Original Research Article

Association of high sensitive-CRP levels with severity of pre-eclampsia

Nilima Patil

Assistant Professor. Department of Biochemistry. ACPM Medical college, Dhule, INDIA.
Email: drnilimapatil01@gmail.com

Abstract

Background: Preeclampsia (PE) is pregnancy specific multisystem disorder that is characterized by development of hypertension, proteinuria and edema after 20 weeks of gestation. The hs-CRP has been suggested to provide better sensitivity in establishing inflammation than levels of CRP and reflects ongoing inflammation and/or tissue damage much more accurately compared to other laboratory parameters of the acute-phase response. **Aim:** To study association of high sensitive-CRP levels with severity of pre-eclampsia. **Material and Methods:** A total of 120 pregnant women between 18 to 35 years visiting the Gynecology and Obstetrics department were included under study. Out of 120 subjects, 80 were the cases of newly diagnosed PE patient and 40 were normal pregnant women as control. Cases were subdivided into separate groups comprising of 40 cases of mild PE 40 cases of severe PE. **Results:** The mean levels of hs-CRP are significantly higher ($p<0.0001$) in severe PE as compared to mild PE and healthy pregnant women.In group II, the hs-CRP was correlated positively with blood pressure (both systolic diastolic BP), while it was correlated negatively with birth weight of baby, while in group III, the hs-CRP was correlated strongly with systolic diastolic BPwhile it was correlated negatively with birth weight of newborn. **Conclusion:** The higher CRP levels in patients with PE delivering earlier in pregnancy could probably be a marker of disease severity and a marker of an excessive inflammatory response in patients with the most severe PE disease delivering prematurely compared with patients with less severe disease who deliver later in pregnancy.

Key Word: Preeclampsia, severity, hs-CRP levels, birth weight

Address for Correspondence:
Dr. Nilima Patil, Assistant Professor. Department of Biochemistry. ACPM Medical college, Dhule, INDIA.
Email: drnilimapatil01@gmail.com
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INTRODUCTION

Preeclampsia (PE) is pregnancy specific multisystem disorder that is characterized by development of hypertension, proteinuria and edema after 20 weeks of gestation.[1] Most severe form of PE is associated with thrombocytopenia, DIC hepatocellular damage.[2] Increasing clinical and biochemical evidence suggests that disturbance of normal endothelial cell function may be a primary cause in the pathogenesis of PE. Endothelial dysfunction is accompanied by elevated levels of inflammatory markers. Indeed, such markers have been shown to be much higher in women with PE than those seen in normal pregnancy as can be expected.[3] C-reactive protein (CRP) is measurement of inflammatory marker may be an alternative method of detecting women at risk of PE. CRP is a marker of systemic inflammation. It has been shown that CRP is elevated in women with PE.[3] The term high sensitivity CRP (hs-CRP) refers to the lower detection limit of the assay procedure being used and is otherwise similar to routine CRP in structure and function. The hs-CRP has been suggested to provide better sensitivity in establishing inflammation than levels of CRP and reflects ongoing inflammation and/or tissue damage much more accurately compared to other laboratory parameters of the acute-phase response.[4]Determination of hs-CRP has been suggested to be more sensitive than conventional measurement of CRP and provides better sensitivity in confirmation of inflammation.[3] The purpose of our study was to compare

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the levels of hs-CRP in normotensive healthy pregnant women and women with PE between 28-40 weeks of gestation and to study whether this parameter has any prognostic significance as in determining severity of preeclampsia.

MATERIAL AND METHODS

This cross sectional study was carried out in the Department of Biochemistry over a period of one year. After written and informed consent, a total of 120 pregnant women between 18 to 35 years visiting the gynecology and obstetrics OPD were included under study. Out of 120 subjects, 80 were the cases of newly diagnosed PE patient and 40 were normal pregnant women as control. Cases were subdivided into separate groups comprising of 40 cases of mild PE 40 cases of severe PE. This classification of PE patient based upon guidelines given by National High Blood Pressure Education Programme (NHBPEP) working group on high blood pressure in pregnancy.[5]

The study groups were made as:

Group I: 40 Healthy normotensive pregnant women as a control.

Group II: 40 cases of mild PE .

Group III: 40 cases of severe PE.

Total size: 120 individuals.

All cases controls were evenly matched for parity and maternal age. Participants were selected on the basis of detailed history, clinical examination and laboratory investigations. While recording Blood pressure either in left lateral or sitting position of the right arm roughly horizontal position at heart level. Detailed history of participants including age, sex, history of any medications, addictions and complete obstetric history was taken.

- Control: were normotensive healthy pregnant women without proteinuria who came to OPD for antenatal follow up in 3rd trimester of pregnancy. Development of hypertension at any time during antenatal follow up is excluded from control group.
- Cases: were those newly diagnosed PE patients in the 3rd trimester (28-40 weeks) admitted to obstetrics ward during study period.
- PE was diagnosed by blood pressure greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic occurring after midpregnancy (20 weeks of gestation) and accompanied by proteinuria (urinary excretion of 0.3 gm of protein or higher in a 24 hr urine specimen which corresponds with 1+ or greater on a urine dipstick test).
- Mild PE: The patients with blood pressure ≥140/90 mmHg but <160/110 mmHg with proteinuria of ≥ 0.3 gm in 24 hrs which corresponds with 1+ or greater on a urine dipstick test without involvement of end organ damage.
- Severe PE: The blood pressure reading is ≥160 mm Hg systolic or ≥110 mm Hg diastolic; her proteinuria is ≥ 5 g of protein in the urine per 24 hours or 3+ or greater on two random samples collected at least 4 hrs apart or other organ systems are involved. She may have headache, visual disturbances or other CNS symptoms; pulmonary edema, cyanosis, other cardiovascular symptoms and abdominal pain.

Inclusion criteria

- Healthy normotensive pregnant women in their 3rd trimester.
- Mild PE and severe PE women in their 3rd trimester.

Exclusion criteria

- H/O Diabetes, renal disease, chronic hypertension, any thyroid disease, dyslipidemia, bad obstetric history and PE.
- H/O any chronic inflammatory disease, systemic lupus erythematosus and cardiovascular disease.
- H/O any metabolic disorder before or during pregnancy.
- H/O any medication that might affect thyroid function.
- H/O any acute illness or any addiction.
- Cases in study group which are in labour or having multiple pregnancy.

Blood pressure (mm of Hg) was measured with mercury sphygmomanometer with patient is either in left lateral or sitting position with the right arm roughly in horizontal position at heart level.Weight (Kg) was measured by weighing pan at nearest Kg.

Estimation of hs-CRP By Immunoturbidimetric Method: After written informed consent, 12 hour fasting venous blood samples were collected from all pregnant women at least 6 hr before delivery. In pre-eclamptic group, blood sample is collected when patient presented for evaluation before initiation of medical therapy in plain bulbs. Serum was separated after 1 hour by centrifugation at 3000 rpm for 10 minutes and was tested for serum hs-CRP by turbidimetric immunoassay. Pipette 400 µl of activation buffer and 100 µl of latex reagent in the measuring cuvette. Mix well and incubate for 5 min at 37° C. Add 5 µl of serum and mix gently. Read absorbance (A1) exactly at 10 sec and absorbance (A 2) again at the end of exactly 4 min.Calculate Δ A (A2 – A1) for the test specimen.

Linearity: 10 mg/l.

Reference range: upto 1 mg/l.

Statistical analysis: emographic and biochemical characteristics of all the participants were analyzed as mean ± Standard Deviation (S.D.). All groups are matched for age and parity. Unpaired t test was applied to analyze the differences of studied characters in study groups. P value was obtained by t Test as > 0.05 not significant, < 0.05 significant and < 0.01 highly significant. Correlation coefficients (r) are calculated among various parameters in preeclamptic and control groups.

RESULTS

A total of 120 participants were enrolled in the study, 40 in each group.
Group I: 40 healthy normotensive pregnant women as a control.
Group II: 40 cases of mild PE.
Group III: 40 cases of severe PE.
Total size: 120 individuals.

Table 1: Demographic parameters in studied groups

Parameters	Group I (control) n=40	Group II (mild PE) n=40	P	Group III (severe PE) n=40	Pa	Pb
Maternal age(yrs)	23.73±2.58	23.25±2.79	0.43	22.45±2.31	0.13	0.10
Gest age at serum sampling(wks)	36.15±1.42	34.33±2.46	0.0001*	33.10±1.68	0.01	<0.0001*
Systolic BP (mm of Hg)	117.55±5.21	150.65±4.54	<0.0001*	168.6±4.08	<0.0001*	<0.0001*
Diastolic BP (mm of Hg)	78±4.75	98.85±3.48	<0.0001*	118.5±3.67	<0.0001*	<0.0001*
Urine protein	Nil	1+		2+		
Birth weight (kg)	2.89±0.17	2.54±0.08	<0.0001*	2.35±0.08	<0.0001*	<0.0001*

[*: Highly significant P value. P: comparison between normal pregnant and mild PE; Pa: comparison between women with mild and severe PE; Pb: comparison between normal pregnant and severe PE women.] There was no significant difference in maternal age in all three groups. However, P values of gestational age, systolic and diastolic BP are significantly higher (P<0.0001) in severe preeclamptic women compare with mild PE and normal pregnant women. While mean value of birth weight are significantly lower (p<0.0001) in severe PE compared with two other groups.

Table 2: hs-CRP level in studied groups

Parameter	Group I (control) n=40	Group II (mildPE) n=40	P	Group III (severePE) n=40	Pa	Pb
hs-CRP(mg/l) (upto1)	1.13±0.21	2.90±0.24	<0.0001*	5.00±0.33	<0.0001*	<0.0001*

The mean levels of hs-CRP are significantly higher (p<0.0001) in severe PE as compared to mild PE and healthy pregnant women.

Table 3: Correlation co-efficientin group II (Mild PE)group III (severe PE)

hs-CRP	Group II		Group III	
	r value	P value	r value	P value
vs Systolic BP	0.36	0.02	0.84	< 0.000
Vs Diastolic BP	0.69	< 0.000	0.88	< 0.000
vs Birth weight	-0.37	0.02	-0.38	0.02

In group II, the hs-CRP is correlated positively with blood pressure (both systolic diastolic BP), while it is correlated negatively with birth weight of baby (r=-0.37), while in group III, the hs-CRP is correlated strongly with systolic diastolic BP(r=0.8) while it is correlated negatively with birth weight of newborn (r=-0.38).

DISCUSSION

PE is a pregnancy specific disease associated with endothelial cell damage. There is an increasing evidence that PE is a systemic inflammatory disease. Activation of haemostatic system and endothelial activation are the key components of systemic inflammatory response. The hs-CRP is an acute phase reactant protein produced by liver in response to inflammation. It act as a sensitive marker of tissue damage and inflammation. Its production is stimulated by inflammatory cytokines, Interleukin-6 and

Tumor Necrosis Factor-α. The hs-CRP plays important role in eliciting the inflammatory processes. It acts as a scavenger and responsible for clearance of membranes and nuclear antigens. The hs-CRP is useful in PE patient is differentiating acute inflammation as well as assessment of severity of inflammation. More severe is inflammation indicated by higher hs-CRP level is associated with more severe PE.[2] In normal pregnancy inflammatory activity is increased leading to increased hs-CRP level; this process starts since early weeks of pregnancy. While this inflammatory activity is exaggerated in PE during early 3rd trimester. In PE cytokines production is increased to stimulate production of hs-CRP. Perhaps in 3rd trimester the maximum growth of foetus occurs that is inhibited by these cytokines leading to low birth weight of foetus.[6] The mean values of maternal age in all three were not statistically significant. Mean values Group I: 23.73±2.58, Group II: 23.25±2.79, Group III: 22.45±2.31).Mean gestational age at the time of serum sampling in normal pregnant women is 36.15±1.42 and it decreases in mild (34.33±2.46) and severe PE (33.10±1.68) having highly significant P value.While SBP and DBP increases with severity of PE as compared to normal pregnant women having highly significant P value (<0.0001). As blood pressure is indicator for the severity of PE because more is SBP DBP more severe is the PE. Urine protein was nil in group I and it increases with severity of PE. Proteinuria and blood pressure are used as parameters for severity of PE.The mean value of birth weight was normal in healthy pregnant women 2.89±0.17 but it decreases in mild PE (2.54±0.08) to more decrease in severe PE (2.35±0.08) having highly significant p value <0.0001. In our study, the mean level of serum hs-CRP in normal pregnant women was slightly raised (1.13±0.21). It increases with severity of PE with mean value in mild PE was 2.90±0.24 and in severe PE was 5.00±0.33.Our findings correlate with Hossein Ayatollahi *et al* study. They studied serum level of hs-CRP in normal and preeclamptic pregnancies in 28-40 wks of trimester. There was a significant difference in the mean hs-CRP between normal pregnant women and mild preeclamptic women (6.7±2 mg/l vs 9.2±7.1 mg/l, p<0.05). Patients with severe PE had a significantly higher means plasma levels (12.8±7.3 mg/l) than normal pregnant (6.7±2 mg/l) and mild preeclamptic women (9.2± 7.1 mg/l) (p<0.05).They found significantly higher levels of hs-CRP in severe PE than mild PE.[3] In our study, hs-CRP is positively correlated with systolic blood pressure in both mild and severe PE (r=0.36, P= 0.02 in mild PE r=0.84, P=<0.000 in severe PE). The hs-CRP is also positively correlated with diastolic blood pressure in both mild and severe PE (r=0.69, P=<0.000 in mild PE r=0.88, P=<0.000 in severe PE). Bargale *et al* study enrolled 60 cases out of which 30 were preeclamptic women 30 were normal healthy pregnant women as control between the age group of 19 - 30 years with gestational age between 28-40 wks. In this study, hs-CRP level was significantly (p<0.001) higher in preeclamptic women (3.733±1.096 mg/L) when compared with normal pregnant women (1.216±0.552 mg/L).They observed gradual increase in hs-CRP level as disease progresses from mild (2.941±0.390) to severe PE (4.769±0.807).The study conclude that hs-CRP levels may be helpful to predict severity of disease.In their study blood pressure is an indicator for the severity of the preeclampsia. Along with blood pressure, hs-CRP and uric acid levels increased with the severity. Therefore, they correlated these two parameters with blood pressure within preeclampsia group. They found, hs-CRP and uric acid levels are significantly (p<0.001) correlated with blood pressure [hs-CRP/SBP r=0.7232, hs-CRP/DBP r=0.7465 and uric acid/SBP r=0.6407, uric acid/DBP r=0.7325] respectively. In addition, they found significant (p<0.001) correlation between hs-CRP and uric acid concentrations in pregnancies complicated with preeclampsia (r = 0.6628). Thus, their findings suggest a strong association between hs-CRP, uric acid levels and blood pressure.[2] These findings in the above study correlate with those of our study. We find a positive correlation between serum levels of hs-CRP, systolic blood pressure, diastolic blood pressure and urine protein excretion in PE. In our study, hs-CRP is negatively correlated with birth weight in mild and severe PE(r= -0.37, P=0.02 in mild PE r=-0.38, P=0.02 in severe PE). These findings in our study correlate with those of following study by Mirzaie *et al* study. Their study group includes mild PE, severe PE and healthy normotensive pregnant women with 43 women in each group in their 3rd trimester. Serum CRP levels in mild and severe PE were markedly higher than those of normal third trimester pregnant women (P =0.003). In mild to severe PE groups, correlation tests show positive correlation between serum CRP levels and systolic blood pressure (r=0.6,*p*=0), diastolic blood pressure (r =0.5, *P*=0). There was a negative correlation between CRP and birth weight (r=-0.09, *P*=0.01) and gestational age (r =-0.4, *P*=0).The study showed higher levels of CRP in women with PE. Elevated serum levels of CRP in PE women are thus correlated with severity of disease.[7] In a study byGuven *et al* patient those affected by PE demonstrated a significantly higher systolic pressure (158±16 mm Hg vs 109±13 mm Hg, *p*<0.001) and a significantly higher diastolic pressure (105±7.0 mm Hg vs 67±9.8 mm Hg, *p*<0.001).There were statistically significant differences between the 3 groups for CRP (*p*=0.012), TNF-α

(p=0.046), IL-6 (p=0.015), homocysteine (p<0.001) and crude fetal birth weight (p<0.001). Indeed, gestational age-adjusted birth weight percentiles were also significantly lower in the groups complicated by PE (p<0.001).Especially in the severe PE group, correlation analysis showed negative correlations between fetal birth weight and serum hs-CRP (r =-0.702, p=0.012), TNF-α (r=0.8, p=0.046), IL-6 (r=0.514, p=0.015) and Homocysteine (r =0.512, p<0.001). The mean fetal weight for normotensive controls, mild and severe PE groups were (3485±365, 2477±746 and 2435±768), respectively.They conclude that, elevated maternal serum levels of hs-CRP, TNF-α, IL-6 and homocysteine in preeclamptic women are associated with fetal birth weight in the early third trimester.[6]

CONCLUSION

The hs-CRP is increases with severity of PE and correlated positively with blood pressure in PE. Is having higher level in severe PE than mild PE and normal pregnant women. The results of this study provide further support to the hypothesis that inflammation contributes to the development of PE and that inflammatory activity is linked with fetal birth weight and severity of the condition. The higher CRP levels in patients with PE delivering earlier in pregnancy could probably be a marker of disease severity and a marker of an excessive inflammatory response in patients with the most severe PE disease delivering prematurely compared with patients with less severe disease who deliver later in pregnancy.

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