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C-reactive Protein Level in Bangladeshi Preeclamptic Patients and Its Comparison with Trimester-Matched Normal Pregnancy

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Abstract

Introduction with objective: *Preeclampsia is a major cause of maternal and fetal morbidity and mortality in Bangladesh. This study aimed to estimate C-reactive protein (CRP) level among patients with preeclampsia and to compare with those of trimester-matched normal pregnancy.* ***Materials and Methods:*** *: This cross-sectional study was done from January 2005 to December 2006 at the different tertiary care hospital at Dhaka. A total of 33 preeclamptic and 33 normal pregnant women in the third trimester were enrolled in the study. The PE patients were divided into two groups: mild hypertension [diastolic blood pressure (DBP) <110 mm Hg] and severe hypertension (DBP ≥110 mm Hg). Similarly the patients were divided into two groups on the basis of proteinuria, group I (2^{+}≥=1gm/l) and group II (3^{+}≥3gm/l). Both PE and control groups were matched for their age and parity. Estimation of serum CRP was done by Turbulometry method.* ***Results:*** *CRP concentration (mg/l) was 4.55±2.83 in control group and 23.52±24.85 in PE group which was significantly higher than in control group. CRP level was significantly higher (p<0.001) in severe PE than in mild PE group. Significant difference was also seen between the groups subdivided on the basis of proteinuria (p<0.05). In the whole population CRP values showed significant positive correlation with systolic and diastolic blood pressure (p<0.001) and significant negative correlation with gestational age at delivery and birth weight (gestational age: p<0.05, birth weight: p<0.001).* ***Conclusion:*** *Maternal CRP concentration was higher in patients with preeclampsia and was correlated with disease severity.*

Keywords: *Preeclampsia, C-reactive protein, Blood pressure, Proteinuria.*

Number of Tables: *03; Number of Figures: 03; Number of References: 19; Number of Correspondences: 04.*

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Introduction:

Preeclampsia (PE) is a disease unique to pregnancy, characterized by hypertension and proteinuria, seen in 5% to 8% of all pregnancies[1]. Hypertension is the most frequent medical complication of pregnancy, occurring in 10% of pregnancies and being the main cause of perinatal mortality and morbidity[2]. Pregnancy induced hypertension (PIH) occurs in around 16- 24% of first pregnancy and 12-15% of subsequent pregnancies. Preeclampsia complicates 3-5% of first pregnancy and 1% of subsequent pregnancies with around 5-10% being severe[3]. Preeclampsia and hypertensive disorder of pregnancy are major causes of maternal, fetal and neonatal morbidity worldwide. The disease may be mild and inconsequential or cause death or significant maternal morbidity from stroke, seizures, cerebral edema, hepatic failure, renal failure, disseminated intravascular coagulation or placental abruption. Fetal and neonatal conse uences include intrauterine growth restriction (IUGR), stillbirth and severe prematurity due to premature termination of pregnancy for maternal indications[2]. In developing countries, due to the lack of proper antenatal check up, poverty, ignorance and poor education, the incidence of PE is much higher in comparison to the developed nations. In Bangladesh, the incidence is high. It is about 8.2% of

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pregnancies[4]. Clinical features of PE include hypertension, proteinuria and varying degrees of ischemic endorgan damage, which are thought to result from diffuse endothelial dysfunction. Although the etiology of endothelial dysfunction in preeclampsia is unknown, it has been postulated to be part of an exaggerated maternal inflammatory response to pregnancy[5]. Redman and colleagues suggest that preeclampsia is not an intrinsically different state of pregnancy but represents the extreme maternal response to pregnancy. According to them, some diseases in pregnancy and especially preeclampsia, are part of a more generalized intravascular inflammatory reaction involving intravascular leucocytes as well as the clotting and complement systems[5]. Activated circulating leucocytes[6,7], increased production of reactive oxygen species[8] and increased release of inflammatory cytokines [9,10], such as tumor necrosis factor-α (TNF-α) and interleukin-6(IL-6), as well as abnormal activation of the clotting system[11] in women with preeclampsia compared with normotensive women. C-reactive protein (CRP) is used mainly as a marker of inflammation. After onset of inflammatory or acute tissue injury, CRP synthesis increases with 4 to 6 hours, doubling every 8 hours and peak at 36 to 50 hours[4]. In this respect CRP can be a potential marker and play a role in eliciting the inflammatory response characteristic of preeclampsia.

The hepatic synthesis of CRP increases in response to inflammatory cytokines such as IL-1, IL-6 and TNF-α, which are responsible for inflammatory response and maternal endothelial activation in preeclampsia. Higher level of CRP may increase blood pressure by reducing nitric oxide production in endothelial cells, causing vasoconstriction and increasing endothelin-1, coagulation function[12]. Although systemic inflammation has been implicated in the pathogenesis of preeclampsia, available data from studies of maternal CRP concentrations and preeclampsia risk have been conflicting. A cross-sectional study reported that CRP concentrations were 66% higher in women with preeclampsia as compared with controls[13]. Another prospective nested case-control study reported that women with CRP concentrations >4.1mg/L experienced 3.5-fold increased risk of preeclampsia as compared with women whose CRP concentrations were <1.1mg/L[14]. The above evidences have shown that there is significant association of elevated maternal serum CRP concentration in peripheral circulation and increased risk of PE and are believed to correlate with preeclamptic process severity, preterm delivery and poor neonatal outcome. Thus remain a need for more exploratory work to be done in this field. This research work intended to determine the association of elevated maternal serum CRP with risk of PE and negative obstetrical outcome. Hence this is being undertaken to explore the association of serum CRP with preeclampsia and the effect of CRP on fetal outcome.

Materials and Methods:

This cross-sectional study was done from January 2005 to December 2006, at Department of Obstetrics and Gynaecology in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka Medical College Hospital (DMCH), Sir Salimullah Medical College and Mitford Hospital (SSMCH) and Department of Microbiology and immunology, BSMMU. Study population was pregnant women of third trimester, preeclamptic (case group) and normotensive (control group) were selected for the study. A total of 66 pregnant women of third trimester were included consecutively for the study. Convenient sampling was applied here. The researcher interviewed the respondents according to her convenience. Patients were divided into two groups; Out of sixty six, PE group consisting of thirty three women with preeclampsia in third trimester of pregnancy with following criteria, blood pressure ≥140/90 mm Hg taken on two occasions 6 hours apart and urinary protein of 0.3gm/l or more were case group and control group consisting of thirty three women with normal pregnancy in third trimester with following criteria, normal blood pressure throughout pregnancy and no proteinuria were control group. Exclusion criteria were history of hypertension and proteinuria prior to conception or before 20 weeks of gestation, diabetes mellitus, thyroid disease. The cases were further subdivided into mild (BP >140/90 mmHg but <160/110 mmHg with proteinuria of 2+ on dip stick reagent strip) and severe (BP ≥ 160/110 mmHg with proteinuria of 3+ or more on reagent strip) PE group according to degree of proteinuria and severity of blood pressure. The interpretation of dipstick test is 0.3gm/l to <1gm/l =1+, 1 gm/l to <3gm/l =2+ and 3gm/l or more = 3+.Two ml of venous blood was drawn from each of the cases and control subjects taking aseptic precautions. The blood was transferred into a clean, dry test tube and taken to laboratory. Blood was allowed stand still for about 30 minutes to clot. Clot was then separated from the test tube by wooden stick and was centrifuged within 1 hour of collection at 2000 rpm for 5 minutes. The separated serum was carefully drawn by micropipette and was stored in micro-centrifuged tube at -70˚c until the analysis was done. Random urine sample was collected in a clean test tube and assayed for presence of protein by dipstick reagent strip. Estimation of serum CRP concentrations was done by liquid phase immunoprecipitation assay by Turbulometry. Ethical clearance was taken from IRB board of BSMMU. Data was collected by interviewing the patients and doing physical examination and relevant biochemical tests were carried out. The results of investigations were reviewed and recorded in a checklist. All these patients were followed up till delivery. Collected data was placed in a master sheet. The descriptive and analytic assessments were done using the software SPSS for Windows. The data are expressed as mean with standard deviation (±SD). P value <0.05 was taken as statistically significant.

Results:

A total of 66 pregnant women participated in the study. Among them 33 were cases of PE and 33 were normotensive pregnant women. Table I showing analysis of age and blood pressure of study populations. The age range in control group was 19-35 years and in the case group (PE group) was 20-33 years. Most of them were between 21-30years in both the groups. The mean age with standard deviation (±SD) in the

case group was 25.45±4.06 years and in the control group was 25.09±4.27 years (p>.50ns). Both the study groups matched in regard to their age range and thereby there was no statistical difference of age in these groups of patients (Table: I). The mean (±SD) SBP in the study group (PE group) was 153.64 ±14.65 mmHg and in the control group the mean (±SD) SBP was 108.03±9.28 mmHg. The women with PE had significantly higher level of SBP (p<0.001) in comparison to the control group. The mean DBP (±SD) in the control group was 74.85±7.45 mmHg and in the study group (PE group) was 104.70±8.65 mmHg respectively. The preeclamptic group had significantly higher DBP (p<0.001) as compared to the control group. In control group 21 (63.6%) were nullipara, 36% were multipara and in the PE group 51.5% were nullipara, 48.5% were multipara. Both the study groups matched in regard to their parity range and thereby there was no statistically significant difference (p>0.10) of parity in these groups of patients (Table: I).

Table-I: Grouping of study subjects with age, blood pressure and parity distribution

Parameter	Case (n=33) Mean±SD	Control (n=33) Mean±SD	t value	P value
Age (years)	25.45±4.o	25.09±4.2	-0.355	>0.50^{ns}
SBP (mmHg)	153.64±14.6	108.03 ±9.2	-15.117	<0.001*
DBP (mmHg)	104.70 ±8.6	74.85±7.4	-15.018	<0.001*
Nulliparous	21 (63.6%)	17 (51.5%)		>0.10**
Multiparous	12 (36.4%)	16 (48.5%)		

**Chi-square test,* **Chi-square test

Table II showing analysis of gestational age and birth weight in study populations. The mean gestational age during delivery in the control group was 39.18±0.92 weeks and in the case group (PE group) was 35.52±2.40 weeks. The PE patients had significantly shorter gestational age (p<0.001) than the control group during delivery. Mean CRP concentration in the control group was 4.55±2.83 mg/L and in the case group (PE group) was 23.52±24.85 mg/L. There was statistically significant (p<0.001) difference in mean serum CRP concentration in PE group than control group. Mean birth weight in study group (PE group) was 2.10±0.38 and in normotensive patients (control group) was 2.86±0.21 respectively, which was significant (Table:II).

Table-II: Comparison of Gestational age at delivery, C-reactive protein levels, birth weight between case and control

	Control (n=33) Mean±SD	Case (n=33) Mean±SD	t value	P value
Gestational age (weeks)				
At delivery	39.18±0.92	35.52±2.40	8.2000	<0.001*
CRP (mg/L)				
Mean±SD	4.55±2.83	23.52±24.85	-4.357	<0.001*
Birth weight				
Mean±SD	2.10±0.38	2.86±0.21	9.944	<0.001*

**Unpaired Student's 't' test,*

Table III showing analysis of C-reactive protein and birth weight status in preeclampsia cases.The mean C-reactive protein concentration with standard deviation (±SD) in mild PE was 12.48±9.11 mg/L and in severe PE was 42.83± 31.72 mg/L which was statistically significantly higher (p<0.001) than mild PE. Mean birth weight in mild PE group was 2.18±0.37 kg and that in severe PE group was 1.95±0.38 kg. The severe PE group had lower birth weight (p>0.10^{ns})in comparison to mild PE group but the difference is not significant (Table: III).

Table III: C-reactive protein and Birth weight levels among preeclampsia cases

	Mild PE (n=21)	Severe PE (n=12)	t value	P value
CRP (mg/L) Mean±SD	12.48±9.1	42.83±31.7	-4.140	<0.001***
Birth weight (kg) Mean±SD	2.18±0.3	1.95±0.3	+1.577	>0.10^{ns}

*Unpaired Student's 't' test, *** = Significant*

These scattered diagrams showing relation between CRP, birth weight and blood pressure.In the total population systolic and diastolic blood pressure were the only variables that showed significant positive correlation with CRP (SBP: r= +0.608, P<0.001; DBP: r= +0.632, p<0.001) (Fig 1, 2).

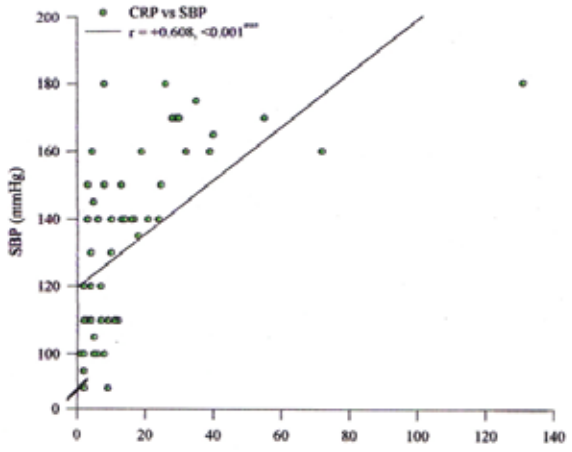

Fig. 1: Relationship between CRP and SBP (Total population, n=66)

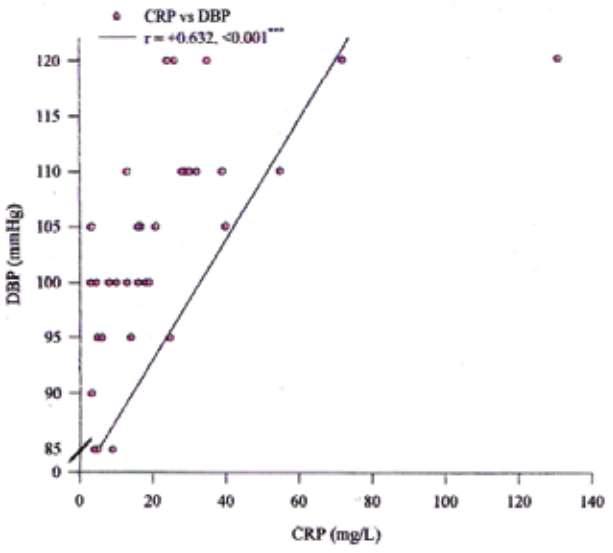

Fig. 2: Relationship between CRP and DBP (Total population, n=66)

Systolic and diastolic blood pressure values were inversely correlated with birth weight of the newborn (SBP: r= -0.744, p<0.001; DBP r= -0.795, p<0.001) (Fig 3). In the whole population multiple regression analysis showed that CRP values were the variables showed significant negative correlation with birth weight (Birth weight: r= -0.492, p<0.001).

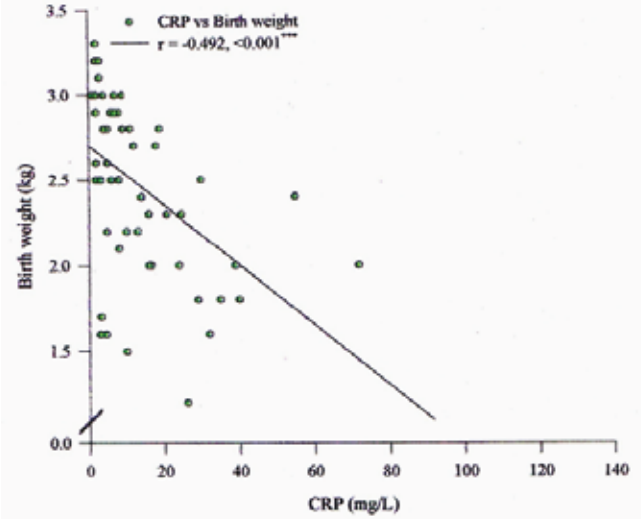

Fig. 3: Relationship between CRP and birth weight (Total population, n=64) There were two stillbirths

Discussion:

Despite intense study, preeclampsia remains a major cause of maternal and perinatal morbidity and mortality and cause remains obscure. In the present study, a total of 66 subjects out of which 33 were preeclamptic and 33 were normal pregnant women. The study group was further classified into 21 mild (DBP<110 mmHg) and 12 severe cases (DBP ≥110 mmHg) according to level of blood pressure.Mean age of the preeclamptic patients (study group) was 25.45±4.06 years with 20 years as minimum and 33 years as maximum. Mean age of normotensive pregnant women (control group) was 25.09±4.27 years with 19 years as minimum and 35 years as maximum. Most of the women were between 21-30 years, which is consistent with the findings by Paternoster et al.[15].They found both the groups matched in regard to age and there was no statistically significant difference with respect to age. Assessing 253 patients in their study they obtained the mean age in preeclamptic patients (n=63) was 32±7 years and in control group (n=190) was 31±5years. In a prospective case control study by Teran et al.traced in their study mean age in preeclamptic patients 24.5±1.6years and 24.4±1.3 years in normal pregnant women[13]. Their finding is almost similar to the findings of this study. Wolf et al. in 2001 explored mean age 29.5 years for normal gestation and in women with preeclampsia[14]. Chunfang et al. in a prospective study analyzed 566 patients and they recorded 70% patients in case group and 72.5% patients in control group and were in the age range of 20-34 years[16]. All these studies showed that there was no statistically significant difference between the groups in respect to age. In this research work, more than half of the women of both groups were nulliparous. In the study group 51.5% were nulliparous and 48.5% were multiparous whereas in control group it was 63.6% and 36.4% respectively. Paternoster et al. assessed 253 patients and showed 43% nulliparous and 57% multipara in control group and 51% and 49% in study group respectively[15]. Chunfang et al. observed 70% nulliparous and 30% multipara in the PE group and 88.3% and 11.7% in the control group respectively[16]. There was no significant statistical difference in parity between the groups in all of these studies, which is consistent with the present study. Mean parity was 2.54±2.04 obtained by Teran et al. in their series[13]. In all the above-mentioned studies subjects were matched in respect to their parity, which corroborate with the findings of the current study. But mean gestational age at delivery for the study group was 35.52±2.40 weeks and 39.18±0.92

weeks in the control group. Preeclamptic patients delivered at a significantly shorter gestational age (t= 8.20, p<0.001). Paternoster et al. observed similar picture in their study. They found gestational age at delivery for the study group and control group were 30.71± 3.69 weeks and 38.01±2.7 respectively[15]. Wolf et al. showed that gestational age at delivery in study group 38±3 weeks and in control group 40±2 weeks. The preeclamptic women delivered at an earlier period of gestation as compared to the normotensive women (p<0.01)[14]. Taking into account of the blood pressure, the study findings showed significant increase in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the preeclamptic patients compared to normotensive women with chronological age and gestational age (p<0.001) enrolled in the study. The mean SBP with standard deviation (± SD) was 153.64±14.65 mm of Hg for the study group and 108.03±9.28 mm of Hg for the control. The mean DBP with standard deviation (± SD) was

104.70±8.65 mm of Hg for study group and 74.85±7.45 mm of Hg for control. Similar blood pressure recordings were observed by many authors. Paternoster et al. found significant difference in SBP and DBP between preeclamptic and normotensive women ($p<0.005$)[15]. According to Teran et al. preeclamptic patients have significantly higher SBP and DBP in comparison to control group[13]. In their prospective study they were convinced by the results that the findings were consistent with other studies. Findings of all these studies are consistent with the present study. The present study was conducted to assess whether CRP level is raised in preeclampsia and to reflect its relation with disease progression. In this study mean CRP in study group is 23.52±24.85 and in control group is 4.55±2.83 mg/L. There is statistically significant difference ($p<0.001$) in CRP concentration between study group and control group. Mean serum CRP was 12.48±9.11 mg/l in mild PE and in sever PE was 42.83±31.72 mg/l. Significant difference ($p<0.001$) in serum CRP concentrations between severe PE and mild PE group was also found. Paternoster et al. showed maternal serum CRP levels were higher in PE group than in the normotensive control group which was statistically significant ($p<0.001$)[15].Their findings came out similar direction as that of current study. Batashki et al. observed a significant difference in plasma concentration of CRP between preeclampsia and those with normal pregnancy in the third trimester ($t=2.92$, $p<0.01$)[17].They concluded that CRP values would be higher in women with preeclampsia and was in agreement with the statement for presence of pronounced inflammation at preeclampsia compared to normal pregnancy and similar to the present series. Wolf et al. in a prospective case control study showed first trimester CRP levels were significantly higher among women in whom preeclampsia subsequently developed compared with controls (4.6 compared with 2.3 mg/L, $p=0.04$)[14]. Teran et al. found similar findings in high risk Andean population[13]. They observed that concentration of C-reactive protein was significantly higher in preeclamptic women (4.11±0.37 mg/dl; $p<0.0001$) in comparison with normal pregnant women (2.49±0.26 mg/dl; $p=0.001$) and non-pregnant controls (1.33±0.15 mg/dl; $p<0.0001$). The difference between normal pregnancy and controls was also significant ($p<0.005$).Wolf et al. reported that women in the highest quartile of CRP experienced a 3.5 fold increased risk of preeclampsia compared with women in the lowest quartile, although after adjusting for prepregnancy BMI in the multivariable model, the OR was greatly attenuated to 1.1[14]. Given that BMI and CRP concentrations were highly correlated and increased BMI and CRP are likely to be in the same causal pathway. Chunfang et al. repeated analyses designed to assess the independent and joint effects of maternal elevated CRP concentrations and prepregnancy overweight status, respectively[16]. They observed that elevated CRP concentrations among lean women were associated with a 2.5 fold increased risk of preeclampsia. Moreover maternal overweight status in the absence of elevated CRP concentration was associated with a 4.9-fold increased risk of preeclampsia. Women who were overweight and who also had elevated CRP concentrations experienced a similar increased risk of preeclampsia (OR = 5.5). Ustun et al. in a case control study done in the third trimester of pregnancy showed plasma CRP levels in mild and severe preeclampsia were significantly higher than that of the normal third trimester pregnant women ($r=0.515$, $p=0.0001$)[18]. This results is consistent with the current study. In this study,preeclamptic mother delivered low birth weight baby than normotensive mother. Mean birth weight in case group was 2.10±0.38 kg and which in control group was 2.86±0.21kg. The difference was statistically significant ($p<0.001$). Birth weight was further analyzed among the case group. Mean birth weight in mild PE cases was 2.18±0.37 kg and in severe PE cases it was 1.95±0.38 kg. Severe PE mother delivered very low birth weight baby than mild PE mother but the difference was not significant statistically ($p>0.10$), small sample size might be the cause. The fact may come out in further studies involving large population. Mean birth weight in the study of Paternoster et al.was 3157.66±7.35.43 and 1342.4±783.3 (g) in normotensive and preeclamptic mother respectively. The difference was highly significant ($p<0.005$)[15].The fact came out in similar direction as in this series. Wolf et al.reported a significant difference in their study regarding birth weight ($p<0.01$). The mean birth weight was 3356±573 and 2986±623 (g) in normal pregnant and preeclamptic mother respectively[14]. Findings of this study is also consistent with the current study. Multiple regression analysis in total population showed that there was strong negative correlation of Systolic and diastolic blood pressure values with birth weight of the newborns (SBP: $r= -0.744$, $p<0.001$; DBP: $r= -0.795$, $p<0.001$).CRP values were inversely correlated with birth weight ($p<0.001$) Higher the CRP levels lower the birth weight during delivery. In the present study CRP level showed significant positive correlation with systolic blood pressure and diastolic blood pressure ($p<0.001$), this is consistent with study done by Paternoster et al[15]. They found similar strong positive correlation of CRP level with systolic and diastolic blood pressure. They also showed in the whole population CRP levels were inversely correlated with birth weight during delivery (Birth weight $p<0.001$) which is similar with the current study. Kumru et al (2005) observed serum hsCRP levels were elevated in women with preeclampsia and showed a strong positive correlation ($r=0.9$, $p=0.05$) with diastolic blood pressure and they also found a negative correlation ($r=0.5$, $p=0.05$) with weight of the newborns[19]. They concluded that hsCRP might be used as a marker for the severity of preeclampsia. Findings of their study corroborate with the data of this study.

Conflict of Interests: None.

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