80$ mmHg, and proteinuria.\textsuperscript{1}

A study conducted by Rozikhan, in Kendal Hospital found that the risk factors of severe preeclampsia were significantly in the presence of history of preeclampsia (p = 0.001), descent (p = 0.001), the first child parity/nullipara (the first pregnancy with a new partner or a previous pregnancy is $\geq 10$ years), a history of preeclampsia at her mother or sister, pregnancy with donor sperm insemination, oocyte or embryo, diastolic blood pressure $\geq 80$ mmHg, and proteinuria.\textsuperscript{6}

To this date, there are various findings of biomarkers that can be used to predict the incidence of preeclampsia, but none of these tests that have high sensitivity and specificity as well as there is no test filters that are reliable, valid and economical.\textsuperscript{3}

C-Reactive Protein (CRP), a sensitive marker for inflammation and tissue damage, can be a potential marker. Plasma level of CRP increases in cases of acute infection, malignancy, and inflammatory diseases. CRP can bind to chromatin, which is released from necrotic cells or apoptotic cells, and to a small ribonudeoprotein nucleus particles. This shows us that the CRP, in the adjustment function, can play a role in inducing the inflammatory response that is characteristic of preeclampsia.\textsuperscript{7}

Based on that study, our study want assessed the relationship levels of C-Reactive Protein in the second trimester of pregnancy with preeclampsia.

METHODS

This study was conducted at the networking of Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Hasanuddin and primary health centers in the city of Makassar. This study was designed as a prospective cohort study. Consecutive sampling by the number of subjects 115 people. Subjects who suited for the criteria sample of pregnant women at trimester II, then were informed about how's the purpose and objective of the study is worked, and who are willing to participate the study will sign a consent form and then examination was performed. After that we do the questionnaires, included the form data of anamnesis, physical examination and laboratory investigation. Blood samples were taken as much as 3 cc by using a tube serum separator tube (SST) and then they will be sent to a laboratory for examination (Prodia Makassar Laboratory) for measure the levels of C-reactive protein. Patients were followed monthly their pregnancy until the labor time. Final data capture and collect include preeclampsia and time of birth. Data analysis using Fisher's Exact test and Mann Whitney test.

The inclusion criteria of this study were pregnant women with second trimester of pregnancy (24-28 weeks) that antenatal and planned deliveries in the city of Makassar, and women with a complete personal identity and has a phone number that can be contacted and volunteered to followed this study.

Pregnant women with history of metabolic diseases such as diabetes mellitus, cardiovascular disease, and coronary heart disease, were excluded. And if the blood sample lysis, the data were incomplete or did not follow the entire procedure, and patients withdrew for certain reasons.

RESULTS

In this study, we got 115 of the second trimester pregnant women, with gestational age range 24-28 weeks who were willing to be the subject of study from the beginning to the end of the study. Of the 115 subjects, obtained 9 (7.8%) of women who become preeclampsia during the study and serve as a research group, and 106 people who did not become preeclampsia used as a control group. From Table 1 we can see the tendency of
preeclampsia occurs at age 20-35 years, women who did not work, and multiparous.

**Table 1.** Distribution of General Characteristic of the Samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia (n = 9)</th>
<th>no Preeclampsia (n = 106)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>&lt; 20 and &gt; 35</td>
<td>2</td>
<td>22.2</td>
<td>28</td>
</tr>
<tr>
<td>20 - 35</td>
<td>7</td>
<td>77.8</td>
<td>78</td>
</tr>
<tr>
<td>Occupation</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Employer</td>
<td>3</td>
<td>33.3</td>
<td>15</td>
</tr>
<tr>
<td>Housewife</td>
<td>6</td>
<td>66.7</td>
<td>91</td>
</tr>
<tr>
<td>Parity</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Nulli/Primipara</td>
<td>4</td>
<td>44.4</td>
<td>74</td>
</tr>
<tr>
<td>Multipara</td>
<td>5</td>
<td>55.6</td>
<td>32</td>
</tr>
</tbody>
</table>

In Table 2, the data stratified by risk factors of preeclampsia. Of the 23 subjects who did not have the risk factors were 2 (8.7%) subjects who developed into preeclampsia, whereas 92 subjects with risk factors obtained 7 subjects who developed into preeclampsia. Between 5 of preeclampsia risk factors identified in the study subjects, subjects with risk factors of age over 40 years (16.7%), Nulli / primiparous (5.1%), history of previous preeclampsia (33.3%), a history of hypertension in pregnancy in mothers or sisters (10%), which later developed into preeclampsia, although not statistically significant (p <0.05).

Table 3 shows the mean value (mean) of C-Reactive Protein in the preeclampsia group and non-preeclampsia group. There is no significant found a relationship between preeclampsia group and non-preeclampsia group instead in case of elevated levels of C-Reactive Protein.

**Figure 1.** Spreading of C-Reactive Protein Level at Various Samples Study
DISCUSSION

The results of this study showed that 115 samples with second trimester of pregnancy whose CRP levels were checked, as much as 9 subjects who develop preeclampsia. Of the 9 patients who develop preeclampsia, a total of 4 patients had higher levels of C-reactive protein, which is categorized as high ($\geq 4.9 \text{ mg} / \text{l}$), 4 patients had medium levels of C-reactive protein, which is categorized as moderate (1.8 – 4.8 mg / l), and there is one patient who had lower levels of C-reactive protein (<1.8 mg / l).

Based on the study results, there is a tendency of patients with preeclampsia had higher levels of C-Reactive Protein. The mean of CRP in patients suffering from preeclampsia is 5.05 mg / l. Of the 9 patients who suffer from preeclampsia, there were two patients who do not have risk factors for preeclampsia. Based on Fisher’s Exact test results conducted between risk factors for preeclampsia with the incidence of preeclampsia, there is not found significantly the relationship between risk factors and the incidence of preeclampsia. This means that the risk factors that exist is not a confounding factor in this study.

The incidence of preeclampsia varies; it is affected by parity, race / ethnicity, genetic predisposition, environment, socioeconomic and other factors. It is reported that the incidence of preeclampsia in nulliparous population ranges from 3 to 10%. In this study, we found as many as 23 subjects who did not have preeclampsia risk factors, but there were 2 (8.7%) of them developed into preeclampsia. It shows how a pregnancy can trigger a state of hypertension remains a mystery although more research is trying to solve it.3

Extremes of maternal age (under 20 years and above 35 years) increases the risk of preeclampsia.5 In this study, 30 subjects belongs in the extreme age and two of them suffered from preeclampsia. Data on demographic characteristics conducted by Qiu et al (2004) reported that no significant difference between preeclampsia and control groups on the age of the subject.4 Duckitt and Harrington (2005), report of 5 cohort study of risk factors for preeclampsia, multipara with a history of preeclampsia increases the risk until seven-fold (RR 7.19 95% CI 5.85 to 8.83) on five cohort studies.8 In this study, we found that between 3 subjects who have risk factors multipara with a history of preeclampsia earlier, gained 1 (33.3%) subjects experienced preeclampsia. Subjects with a history of preeclampsia in their mother and sister of three-fold increase risk (RR 2.90 95% CI 1.49 to 6.77), and 10 cases obtained 1 (10%) incidence of preeclampsia, although not statistically there is no significance result ($p <0.05$).1,8 It is associated with genetic factors, hereditary tendency due to the interaction of hundreds of genes inherited from both father and mother which controls a number of metabolic and enzymatic functions in every organ, clinically manifest in women who develop preeclampsia.3

According Gammill et al (2010), the role of CRP is particularly interesting in the case of obesity, because CRP is closely related to BMI and is also directly affected by the endocrine function of adipose tissue.9 Benyo et al (2001), shows that there is no difference between the expression of pro-inflammatory cytokines in the placenta of women with preeclampsia compared with controls, so we could say that the increase in inflammatory markers in preeclampsia maternal derived from non-placental source.10 The main CRP is produced by hepatocytes, under the influence of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-\alpha). Both of pro-inflammatory cytokines are produced by adipose tissue. Interestingly, IL-6 and TNF-\alpha also increased in preeclampsia which is clinically manifested.

The association between obesity and preeclampsia has been investigated. In a study aiming to...
understand how the mechanisms by which obesity predispose to preeclampsia, Bodnar et al (2005), found that increased of inflammation (measured by CRP), with a combination of hypertriglyceridemia, covering about a third of the increase in such risks.\textsuperscript{11} Never the less, in this study, BMI measurement in the second trimester of pregnancy can not be used as a source of data that can be associated with CRP because the measurement based on height and weight during pregnancy is also associated with fetal weight, so they were difficult to assess the real IMT, unlike the BMI measurement before pregnancy or early in pregnancy.

It has been proposed that CRP, in accordance with its function, is able to elicit the inflammatory response characteristic of preeclampsia.\textsuperscript{12} CRP is increased in those with preeclampsia; however, there is still debate regarding the potential utility of CRP as an early marker for preeclampsia.\textsuperscript{13} Wolf et al showed that elevated levels of CRP during the first trimester in women suffering from preeclampsia, where Savvidou et al (2002), showed that CRP levels at the end of the second trimester was not associated with preeclampsia.\textsuperscript{14,15}

In this study of 115 subjects showed whom CRP levels were examined in the second trimester of pregnancy, 9 subjects with preeclampsia was 4 of which have high levels of CRP, and there is one that is low CRP levels but experienced preeclampsia. In addition, of the 106 subjects who did not develop preeclampsia, a total of 26 subjects have high levels of CRP but did not develop preeclampsia. This suggests that the increasing of CRP was not significantly different with the incidence of preeclampsia which was obtained $p > 0.094$.

**CONCLUSIONS**

In this study, there were 9 cases of preeclampsia among 115 subjects studied, where there is a tendency of increase in the incidence of preeclampsia in pregnant women with risk factors for age over 40 years, nulli / primiparity, previous history of preeclampsia, and family history of hypertensive disorder in pregnancy. CRP levels in the preeclampsia group on average higher than those not preeclampsia, but these results can not be used as value for predicting preeclampsia. Further research needs to be carried out by using other parameters to determine the extent of C-reactive protein is able to identify women at high risk of developing preeclampsia.

**REFERENCES**