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ORIGINAL ARTICLE

Serum C-reactive protein in Preeclamptic women in Jos Nigeria

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ABSTRACT

Background: Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality and is thought to result from exaggerated inflammatory response. C-reactive protein (CRP) is a marker of tissue damage and inflammation. We sought to compare the serum level of CRP in women with preeclampsia with those of normal pregnancy. **Method**: A comparative study between 25 pregnant women with preeclampsia and 25 normotensive controls was carried out over a 6-month period between January- June 2012 in the antenatal ward of JUTH. Venous blood for CRP levels was taken at diagnosis prior to commencement of medical therapy. The cases and control were matched for age, parity, gestational age and educational status. The CRP concentration was measured using ELISA. Data was analyzed using STATA version 11.0, College station Texas USA. Student t-test was done to determine the difference in the mean serum CRP levels of preeclamptics compared with normotensive control. Bonferroni's pairwise comparison test was used to compare the level of CRP between those with mild or severe preeclampsia. The level of significance was set at $\alpha < 0.05$. Categorical variables were compared using chi square test or Fisher exact test where applicable. **RESULTS:** There was significant difference in CRP levels between those that had preeclampsia and the control (p-0.001). However, there was no difference in CRP levels between those with mild or severe preeclampsia (p-0.184). There was a strong correlation between the levels of CRP and maternal weight (p-0.003). **CONCLUSION**: Significant difference exists between levels of CRP in women with preeclampsia compared with the normotensive controls, however no difference in the levels of CRP amongst women who had severe and mild preeclampsia. Raised serum CRP could be a useful marker of preeclampsia.

Keywords: C-reactive protein; Preeclampsia; Pregnancy

INTRODUCTION

Preeclampsia is a human-pregnancy-specific disorder [1, 2] characterized by the occurrence of hypertension and significant proteinuria after the 20th week of gestation in a previously normotensive and non-proteinuric woman [3]. It complicates 2-8% of pregnancies [4] and is one of the leading causes of maternal and perinatal morbidity and mortality [2]. It is a complex disorder characterized by generalized vasospasm, intravascular volume contraction, reduced organs perfusion and activation of coagulation cascade. It precedes the onset of eclampsia in most cases [5].

The aetiology of preeclampsia remains unknown [6]. The risk factors for the development of preeclampsia includes, nulliparity, age below 20 years or greater than 35 years, black race, family history, molar pregnancy, multiple

gestation, Diabetes mellitus, chronic hypertension, renal disease, antiphospholipid antibody syndrome, collagen vascular disorder and previous history of preeclampsia [1,4].

The pathophysiology of preeclampsia remains unknown; hence it has been tagged a disease of theories [5,7]. Many theories have been suggested, some of which include abnormal placentation, immunologic intolerance between maternal and fetal tissues, maladaptation to cardiovascular changes, genetic abnormalities and dietary deficiencies [8]. Central to these disorders is placental ischemia leading to the release of circulating factors which causes widespread endothelial cells damage and activation of coagulation system [5].

The features of preeclampsia which include hypertension, proteinuria and varying degrees of ischemic end-organs damage, are thought to result from diffuse endothelial dysfunction [1, 9]. The aetiology of endothelial dysfunction in preeclampsia is not known, but it has been postulated to be part of an exaggerated maternal inflammatory response to pregnancy [10], and increased released of inflammatory cytokines, such as TNF_{α} and IL-6[11]. C-reactive protein is an objective and sensitive index of overall inflammatory activity in the body [12, 13]. For a long time, a role of CRP in preeclampsia has been conceived [12]. It has been shown that CRP is elevated in women with overt preeclampsia [14], however, little is known about whether or not there is a correlation with the severity of the disease.

It has been suggested that CRP, in accordance with its proposed function, may play a role in eliciting the inflammatory response characteristics of preeclampsia [10]. This study therefore sought to compare the serum levels of CRP among preeclamptics with normal pregnant women as well as correlation between CRP and severity of preeclampsia in Jos university teaching hospital (JUTH).

METHODS

A cross-sectional, hospital-based study was done in the antenatal ward of JUTH, a tertiary health institution situated in the central part of Jos. The study population comprised of pregnant women with clinical diagnosis of preeclampsia as cases and women with normal blood pressure without a medical complication as controls. Enrollment was done within a period of 6 months from January – June 2012.

Women with singleton pregnancies with diagnosis of preeclampsia (cases) and normotensive women with singleton pregnancies at similar gestational ages (controls) were sampled. Patients with history of Diabetes mellitus, other cardiovascular illness, symptomatic infectious diseases, premature rupture of membranes or Chorioamnionitis, patients in labour and those with eclampsia were excluded.

C-reactive protein concentration was measured by ELISA method using diagnostic automated kit (Accu Bind Elisa Microwells). Ethical approval was obtained by the institution research and ethical committee. Eligible, cases and matched controls (age, occupation, level of education, socioeconomic status, weight, parity and gestational age) were sampled. The procedure was explained to all subjects and a written consent was obtained. Data was collected from each subject using a questionnaire administered by the researcher and entered into the pro forma. When taking the blood pressure, the woman was rested for 5mins and sitting at a 45-degree angle. The sphygmomanometer cuff of appropriate size was applied around the upper arm at the level of the heart. The mercury sphygmomanometer was used for blood pressure measurement and the Korotkoff sound V (disappearance of the sound) was used to get the diastolic blood pressure. Two blood pressure measurements were taken at least five minutes apart and the average of these was calculated. Sustained elevation of blood pressure was ensured by repeating the above procedure at least four hours later. Urine protein estimation was carried out using dipstick measurement of clean catch mid-stream urine specimen. Five millilitres (ml) of venous blood sample for the serum levels of C-reactive protein estimation was drawn from the cubital vein and sent for laboratory analysis.

The sample size of 22 was calculated using

$2N=4(Z\alpha +Z\beta)^2d^2 /\Delta^2$

Where

Zα- two-sided Z value (e.g. Z=1.96 for 95% confidence interval).

Zβ- Power- 0.80 or 80% =2.84

d- Variance of distribution of mean serum levels of C-reactive protein=65.6%

Δ- The mean difference in serum levels of C-reactive protein,

10-7mg/l=3mg/l

2N=44 So, n=22

RESULTS

The Socio-Demographic, clinical and biochemical characteristics of preeclamptics and normotensive controls as showed in Table 1. These baseline socio-demographic characteristics were similar between control and study groups. Their level of education was also comparable (p-value 0.29).

There was significant difference in the mean weight between controls and cases (69.54 ± 9.9 versus 78.46 ± 17.1; p-value 0.029). Our data also showed marked significant difference in the mean systolic and diastolic blood pressures between controls and cases (106.8 ± 8.0mmHg, 67.6 ± 6.6mmHg verses 165.2 ± 17.3mmHg, 107.2 ± 11.0mmHg respectively; p-value 0.001). The mean values of CRP of the controls and cases were 1.07 ± 1.39 and 7.07 ± 6.65 respectively, p-value 0.001. There was a significant difference in CRP between those that had the disease and the controls. However, using the Bonferroni's pairwise comparison test, our data showed no difference in CRP levels between those with mild or severe preeclampsia (p-value 0.184).

Table 1. Socio-Demographic, clinical and biochemical characteristics

	Controls (n=25)	Cases (n=25)	P-value
	Mean ± SD	Mean ± SD	
Age (year)	28.84 ± 4.48	28.0 ± 5.64	0.97
Parity	0.68 ± 1.14	0.60 ± 1.11	0.90
G A (weeks)	36.84 ± 2.7	36.52 ± 3.1	0.69
Level of Education			
None	1	1	0.29
Primary	2	1	
Secondary	9	4	
Tertiary	13	19	
Weight (Kg)	69.54 ± 9.9	78.46 ± 17.1	0.029
SBP	106.8 ± 8.0	165.2 ± 17.3	0.001
DBP	67.6 ± 6.6	107.2 ± 11.0	0.001
CRP	1.07 ± 1.39	.07 ± 6.55	0.001

CRP, C-reactive protein; DBP, diastolic blood pressure; GA, gestational age; SBP, systolic blood pressure; SD, standard deviation.

Table 2. Multivariate regression of CRP and predictive factors

Predictive factor	Regression co-efficient	P-value	95% CI
Weight (Kg)	0.140	0.003	0.05-0.22
SBP (mmHg)	0.042	0.514	-0.09-0.17
DBP (mmHg)	0.055	0.563	-0.14-0.24
Constant	-16.99	0.001	-24.26-9.72

Table 2 showed the relationship between CRP as a response variable and possible predictive variables in a multivariate regression model. In this model, only weight was independently predictive of CRP level (regression coefficient highly significant after controlling for other covariates in the model; p-value 0.003).Fig. 1 showed a scattered plot with fitted line and lowess regression smoothing of the linear relationship between maternal weight and CRP in our study population.

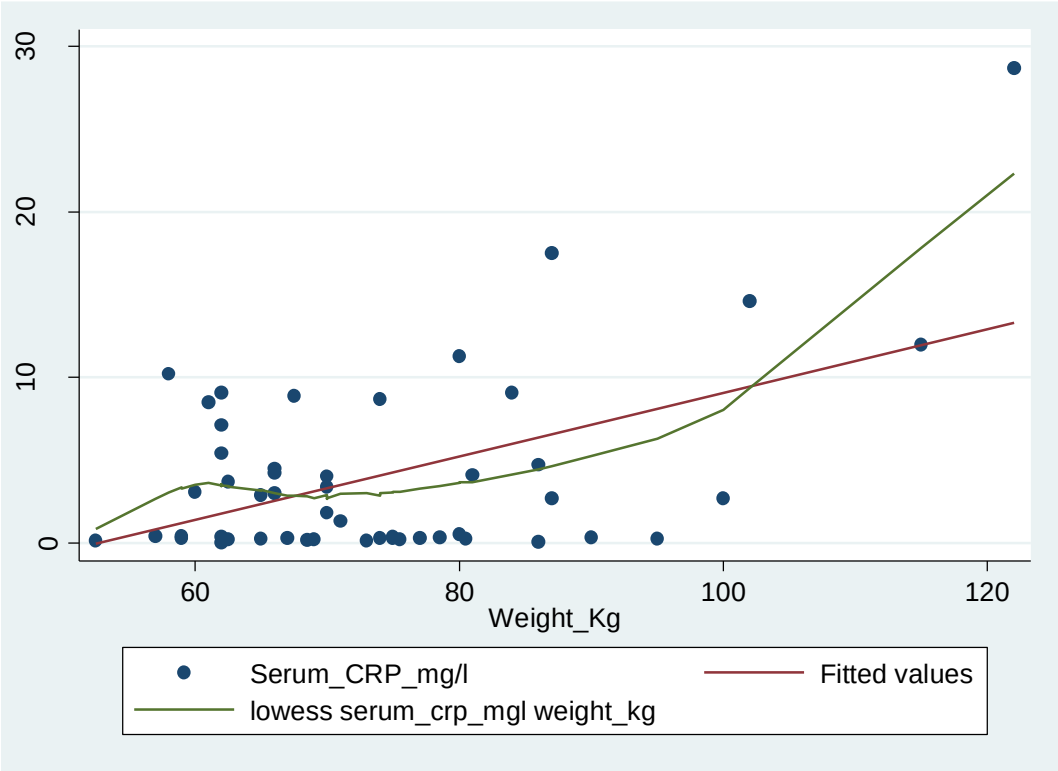

Fig 1: Lowess regression curve

Using the multivariate regression model of CRP as response variable and maternal weight, SBP and DBP as predictive variables, the predictive regression equation below shows the relationship between CRP and maternal weight, DBP and SBP. This means that holding SBP and DBP constant, for every unit change in weight, there is a corresponding change in CRP of 0.14mg/l. CRP (mg/l) = -16.99 + 0.14Xweight (kg)+ 0.042 X SBP + 0.055 X DBP.

DISCUSSION

There is increasing evidence that preeclampsia is a systemic inflammatory disease [15]. Activation of the haemostatic system and endothelial activation are components of systemic inflammatory response [16]. Studies have shown that markers of endothelial activation or inflammation have an active role in preeclampsia [15]. In this study, the mean ages, parity, and gestational ages between the cases and control were comparable. There was no statistically significant difference in their levels of education. However, there was statistical difference in the mean weight, systolic and diastolic blood pressures between the cases and the controls.

In this study, we found that the serum levels of C-reactive protein were higher in women with preeclampsia compared with normotensive controls. This was similar to studies reported in Turkey and Andean women [14,17-20]. Also, comparable results were reported from studies in South Korea, Bulgaria, Sweden and South Africa [21-24]. This is a pointer to the fact that preeclampsia is associated with inflammatory changes. However, another study reported in Lund, Sweden found no difference in the serum levels of C-reactive protein in preeclamptics and normal pregnant women [25]. This may be probably due to the difference in the method of laboratory analysis.

In this study, there was no significant difference between the levels of C-reactive protein in women who had mild and severe preeclampsia. This contrasted with what was reported in Van, Edirne, Kahramanmaras Turkey, Italy and Kerman Iran [15, 19, 26-30]. Here the Mean Arterial Pressure (MAP) were used to indicate the severity of preeclampsia as against the absolute value of blood pressure used in our study. Also, different statistical analyses were used which might account for the differences.

In this study, we found the level of C-reactive protein was greatly associated with

maternal weight. Holding SBP and DBP constant, for every unit change in weight, there is a corresponding change in CRP of 0.14mg/l. This association might explain part of the excess cardiovascular risk linked to obesity [31], and supported the fact that obesity is a validated independent risk factor for preeclampsia [32]. Obesity has an association with hypertension and endothelial dysfunction causing activation of inflammatory mechanism [33]. It has been shown that increase BMI causes increase in C-reactive protein [34]. However, it is not known whether inflammation might be one pathway through which obesity predisposes to preeclampsia [35].

In contrast to our study, Chung Fang Qiu et al reported that lean women with elevated C-reactive protein were associated with 2.5-fold increased risk of preeclampsia, but no similar association was observed in overweight women [36]. A similar study in Turkey also found serum levels of C-reactive protein were negatively correlated with maternal weight [18]. This may be attributed to the methodology. Body mass index (BMI) was used as compared to absolute weight used in our study.

In this study, there was no independent correlation between C-reactive protein levels with either systolic or diastolic blood pressure. This was in contrast with the study in Turkey which showed a strong positive correlation between CRP levels and diastolic blood pressure [18]. This may be due to the differences in the method of laboratory analysis.

LIMITATIONS OF THE STUDY

Proteinuria was defined using the dipstick method instead of a 24-hour urinary protein estimation which is a more objective test. Sub-clinical infection screen was not done which might have affected the levels of CRP.

CONCLUSION

C-reactive protein often associated with inflammatory changes is significantly increased among women with PE which suggest that increased CRP may reflect endothelial cell dysfunction in preeclampsia. There was also a strong correlation between maternal weight and the levels of CRP. Further studies are needed to ascertain the role of anti-inflammatory agents and weight reduction in the prevention or management of preeclampsia.

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