International Journal of Research in Medical Sciences
*Sayyed AAK et al. Int J Res Med Sci. 2020 Aug;8(8):3002-3006*
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20203454

**Original Research Article**

# High sensitive C reactive protein as an inflammatory indicator in preeclampsia

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**Received:** 11 June 2020
**Accepted:** 06 July 2020

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## ABSTRACT

**Background:** Preeclampsia is one of the most serious complications of pregnancy and one of the leading cause of maternal, prenatal morbidity and mortality. The present study was carried out to estimate serum high sensitive C-reactive protein in both mild and severe preeclampsia as an indicator of inflammation and to correlate Hs-CRP with blood pressure.
**Methods:** A case control study was conducted in the Department of Biochemistry and Department of Obstetrics and Gynecology, MIMER Medical College and Bhausaheb Sardesai Rural Hospital Talegaon Dabhade, Pune. The study group include 50 cases of normal pregnant women, 43 clinically diagnosed cases of mild preeclampsia and 7 cases of severe preeclampsia in second and third trimester of pregnancy. 2 ml venous blood samples was collected from all the study participants for estimation of Hs-CRP by ultra-sensitive immunoturbidometric assay spin react method.
**Results:** There was significant increase in the mean serum Hs-CRP levels in normal pregnant women and mild preeclamptic women ($p<0.001$). Serum Hs-CRP levels were significantly higher in severe preeclamspia than mild preeclamptic women ($p<0.001$). The degree of inflammation increases as HsCRP rises. Hence, present study shows that HsCRP levels increases as disease progresses from mild to severe condition. Significant positive correlations was found between Hs-CRP and Blood Pressure in preeclampsia.
**Conclusions:** In preeclampsia there is an exaggeration of systemic inflammatory response that might induce reactive oxygen species which further induces endothelial dysfunction. This leads to clinical symptoms of hypertension and proteinuria in preeclampsia. Early detection might minimise systemic complications and maternal death due to preeclampsia. Hence, HsCRP may be used as an important indicator of severity of preeclampsia.

**Keywords:** Blood Pressure, HsCRP, Preeclampsia

## INTRODUCTION

Preeclampsia is a complex systemic condition, which is not attributed due to any single cause. Etiology of preeclampsia is still unknown. According to National Health Portal 2016 prevalence of hypertensive disorders of pregnancy was 7.8%, out of which preeclampsia contribute 5.4% of the study population.[1] Preeclampsia complicates 3-8% of all pregnancies, 3-7% of nulliparas and 1-3% of multiparas in western countries.[2] Preeclampsia is the leading cause of maternal morbidity and mortality. Preeclampsia is defined as a pregnancy specific syndrome observed after 20th of week of gestation with blood pressure ≥140/90 mmHg accompanied by significant proteinuria.[3]

The exact pathogenesis of preeclampsia is not yet known. It has been observed that imbalance of angiogenic factors, hypoxia, impaired immunity and inflammatory markers associated with the occurrence of preeclampsia. There is extensive evidence that activation of inflammation is considered as an important contributor in

the pathogenesis of preeclampsia. It is seen that during normal pregnancy, the innate immune system is activated and maternal inflammatory response is stimulated. In preeclampsia, the systemic maternal inflammatory response is enhanced and it is also characterized with more generalized intravascular inflammatory reaction.[4-6]

The studies have suggested that low grade, chronic systemic inflammation can be assessed by High sensitive C- reactive protein (HsCRP) which may be involved in the pathogenesis of preeclampsia.[7,8] Since there is controversy in serum HsCRP levels and severity of preeclampsia, present study was undertaken to determine HsCRP level in preeclampsia and its relation with the severity of the disease.

## METHODS

A case control study was carried out on 100 participants. Sample size was calculated in Winpepi software version 22.0, with 80% power and 95% confidence interval. Out of 100 participants, 50 were clinically diagnosed preeclamptic women with gestational age of ≥20 weeks and 50 normal pregnant women in the same gestational age were included as control. These study participants were further divided into three groups as Group I: 50 normal pregnant women, Group II: 43 women with mild preeclampsia and Group III: 7 women with severe preeclampsia. Mild and Severe preeclampsia were classified according to American College of Obstetrics and Gynecology (ACOG) criteria.[4] Mild preeclampsia: Blood pressure (BP) ≥140/90 mmHg after ≥20 weeks of gestation and proteinuria ≥ 300 mg /24 hours or 1+ dipstick and Severe preeclampsia: According to ACOG one of these parameters should be used to define severe preeclampsia.

BP ≥ 160/110 mm Hg on two occasion 6 hours apart while patient is on bed rest and proteinuria 2 gm or higher on 24 hour urine or 2+ or greater on two random urine sample 4 hours apart or severity of evidence such as persistent headache or other cerebral or visual disturbances, upper abdominal pain, oliguria, elevated serum creatinine, thrombocytopenia, marked liver enzyme elevation and pulmonary edema. These patients attended the Obstetrics and Gynecology department in Bhausaheb Sardesai rural tertiary care Hospital.

The study participants belong to age group ≥18 years and both primigravida and multigravida in second and third trimester of pregnancy were included.[3,4]

This study was approved by the Institutional Ethical Committee (IEC). A written informed consent was taken from the each participant prior to blood sample collection. 2 mL of venous blood sample was collected under aseptic conditions in plain bulb from the preeclamptic and normotensive pregnant women visiting to the Department of Obstetrics and Gynecology, ≥20 weeks of gestation period. The blood samples were allowed to clot and centrifuged at 3000 rpm for 10 minutes to obtain the clear serum. Thus obtained clear serum sample was used for the estimation of HsCRP by ultra-sensitive immunoturbidimetric method using commercially available kit (Roche, Germany).

Women having history of premature rupture of membranes, renal diseases, liver diseases, cardiovascular diseases, severe anemia, diabetes mellitus and other systemic or endocrine disorders were excluded. HsCRP was estimated by ultra-sensitive immunoturbidimetric method using commercially available kit (Roche, Germany).

### *Statistical analysis*

Data was analysed in SPSS statistical software (Version 11.43). Results obtained were expressed in mean±standard deviation (SD). Unpaired student's t- test was used for comparison of the study groups. Pearson's coefficient correlation (r) was used to show the relation between HsCRP and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

## RESULTS

Comparison of age and gestational age were shown in Table 1. The mean age (years) and gestational age (weeks) were not statistically in both mild and severe preeclampsia as compared to normal pregnant women.

Serum HsCRP levels were significantly higher in severe preeclampsia patients as compared to mild preeclampsia ($p \leq 0.001$) (Table 1 and 2).

**Table 1: Mean±SD of clinical parameters in study groups.**

| Parameters | (Group I) Normal pregnant women (n=50) | Patients | | | p value |
|---|---|---|---|---|---|
| | | Preeclampsia (overall) | (Group II) mild preeclampsia (n= 43) | (Group III) severe preeclampsia (n=7) | |
| Age (years) | 22.9±3.5 | 23.9±2.7 | 23.8±3.3 | 24±2.14 | 0.17 |
| Gestational age | 30±6.7 | 31.9±2.2 | 32.5±3.5 | 32.9±4.5 | 0.14 |
| Systolic BP (mmHg) | 116.5±4 | 142.4±13 | 140.8±17.4 | 144±9 | < 0.001* |
| Diastolic BP (mmHg) | 76.9±4.5 | 101.2±9.2 | 92.1±9.2 | 110±9.4 | < 0.001* |

*Significant, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

**Table 2: Mean±SD of serum HsCRP (mg/l) in study groups.**

| Parameter | (Group I) Normal pregnant women (n=50) | Study groups | | | p value |
|---|---|---|---|---|---|
| | | Overall preeclampsia | (Group II) mild preeclampsia (n= 43) | (Group III) severe preeclampsia (n=7) | |
| HsCRP level (mg/l) | 1.47±0.59 | 3.09±1.77 | 2.89±1.12 | 4.3±0.58 | < 0.001* |

SBP and DBP were significantly higher in preeclampsia as compared to normal pregnant women. Both SBP and DBP were positively correlated with HsCRP level in preeclampsia (Table 1, Figure 1 and Figure 2).

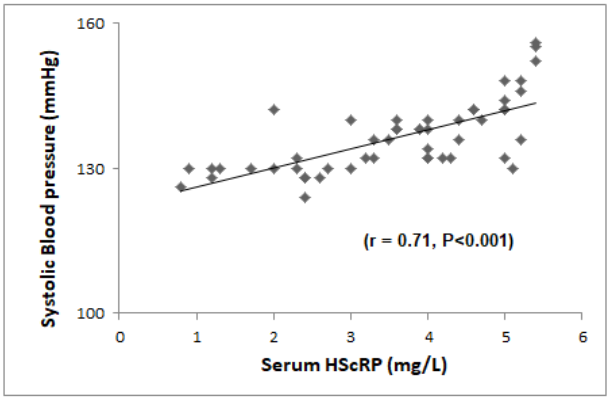


**Figure 1: Correlation of HsCRP with systolic blood pressure.**

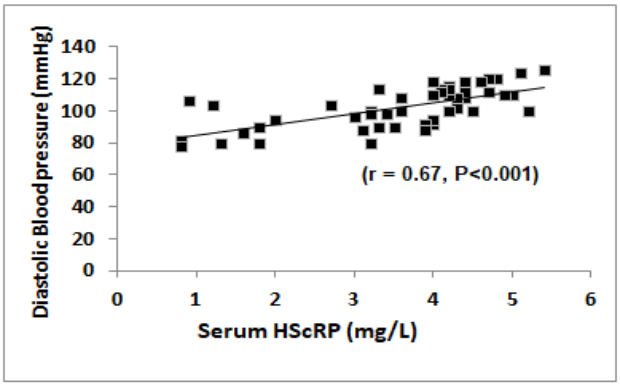


**Figure 2: Correlation of HsCRP with diastolic blood pressure.**

## DISCUSSION

Preeclampsia is a disease of pregnancy associated with systemic inflammation.[3,8-10] HsCRP was discovered by Tillett and Francis in 1930 in the serum of patients suffering from the acute stage of Pneumococcus infection and was named for its reaction with the capsular (C) - polysaccharide of Pneumococcus.[11,12] HsCRP is an acute phase protein that increases multi-folds at the sites of inflammation. It is synthesized as a homopentameric protein mainly in liver, smooth muscle cells, macrophages, endothelial cells, lymphocytes and adipocyte. In the presence of calcium, CRP binds to polysaccharides such as phosphocholine (PCh) on microorganisms and triggers the classical complement pathway of innate immunity by activating C1q.[12-15] Numerous theories have been suggested to explain cause of preeclampsia.[3,10] A possible hypothesis for pathogenesis of preeclampsia is reduced placental perfusion as a result of shallow invasion. This leads to increased oxidative stress and activation of neutrophils and macrophages, this ultimately promotes cytokine production.[4,14,16,17] The production of HsCRP is induced by pro-inflammatory cytokines, Interleukin - 1, Interleukin - 6, Interleukin - 17 and Tumor Necrosis Factor - α in the liver, although extra hepatic production can contribute to systemic concentrations.[18,19] The cytokines bring out biological effects on HsCRP by signalling through their receptors on hepatic cells. It activates different kinases and phosphatases leading to the translocation of various transcription factors on the HsCRP gene promoter and ultimately leads to production of HsCRP.[19] Placental dysfunction or fat tissue leads to the expression of the C-reactive protein in the liver or the placenta. HsCRP binds to phosphocholins which are transferred to neurokinin B thereby enhancing activation of the neurokinin 3 receptor. This leads to organ damage and arterial hypertension.[20] These cytokines are responsible for inflammatory responses causing maternal endothelial dysfunction and activation of hemostatic system in preeclampsia.[21,22,19]

In present study HsCRP levels were significantly elevated in preeclampsia when compared to normal pregnant women (Table 2). Further HsCRP levels were significantly higher in severe preeclampsia as compared to mild preeclamspia this findings are in consistent with Bargale A et al, and Behboudi S et al.[9,22]

Higher levels of HsCRP may increase blood pressure by reducing nitric oxide production in endothelial cells, causing vasoconstriction and increasing endothelin-1 production. this findings are in consistent with.[4,21,23] Therefore, significant positive correlation was observed between HsCRP levels and blood pressure which shows the elevation of HsCRP level in proportion to severity of preeclampsia. Hence, HsCRP may be used as an indicator of severity of disease. This findings was inconsistent with Khairy A et al.[24] However, further more studies are required to assess severity of preeclampsia and inflammatory markers in preeclampsia.

## CONCLUSION

Preeclampsia is an exaggeration of systemic inflammatory response that might induce reactive oxygen species which further induces endothelial dysfunction. This leads to clinical symptoms of hypertension and proteinuria in preeclampsia. Early detection might help in minimizing systemic complications and maternal death due to preeclampsia. HsCRP was highly elevated in severe preeclampsia as compared with mild preeclampsia, hence HsCRP may be useful indicator of severity of preeclampsia. However further studies on inflammatory markers are recommended in future.

limitation of this study is other inflammatory biomarkers such as Interleukin - 6, Tumor Necrosis Factor -α were not done in this study.

## ACKNOWLEDGEMENTS

Authors would like to thank Aishwarya Gade, IV Year MBBS student of MIMER Medical College, Talegaon for providing us technical help in sample collection. Authors express this special thanks to the management for encouraging us to carryout active research in this field.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Sayyed AAK, Pratinidhi SA. High sensitive C reactive protein as an inflammatory indicator in preeclampsia. Int J Res Med Sci 2020;8:3002-6.