OPEN ACCESS

Scholars International Journal of Obstetrics and Gynecology

Abbreviated Key Title: Sch Int J Obstet Gynec
ISSN 2616-8235 (Print) |ISSN 2617-3492 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

High Sensitivity C-Reactive Protein as an Independent Risk Factor for Preeclampsia with Severe Features

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DOI: 10.36348/sijog.2024.v07i04.006 | **Received:** 29.02.2024 | **Accepted:** 08.04.2024 | **Published:** 13.04.2024

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Abstract

***Background*:** One of the most dangerous complications of pregnancy and a major contributor to maternal and perinatal morbidity and death is preeclampsia. The goal of the current study was to measure the level of inflammation in severe preeclampsia by measuring serum high-sensitive C-reactive protein (hs-CRP) and establishing a relationship between hs-CRP and blood pressure. ***Objective*:** The aim of this study is to evaluate the impact high sensitivity C-reactive protein as an independent risk factor for preeclampsia with severe features. ***Methods*:** The cross-sectional study was carried out in the Department of Obstetrics & Gynecology of Dhaka Medical College Hospital, Dhaka, from July 2022 to June 2023. A total of 200 patients were enrolled and analyzed in this study. The questionnaire was pretested, corrected and finalized. Data were collected by face-to-face interview and analyzed by appropriate computer based programmed software Statistical Package for the Social Sciences (SPSS), version 24. ***Results*:** In this study, majority 95 (47.5%) of the patients were in 21 – 30 years age group and 60 (30.00%) patients were in >30 years age group, Mean±SD of age was 27.12 ± 4.12 years. Most of the patients 150 (75.00%) were housewife and 50 (25.00%) patients were service holder. About 55 (27.5) patients were completed their graduation, 50 (25.00%) were completed higher secondary and 20 (10) were illiterate, most of the patients 145 (72.5%) came from rural area and 55(27.5) patients came from urban area. Nullipara was found in 75 (37.5%) patients and multigravida was found in most of the patients 110 (55.00%). Antenatal care was found irregular in 105 (52.5%) patients. Preterm pregnancy was found in majority 145 (72.5%) of the patients. Systolic and diastolic blood pressure were found higher and hsCRP was also found higher in PE with severe features. APGAR score was found less in 65 (32.5%) neonate at birth and APGAR score was found good in 55 (27.5%) neonate at 5 minutes. Average birth weight was found in 75 (37.5%) neonates, LBW was found in 85 (42.5) neonates and very LBW was found in 40 (20.00%) neonates of PE with severe features patients. Intrauterine growth retardation and prematurity were found in 75 (37.5%) and 20 (10.00%) neonates, admission to NICU was needed for 45 (22.5%) neonates, birth asphyxia was found in 15 (7.5%) neonates and stillbirth was occured in 35 (17.5%) cases. ***Conclusion*:** An exaggerated systemic inflammatory response, which may produce reactive oxygen species and worsen endothelial dysfunction, is present in preeclampsia. Clinical signs

of hypertension and proteinuria in preeclampsia result from this. Preeclampsia-related maternal mortality and systemic complications may be reduced with early identification. hsCRP may therefore be a valuable gauge of preeclampsia severity.
Keywords: Blood Pressure, hsCRP, Preeclampsia.

INTRODUCTION

Preeclampsia is a complicated systemic illness for which there is no one identifiable cause. Preeclampsia's etiology is yet unclear. Preeclampsia accounts for 5.4% of the studied population, with hypertensive disorders of pregnancy having a frequency of 7.8% according to the National Health Portal for 2016 [1]. In western countries, preeclampsia complicates 3-8% of all pregnancies, 3-7% of nulliparas, and 1-3% of multiparas [2].

The most common cause of illness and mortality among mothers is preeclampsia. Preeclampsia is characterized as a pregnancy-specific illness that manifests after the 20th week of gestation, with substantial proteinuria and blood pressure ≥140/90 mmHg [3].

Preeclampsia's precise etiology is still unknown. Preeclampsia has been found to be connected with an imbalance of angiogenic factors, hypoxia, weakened immunity, and inflammatory markers. There is a lot of evidence to support the theory that inflammatory activation plays a significant role in the pathophysiology of preeclampsia. It has been observed that a typical pregnancy stimulates the mother's inflammatory response and activates the innate immune system. Preeclampsia is characterized by a more widespread intravascular inflammatory response as well as an elevated systemic maternal inflammatory response [4-6].

As an acute phase protein first synthesized in the liver in response to inflammatory stimuli, C-reactive protein is a crucial part of the innate immune system [7]. Acute phase protein C-reactive protein is frequently utilized as a diagnostic tool for inflammatory and infectious diseases. It has historically been employed as a disease activity marker and as an additional test for inflammation [8].

C-reactive protein levels in normal human blood are less than 10 mg/L, and they rise with age without changing for gender [9]. Late pregnancy is associated with slightly greater levels [10]. Elevations of 10–40 mg/L are caused by mild inflammation and viral infection, whereas 40–200 mg/L are produced by moderate inflammation and bacterial infection. Severe bacterial infections and burns are associated with levels exceeding 200 mg/L [11, 12]. According to Redman and colleagues, preeclampsia is a more widespread activation of intravascular leucocytes, the clotting and complement systems, and the mother's excessive reaction to pregnancy rather than an inherently distinct condition of pregnancy.

The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines preeclampsia, and FIGO uses this definition [13]. Preeclampsia, as defined by the ISSHP, is characterized by one or more of the following new onset conditions at or after 20 weeks of gestation and is accompanied by systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg on at least two occasions measured 4 hours apart in previously normotensive women: Proteinura (i.e., ≥30 mg/mol protein creatinine ratio; ≥300 mg/24 hours; or ≥2+ dipstick). Evidence of other maternal organ dysfunction including acute kidney injury (creatinine ≥1 mg/dL). Liver involvement (elevated alanine aminotransferase or asparate aminotransferase more than 40 IU/L) with or without right upper quadrant or epigastric abdominal pain; neurological complication (e.g: eclampsia, altered mental status, blindness, stroke, clonus, severe headaches and persistent visual scotomata; or hematological complication (thrombocytopenia-intravascular coagulation, hemolysis) or Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis or stillbirth).

This studies have indicated that highly sensitive C- reactive protein (hsCRP), which may play a role in the pathophysiology of preeclampsia, can be used to measure low grade, chronic systemic inflammation [14, 15]. The goal of the current study was to assess the high sensitivity c-reactive protein as an independent risk factor for preeclampsia with severe features.

METHODOLOGY

The cross-sectional study was carried out in the Department of Obstetrics & Gynecology of Dhaka Medical College Hospital, Dhaka, from July 2022 to June 2023. A total of 200 patients were enrolled and analyzed in this study. Patients who matched the inclusion and exclusion criteria were approached for participation in the study. Patients who were not willing to give consent were excluded. Purposive sampling was done according to the availability of the patients who fulfilled the selection criteria. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. Statistical evaluation of the results used to be

obtained via the use of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS-24).

RESULT

Table I shows that, majority 95 (47.5%) of the patients were in 21 – 30 years age group and 60 (30.00%) patients were in >30 years age group, Mean±SD of age was 27.12 ± 4.12 years

Table I: Distribution of the patients according to age (n = 200)

Age group	Frequency	%
≤20	45	22.5
21 - 30	95	47.5
>30	60	30
Total	**200**	**100.0**
Mean ± SD: 27.12 ± 4.12 Years		

Table II shows that most of the patients 150 (75.00%) were housewife and 50 (25.00%) patients were service holder.

Table II: Distribution of the patients according to occupation (n = 200)

Occupation	Frequency	%
Housewife	150	75
Service	50	25
Total	**200**	**100.0**

Table III shows that, 55 (27.5) patients were completed their graduation, 50 (25.00%) were completed higher secondary and 20 (10) were illiterate

Table III: Distribution of the patients according to educational status (n = 200)

Education	Frequency	%
Illiterate	20	10
Primary	35	17.5
Secondary	40	20
Higher Secondary	50	25
Graduate	55	27.5
Total	**200**	**100.0**

Table IV shows that, most of the patients 145 (72.5%) came from rural area and 55(27.5) patients came from urban area.

Table IV: Distribution of the patients according to residence (n = 200)

Residence	Frequency	%
Urban	55	27.5
Rural	145	72.5
Total	**200**	**100.0**

Table V shows that, Nullipara was found in 75 (37.5%) patients and multigravida was found in most of the patients 110 (55.00%). Antenatal care was found irregular in 105 (52.5%) patients. Preterm pregnancy was found in majority 145 (72.5%) of the patients.

Table V: Distribution of the patients according to obstetric parameters (n = 200)

Obstetric Parameters		Frequency	Percent
Parity	Nullipara	75	37.5
	Primipara	35	17.5
	Multipara	90	45
Gravidity	Primigravida	90	45
	Multigravida	110	55
Antenatal care	Regular	55	27.5
	Irregular	105	52.5
	Not done	40	20
Gestational age	Preterm (<37 weeks)	145	72.5
	Term (≥37 weeks)	55	27.5

Table VI shows that, Systolic and diastolic blood pressure were found higher and hsCRP was also found higher in PE with severe features.

Table VI: Distribution of the patients according to clinical parameters (n = 200)

Clinical Parameters			p-value
Blood pressures	Systolic BP (mmHg)	169.67 ± 12.73	<0.001
	Diastolic BP (mmHg)	115.00 ± 7.31	<0.001
hsCRP level	hsCRP	13.90 ± 3.16	<0.001

Table VII shows that, APGAR score was found less in 65 (32.5%) neonate at birth and APGAR score was found good in 55 (27.5%) neonate at 5 minutes.

Table VII: Distribution of the patients according to APGAR score (n = 200)

APGAR score		Frequency	Percent
At birth	Good (≥ 7)	45	22.5
	Low (Less than 7)	65	32.5
At 5 minutes	Good (≥ 7)	55	27.5
	Low (Less than 7)	35	17.5

Table VIII shows that, Average birth weight was found in 75 (37.5%) neonates, LBW was found in 85 (42.5) neonates and very LBW was found in 40 (20.00%) neonates of PE with severe features patients.

Table VIII: Distribution of the patients according to birth weight (n = 200)

Birth weight	Frequency	%
Average birth weight	75	37.5
LBW	85	42.5
Very LBW	40	20
Total	**200**	**100.0**

Table IX shows that, Intrauterine growth retardation and prematurity were found in 75 (37.5%) and 20 (10.00%) neonates, admission to NICU was needed for 45 (22.5%) neonates, birth asphyxia was found in 15 (7.5%) neonates and stillbirth was occured in 35 (17.5%) cases.

Table IX: Distribution of the patients according to other fetal outcome (n = 200)

Fetal outcome	Frequency	%
Stillbirth (fresh)	35	17.5
Intrauterine growth retardation	75	37.5
Need admission to NICU	45	22.5
Birth Asphyxia	15	7.5
Prematurity	20	10

DISCUSSION

There are numerous etiologies that have been linked to preeclampsia development. In the first trimester of pregnancy, PE is linked to placental malfunction [16], and there is mounting evidence that endothelial cell injury may play a key role in the etiology of the condition. Elevated inflammatory markers are associated with endothelial damage [17], and these indicators may be a helpful early diagnostic tool for PE. These markers may be crucial to the pathophysiology of PE. It has been suggested that CRP, a sensitive low-grade immune response marker, may contribute to the elicitation of preeclampsia's immune response features [18]. Interestingly, there is evidence that normal pregnancy itself stimulates the maternal infl ammatory response and CRP levels are elevated in healthy pregnant women compared with nonpregnant women, although to a lesser extent than that seen in PE [19].

The cross-sectional study was carried out in the Department of Obstetrics & Gynecology of Dhaka Medical College Hospital, Dhaka, from July 2022 to June 2023. A total of 200 patients were enrolled and analyzed in this study.

In this study, majority 95 (47.5%) of the patients were in 21 – 30 years age group and 60 (35.3%-30.00%) patients were in >30 years age group, Mean±SD of age was 27.12 ± 4.12 years. Most of the patients 150 (75.00%) were housewife and 50 (25.00%) patients were service holder. About 55 (27.5) patients were completed their graduation, 50 (25.00) were completed higher secondary and 20 (10.00%) were illiterate, most of the patients 145 (72.5%) came from rural area and 55 (27.5%) patients came from urban area. Nullipara was found in 75 (37.5%) patients and multigravida was found in most of the patients 110 (55.00%). Antenatal care was found irregular in 105 (52.5%) patients. Preterm pregnancy was found in majority 145 (72.5%) of the patients. Systolic and diastolic blood pressure were found higher and hsCRP was also found higher in PE with severe features. APGAR score was found less in 65 (32.5%) neonate at birth and APGAR score was found good in 55 (27.5%) neonate at 5 minutes. Average birth weight was found in 75 (37.5%) neonates, LBW was found in 85 (42.5%) neonates and very LBW was found in 40 (20.00%) neonates of PE with severe features patients. Intrauterine growth retardation and prematurity were found in 75 (37.5%) and 20 (10%) neonates, admission to NICU was needed for 45 (22.5%) neonates, birth asphyxia was found in 15 (7.5%) neonates and stillbirth was occured in 35 (17.5%) cases. In another study shows that elevated hs-CRP levels in the first half of pregnancy can predict the subsequent development of preeclampsia. In another study, Tjoa *et al.*, [20] found the same result. They demonstrated that CRP levels were elevated between weeks 10 and 14 in pregnant women who developed PE or delivered a growth restricted baby. However, Savvidou *et al.*, [21] did not find a relationship

between CRP concentration in the late second trimester of pregnancy and PE.

It is difficult to predict the severity of preeclampsia clinically. There are few studies concerning the correlation of CRP levels with the severity of PE. Our result demonstrated that after adjustment for maternal age, prepregnancy BMI, parity, and calcium supplementation, hs-CRP levels remained higher in severe preeclampsia patients. The optimal cutoff values of maternal serum hs-CRP for severe PE were > − 5 mg/L. This threshold could predict PE with high sensitivity and reasonable specificity in the fi rst half of gestation. It has been identifi ed that subclinical elevations of hs-CRP (> 3 mg/L) can be used as a marker for endothelial damage and cardiovascular disease in non-pregnant patients [4]. Our result suggested that this acute phase reactant could be a sensitive and specifi c predictor for PE. Ustun *et al*., [22] and Deveci *et al*., [23] found cutoff levels of CRP for disease severity in the third trimester to be 11.5 and 10.9 mg/L, respectively. These were significantly higher than those used in our study, consistent with the elevations in CRP seen in the third trimester, although differences in geographic and socioeconomic status and interlaboratory variation could have contributed.

In another study, we found a negative correlation between serum hs-CRP levels and weight of the newborns. It seems likely that placental dysfunction plays a role in both conditions, and the elevation of acute phase reactants such as CRP in both conditions' hints at common pathways in their pathogenesis. A limitation of this study was our inability to follow up the patients after delivery. Longer-term outcomes would be of great interest, especially in children with low birth weight (LBW). Small numbers of patients in the preeclamptic groups decreased the effectiveness of this study. Studies with larger samples size would be better for determining a screening threshold. Larger numbers would be needed to examine this relationship properly, including whether the threshold values should be different for these patients. These conditions may lead themselves to differences in the levels of hs-CRP as potential marker of subclinical systemic inflammation, independently on the development of preeclampsia.

CONCLUSION

An exaggerated systemic inflammatory response known as preeclampsia may produce reactive oxygen species, which in turn may cause endothelial dysfunction. Clinical signs of hypertension and proteinuria in preeclampsia result from this. Preeclampsia-related maternal mortality and systemic complications may be reduced with early identification. Since hsCRP was much higher in severe preeclampsia, hsCRP may be a helpful marker of preeclampsia severity. In the future, more research on risk factor for preeclampsia is advised.

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