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High Sensitive- C Reactive Protein (hs-CRP) as a vital tool for grading of Preeclampsia: A Case Control Study

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ABSTRACT

Introduction: High blood pressure (140/90 mmHg or higher), presence of protein in urine and swelling due to fluid retention are symptoms of preeclampsia, a disease that affects pregnant women after the 20th week of gestation. Chronic inflammation is understood to significantly contribute to the development of preeclampsia. This study strived to evaluate serum highly sensitive C-reactive protein levels in women with preeclampsia, as well as to compare the hs-CRP levels across various groups of preeclamptic patients and healthy individuals. **Aims & Objective:** The goals of this study are to ascertain the blood hs-CRP levels of preeclamptic women, to assess and analyze these levels, to compare hs-CRP levels in different groups of preeclampsia patients and healthy controls, and to examine the role of CRP in preeclampsia severity ratings. **Materials & Methods**: The research included 105 pregnant women in their third trimester (28 to 40 weeks) ranging in age from 18 to 35. Mild preeclampsia affected 35 pregnant women and severe preeclampsia affected 35 pregnant women were taken as cases. For the control group, we used 35 identically aged pregnant women whose blood pressure was within the usual range. All subjects were asked to sign an informed consent form before participating in the study. The serum hs-CRP concentration was determined using the turbidimetry technique on the Biosystem BA400 Biochemistry fully automated analyzer. **Results:** The mean hs-CRP level in the control group was 1.73 ± 0.46 mg/l, whereas in mild preeclampsia it was 2.74 ± 0.53 mg/l, and in severe preeclampsia it reached 5.77 ± 1.04 mg/l. The detected difference was statistically significant, suggesting that preeclamptic women, compared to the control group, had a higher level of hs-CRP. **Conclusion:** Increased blood hs-CRP levels are associated with more severe preeclampsia, according to this study's results. Therefore, it may be crucial to determine hs-CRP levels in preeclamptic women early on so that these patients may get the right treatment and reduce the morbidity and mortality associated with these disorders.

Keywords: Inflammation, Preeclampsia, high sensitive C reactive protein (hs-CRP).

INTRODUCTION

Proteinuria (i.e., 300 mg or more in a 24-hour urine collection or 1+ on a dipstick) and hypertension (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg after 20 weeks of gestation) are the hallmarks of preeclampsia. To identify severe preeclampsia, clinical criteria such as diastolic blood pressure of 110 mm Hg or higher, considerable proteinuria (dipstick measurement of 2+), or the presence of symptoms such as headache, convulsions, raised serum creatinine, thrombocytopenia, notable elevation of liver enzymes, and pulmonary edema were examined. [(1)] The global incidence of preeclampsia ranges from 3-10%, with India reporting an 8-10% occurrence. Preeclampsia significantly contributes to maternal and perinatal mortality, impacting 5–7% of expectant mothers. [(2)]

The precise pathogenesis of preeclampsia remains unclear as of now. [(3)] Numerous studies have indicated that a toxic blend of angiogenic factor imbalance, hypoxia, compromised immunity, and inflammation are responsible for the development of Preeclampsia. [(4)] In individuals with preeclampsia, there is an amplified systemic inflammatory response from the mother. Several investigations have revealed elevated levels of inflammatory cytokines in those with preeclampsia compared to normal pregnancies. [(5,6,7)] Accumulating evidence supports that preeclampsia is caused by a complex interplay of immune system issues, genetic predisposition, inflammation and malfunction of the maternal vascular endothelial cells, hypoperfusion of the placenta, and abnormal invasion of trophoblasts. Endothelial cell dysfunction and inflammation play critical roles in the pathophysiology of preeclampsia. C-reactive protein (CRP) is an as a prominent acute-phase reactant in humans, activating the complement system and aiding in the phagocytic clearance of pathogens, thus functionally serving as a key first line defense molecule. [(8,9)] Given that preeclampsia arises due to an exaggerated systemic inflammatory response in mothers during pregnancy, it serves as a predictor for preeclampsia. [(10,11)] High sensitivity CRP (hs-CRP) maintains similarity to routine CRP in both structure and function and indicates the lower detection limit of the employed assay technique. It has been proposed that heightened hs-CRP levels indicate ongoing inflammation and tissue damage with greater precision than other acute phase laboratory parameters. The hs-CRP serves as a sensitive indicator of tissue damage and inflammation. It is beneficial for distinguishing acute inflammation and assessing the severity of the inflammatory response. [(12)] This study primarily aims to evaluate and measure this inflammatory biomarker in preeclamptic women and to compare its level among various groups of preeclampsia patients and healthy controls, aiding in the early identification of this pregnancy complication which lacks a specific diagnostic marker, thus potentially preventing associated morbidities and mortalities.

MATERIAL AND METHODS

Under the condition that they had obtained ethical approval, the case-control study was carried out by the departments of obstetrics and gynaecology and clinical biochemistry at CIMS Chhindwara M.P. India (ethical clearance was obtained on 31/08/2022 with reference no. CIMS/Ethics committee/2022/6400). Total 105 pregnant ladies, ranging in age from eighteen to thirty-five, were scouted from the obstetrics and gynaecology department of CIMS Chhindwara M.P. Mild preeclampsia affected 35 pregnant and severe preeclampsia affected 35 pregnant women were taken as cases. For the control group, we used 35 identically aged pregnant women whose blood pressure was within the usual range. Every participant in the study gave their written informed consent.

The criteria for inclusion were: Each case happened in the third trimester of pregnancy and included a singleton, a woman's age being between 18-35, a woman's blood pressure being normal during the first 20 weeks of gestation, and a woman's history of not having hypertension. (> 28 weeks of gestation). **Exclusion criteria included**: A chronic renal or hepatic problem, an infection, chorioamnionitis, an infection of the urinary system, or a similar condition, combining drinking and smoking, medication for diabetes, and having more than one fetus throughout a pregnancy.

A fasting blood sample of 5ml was obtained and serum hs-CRP levels were assessed on the biosystem BA400

biochemistry analyzer by turbidimetry method.

Statistical Analysis: The IBM SPSS program version 15 and a Microsoft Excel sheet were used to conduct quantitative and statistical studies. The data were presented as the mean, with a standard deviation of ±. The two groups' means were compared using the unpaired t-test. After running the data using one-way analysis of variance and post hoc Tukey, we compared the means of more than two groups. If the P-value was less than 0.05, we considered it statistically significant.

RESULT AND OBSERVATIONS

Table 1 and Graph 1 show the biochemical and demographic traits of the research participants. Table 1 indicates that subjects with severe preeclampsia exhibited a significantly elevated average blood pressure of 161.20/116.86 mmHg. For mild preeclampsia patients, it was 138.97/90.06 mmHg, and for normotensive pregnant women, it was109.14/75.82 mmHg. Serum uric acid levels in those with severe preeclampsia averaged 6.49 ± 0.87, while those with mild preeclampsia had 4.65 ± 0.57, and normotensive subjects averaged 3.46 ± 0.45 mg/dl. Urine albumin levels for women with severe preeclampsia were 1.07± 0.35, while those for mild preeclampsia were 0.62 ± 0.11, and for normotensive women, it was 0.19 ± 0.05 gm/day. A statistically significant difference was observed in mean blood pressure, serum uric acid, and urine albumin levels among severe preeclampsia, mild preeclampsia, and normotensive pregnant women ($p<0.00001$). Table 2 & Graph 2 depict the comparison of serum hs-CRP between case and control groups. The average serum hs-CRP level in the control group was 1.73 ± 0.46 mg/l, but in the case group it was 4.26 ± 1.73mg/l. By comparing the case group to the control group, an examination of the data showed that the former had a significantly higher blood hs-CRP level ($P < 0.00001$). Table 3 & Graph 3 illustrate the comparative analysis of mean serum hs-CRP among normotensive, mild, and severe preeclamptic women. The mean serum hs-CRP were 2.74 ± 0.53 mg/l in mild preeclampsia and 5.77 ± 1.04 mg/l in severe preeclampsia. In contrast, 1.73 ± 0.46 mg/l values were discovered in healthy pregnant women who were otherwise normal. A statistically significant difference was seen between these three groups of pregnant women when the blood hs-CRP levels were analyzed. ($P< 0.00001$). Table 4 shows a paired comparison of the study participants' blood hs-CRP levels. A statistically significant result ($P < 0.00001$) was obtained when comparing mild preeclampsia's mean serum hs-CRP levels with normotensive preeclampsia. Normotensive pregnant women had lower hs-CRP levels than those with mild preeclampsia, according to this study.A statistically significant result was obtained by comparing the mean serum hs-CRP levels between the normotensive and severe preeclampsia ($P < 0.00001$). The results showed that severe preeclampsia had a greater level of hs-CRP.A greater hs-CRP level was found in cases of severe preeclampsia as compared to cases of mild preeclampsia.

Table 1- Comparison of Demographic & Clinical profile between cases and controls.

Variables	Normotensive Pregnant women (n=35)	Pregnant Women with Mild Preeclampsia PE (n=35)	Pregnant Women with Severe Preeclampsia (n=35)	F Value	P Value
Age (years)	24.37 ± 1.40	24.20 ± 4.26	23.17 ± 1.74	1.9113	0.1531
Systolic Blood Pressure(mmHg)	109.14 ±7.08	138.97 ±5.41	161.20 ± 7.31	539.032	P < 0.00001
Diastolic Blood Pressure(mmHg)	75.82 ± 5.95	90.06 ± 6.09	116.86 ± 5.72	433.139	P < 0.00001

Serum Uric acid (mg/dl)	3.46 ± 0.45	4.65 ± 0.57	6.49 ± 0.87	189.075	P < 0.00001
Urine albumin (gm/day)	0.19 ± 0.05	0.62 ± 0.11	1.07 ± 0.35	150.461	P < 0.00001

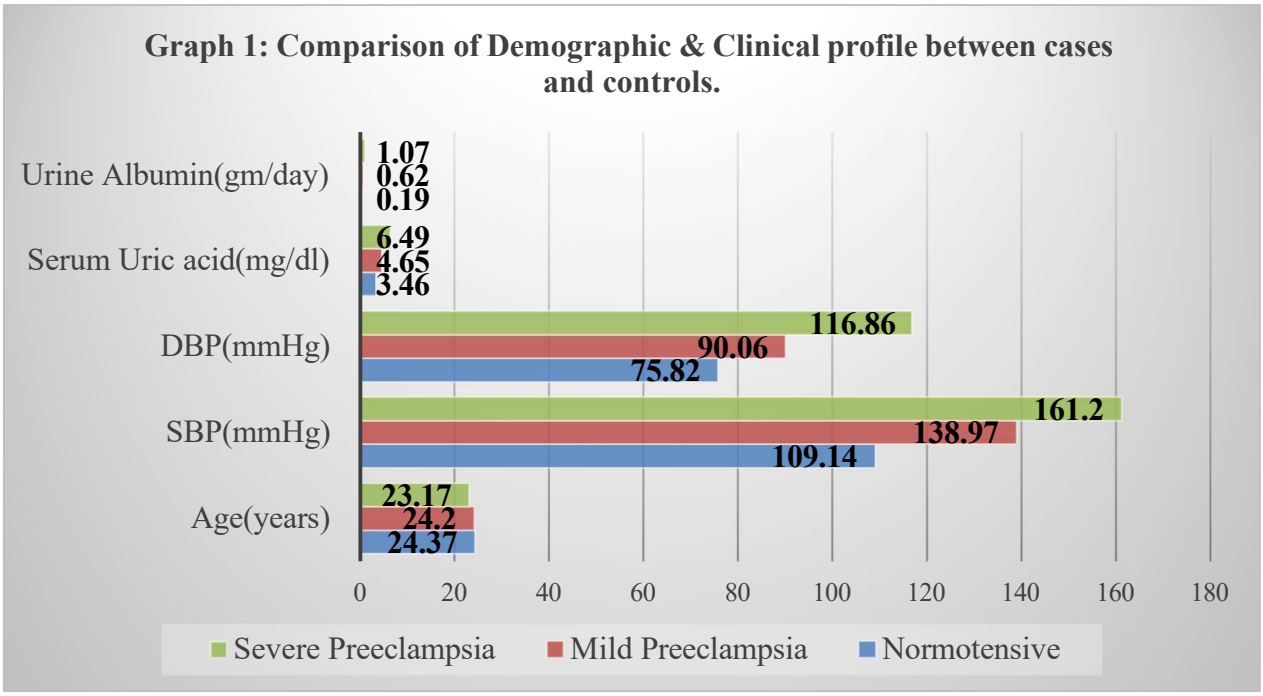

Table 2: Comparison of Serum hs-CRP between the case and control groups

Parameter	Case group (n=70) (Mean ± SD)	Control group (n=35) (Mean ± SD)	T value	P value	Result
Serum hs-CRP (mg/l)	4.26 ± 1.73	1.73 ± 0.46	8.47	< 0.00001	statistically significant

Unpaired 't' test applied. P value <0.05 was taken as statistically significant.

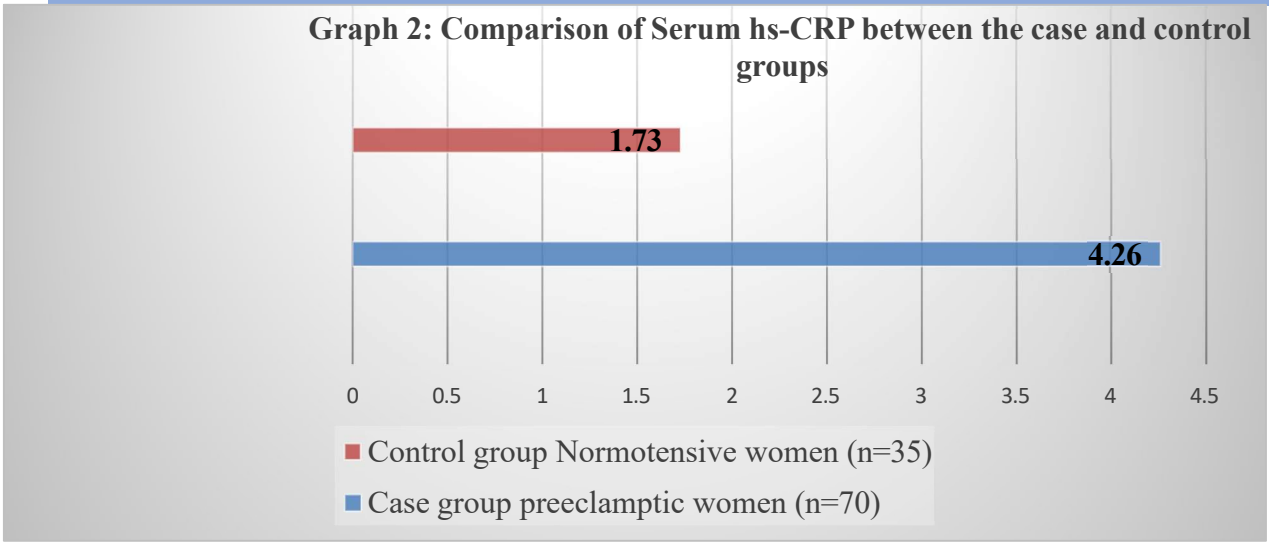

Table 3: Comparison of mean Serum hs-CRP in study subjects.

Pregnant Women	N	Mean hs-CRP (mg/l)	Std. Deviation	F Test	P Value	Result
Normotensive	35	1.73	0.46	290.2188	0.0000	statistically significant
Mild Preeclampsia	35	2.74	0.53			
Severe Preeclampsia	35	5.77	1.04			

One – way ANOVA applied. P value <0.05 was taken as statistically significant.

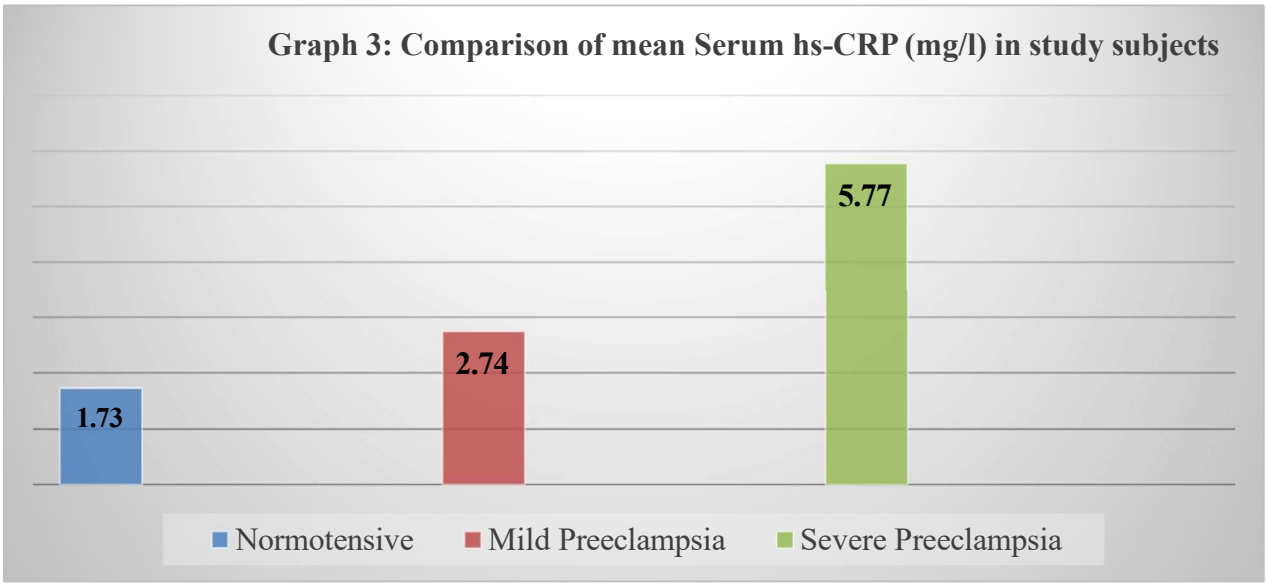

Table 4: Pair-wise comparison of Serum hs-CRP by Post-hoc Tukey test

Pair	F factor	P value	Interpretation
Normotensive-Mild Preeclampsia	72.83534	< 0.00001	Significant
Normotensive-Severe Preeclampsia	434.68769	< 0.00001	Significant
Mild Preeclampsia -Severe Preeclampsia	231.06526	< 0.00001	Significant

DISCUSSION

Our study unveiled several pivotal discoveries: (1) Women with mild preeclampsia exhibit heightened serum hs-CRP levels compared to those experiencing a normal pregnancy. (2) Women with severe preeclampsia display even more pronounced hs-CRP levels than those with mild preeclampsia and normotensive pregnancies. Preeclampsia is defined by endothelial cell impairment and inflammation, both of which are deemed critical in the pathophysiological framework of preeclampsia. [13] **Redman et, al.** [14] proposed that preeclampsia emerges from an excessive maternal intravascular inflammatory reaction to gestation, potentially stemming from either an overly strong stimulus or maternal response, involving both innate and adaptive immune systems. **Greer et, al.** [15] demonstrated that neutrophil activation is restricted to the maternal circulation in pregnancy-induced hypertension, where it may play a role in vascular injury. CRP serves as an objective and sensitive indicator of inflammatory activity in our body. [16] It has been posited that CRP may contribute to triggering the inflammatory response specific to preeclampsia. [17]

In this investigation, we concentrated on the potential role of hs-CRP in preeclampsia. Our results align with the findings of **Kucukgoz Gulec et al.,** [18] **Hossein Ayatollahi et al.,** [19] **Teran et al.,** [20] and **Batashki I et al.,** [21]. All of these researchers observed increased levels of C-reactive protein in patients suffering from severe preeclampsia.

CONCLUSION

Pregnant women who are at risk of getting preeclampsia must be identified as soon as possible because they need to be closely monitored and treated appropriately to improve the quality of their pregnancy. Clinical criteria, which are based on clinical presentation, are often used to diagnose preeclampsia. Currently, there isn't a clinically accepted standard diagnostic test.

Our study's findings indicate that a higher blood hs-CRP level is linked to the severity of preeclampsia. They may be used as a prognostic indicator starting in the first trimester. All pregnant women may thus have their blood hs-CRP levels evaluated to predict preeclampsia, and high-risk pregnant women may benefit from routine serum hs-CRP level monitoring for early diagnosis and management to reduce maternal and fetal morbidity and death.

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