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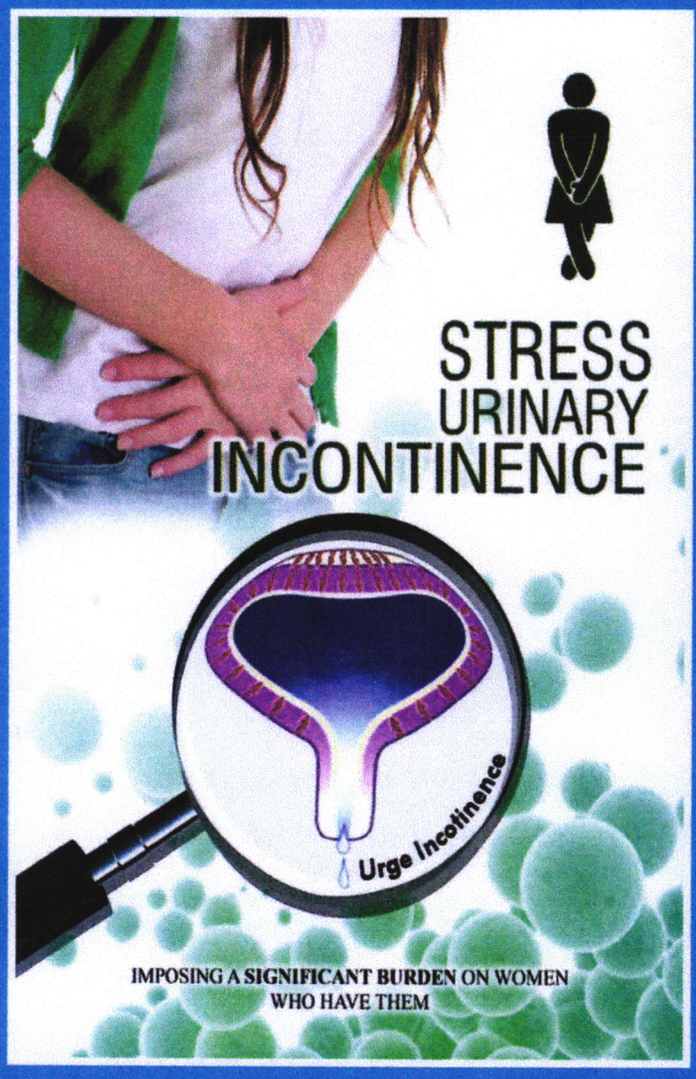

Editorial

Research Articles

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Research Article

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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Abstract

Objective: To determine C-reactive protein in second trimester of pregnancy women who preeclamptic and non-preeclamptic women, and to determine the relationship between the level of C-Reactive protein of trimester two pregnancy and preeclampsia occurrence.

Methods: This was a prospective study conducted at the policlinics of network of academic hospitals of the Department of Obstetrics and Gynecology of Faculty of Medicine, Universitas Hasanuddin and policlinic of child and mother, and some Public Health Centers in Makassar city from September 2015 - April 2016. The C-reactive protein 115 level of pregnant women in pregnancy age of 24-28 weeks was checked, whether the subjects underwent preeclampsia until the childbirth process. Statistics analysis used Fisher's exact test and Mann Whitney test.

Results: The result indicate that 9 subjects (7.8%) developed preeclampsia and 106 subjects did not become preeclampsia. The level of C-Reactive protein increased in preeclampsia group compared to non preeclampsia group i.e 5.05 ± 1.153 : 3.36 ± 0.265, but statistically the result is not significant (value p>0.05).

Conclusion: The average score of C-Reactive protein of preeclampsia group is 33.5% higher than non-preeclampsia group, even though these results cannot be used as the score to predict the preeclampsia occurrence.

[Indones J Obstet Gynecol 2018; 6-1: 18-22]

Keywords: C-reactive protein, preeclampsia, second trimester pregnancy

Abstrak

***Tujuan**: Mengetahui kadar C-Reactive Protein perempuan hamil trimester dua yang menjadi preeklamsia dan bukan preeklamsia, serta mengetahui hubungan antara kadar C-Reactive Protein kehamilan trimester dua dengan kejadian preeklamsia.*

***Metode**: Penelitian ini menggunakan rancangan kohort prospektif, dilaksanakan di Poliklinik RS jejaring pendidikan Departemen Obstetri dan Ginekologi FK UNHAS dan Poliklinik Kesehatan Ibu dan Anak dan beberapa Puskesmas Kota Makassar selama September 2015 - April 2016. Dilakukan pemeriksaan kadar C-Reactive Protein 115 ibu hamil pada usia kehamilan 24 - 28 minggu, kemudian diamati apakah subjek mengalami preeklamsia hingga proses persalinan. Analisis statistik menggunakan uji Fisher's exact dan uji Mann Whitney.*

***Hasil**: Didapatkan hasil 9 subjek (7,8%) berkembang menjadi preeklamsia dan 106 subjek tidak menjadi preeklamsia. Terjadi peningkatan kadar C-Reactive Protein pada kelompok preeklamsia dibanding kelompok bukan preeklamsia yaitu 5,05 ± 1,153 : 3,36 ± 0,265 tapi hasilnya tidak bermakna secara statistik (nilai p>0,05).*

***Kesimpulan**: Nilai rerata kadar C-Reactive Protein kelompok preeklamsia 33,5% lebih tinggi dibandingkan dengan kelompok bukan preeklamsia, namun hasil ini belum dapat digunakan sebagai nilai untuk memprediksi kejadian preeklamsia.*

[Maj Obstet Ginekol Indones 2018; 6-1: 18-22]

***Kata kunci**: C-Reactive Protein, kehamilan trimester dua, 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 ≥ 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 ≥ 0.3 or presence of protein as much as 30 mg / dl (1+) in a random sample of urine is settled.[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 ≥ 35 kg/m^2, vascular diseases, maternal age ≥ 40, nullipara (the first pregnancy with a new partner or a previous pregnancy is ≥ 10 years), a history of preeclampsia at her mother or sister, pregnancy with donor sperm insemination, oocyte or embryo, diastolic blood pressure ≥ 80 mmHg, and proteinuria.[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 (p = 0.001).[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.[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 ribonucleoprotein 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.[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

Characteristic	Preeclampsia (n = 9)		not Preeclampsia (n = 106)		p
	n	%	n	%	
Age (years)					
< 20 and > 35	2	22.2	28	26.4	0.569
20 - 35	7	77.8	78	73.6	
Occupation					
Employer	3	33.3	15	14.1	0.147
Housewife	6	66.7	91	85.9	
Parity					
Nullipara/ primipara	4	44.4	74	69.8	0.118
Multipara	5	55.6	32	30.2	

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.

Table 3. Correlation between C-Reactive Protein with Preeclampsia

	Preeclampsia (n = 9)	No Preeclampsia (n = 106)	p
CRP level	5.05 ± 1.153	3.36 ± 0.265	0.094

In addition, the mean CRP levels in those with preeclampsia was 33.5%, higher when compared with the group with not preeclampsia. Figure 1 shows the distribution of CRP levels in the study subjects. Figure 2 shows the difference in CRP between groups of preeclampsia and non-preeclampsia. In the plot of these data, it appears that CRP levels are not evenly distributed well. It looks at the median value which is not precisely in the middle of the box and whisker at the top and bottom do not have the same length, one of another has a length more than others. It can be concluded that CRP levels are not distributed normally.

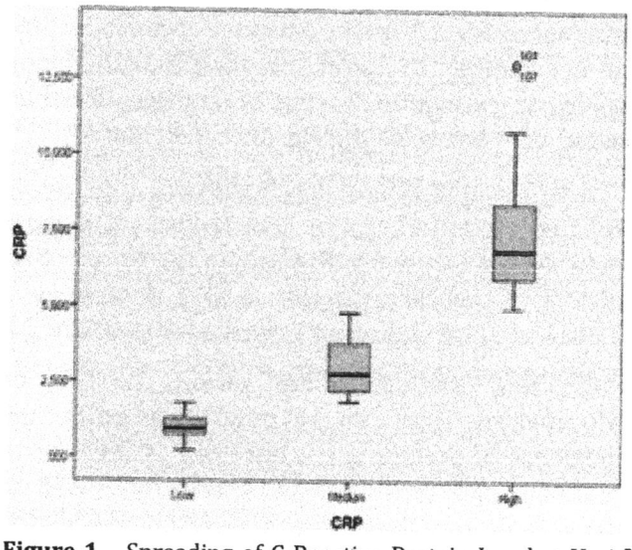

Figure 1. Spreading of C-Reactive Protein Level at Various Samples Study

Table 2. Characteristic Datas of the Risk Factors of Preeclampsia

Characteristic	Preeclampsia		no Preeclampsia		Total	p
	n	%	n	%		
No risk factor	2	8.7	21	91.3	23	0.572
Age > 40 y.o	1	16.7	5	83.3	6	0.394
Nulli/Primipara	4	5.1	74	94.9	78	0.118
History of prior preeclampsia	1	33.3	2	66.7	3	0.219
History of hypertension in pregnancy at their mothers or sisters	1	10	9	90	10	0.573
Gemelli delivery	0	0.0	2	100	2	0.849

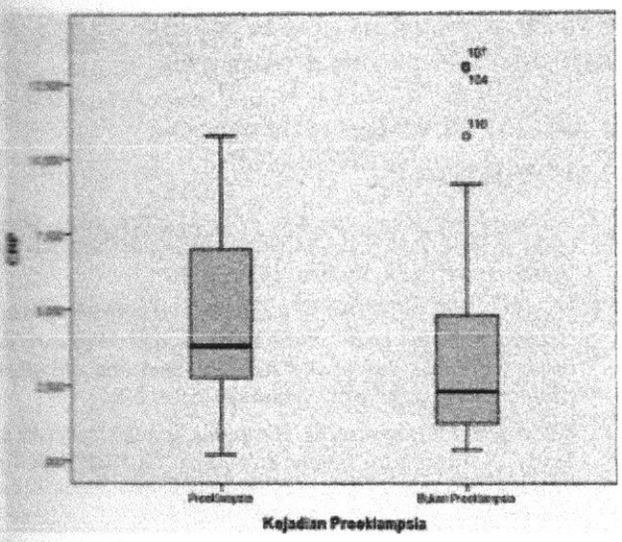

Figure 2. The Difference between CRP Level of Pre-eclampsia Group and non-Preeclampsia Group

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 (≥ 4.9 mg / 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, socioeconomy 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 pre-eclampsia.[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 multi-para 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 8.67), 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-α). Both of pro-inflammatory cytokines are produced by adipose tissue. Interestingly, IL-6 and TNF-α also increased in preeclampsia which is clinically manifested.

The association between obesity and preeclamp-sia 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.[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 elicite the inflammatory response characteristic of preeclampsia.[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.[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.[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.

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