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Association of Highly Sensitive C-Reactive Protein with the Severity of Preeclampsia and Fetal Outcome

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Abstract

Background: Preeclampsia is one of the most common complications of pregnancy and leading cause of maternal mortality and morbidity as well as neonatal mortality and morbidity. There is exacerbated inflammation and endothelial dysfunction in preeclampsia.

Objectives: The aim of the study was to evaluate the association between highly sensitive C-reactive protein and the severity of preeclampsia and fetal outcome in a tertiary care hospital.

Methods: This case-control study was carried out in the Department of Obstetrics & Gynecology of Dhaka Medical College Hospital, Dhaka. A total of 60 preeclampsia patients 30 PE with severe features (cases group) and 30 PE without severe features (controls group) having gestational age between 32 to 40 weeks admitted in the Department of Obstetrics and Gynecology, fulfilled the selection criteria were enrolled in this study.

Results: Maximum study subjects were in 21 – 30 years age group. Mean age of the study subjects was 28.13 ± 6.02 and 26.07 ± 5.44 years in PE with severe features and PE without severe features respectively. There was significant positive correlation of hsCRP with systolic BP and diastolic BP. hsCRP was found significantly higher in PE with severe features (13.90 ± 3.16 mg/L) than PE without severe features (7.59 ± 2.41 mg/L). In this study hsCRP found significantly higher in neonates with low APGAR score, IUGR, Stillbirth, LBW, Prematurity

Conclusion: Raised highly sensitive C- reactive protein has a significant association with severity of preeclampsia and adverse fetal outcome.

Keywords: hsCRP; PE; Fetal outcome

Introduction

Preeclampsia is one of the most common complications after 20 weeks of gestation and characterized by high systemic blood pressure and proteinuria (ACOG practice bulletin 2002) [1]. It affects 2-8% of the obstetrics population worldwide and associated with higher maternal mortality and morbidity as well as neonatal mortality and morbidity (Duley et al., 2009) [2]. Globally 76,000 women and 500,000 babies die each year from this disorder (Kuklina et al., 2009) [3]. Furthermore, women in low resource countries are at a high risk of developing preeclampsia compared with those in high resource countries (Poon et al., 2019) [4]. In Bangladesh the incidence is alarmingly high and about 24% maternal death is associated with Eclampsia, a complication of preeclampsia Other major complications of preeclampsia is premature delivery and need for NICU utilization with its inherent problem [5]. About 10% of women with

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preeclampsia/eclampsia develop HELLP syndrome. The disease may be mild and inconsequential or may be severe enough to cause death or significant maternal morbidity from stroke, seizures, cerebral oedema, hepatic failure, renal failure, HELLP syndrome (haemolysis elevated liver enzymes and low platelet count), disseminated intravascular coagulation (DIC), abruptio placentae. Fetal and neonatal consequences include intrauterine growth retardation (IUGR), still birth and severe prematurity due to premature termination of pregnancy for maternal indication (Deirdre, 2004) [6]. FIGO adopts the definition of preeclampsia which is provided by the International Society for the Study of Hypertension in Pregnancy (ISSHP) (Poon et al., 2019) [7].

The cause of preeclampsia remains unknown but many factors seem to be associated with its development (Sibai et al., 2005) [8]. The exact pathogenesis of preeclampsia is not determined so far. It is suggested that toxic combination of imbalance of angiogenic, hypoxia, impaired immunity and inflammations are associated with the occurrence of preeclampsia. C-reactive protein is an important component of the innate immune system and is initially produced in the liver as an acute phase protein in response to inflammatory stimuli (Black et al., 2004) [9]. C-reactive protein is an acute phase protein widely used as an indicator of infectious or inflammatory conditions. Traditionally it has been used as an adjunctive test for inflammation and as a marker of disease activity (Azizia et al.,2005) [10].

Normal human serum contains C-reactive protein <10 mg/L and this value increases with age but no difference between sexes (Palosuo et al., 1986) [11]. Slightly higher levels are found in late pregnancy mild inflammation and viral infection causes elevation in the range of 10-40 mg/L, while moderate inflammation and bacterial infection may produce level of 40-200 mg/L. Level over 200 mg/L are found in severe bacterial infections and burns [12]. C-reactive protein being a sensitive marker of tissue damage and inflammation, can be a potential marker and play a role in eliciting the inflammatory response characteristics of preeclampsia (Paternoster et al., 2006) [13].

Methodology

This case-control study was carried out in the Department of Gynaecology and Obstetrics, Dhaka Medical College Hospital, during July 2019 to June 2021. A total of 60 patients were participated in the study. Patients admitted into indoor of Obstetrics and Gynecology Department, Dhaka Medical college Hospital fulfilling the selection criteria were included in this study. Study sample included preeclampsia with severe features (Case group) and preeclampsia without severe features (Control group). After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

Results

Table I shows Age distribution of the study population. Maximum study subjects were in 21 – 30 years age group. Mean age of the study subjects was 28.13 ± 6.02 and 26.07 ± 5.44 years in PE with severe features and PE without severe features respectively. There was no significant difference among the groups.

Table II shows obstetrics parameters of the study subjects. Nullipara was higher in PE with severe features and multigravida was higher in PE without severe features. Antenatal care was found more irregular in PE patients with severe features subjects than without severe features. Preterm pregnancy was higher in PE with severe features than PE without severe features. There were no significant differences in parity, gravidity, antenatal care and gestational age between the groups.

Table III shows systolic and diastolic blood pressure were found significantly higher in PE patients with severe features than without severe features. hsCRP was found significantly higher in PE with severe features than PE without severe features.

Table IV shows APGAR score of the neonate was significantly better of PE patients without severe features than with severe features patients both at birth and at 5 minutes. Average birth weight of the neonate was found significantly higher of the PE patients without severe features than with severe features patients. There was 5 (16.7%) very LBW of neonates of PE with severe features patients but none in PE without severe features patients. Intrauterine growth

Table-I: Age distribution of the study population

Age (year)	PE with severe features (n=30)	PE without severe features (n=30)	p-value
≤20	4 (13.3)	6 (20.0)	0.367
21 - 30	14 (46.7)	17 (56.7)	
>30	12 (40.0)	7 (23.3)	
Mean ± SD	28.13 ± 6.02	26.07 ± 5.44	

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Table-II: Obstetric characteristics of the study subjects (N=60)

Obstetric Parameters	PE with severe features (n=30)	PE without severe features (n=30)	p-value
Parity			
Nullipara	15 (50.0)	11 (36.7)	0.311
Primipara	5 (16.7)	10 (33.3)	
Multipara	10 (33.3)	9 (30.0)	
Gravidity			
Primigravida	13 (43.3)	9 (30.0)	0.284
Multigravida	17 (56.7)	21 (70.0)	
Antenatal care			
Regular	9 (30.0)	14 (46.7)	0.386
Irregular	16 (53.3)	13 (43.3)	
Not done	5 (16.7)	3 (10.0)	
Gestational age			
Preterm (<37 weeks)	21 (70.0)	18 (60.0)	0.417
Term (≥37 weeks)	9 (30.0)	12 (40.0)	

Table III: Blood pressure, hsCRP of the study subjects (N=60)

hsCRP	PE with severe features (n=30)	PE without severe features (n=30)	p-value
Systolic BP (mmHg)	169.67 ± 12.73	146.67 ± 7.11	<0.001
Diastolic BP (mmHg)	115.00 ± 7.31	96.33 ± 4.90	<0.001
hsCRP	13.90 ± 3.16	7.59 ± 2.41	<0.001

Table IV: Fetal outcome of the study subjects (N=60)

	PE with severe features (n=30) n(%)	PE without severe features (n=30) n(%)	p-value
APGAR score (At birth)			
Good (More than or equal to 7)	9 (30.0)	17 (56.7)	0.037
Low (Less than 7)	21 (70.0)	13 (43.3)	
At 5 minutes			
Good (more than or equal to 7)	19 (63.3)	27 (90.0)	0.015
Low (Less than 7)	11 (36.7)	3 (10.0)	
Birth weight			
Average birth weight	11 (36.7)	20 (66.7)	0.016
LBW	14 (46.7)	10 (33.3)	
Very LBW	5 (16.7)	0 (0.0)	
Others Fetal outcome			
Stillbirth (fresh)	3 (10.0)	0 (0.0)	0.237
Intrauterine growth retardation	16 (53.3)	7 (23.3)	0.017
Need admission to NICU	10 (33.3)	8 (26.7)	0.573
Birth Asphyxia	8 (26.7)	3 (10.0)	0.095
Prematurity	15 (50.0)	3 (10.0)	0.001

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retardation, and prematurity were found significantly higher in PE with severe features patients comparing PE without severe features.

Figure I show the bar diagram showing hsCRP level in PE patients with and without severe features. Here hsCRP of PE patients with severe features was 13.9 mg/l and PE patients without severe features was 7.5 mg/l.

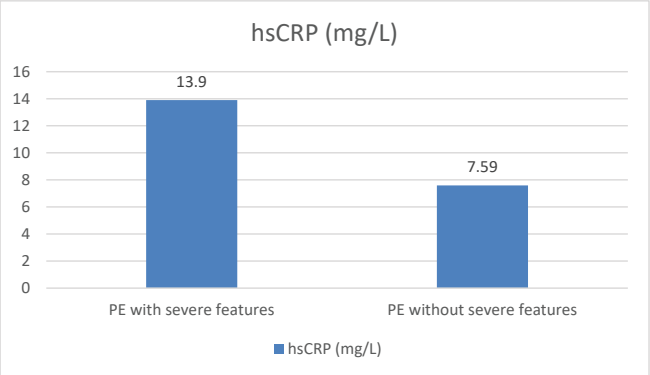

Figure I: Bar diagram showing hsCRP level in PE patients with and without severe features

Table V shows correlation of hsCRP with blood pressure. There was significant positive correlation of hsCRP with systolic BP and diastolic BP.

Table VI shows Association of APGAR score of the neonate with mother's hsCRP in PE patients. hsCRP found significantly higher in neonates with low APGAR score both at birth and at 5 minutes.

Table VII shows Association of hsCRP with Birth weight of the neonate. hsCRP was significantly lower at average birth weight cases comparing LBW and very low birth weight cases.

Table VIII shows association of hsCRP with others Fetal outcome in PE patients. hsCRP was significantly higher in stillbirth(fresh), intrauterine growth retardation, birth asphyxia and prematurity cases.

At a cut- off point > 10.01 true positive was found 27 (90), false positive was 1 (3.3), false negative was 3 (10) and true negative was 29 (96.7) which was significant.

Table X shows diagnostic efficacy parameters for the use of hsCRP levels in the diagnosis of severity of preeclampsia at a cut-off point >10.01. Sensitivity, specificity, PPV and NPV of hsCRP were 90.0%, 96.7%, 96.4% and 90.6% respectively.

Table V: Correlation of hsCRP with blood pressure (N=60)

	r	p-value
Systolic BP	0.538	<0.001
Diastolic BP	0.645	<0.001

Table VI: Association of APGAR score of the neonate with mother's hsCRP in PE patients (N=60)

APGAR score	hsCRP	p-value
At birth		
Good(more than or equal to 7)	8.33 ± 3.55	<0.001
Low (Less than 7)	12.58 ± 3.77	
At 5 minutes		
Good(more than or equal to 7)	9.77 ± 3.90	0.001
Low (Less than 7)	13.92 ± 3.72	

Table VII: Association of hsCRP with Birth weight of the neonate (N=60)

Birth weight	hsCRP	p-value
Average birth weight	9.34 ± 4.64	0.015
LBW	11.90 ± 3.28	
Very LBW	13.93 ± 1.96	

Table VIII: Association of hsCRP with others Fetal outcome (N=60)

Others fetal outcome	hsCRP (mean±SD)	p-value
Stillbirth (fresh)	18.36 ± 2.28	0.001
Live birth	10.34 ± 3.91	
IUGR	12.85 ± 3.18	0.002
Healthy neonate	9.43 ± 4.29	
Need Admission to NICU	11.17 ± 5.18	0.615
No need admission to NICU	10.56 ± 3.78	
Birth Asphyxia	13.52 ± 3.57	0.015
Non birth asphyxia	10.12 ± 4.13	
Prematurity	13.03 ± 3.27	0.005
Maturity	9.76 ± 4.23	

Discussion

Preeclampsia is a pregnancy disease characterized by systemic inflammation. Tillett and Francis discovered C-reactive protein (CRP) in the serum of patients suffering from the acute stage of Pneumococcus infection in 1930 [14]. hsCRP is an acute phase protein that multiplies at sites of inflammation. It is primarily produced in the liver, smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes as a homopentameric protein. The aim of this study was to evaluate the association between hsCRP and the severity of preeclampsia and fetal outcome in a tertiary care hospital.

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Maximum study subjects were in 21 – 30 years age group. Mean age of the study subjects was 28.13 ± 6.02 and 26.07 ± 5.44 years in PE with severe features and PE without severe features respectively. There was no significant difference among the groups. Similar age was observed in the study of Ertas et al. (2010) where mean age of PE without severe features and PE with severe features was 27.6 ± 3.6 and 25.4 ± 7.2 years respectively [15]. Similar observations were made by Kara and Gharib [16,17].

In this study, Primigravida was 13 (43.3%) PE with severe feature and 9 (30%) PE without severe features. Multigravida was 17 (56.7%) in in PE with severe features patients and 21 (70%) in PE without severe features. There was no significance difference among the groups. In this study, nullipara was 15 (50.0%) in PE with severe feature and 11 (36.7%) in PE without severe features and Primipara was 5 (16.7%) in PE with severe features and 10 (33.3%) in PE without severe features. Multipara was 10 (33.3%) and 9(30.0%) in PE with and without severe features. In the study of Ertas et al. (2010), nulliparity was 54.0% in PE without severe features and 71.0% in PE with severe features.[5] Behboudi-Gandevani (2016) found nulliparity was 83.0% and 90.0% in PE without severe features and PE with severe features respectively [18].

Mean systolic BP was 169.67 ± 12.73 mmHg and 146.67 ± 7.11 mmHg in PE with severe features and PE without severe features respectively. Mean diastolic BP was 115.00 ± 7.31 and 96.33 ± 4.90 mmHg in PE with severe features and PE without severe features respectively. Similar blood pressure was observed in the study of Ertas et al. (2010) where they revealed that mean systolic BP was 148 ± 16 mmHg and 162 ± 14 mmHg in PE without severe features and PE with severe features respectively; mean diastolic BP was 96 ± 6.2 mmHg and 114 ± 7.2 mmHg in PE without severe features and PE with severe features respectively. [15]. In a similar study of Kumru, systolic and diastolic blood pressure were 172 ± 15 mm Hg and 108 ± 12 mm Hg respectively. [19]. There was significant positive correlation of hsCRP with systolic BP and diastolic BP in both PE with and without severe features.

hsCRP was found significantly higher in PE with severe features (13.90 ± 3.16 mg/L) than PE without severe features (7.59 ± 2.41 mg/L). Similar observation was made by Ertas et al. (2010) who found mean hsCRP in PE without severe features was 9.6±7.1 mg/L and in PE with severe features was 23.4±16.5 mg/L. [15] Behboudi- Gandevani (2016) revealed hsCRP level in PE without severe features and PE with severe features was 7.2 ± 2.2mg/L and 9.4 ± 3.95 mg/L respectively. [18] In a similar study, Kumru et al. (2005) found significantly higher level of hsCRP in preeclampsia patients (9.5±0.8 mg/L) than normal pregnant women (3.9±2.5 mg/L) [19]. Jannesari and Kazemi also found significantly higher level of hsCRP in PE patients (7.71±6.19 ng/ml) than normal pregnant women (5.44±3.94ng/ml), they also revealed significantly higher level of hsCRP in pregnant women with PE with severe features (8.90±7.27 mg/L) than pregnant women with PE without severe features (6.70 ± 5.06 mg/L) [20].

The average neonatal birth weight of PE without severe features was found to be significantly higher than that PE with severe features patients. There were 5 (16.7%) very LBW neonates in PE with severe features patients, but none in PE without severe features patients. Ertas revealed significantly lower birthweight in PE with severe features than PE without severe features [15]. hsCRP was significantly lower at average birth weight cases comparing LBW cases. According to Ertas, fetal birthweight was significantly higher in low hsCRP cases. [15] Kumru et al. (2005), in a similar study, found significantly lower birthweight in PE patients (2520±402.8 gm) than normal pregnant women (3125±735.5 gm), they also found elevated level of hsCRP was associated with low birth weight [19].

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

Conclusion

This study showed that the maternal hsCRP level was significantly higher in preeclampsia with severe features patients than PE without severe features patients. hsCRP was significantly higher in low birthweight, low APGAR score, stillbirth (fresh), intrauterine growth retardation, birth asphyxia and prematurity cases.

Recommendation

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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Declaration

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Conflict of interest: None declared.

Ethical approval: The study was approved by the ethical committee of Dhaka Medical College Hospital, Dhaka, Bangladesh.

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