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High level of highly sensitivity c-reactive protein levels (hs-CRP) as a risk factor for preterm delivery

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ABSTRACT

Introduction: Preterm labor is still a global problem because it affects perinatal morbidity and mortality, especially in developing countries. An increase in hs-CRP in pregnant women is associated with the incidence of preterm labor. This study was conducted to prove that high serum hs-CRP levels are a risk factor for preterm labor.
Method: The method used in this study is an observational case-control study, in which pregnant women with preterm labor are in cases group, whereas preterm pregnant women that are not in labor, included in control group. Cases and controls were not matched in the gestational age variable. In both groups blood samples were taken. Blood sampling was taken in the cubital vein to examine the serum levels of hs-CRP. From the data collected, data analysis was performed using SPSS version 23.0. In this study, after the data normality test was performed using the Shapiro-Wilk test, the result p values <0.05 or abnormal distribution data, the Mann Whitney test was chosen. A Chi-square test was performed to determine the increase in serum hs-CRP levels as a risk of preterm labor.
Result: hs-CRP levels as a risk of preterm labor. Calculation of the OR is 19.46 times with 95% CI: 2.25–168.27.
Conclusion: it can be concluded that high levels of hs-CRP as a risk factor for preterm labor.

Keywords: preterm, risk, inflammation, c-reactive protein, outcome.
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INTRODUCTION

Preterm delivery is still a global problem because it affects perinatal morbidity and mortality, especially in developing countries. Preterm labor occurs due to infection and/or systemic inflammation of the decidua-chorion-amniotic, maternal stress that activates the hypothalamic-pituitary-adrenal (HPA) axis corticotropin-releasing hormone (CRH) and corticosteroids, decidual bleeding, placental abruption and uterine overstretching. Due to polyhydramnios or multiple pregnancies that cause increased prostaglandins and collagenases, uterine incompetence and inflammatory reactions associated with elevated levels of high sensitivity C-reactive protein (hs-CRP) can cause preterm labor.

The causes of preterm labor are multifactorial, including ascending infection, ischemic damage of the uteroplacental unit, chronic stress, and fetal and uterine development malformations. The incidence of preterm labor is different in each country, in developed countries for example in Europe and the United States the incidence ranges from 5-11.9%, in Australia the incidence is around 7%. In developing countries, the incidence is higher, for example in India (30%), in Malaysia at 10%.[1,2] Meanwhile, in Indonesia, there is still no accurate data available, but the incidence of low birth weight (LBW) can roughly reflect the incidence of prematurity. The national incidence of LBW in hospitals is 27.9%.[3] In Ujung Berung, West Java, the incidence rate was 14.7%, the incidence rate at Hasan Sadikin Hospital in Bandung was 17.4%, Kariadi Hospital Semarang in 2000 10% and not much change over the last 10 years.[1,4]

The mechanism of preterm labor itself has several stages, such as 1) activation, related to uterine stretching and activation of the fetal HPA pathway; 2) stimulation, refers to the stimulation of the uterus which is activated by various compounds including CRH, oxytocin and prostaglandins. At this stage, inflammatory mediators such as interleukin-1 (IL), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) can be found. 1 It is this CRP that will be discussed in more detail regarding its association with preterm labor.[3]

C-reactive protein is produced in the acute phase of systemic inflammatory reactions, is a sensitive and objective marker for inflammation, and is the first acute-phase protein that has been studied. Associated with inflammation.[5] Research conducted at Sanglah General Hospital (Central General Hospital) found that high CRP levels in preterm patients with labor were higher when compared to CRP levels in preterm patients who had not yet labored.[6]

Highly sensitive C-reactive (hs-CRP) protein is an antibody protein

that is measured using enzyme-linked immunosorbent assay (ELISA) and fluorescence compounds or polystyrene antibodies. Determination of hs-CRP levels has been proposed as a more sensitive measure than conventional CRP measurements and provides better sensitivity in establishing the presence of inflammation. The study aims to prove that high serum hs-CRP levels are a risk factor for preterm labor.

METHOD

The research design used in this study was observational with a case-control study. Pregnant women with preterm delivery were cases, while preterm pregnant women did not give birth as controls. Cases and controls were not controlled for the gestational age variable. In both groups, blood samples were taken for further examination of serum hs-CRP levels. The research ethics commission has approved this research of the medical faculty of Udayana University/Sanglah Denpasar General Hospital.

RESULT

During the period January 2018 to September 2018 there were 48 pregnant women with a gestational age range of 20 to <37 weeks at Sanglah Hospital Denpasar who met the inclusion and exclusion criteria. This study consisted of 24 pregnant women who checked themselves in the Obstetrics and Gynecology section of the Polyclinic as controls and 24 pregnant women who gave birth in the IRD Obstetrics and Gynecology maternity ward Sanglah Hospital Denpasar as cases. In this study, after testing the normality of the data using the Shapiro-Wilk test on the three variables (mother's age, gestational age and parity) the p-value <0.05 or the data was not normally distributed, therefore the Mann Whitney test was chosen to compare the three variables in the study.

Then from the test, the median age of the mother in the control group was 28 years with a minimum age of 17 years and a maximum age of 34 years, the median value in the case group was 27 years with a minimum age of 17 years and a maximum age of 34 years, the p-value was 0.684 or not significantly different. Between maternal age in the control and case groups. The mean gestational age in the control group was 33.5 weeks with a minimum gestational age of 24 weeks and a maximum of 36 weeks, while the mean gestational age in the case group was 35 weeks with a minimum gestational age of 24 weeks and a maximum of 36 weeks, with a p-value 0.013 or significantly different between the gestational age of the control and case groups. The mean parity value in the case and control groups was 0.00 with a minimum value of 0.00 and a maximum of 2.00, the p-value > 0.713 or no significant difference between the parity values between the control and case groups (Table 1).

Table 1. Study participant characteristics.

	Case (n = 24)	Control (n = 24)	*p*
Age (years)	27 (17 – 34)	28 (17 – 34)	0.684
Gestational age (minggu)	35.00 (24 – 36)	33,50 (24 – 36)	0.013
Parity	0.00 (0.00-2.00)	0.00 (0.00-2.00)	0.713

Table 2. Risk analysis table for hs-CRP levels with preterm delivery.

High level of hs-CRP	Persalinan preterm		Total	OR (CI 95%)	*p*
	Yes	No			
Yes	23	13	36		
No	1	11	12	19.46 (2.25 – 168.27)	0.001*
Total	24	24	48		

*Significant (p<0.05)

In this study, from 24 pregnant women in the control group, 11 pregnant women with low hs-CRP levels and 13 pregnant women with high hs-CRP levels were found. Meanwhile, out of 24 pregnant women in the case group, one subject had low levels of hs-CRP. The Chi-Square test obtained significant results with a p-value of 0.001 (Table 5.2). The calculation of the odds ratio (OR) is determined by 19.46 times with 95% CI: 2.25–168.27 (Table 2).

DISCUSSION

Study characteristics

In this study, it was found that there was no significant difference in the mean value of the maternal age variable. This study found the median age of the mother in the case group was 27 years and the control group was 28 years. The study by Manoppo et al. showed the same thing. There was no difference in maternal age between the two groups, namely 29.4 years.[7,8] Another study conducted in India also showed that maternal age in the two groups was also not significantly different, namely 25.33 years and 24.95 years in the case and control groups, respectively. In this study, mothers who were less than 16 years old and more than 35 years old were excluded, so it was hoped that there would be no bias in the study results. According to Behrman et al.[9] teenage pregnancy aged <16 years, especially those with a young gynecological history (adolescents who received menstruation <2 years before their pregnancy) will increase the incidence of preterm labor at gestational age <33 weeks and according to Astolfi et al.[10] women aged >35 years will increase preterm delivery by 64%. Women of productive age in Indonesia are around 27 years old, so many samples are obtained and studied at this age group.

Variable gestational age in this study found the median of the case group was 33.50 weeks, while in the control group it was 35.00 with a range of 24 to 36 weeks. Another study conducted by Nakishbandy et al. showed similar results, with gestational age ranging from 32 to 36 weeks by 56%.[11]

There was a significant difference in hs-CRP levels in the case and control groups, namely the mean hs-CRP level in the case group was 38. while in the control group was 4.80, with a p-value of 0.000. This finding is similar to the results of Elmegeed et al.[12] study, which showed a significant difference in hs-CRP levels in the case group of pregnant

women with gestational age 26-34 weeks who experienced premature rupture of membranes in preterm pregnancy (median hs-CRP level 8.1 mg/dL) compared with control group of pregnant women with gestational age 26-34 weeks with intact membranes and no uterine contractions (median hs-CRP level 1.9) with a p-value of 0.001 (<0.005).[12] In this study, the parity variable obtained a p-value >0.713 or not significantly different parity values between the control and case groups, so it cannot be proven that preterm labor is more common in the first pregnancy and its incidence will decrease with increasing the number of parity at term.[12,13]

High Hs-CRP Levels as a Risk Factor for Preterm Labor

Analysis using Chi-Square test by classifying hs-CRP levels between cases and controls showed a significant difference (p 0.001) between cases and controls. The odds ratio in our study is 19.46 (95% CI 2.25–168.27). This indicates that high levels of hs-CRP can be a risk factor for preterm labor by 19.46 times greater than those of low hs-CRP.

Research conducted by Nakishbandy and Barawi in Iraq reported that of 100 pregnant women in the case group who experienced early uterine contractions, 93% had elevated hs-CRP levels. They also reported a significant association between high hs-CRP levels and preterm delivery when hs-CRP levels increased above 1 mg/dL in the case group compared to the control group (p-value 0.001).[11]

Research conducted by Alghazali et al.[14] showed the average value of hs-CRP levels from the case group, namely 50 pregnant women with preterm delivery of 14.52 mg/dL. In contrast, the control group was pregnant women with preterm pregnancies, but not yet. delivery at 6.36 mg/dL. The results of this study reported high levels of hs-CRP in the preterm delivery group compared to the control group which could significantly indicate the effect of hs-CRP that may play a role in the development and pathogenesis of preterm labor.

Research by Bastek et al.[4] showed that high levels of hs-CRP (≥4.34) increased the risk of preterm delivery twofold (OR: 2.32, 95% CI: 0.93-5.76).[4] High levels of hs-CRP are associated with the risk of preterm labor in this study, hs-CRP which is synthesized by hepatocytes and is an acute-phase protein inflammatory reaction is activated by inflammation that occurs due to preterm labor which then hs-CRP activates the classical complement pathway and is responsible for to eliminate foreign bodies and debris from the blood circulation. Another study showed that hs-CRP enhances opsonization and phagocytosis of apoptotic cells. After the cell undergoes necrosis, the effect of hs-CRP will decrease hs-CRP levels that increase 4-6 hours after the first tissue damage and will continue to increase hundreds of times in 24-48 hours, so that hs-CRP levels will remain high in the acute phase response and return to normal along with structural restoration. and function of the affected tissue.[15] In recent decades high CRP levels measured during pregnancy have been associated with preeclampsia and fetal growth restriction and have been related to the presence of intrauterine infection. Systemic maternal infection can cause cervical ripening and preterm labor via inflammatory cytokines which then produce prostaglandins.

CONCLUSION

From the results of this study, it can be concluded that high hs-CRP levels are a risk factor for preterm delivery. The use of hs-CRP as an inflammatory marker in determining the risk of preterm labor is expected to be an early detection in the context of preventing preterm labor. In addition, larger-scale studies are needed to determine the limits of serum hs-CRP levels in increasing the risk of preterm labor, premature rupture of membranes and other risk factors.

CONFLICT OF INTEREST

All author declares there is no conflict of interest regarding publication of this study.

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ETHICAL STATEMENT

The ethical committee Faculty of Medicine approved this study, with ethical clearance references number LB.02.01/ XIV.2.2.1/2883/2018.

AUTHOR CONTRIBUTION

All authors had contributed to writing the original draft and agreed to the final version of the manuscript for publication.

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