ORIGINAL ARTICLE

Correlation of CRP Levels in Third Trimester with Fetal Birth Weight in Preeclamptic and Normotensive Pregnant Women

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ABSTRACT

Objective: To evaluate the levels of C-reactive protein, an inflammatory marker in preeclamptic and normotensive pregnant women and to determine its correlation with fetal birth weight.

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Unit of Obstetrics and Gynaecology, Shaikh Zayed Hospital and Gynaecological Unit II of Jinnah Hospital, Lahore, from December 2011 to May 2012.

Methodology: The participants included 60 cases with preeclampsia and 60 normotensive pregnant women, all in their third trimester. All the participants 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 Immunosorbent Assay. Statistical analysis was done using SPSS (version 15). The values were considered significant at 0.05 level of significance.

Results: C-reactive protein levels were significantly high ($p < 0.001$) in the preeclamptic group with a median value of 8.8 (0.3 - 25.5) as compared to 5.4 (0.24 - 9.8) mg/l in the normotensive women. The birth weight of babies was also significantly low in the preeclamptic group. The high CRP levels were negatively correlated with fetal birth weight in preeclamptic group.

Conclusion: Elevated C-reactive protein levels in the preeclamptic pregnant women is a part of an exaggerated maternal systemic inflammatory response, and correlates with low fetal birth weight.

Key Words: *Preeclampsia. C-reactive protein. Pregnancy. Third trimester.*

INTRODUCTION

Preeclampsia is a common hypertensive disorder of pregnancy characterized by hypertension that occurs after 20 weeks of gestation in a woman with previously normal blood pressure accompanied by proteinuria.[1] Placenta is central to preeclampsia and poor placentation with failure of trophoblastic invasion of spiral arteries is thought to be the 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. This chronic oxidative stress in placenta leads to severe inflammatory response in the mother.[2] Release of toxic substances result in endothelial injury thus increasing vascular permeability and sensitivity to vasopressin substances.[3] There is increasing evidence that preeclampsia is a systemic inflammatory disease with activation of the haemostatic system and endothelial activation.[4]

C-reactive Protein (CRP) is an acute phase protein with a known inflammatory role. It has been proposed that it may contribute to the inflammatory response seen in preeclampsia. Higher levels of hsCRP are found in third trimester in pregnancies complicated with severe preeclampsia as compared to controls and cases of mild preeclampsia. Also adverse outcomes for hemolysis, HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome and intra uterine growth restriction were found to be higher in group with high levels of hsCRP.[5] Preeclampsia is a well-known risk factor for poor fetal growth and prematurity. Along with eclampsia, it is one of the leading causes of perinatal morbidity and mortality.[6]

Defective placentation with uteroplacental insufficiency in preeclampsia results in a compromise of blood flow to fetus and intra uterine growth retardation. In severe preeclampsia, the effect on fetal growth is more pronounced, resulting in 12% lower birth weight than expected.[7]

The aim of this study was to determine the correlation of C-reactive Protein (CRP) levels in third trimester of pregnancy with fetal birth weight in preeclamptic and normotensive pregnant women.

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METHODOLOGY

This cross-sectional analytical study was conducted in Shaikh Zayed Medical Complex, Lahore in collaboration with Jinnah Hospital, Lahore. The study was approved by the respective Ethical Review Boards of these institutions. Study population consisted of 60 normotensive and 60 preeclamptic pregnant women aged 20 - 40 years, in their third trimester of pregnancy. The sample size was calculated by using 5% level of significance and 80% power of test with expected fetal birth weight of 2.5 ± 0.75 and 2.8 ± 0.41 kg for preeclamptic and normotensive groups respectively. Both groups were matched for BMI and all were in the range of 18 - 25 years. Women with history of smoking, diabetes, renal disease, arthritis, inflammatory bowel disease, chronic hypertension, other cardiovascular illnesses and symptomatic infectious diseases (bacterial and viral) were excluded. Women on antibiotic therapy were also excluded. None of the participants were in labour.[8]

All participants were briefed about the nature of the study and an informed consent was taken from each of them. Blood pressure reading and blood samples were obtained from the subjects. Serum was aliquoted and kept at -20°C. Standard commercial ELISA-based kits (manufactured by Bio check Inc., Foster city) were used for estimation of serum C-reactive Protein (CRP). Laboratory work was performed at National Health Research Council Laboratory, PGMI, Lahore. Data was entered and analyzed by using SPSS version 15.0. The data regarding CRP levels and fetal birth weight was deviating from normality hence non-parametric tests of significance (Mann Whitney U-test) were applied for comparison between the two groups. P-value ≤ 0.05 was considered statistically significant. Spearman correlation coefficient was used to study nature of relation between variables and linear and binary logistic regression analyses were used to see collinearity of various variables.

RESULTS

Data was divided into two groups: Group I consisted of 60 preeclamptic women and group II of 60 normotensive pregnant women. C-reactive protein levels were significantly high (p-value < 0.001) in the preeclamptic group with a median value of 8.8 (0.3 - 25.5) as compared to 5.4 (0.24 - 9.8) mg/l in the normotensive women. The birth weight of babies was also significantly low for preeclamptic women. Spearman correlation coefficient between CRP and birth weight was -0.412 in the preeclamptic group (p=0.001, Figure 1) and 0.111 in the normotensive group (p=0.397, Table I). It explains that the CRP level has a moderate reverse relationship with fetal birth weight in the preeclamptic group. When data were combined for the 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 39.7 ± 0.7 weeks in preeclamptic 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).

When birth weight was regressed on CRP along gestational age at birth it was recorded that the (FBW = - 4.81 - 0.009 CRP + 0.20 GAB). The coefficient of CRP

Table I: Correlation between CRP levels and fetal birth weights by groups.

Group	Spearman's rho	p-value
Preeclamptic	-0.412	0.001
Normal	0.111	0.397
Comparison	Z = -2.933	0.003
Together	-0.349	< 0.001

Table II: Predictability of CRP for fetal birth weight.

	Predicted		Percentage correct
	Low weight	Normal +	
Observed			
Low weight	0	26	0.0
Normal +	0	94	100.0
Overall percentage			78.3

Binary logistic regression with CRP as single predictor

	B	S.E.	Wald	df	Sig.	OR
High CRP	2.873	0.765	14.086	1	< 0.001	17.684
Constant	-2.413	0.889	7.373	1	0.007	0.090

Table III: Predictability of CRP for fetal birth weight keeping gestational age as confounder.

	Predicted		Percentage correct
	Low weight	Normal +	
Observed			
Low weight	11	15	42.3
Normal +	1	93	98.9
Overall percentage			86.7

Binary logistic regression with CRP as predictor and gestational age at birth as confounder

	B	S.E.	Wald	Df	p-value	OR
High CRP	2.688	0.812	10.960	1	0.001	14.696
GAB < 37 weeks	2.848	0.804	12.532	1	< 0.001	17.252
Constant	-7.40	1.866	15.72	1	0.000	0.001

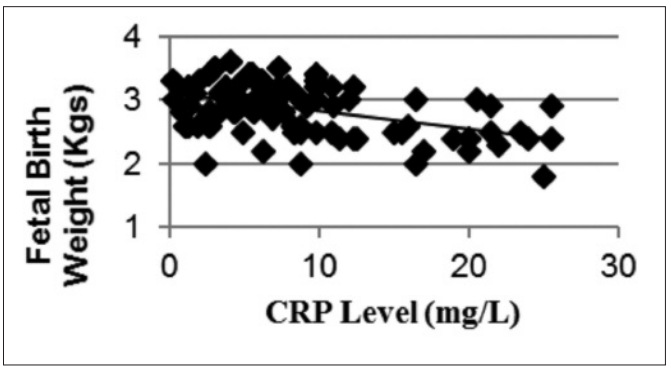

Figure 1: Correlation of CRP with fetal birth weight in preeclamptic group, r = -0.412, p < 0.001 (Spearman's rank correlation test showing moderate negative correlation between CRP levels and fetal birth weight).

was insignificant but borderline (p=0.058) and that for the gestational age was significant (p < 0.001). When birth weight was regressed 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 odd ratio of 17.68 (3.95 - 79.27, Table II). When adjusted for gestational age, the accuracy in prediction of birth weight improved to 86.7% with odds ratio of 14.7 and underweight prediction accuracy of 42.3% and normal weight prediction of 98.9% (Table III). This indicated that if the effect of gestational age at birth was controlled, there was 14.7 times increased chance of low fetal birth weight with high levels of C-reactive Protein (CRP) in the third trimester of pregnancy.

DISCUSSION

It was found that there were high levels of CRP, an inflammatory marker, in third trimester in the preeclamptic pregnant women. It was further observed that CRP levels were negatively correlated with fetal birth weight. These results are consistent with a number of studies, which support the hypothesis that persistent and exaggerated systemic inflammation during pregnancy leads to endothelial dysfunction and preeclampsia.[4,9-11] The etiology of preeclampsia is still unknown. The commonest concept is that poor implantation leads to placental hypoxia, is thought to amplify the release of inflammatory stimuli into maternal circulation which in turn stimulates the production of pro-inflammatory cytokines by the placenta.[5]

CRP is an acute phase reactant produced by the liver in response to such placental pro-inflammatory cytokines, especially IL-6 and TNF-α.[12,13] Elevated levels of C-reactive protein in preeclampsia 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 nonpregnant women because even normal pregnancy is accompanied by mild systemic inflammatory response.[15] High levels of hsCRP were reported in mild and severe preeclamptics as compared to normotensive controls in 2005 by Ustun and colleagues.[4] They used nephlometric assay to measure CRP levels and reported positive correlation between CRP and mean arterial pressure. Hwang and colleagues in 2007 measured serum CRP levels in preeclamptic and normal pregnant women and found similar results. They reported that the levels of hsCRP were significantly high in the preeclamptic group and correlated with severity of the disease.[16] These results were supported by another study in 2009 by Devici and colleagues who found higher levels of hsCRP in preeclamptic pregnant women in the third trimester as compared to healthy normotensive controls.[11]

In 2010, Ertas *et al*. after studying groups of patients stratified by severity of disease as mild and severe preeclamptics concluded that elevated CRP level is useful parameter in severity of preeclampsia.[5] The hsCRP levels were measured using standard ELISA kit in accordance with Can and colleagues (2011) who reported higher levels of hsCRP in severe preeclamptics as compared to normal controls and cases with mild disease.[9]

Contrarily, these results are in contrast to some studies which did not find a significant role of CRP in pregnancies complicated by preeclampsia as compared to normotensive pregnant women.[17-19] Differences in sample size, timing of sample collection and CRP detection technique followed by these studies may be the cause of these results.

In addition to serum hsCRP levels, we studied the correlation of CRP with fetal birth weight and found a moderate inverse relationship between CRP and fetal birth weight in the preeclamptic group. Researchers have found high levels of CRP in severe preeclamptics along with low fetal birth weight.[9,10,16] These results are consistent with the studies by Given (2009) and Gandevani (2012) who reported higher levels of hsCRP in preeclampsia and found negative correlation between CRP and fetal birth weight especially in severe preeclamptics.[20,21] Though the fetal birth weight was significantly low in the preeclamptic cases but this can be due to the 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 fetal birth weight with high levels of CRP in the third trimester of pregnancy.

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

Longitudinal studies with serial measurements of serum CRP would help to elucidate the pathophysiologic consequences of excess CRP during preeclampsia. Preeclamptic mothers with high serum CRP can be screened to have repeated ultrasonography scans and strict follow-up to prevent low fetal birth weight. In future, further research is recommended to find whether therapeutic lowering of the CRP levels will improve fetal birth weight. This would be a milestone in improving fetal health in preeclamptic mothers. Furthermore, correlation of CRP with severity of preeclampsia may also yield interesting results.

CONCLUSION

Significantly high levels of CRP were found in third trimester in pregnancies 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 preeclamptic group.

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