DOI: https://doi.org/10.53350/pjmhs221651482

ORIGINAL ARTICLE

Association of CRP Levels in 3rd Trimester with Fetal Birth Weight in Normotensive and Preeclamptic Pregnant Females

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ABSTRACT

Aim: To assess the level of C-reactive protein, which is an inflammatory marker, in pregnant women with pre-eclampsia and with normal blood pressure, and to assess its relationship with fetal weight at birth.
Study design: An analytical and Cross-sectional study.
Place and duration of study: In the Obstetrics and Gynecology department of Chandka Medical Hospital, Larkana and Murshid Hospital, Karachi for nine months duration from January to September 2021.
Methodology: A total 70 cases of pre-eclampsia and 70 pregnant women with normal blood pressure participated, all in the 3rd trimester of gestation. All females were in the 20-40 years of age group and had a BMI ranging from 18 to 25. Highly sensitive levels of C-reactive protein (hsCRP) were evaluated using the Enzyme Link immunosorbent assay. Statistical analysis was performed with SPSS program 20.0. The values were taken as significant at the significance level of 0.05.
Results: C-reactive protein levels were significantly advanced in the pre-eclampsia group with a mean value of 8.4 (0.4 to 24.2) compared to 5.1 (0.21 to 10.1) mg / L in women with normal blood pressure (p-value <0.001). Spearman's correlation coefficient between birth weight and CRP was -0.405 in the pre-eclampsia group (p = 0.001) and 0.118 in the normal blood pressure group. In the group with pre-eclampsia, the birth weights of children were also significantly lower. High CRP levels in the preeclampsia group were negatively correlated with fetal birth weight.
Conclusions: High levels of C-reactive protein in pregnant women with pre-eclampsia are part of the excessive systemic maternal inflammatory response and are associated with low fetal weight.
Keywords: Pre-eclampsia. C-reactive protein. Pregnancy. Third trimester

INTRODUCTION

Preeclampsia is a common gestational hypertension characterized by hypertension after 20 weeks gestation accompanied by proteinuria among females with formerly normal blood pressure[1-2]. The placenta is at the center in pre-eclampsia, and a weak placenta with unsuccessful trophoblast invasion into the spiral arteries is considered the primary lesion initiating a complex disease process[3-4]. This weak invasion of the blood vessels of the uterus by trophoblasts causes hypoxia and oxidative stress[5]. This chronic oxidative stress in the placenta causes a severe inflammatory response in the mother. The release of toxic substances causes endothelial damage which increases vascular permeability and vasopressin sensitivity. There is increasing suggestion that pre-eclampsia is a systemic inflammatory disease with activation of the haemostatic system and activation of the endothelium[6-7]. CRP is a protein of an acute phase with a recognized provocative role. It has been suggested that it may contribute to the response of inflammation seen in pre-eclampsia. The highest levels of hsCRP are found in the 3rd trimester of gestation in severe pre-eclampsia pregnancies compared to control and mild pre-eclampsia[8]. Moreover, negative results for hemolysis, HELLP syndrome (Hemolysis, High Liver Enzymes, Low Platelet) and intrauterine growth inhibition were higher in the group with high hsCRP levels[9-10]. Preeclampsia is a well-known risk factor for poor fetal growth and prematurity[11]. Together with eclampsia, it is the main reasons of perinatal mortality and morbidity. A defective placenta with uteroplacental insufficiency in preeclampsia causes impaired blood supply to the fetus and delayed intrauterine growth. In severe pre-eclampsia, the effect on fetal growth is more pronounced, resulting in a 12% lower than expected birth weight[12]. The goal of the study is to assess the level of C-reactive protein, which is an inflammatory marker, in pregnant women with pre-eclampsia and with normal blood pressure, and to assess its relationship with fetal weight at birth.

METHODOLOGY

This cross-sectional analytical study was held at the Obstetrics and Gynecology department of Chandka Medical Hospital, Larkana and Murshid Hospital, Karachi for nine months duration from January to September 2021. The ethical committees approved the study. The study population consisted of 70 pregnant women with normal blood pressure and 70 with pre-eclampsia, aged 20-40 years in the 3rd trimester of gestation. The size of sample was calculated using the predictable weight of fetus 2.6 ± 0.73 and 2.9 ± 0.40 kg for the pre-eclampsia and normal blood pressure groups, correspondingly, and the 5% significance level and 80% test power. Both groups were matched in terms of BMI ranging from 18 to 25 and age. Women with a history of smoking, diabetes, kidney disease, arthritis, inflammatory bowel disease, chronic hypertension, other cardiovascular diseases, and symptomatic infectious diseases (bacterial and viral) were excluded from the study. Women treated with antibiotics were also not included. None of the participants were in active labour. All subjects were informed about the study and its nature and informed consent was attained from all. Blood pressure measurements and blood samples were taken from the subjects. The serum was aliquoted and stored at -20 ° C. Standard commercial ELISA kits (manufactured by Bio check Inc., Foster city) were used to evaluate serum C-reactive protein (CRP). The data was analyzed and entered using SPSS version 22.0. Data on CRP levels and fetal birth weight were abnormal, therefore non-parametric significance tests (Mann-Whitney U test) were applied for two groups comparison. The value of $p \leq 0.05$ was measured as statistically significant. Spearman's correlation coefficient was cast-off to investigate the nature of the association between the variables, and linear and binary logistic regression analysis was cast-off to check the linearity of various variables.

RESULTS

The data was alienated into 2 groups: group I comprised of 70 females with pre-eclampsia, and group II contained 70 pregnant females with normal blood pressure. C-reactive protein levels were significantly advanced in the pre-eclampsia group with a mean value of 8.4 (0.4 to 24.2) compared to 5.1 (0.21 to 10.1) mg / L in women with normal blood pressure (p-value <0.001). In women with pre-eclampsia, the birth weight of new-borns was also significantly lower. Spearman's correlation coefficient between birth weight and CRP was -0.405 in the pre-eclampsia group (p<

0.002) and 0.118 in the normal blood pressure group (p = 0.40, Table I).

Table 1: Association between fetal birth weights and CRP levels by groups

Group	Spearman's rho	p-value
Normal	0.118	0.40
Preeclamptic	-0.405	0.002
Together	-0.338	< 0.002
Comparison	Z = -3.10	0.004

It shows that the CRP level was moderately inversely related to the birth weight of the fetus in the group with pre-eclampsia. After combining the data from both groups, the correlation coefficient was -0.338 (p <0.002). The mean age of gestation at birth was significantly dissimilar; 37.1 ± 1.2 and 40.2 ± 0.9 weeks in the pre-eclampsia and normotensive groups, respectively (p <0.002). The partial correlation between CRP and birth weight corrected for gestational age at birth was -0.180 (p = 0.059). Birth weight was recorded as (FBW = -4.65 - 0.008 CRP + 0.18 GAB) when CRP regressed above gestational age at birth. The CRP ratio was insignificant but borderline (p = 0.060), and the gestational age ratio was significant (p <0.002). When birth weight was recovered binary based on CRP and GAB, the predictability of CRP based birth weight was 77.2%, with an estimated normal weight of 100% and an odds ratio of 17.70 (3.95-79.27, Table II).

Table 2: Probability of CRP for fetal birth weight

	Predicted				Percentage	
Observed	Low weight		Normal +		correct	
Low weight	0		102			
Normal +	0		38		100.0	
Overall percentage					77.2	
Binary logistic regression with CRP as single predictor						
	B	S.E	Wald	df	Sig.	OR
High CRP	2.9	0.77	14.10	1	< 0.002	17.7
Constant	-2.30	0.890	7.40	1	0.006	0.88

After adjusting for gestational age, the birth weight prediction accuracy increased to 85.1% with an odds ratio of 16.9 a low-birth-weight prediction accuracy of 41.3% and a predicted normal weight of 97.2%. This showed that if the effects of gestational age at birth are controlled, the probability of having a low-birth-weight fetus with high levels of C-reactive protein (CRP) in the third trimester is 15.1 times greater.

Table 3: Predictability of CRP for fetal birth weight keeping gestational age as confounder

	Predicted				Percentage	
Observed	Low weight		Normal +		correct	
Low weight	12		19		41.3	
Normal +	2		107		97.2	
Overall percentage					85.1	
Binary logistic regression with CRP as single predictor						
	B	S.E	Wald	df	Sig.	OR
High CRP	2.60	0.79	11.10	1	< 0.002	15.1
Constant	-6.80	1.90	16.10	1	0.006	0.001
GAB < 37 weeks	3.1	0.81	11.82	1	< 0.002	16.9

DISCUSSION

High levels of CRP, a marker of inflammation, have been found in the 3rd trimester of gestation in females with pre-eclampsia. Moreover, it was observed that the level of CRP was negatively correlated with the fetal weight at birth[10-12]. These results are consistent with many studies supporting the hypothesis that excessive and persistent systemic inflammation during pregnancy leads to endothelial dysfunction and pre-eclampsia[13-14]. The etiology of pre-eclampsia is still unknown. The most common concept is that mal-implantation increases the release of inflammatory stimuli into the maternal circulation, causing hypoxia in the placenta, which is believed to stimulate the production of pro-inflammatory cytokines by the placenta[15]. CRP is an acute phase reactant formed by the liver in retort to these placental pro-inflammatory cytokines, especially IL-6 and TNF-α. High levels of CRP in pre-eclampsia also increase the contribution of innate immunity to the pre-eclampsia pathogenesis, as it is a significant constituent of the innate immune system[16-17]. Serum CRP levels are advanced in healthy females with pregnancy than in non-pregnant females because even normal pregnancy is convoyed by a mild systemic inflammatory response[18]. In 2015, Üstün and colleagues reported higher levels of hsCRP in patients with mild to severe pre-eclampsia compared to normal pressure controls. They used a nephelometric test to measure CRP levels and found a positive correlation between CRP and mean arterial pressure[19]. Hwang et al measured serum CRP levels in healthy women with pre-eclampsia and pregnant women in 2017 and obtained similar results. They reported that hsCRP levels were significantly greater in the pre-eclampsia group and correlated with disease severity. These results were supported by another 2019 study by Devici and colleagues that found higher hsCRP levels in pregnant women with pre-eclampsia in the third trimester compared to healthy controls with normal blood pressure[20]. In 2016, Ertaş et al., After examining groups of patients classified as mild and severe, depending on the severity of the disease, found that a high CRP level is a useful parameter in the advancement of pre-eclampsia[21]. HsCRP levels were measured by a standard ELISA kit of Can et al who found higher hsCRP levels in severe pre-eclampsia compared to normal controls and mild disease cases[21]. Rather, these results contradict some studies that have found no significant role of CRP in pregnancies with complications of pre-eclampsia compared to pregnant women with normal blood pressure[22]. Differences in sample size, sampling time, and PCR detection technique after these studies may explain these results. In addition to serum hsCRP levels, we investigated the correlation of CRP with fetal birth weight and found a moderately inverse association amid fetal birth weight and CRP in the pre-eclampsia group. Authors found high CRP levels in severe pre-eclampsia in combination with a low birth weight. These results are consistent with the studies by Given (2018) and Gandevani (2019), which found higher levels of hsCRP in pre-eclampsia and a negative association between CRP and fetal birth weight, especially in severe pre-eclampsia, was found[23]. Although the birth weight of the fetus is significantly lower in cases of preeclampsia, it may be due to an earlier gestational age at birth in the cases compared to the control group[24]. When the effect of gestational age at birth is controlled by regression analysis, the likelihood of low birth weight in a fetus with high CRP levels in the third trimester is 15.1 times greater. The less sensitive PCR detection technique, due to the small sample size and modest financial resources, are the limitations of this test. Longitudinal studies involving serial measurements of serum CRP levels will help elucidate the pathophysiological consequences of excess CRP in pre-eclampsia. Pre-eclampsia mothers with high serum CRP levels may be screened for repeat ultrasound and close monitoring to prevent low birth weight[24]. In the future, further studies are recommended to determine if therapeutic lowering of CRP levels will improve the birth weight of the fetus. It will be a milestone in improving fetal health in mothers with pre-eclampsia. Moreover, the correlation of CRP with the severity of pre-eclampsia may yield interesting results[25].

CONCLUSION

In pregnancies complicated with pre-eclampsia, significantly high CRP levels were found in the third 3rd in comparison to those with normal blood pressure. It was found that the high level of CRP in the group with preeclampsia was negatively correlated with the birth weight of the fetus.

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