Serum C-reactive Protein Concentration in Preeclamptic Women: Effect on Pregnancy Outcome

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Abstract:

Background: Preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mm of Hg or more with proteinuria after the 20th gestational week in a previously normotensive and non protein uric women1. According to the National High blood presure Working group (NHBPEP) and American college of obstetricans and Gynecologiests (ACOG) hypertension in pregnancy is defined as a diastolic blood pressure of 90 mm Hg or higher after 20 weeks of gestation in a woman with previously normal blood pressure (NHBPEP, 2000; ACOG, 2002)2 If the disease is allowed to progress to the HELLP syndrome or eclampsia, maternal morbidity and mortality increases. The majority of perinatal losses are related to placental insufficiency, which causes intrauterine growth retardation, prematurity associated with preterm delivery, or abruptio placentae. **Objectives:** This study tried to explore the effect of serum C reactive protein concentration in preeclamptic women and its effect on pregnancy outcome. **Methods:** This case control study included 60 third trimester pregnant women (30 normotensive and 30 preeclamptic) who attended Department of Obstetrics and Gynaecology, BIRDEM and DMCH, during July 2009 and June 2010. Estimation of serum C reactive protein (CRP) concentrations was done by liquid phase immunoprecipitation assay and turbulometry at DMC. **Results:** Mean (±SD) age showed no significant difference between groups; however, BMI, SBP, DBP and CRP were significantly (P<0.001) high in case group. Gravidity and ANC showed no significant variation between groups. CRP concentration was significantly high case group. Gestational age was significantly low in case group resulting in higher preterm delivery. No significant variation was observed regarding fetal outcome; however, birth weight was significantly low and neonatal complication was also significantly high in case group. **Conclusion:** CRP concentration was high in preeclamptics resulting in adverse pregnancy outcome.

Key words: CRP, Preeclampsia, Pregnancy outcome

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Introduction:

Preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mm of Hg or more with proteinuria after the 20th gestational week in a previously normotensive and non protein uric women[1]. Preclampsia is a very serious disease and is the second leading cause of maternal mortality (National High Blood Pressure Education Program Working Group, 2000; USDHHS, 2000), accounting for 16 to 18 percent of all maternal death (ACOG,2002; Cox et al,2004).[2]

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Preeclampsia is the second leading cause of maternal mortality, accounting for 16 18% of all maternal death.[3] If the disease is allowed to progress to the HELLP (hemolysis, elevated liver enzyme and low platelet count) syndrome or eclampsia, maternal mortality increases to as high as 24%, and morbidity levels are even higher. The most common causes of mortality or morbidity are related to abruptio placentae, pulmonary edema, stroke, renal or hepatic failure, myocardial infarction, disseminated intravascular coagulation (DIC) and cerebral hemorrhage.[7]

The majority of perinatal losses are related to placental insufficiency, which causes intrauterine growth retardation (IUGR), prematurity associated with preterm deliv-

ery, or abruptio placentae.[8]

Proteimuria: It is defined as the urnary excretion of 300 mg/L or more of protein in a 24-hour urine collection. This usually correlates with>30 mg/dl (1+by qualitative estimtion using reagent strips). A diluted (<1010 sp.gr) or concentrated (>1030 sp.gr) urine or an alkaline speciemen (pH>8.0) may prodcue false reslults when tested with the reagent strips.

Chronic hypertension: It is defined as hypertension present before the 20th week of preganncy or that present before preganncy (ACOG,2001) Hypertension should be documented on at least two occasions measured at least 4 hours apart (Sibai,2002). Chronic hypertension with superimposed preclampsia: It is defined as proteinuria developing for first time during prenancy in a woman with known chronic hypertension.

Gestational hypertension: Hypertension without proteinuria, develoiping after 20 weeks of gestation, during labor, or the puerperium in a previously normotensive nonproteinuric woman.

Preclampsia: Hypertension associated with proteinuria, greater than 0.3 g/L in a 24 hour urine collection or 1+by qualitative urine examination, after 20 weeks of gestation. Eclampsia: Convulsions occurring in a patient with preclampsia are known as eclampsia.

HELLP syndrome: Severe form of preclampsia characterized by hemolysis abnormal peripheral blood smear, bilirubin>1.2 mg/dl, thrombocytopenia (<100, 000/mm3), and elevated liver enzymes (AST>70U/L, LDH>600 U/L).

Preeclampsia and eclampsia are the most serious complications of pregnancy. A maternal mortality of 2 3% and perinatal mortality of 15% still occurs even in countries with modern obstetric services. In the western countries, the incidence of preeclampsia is about 6% of the general population; the incidence varies with geographic location.[5] Among the American people, highest incidence of eclampsia occurs in the south, and estimated incidence of eclampsia is 1:250 to 1:500 deliveries.[10]

Raised serum C-reactive protein is associated with preeclampsia. The present study was aimed to explore the effect of serum C reactive protein (CRP) concentration in preeclamptic women and its effect on pregnancy outcome.

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in responw to inflammation (an acute-phase protien). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells, (an some types of bacteria) in order to activate the complement system iva clq. CRP is synthesized by the liver in response to factors released by fat cells (adipocytes). It is a member of the pentraxin family or proteins. It is not related to C-peptide or protein C.

CRP was orginally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with C polysaccharide of pneumococcus. Initially it was thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illness including cancer, however, discovery of hepatic synthesis demonstrated that it is a native protein.

The CRP gene is located on the first chromosome (1q21-q23). CRP is a 224-reside protein with monomer molar mass of 25106 dalton. The protein is an annular pentameric disc in shape and a member of the small pentraxins family.

A cross-sectional study reported that CRP concentrations were 66 percent hight in women with preeclampsia as compared with controls (Teran et al, 2001). Another prospective nested case-control study reported that women with CRP concentration >4.1 mg/L experienced 3.5-fold increased risk of preeclampsia as compared with women whose CRP concentrations were <1.1 mg/L (Wolf et al, 2001).[11]

The Aim and Objectives of this study is to find out the association between serum C-reative protein (CRP) and preeclampsia.

Methods:

This case control study included 60 pregnant women in third trimester (30 normotensive and 30 preeclamptic) who attended Department of Obstetrics and Gynaecology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), and Dhaka Medical College Hospital (DMCH), during July 2009 and June 2010.

Inclusion criteria for control subjects were (a) normal blood pressure throughout pregnancy, and (b) no proteinuria, and for case subjects were (a) blood pressure ☒140/90 mmHg taken on two occasions, 6 hours apart after the gestational age 20 weeks, and (b) urinary protein 0.3 g/L or more. Exclusion criteria for both control and case subjects were (a) history of hypertension and/or proteinuria prior to conception or before 20 weeks of gestation, (b) renal disease, (c) diabetes mellitus, (d) any infection, and (e) thyroid disease. Informed written consents were obtained from each study subjects.

Collection of blood and urine

With aseptic precautions, 2 ml venous blood was drawn from each of the study subjects. The blood was transferred into a clean, dry test tube and taken to laboratory. Blood was allowed to stand still for about 30 minutes to clot. Clot was then separated from the test tube by wooden stick and was centrifuged within one hour of collection at 2000 rpm for 5 minutes. The separated serum was carefully drawn by micropipette and was stored in a microcentrifuged tube at 70oC until the analysis was done. Random urine sample was collected in a clean test tube and analyzed for presence of protein by dipstick reagent strip.

Estimation of serum C reactive protein concentrations was done by liquid phase immunoprecipitation assay and turbulometry at DMC.

The data obtained from each individual study subject was included in a predesigned data collection sheet. Collected data was compiled and appropriate analyses were done using computerbased software, Statistical Package for Social Science (SPSS).

Results:

Table I shows characteristics of the study subjects. Age (mean±SD) was 23.23±4.58 and 29.30±3.380 years (no significant difference), BMI 21.81±1.45 and 23.37±1.47 kg/m2 (P<0.001), systolic blood pressure 108.00±7.14 and 148.33±13.41 mmHg (P<0.001), diastolic blood pressure 69.67±5.56 and 106.67±6.99 mmHg (P<0.001), and C reactive protein 0.63±0.49 and 10.57±6.71 mg/dl (P<0.001) in control and case groups, respectively. Statistically, age showed no significant difference between groups, however, BMI, SBP, DBP and CRP were significantly (P<0.001) high in case group.

In control and case group, respectively, gravidity was primi in 12 (40%) and 15 (50%), and multi in 18 (60.0%) and 15 (50.0%); and antenatal care was regular in 5 (7.9%) and 3 (8.1%), irregular in 13 (20.6%) and 10 (27.0%), and none in 23 (36.5%) and 10 (27.0%). None of these parameters showed significant variation between groups. C reactive protein was normal (☒0.8 mg/dl) in 25 (83.3%) and 2 (6.7%), and raised (>0.8 mg/dl) in 5 (16.7%) and 28 (93.3%) control and case subjects, respectively; statistically the distribution was significant (P<0.001).

Table II shows pregnancy outcome. Gestational age (mean±SD) at delivery was significantly low (P<0.001) in case group (35.24±2.33 weeks) compared to control (37.49±2.53 weeks). In control and case group, respectively preterm delivery was in 16 (25.4%) and 27 (73.0%), and term delivery in 47 (74.6%) and 10 (27.0%); the distribution is significant (P<0.001).

Fetal outcome shows no significant variation between groups; in control all 30 (100%) babies were livebirths, and in case 27 (90%) livebirths and 3 (10%) IUD/stillbirth; statistically no significant variation. Overall birth weight (mean±SD) was significantly low

(P<0.001) in case group (n=27, 2.40±0.27 kg) compared to control (n=30, 2.76±0.30 kg). In control group low birth weight babies (<2.5 kg) were 3 (10%) compared to 8 (29.6%) in case; and normal birth weight (⊠2.5 kg) babies were 27 (90%) and 19 (70.4%); statistically no significant variation. In control group (n=30), none of the babies suffered from any neonatal complication, however, 5 (18.5%) babies of case group (n=27) suffered asphyxia; which is statistically significant (P<0.05).

Table-I

Characteristics of the study subjects (n=60)

Parameters	Control (n=30)	Case (n=30)
Age (years)		
	23.23±4.58	23.90±3.80
	(17.00 32.00)	(18.00 32.00)
Body mass index (kg/m2)	21.81±1.45	23.37±1.47***
	(18.75 24.46)	(20.45 26.40)
Systolic blood pressure (mmHg)	108.00±7.14	148.33±13.41***
	(100-120)	(130-180)
Diastolic blood pressure (mmHg)	69.67±5.56	106.67±6.99***
	(60-80)	(100-120)

Date Presented in mean±SD figare in Paretnesis in dicate ranogs, ***=p<0.00.

Table-II

Frequencing % by Gravidity, Anternl case & C-reactive protein (n=60)

Values in parenthesis Indicate range	Control No.(%)	Case No.(%)
Gravidity		
Primi	12 (40.0)	15 (50.0)
Multi	18 (60.0)	15 (50.0)
Antenatal care		
Regular	5 (7.9)	3 (8.1)
Irregular	13 (20.6)	10 (27.0)
None	23 (36.5)	10 (27.0)
C reactive protein (mg/dl)		
Normal (0.8)	25 (83.3)	2 (6.7)**
Raised (>0.8)	5 (16.7)	28 (93.3)
Mean±SD	0.63±0.49	10.57±6.71***
Range	0.02 1.60	0.08 25.00

Unpaired Student's 't' test/Chi square test, **=P<0.00, ***=P<0.001

Discussion:

In Inflammatory or acute tissue injury, CRP synthesis increases with 4 to 6 hours, doubling every 8 hours and peak at 36 to 50 hours.[12] The peak level is as much as 0.4 g/L within 24 to 48 hours. CRP levels remain elevated with ongoing inflammation and tissue destruction but with resolution they decline rapidly, because of a relatively short half life of 17 hours.[13] A cross sectional study reported that CRP concentrations were higher 66% in women with preeclampsia as compared with controls.[14] Another prospective nested case control study reported that women with CRP concentration >4.1 mg/L experienced 3.5 fold increased risk in preeclampsia as compared with women whose CRP concentrations were <1.1 mg/L.[15] These findings show that there is significant association of elevated maternal serum C reactive protein concentration in peripheral circulation and increased risk of preeclampsia and are believed to correlate with preeclamptic process severity, preterm delivery and poor neonatal outcome. The present work was intended to find out effect of maternal CRP in preeclamptic women on fetal outcome in our country.

Mean age of case group was 23.90±3.80 years (range 18 32), and control group was 23.23±4.58 years (range 17 32, which is consistent with the findings of Paternoster et al.[16] They found that 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 case (n=63) group as 32±7 years and in control (n=190) group as 31±5 years. In a case control study, Teran et al. reported mean age in case group as 24.5±1.6 years and control group as 24.4±1.3 years.14

Table-III
Pregnancy outcome (n=60)

Parameters	Control (n=30)	Case (n=30)	P value
Gestation (weeks)			
Mean±SD	38.47±0.97	36.27±0.91	0.0001 ***
Range	37.00 -40.00	34.00 -38.00	
	No. (%)	No. (%)	
Birth weight (kg)	(n=30)	(n=27)	
Mean±SD	2.76±0.30	2.40±0.27	0.0001 ***
Range	1.90 -3.20	1.80 -2.90	
Delivery (weeks)			0.0001 ***
Preterm (<37)	0	20 (66.7)	
Term (≥37)	30 (100.0)	10 (33.3)	
Fetal outcome			0.076 ns
Livebirth	30 (100.0)	27 (90.0)	
IUD/Stillbirth	0	3 (10.0)	
Low/Normal birth weight		0.061 ns	
Low <2.5)	3 (10.0)	8 (29.6)	
Normal (≥2.5)	27 (90.0)	19 (70.4)	
Neonatal complication			0.014 *
None	30 (100.0)	22 (81.5)	
Asphyxia	0	5 (18.5)	

Chi -square test/Unpaired Student's 't' test, ns = Not significant, * = P<0.05, *** P<0.001.

Their finding is almost similar to our finding. BMI in control and case groups were mean (±SD) 21.81±1.45 and 23.37±1.47 kg/m2, respectively.

In our study, half (50%) of the women of case group were primigravida and half of the women were multigravida. In the control group 40% were primigravida and the rest 60% multigravida Paternoster et al. assessed 253 patients and found 43% primigravida and 57% multigravida in control group, and 51% and 49% in case group respectively.[15] Chunfang et al. observed 70% primigravida and 30 multigravida in preeclampsia group and 88.3 and 11.7%, respectively, in control group.[18] There was no significant statistical variation in parity between the groups in all these studies, which is consistent with the present study.

The present study was carried out to assess whether CRP

level is raised in preeclampsia. In the present study, mean (±SD) CRP was significantly raised (P<0.001) in case group was 10.57±6.71 mg/dl compared to control group 0.63±0.49 mg/dl, which is consistent with the findings of Paternoster et al. showed maternal serum CRP levels were higher in preeclampsia group than in the control group (P<0.001).[15] Batashki et al. observed a significant difference (P<0.01) in plasma concentration of CRP between case and control group in their third trimester.[16] 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, which is similar to the present study.

Teran et al. showed similar results in high risk Andean population.[18] They observed that concentration of CRP was significantly higher in preeclampsia women (4.11±0.37 mg/dl; P<0.001) in comparison to normal pregnant women (2.49±0.37 mg/dl; P<0.01) and nonpregnant control (1.33±0.15 mg/dl; P<0.001). The difference between normal pregnancy and control was also significant (P<0.01).

Recent studies demonstrated increased levels of CRP in women with preeclampsia.[13,18]

Mean birth weight in the study by Paternoster et al. was significantly high (P<0.001) in control (3.16±0.74 kg) and compared to case (1.34.0.40±0.78 kg), which is consistent with our findings (control: 2.70±0.23; case: 2.56±0.27; P<0.001).[15]

Findings of the present study also showed elevated CRP in women with preeclampsia and adverse pregnancy outcome.

Conclusion:

Current research suggest that elevated maternal CRP level is associated with preeclampsia and may be the cause or the effect of preeclampsia. Therefore, identification of raised CRP levels and appropriate measures like intervention, close monitoring, if delivery is not chosen, should be done for maternal and fetal complications, such as IUGR and uteroplacental insufficiency. These might affect the occurrence and severity of the morbidity and mortality associated with preeclampsia. Persisting high CRP level is an area of concern, where obstetricians can focus their attention, and in this respect, CRP levels may be clinically useful to monitor disease activity response to treatment in preeclampsia patients.

Further studies involving larger sample size, in which CRP and other inflammatory markers are assayed at multiple time points in pregnancy and postpartum period are needed to support the findings of the present study. Multicentric study may answer the correlation and mechanism how CRP levels are altered in preeclamptic women in terms of geographic variation. Present study was undertaken in women with established preeclampsia and was not possible to determine whether the increase of CRP was a cause or consequence of the disease. Therefore, it would be necessary to undertake a longitudinal study of CRP from early pregnancy before onset of preeclampsia.

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