

Relationship of CRP Levels in Pre-Eclamptic and Normotensive with Foetal Birth Weight

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ABSTRACT

Background and Objectives: Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality. It affects the multiple organ systems of the maternal body and may also cause preterm labour, small for gestational age infants, low birth weight, retardation and fetal growth restriction. So, the objective is to determine the level of inflammatory marker i.e. C-reactive proteins in pre-eclamptic and normotensive pregnant women and to find out its correlations with foetal birth weight.

Methods: Analytical study was conducted in the different units of Obstetrics & Gynaecology, Sir Ganga Ram Hospital, Hussain Memorial Hospital and Surraya Azeem Hospital, Lahore from February 2018 to March 2019. The study included 59 cases with preeclampsia and 59 normotensive pregnant women, all in their 3rd trimester. All the females were in the age group of 20-40 years and had a BMI range of 18-25. High sensitive C-reactive protein (hsCRP) levels were measured by Enzyme Link Immunosorbant Assay (ELISA). Statistical analysis was done using SPSS (version 15). The values were significant at the 0.05 level of significance.

Results: C-reactive protein levels were significantly high ($P < 0.001$) in the pre-eclamptic group with a median value of 8.8 (0.3 to 24.5) as compared to 5.4 (0.24 to 9.8) mg/l in the normotensive women. The birth weight of babies was low in the pre-eclamptic group. The high CRP levels were negatively correlated with foetal birth weight in the pre-eclamptic group.

Conclusion: Elevated C-reactive protein level in pregnant women is part of an increased maternal systemic inflammatory response and correlates with low foetal birth weight.

KEYWORDS: Pre-eclampsia, C-reactive protein, Third trimester, Birth weight.

INTRODUCTION

Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality with an estimated worldwide incidence between 3 to 10% of all pregnancies.¹ In Pakistan the incidence of preeclampsia is 19%.² Preeclampsia is a common hypertensive disorder of pregnancy characterized by hypertension that occurs after 20 weeks of gestation in women with previously normal blood pressure accompanied by proteinuria.¹ Placenta is main cause of pre-eclampsia and poor placentation with failure of trophoblastic invasion of spiral arteries is thought to be a primary insult that initiates the complex process of the disease. This poor invasion of uterine blood vessels by the trophoblasts results in hypoxia and oxidative stress. The chronic oxidative stress in placenta leads to severe inflammatory response in the mother.^{3,4} Release of toxic substances results in endothelial injury thus increasing vascular permeability and sensitivity to Vasopressin.⁴ There is

increasing evidence that preeclampsia is a systemic inflammatory disease with activation of haemostatic system and endothelial activation.⁵

C-reactive protein (CRP) is an acute-phase protein with a known inflammatory role. Higher levels of hsCRP are found in third trimester of pregnancies complicated with severe preeclampsia as compared to controls and cases of mild preeclampsia. Adverse outcomes for HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome and intrauterine growth restriction was found to be higher in group with high levels of hsCRP.⁶ Pre-eclampsia is a known risk factor for prematurity and poor foetal growth. It is one of the leading causes of perinatal morbidity and mortality.⁷ Poor placentation with uteroplacental insufficiency in preeclampsia results in compromised blood flow to the foetus which is responsible for intrauterine growth retardation. In severe preeclampsia, the effect on foetal growth is more significant resulting in 12% lower birth rate than

expected.⁸ The objective of the study was to find out the correlation of C-reactive protein (CRP) levels in third trimester of pregnancy with foetal birth weight in pre-eclamptic and normotensive pregnant women.

METHODS

After obtaining approval by ethical committee and institutional review board vide letter No. (H12017/ERC/109), this cross-sectional comparative study was conducted in three hospitals including Hussain Memorial Hospital Lahore, Sir Ganga Ram Hospital Lahore and Surraya Azeem Hospital Lahore. Study population consisting of 59 pre-eclamptic women between 20 to 40 years age in their third trimester of pregnancy and 59 normotensives. The size of the sample was determined by adopting 5% level of significance and 80% power of the test with an expected foetal birth weight of 2.5 ± 0.75 and 2.8 ± 0.41 kg for pre-eclamptic and normotensive respectively. Both groups were matched for BMI and all were in the range of 18 to 25. Women below 20 years and above 40 years were excluded from the study. Known cases of diabetes mellitus, arthritis, renal disease, chronic hypertension, cardiovascular diseases, inflammatory bowel disease and symptomatic infectious diseases (bacterial and viral) were excluded. Women on antibiotic therapy were also excluded. Females in first and second trimester were not included in the study. None of the participants was in labour.

All participants were explained about the nature of this study. Also, written informed consent was taken from the participants prior to the recruitment for the study. Blood pressure reading and blood samples were obtained from the subjects. Liquots of serum samples were kept at -20°C . Standard ELISA – based kits were used for the estimation of serum C-reactive protein (CRP).

STATISTICAL ANALYSIS

Data were analyzed by Statistical Package for the Social Sciences (SPSS) (Version 22.0). The data regarding foetal weight and C-reactive protein level was deviating from normality hence non-parametric test of significance were employed to achieve the objective of the study. The two study groups were compared using Mann-Whitney U test where test results were considered significant with $P\text{-value} \leq 0.05$. Moreover, Spearman correlation was rendered to explore the relationship between variables and linear as well as binary logistic regression analysis to see collinearity of various variables.

RESULTS

Of the 118 patients, 59 pre-eclamptic women and 59 normotensive pregnant women were divided into two groups, respectively. C-reactive protein level was

significantly high in the pre-eclamptic group with median value of 8.8 as compared to 5.4 mg/l in the normotensive women as shown in Table-1. The birth weight of babies was also significantly low for pre-eclamptic mothers. Spearman correlation coefficient between CRP and birth weight was 0.412 in the pre-eclamptic group ($P=0.001$) and 0.111 in the normotensive group ($P=0.397$). It explains that the CRP level has a moderate reverse relationship with foetal birth weight in the pre-eclamptic group (Fig: 1.).

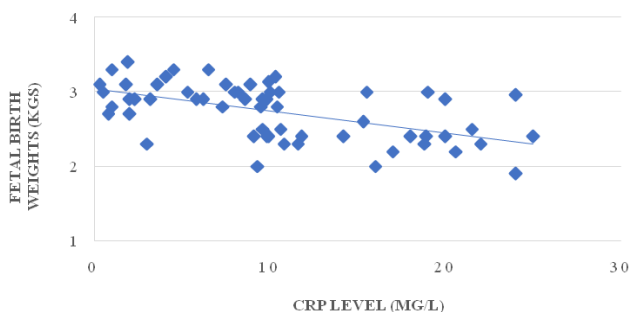


Fig: 1. Correlation between CRP levels and fetal birth weight of pre-eclamptic patients (n = 59).

When data were combined for two groups, the correlation coefficient was -0.349 ($P < 0.001$). The average gestational age at birth was significantly different, 38.0 ± 1.0 and 39.6 ± 0.6 weeks in pre-eclamptic and normotensive groups respectively ($P < 0.001$). The partial correlation between CRP and birth weight adjusted for gestational age at birth was -0.174 ($P = 0.058$).

Table-1: Comparison of CRP levels in two study groups.

Study Groups	CRP Median (mg/l)	P-value
Cases (n = 59)	8.8 (0.3 – 25.5)	0.001
Controls (n = 59)	5.4 (0.24 – 9.8)	

Table-2: Correlation between CRP levels and birth weight.

Study groups	Correlation Coefficient	P-value
Cases (n = 59)	.412	0.001*
Controls (n = 59)	.111	0.397

*P-value ≤ 0.05 is statistically significant

When birth weight was assessed on CRP along with gestational age at birth, it was recorded that the (FBW = $-4.81 - 0.009$ CRP + 0.20 GAB). The coefficient of CRP was insignificant but borderline ($P = 0.058$) and that for the gestational age was significant

($P < 0.001$). When birth weight was assessed on CRP and GAB in binary form, the predictability of birth weight on the basis of CRP was 78.3% with 100% normal weight prediction and odds ratio of 17.68. When adjusted for gestational age, the accuracy in prediction of birth weight improved to 86.7% with an odds ratio of 14.7 and underweight prediction accuracy of 42.3% and normal weight prediction of 98.7%. This showed that if the effect of gestational age at birth was controlled, there were 14.7 times increased chance of low foetal birth weight with high level of C-reactive protein in third-trimester pregnancy.

DISCUSSION

It was determined that in pre-eclamptic women, there were high levels of CRP in the third trimester of pregnancy. It was further observed that C-reactive protein levels were negatively related to foetal birth weight. There are multiple studies which support the hypothesis that persistent and significant systemic hypertension during pregnancy leads to endothelial dysfunction and pre-eclampsia.⁹⁻¹¹ The etiology of preeclampsia is still unknown. The common concept is that poor placentation leads to placental hypoxia which in turn increases the release of inflammatory stimuli into maternal circulation that stimulates the production of pro-inflammatory cytokines by the placenta.

CRP is an acute-phase reactant produced by the liver in response to placental pro-inflammatory cytokines especially IL-6 and TNF- α .^{12,13} Elevated levels of C-reactive proteins in pre-eclampsia also augment the contribution of innate immunity in the pathogenesis of preeclampsia, as it is an important component of innate immune system.¹⁴ Serum levels of CRP are higher in healthy pregnant women as compared to non-pregnant women because even normal pregnancy is accompanied by mild systemic inflammatory response.¹⁵ Higher level of hsCRP were reported in severe preeclampsia as compared to normotensive controls in 2005 by Ustum and colleagues.⁹ They measured CRP levels and reported positive correlation between CRP and Mean arterial pressure. Hwang and colleagues measured serum CRP in normal pregnant women and found similar results. In 2010, Ertas et al.⁶ after studying groups of patients with mild to severe disease, also concluded the same result. They used standard ELISA kit for measurement of CRP levels.

There are few studies which showed an insignificant role of CRP in pregnancies complicated by pre-eclampsia as compared to normotensive pregnant women.^{16,17} It might be owing to the timing of sample collection, variations in sample size and CRP detection technique may be the cause of these results.

In addition to serum hsCRP levels, we studied the correlation of CRP with foetal birth weight and found a

moderate inverse relationship between CRP and foetal birth weight in the pre-eclamptic group which are consistent with the studies conducted by Given (2009) and Gandevani (2012).¹⁸⁻²⁰ The low foetal birth weight may be due to early gestational age at birth in cases as compared to controls. When the effect of gestational age at birth is controlled by regression analysis, there are 14.7 times increased chances of low foetal birth rate with high levels of CRP in third trimester.

CONCLUSION

Significantly high levels of CRP were found in the third trimester in pregnancy complicated by preeclampsia as compared to normotensive pregnant women. The high levels of CRP were found to be negatively correlated with fetal birth weight in the pre-eclamptic group. Further studies with large sample size and improved CRP detection techniques are recommended for the future.

LIMITATIONS OF STUDY

A small sample size and less sampling CRP detection technique due to modest financial resources were the limitations of this study.

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AUTHOR'S CONTRIBUTION

NM, AT and ZIB: Collected data, drafting the article, analysed data and approved the final draft of the manuscript.

MTR, HMD and AS: Conceived idea, analysed data, article drafting, proofread and approved the final draft.

CONFLICT OF INTEREST

None to declare.

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None to disclose.

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