

## Original Article

### Serum Level of High Sensitive C-Reactive Protein in Normal and Preeclamptic Pregnancies

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#### ABSTRACT

**Background and Objective:** The aim of this study was to determine the level of plasma high sensitive c-reactive protein (hs-CRP) in preeclampsia and to compare hs-CRP levels between normal pregnant women, mild preeclamptic, and severe preeclamptic women.

**Materials and Methods:** Serum hs-CRP levels were investigated in 40 cases of normal pregnant women, 37 cases with mild preeclampsia and 38 cases with severe preeclampsia in the third trimester of pregnancy. Venous blood samples were collected at admission to the hospital at least 6h before delivery for measurement of hs-CRP by immuno turbidometric method. The student t-test was used for comparison of proportions.

**Results:** There were significant difference in the means serum hs-CRP between normal pregnant women and mild preeclamptic women ( $P<0.05$ ). Serum concentration of hs-CRP were significantly higher in severe preeclampsia ( $p<0.05$ ) than normal pregnancy.

There were also significant differences in hs-CRP levels between mild and severe preeclampsia ( $P<0.05$ ).

**Conclusion:** We found higher levels of hs-CRP in mild and severe preeclampsia than normal pregnancy and also these results suggest that hs-CRP are increased more in severe preeclampsia than mild preeclampsia, and may be useful in prediction and diagnosis of the severity of preeclampsia.

**Key words:** C-reactive protein receptor, Pre-Eclampsia, Pregnancy

#### Introduction

Preeclampsia is a complication of pregnancy constituting a major cause of maternal and fetal morbidity and mortality (1). Preeclampsia

(PE) develops in 4–5% of human pregnancies. It is characterized by an elevated blood pressure and proteinuria and develops after 20 weeks of gestational age. PE can result in eclampsia when convulsions develop or manifest as the hemolysis, elevated

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liver enzymes and low platelet count (HELLP) syndrome. Several etiologies have been implicated in the development of preeclampsia. Some of them include abnormal trophoblast invasion of uterine blood vessels, immunological intolerance between fetoplacental and maternal tissues, maladaptation to the cardiovascular changes or dietary deficiencies and genetic abnormalities (2). Endothelial cell dysfunction and inflammation are considered to have a crucial role in the pathophysiological mechanism of preeclampsia (3).

Increasing clinical and biochemical evidence suggests that disturbance of normal endothelial cell function may be a primary cause in the pathogenesis of PE (4).

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 (5) as can be expected. C-reactive protein (CRP) is a marker of systemic inflammation (6). It has been shown that CRP is elevated in women with PE (7). High-sensitive (hs) CRP is a protein measured by either antibodies that are labeled with an enzyme (ELISA) or a fluorescent compound or antibody-coated polystyrene beads. Determination of hsCRP has been suggested to be more sensitive than conventional measurement of CRP and provides better sensitivity in confirmation of inflammation (8). Recently, several studies have conducted to elucidate a relationship between PE and serum hsCRP levels. However, little is known about whether or not there is a relationship with the severity of disease.

Therefore, the aim of this study was to determine the level of serum CRP in preeclampsia and its relationship with the severity of the disease.

## Materials and Methods

The cross-sectional strategy of this study was designed to compare the plasma concentration of hs-CRP in peripheral blood obtained from normal pregnant women and pregnant patients with preeclampsia at the Departments of Obstetrics and Gynecology of the Ghaem hospital (Mashhad University of Medical Sciences, Mashhad, Iran).

Preeclampsia was defined as hypertension (systolic blood pressure  $\geq 140$  mmHg and diastolic blood

pressure  $\geq 90$  mmHg 20 weeks after gestation) and proteinuria ( $\geq 300$  mg in a 24-hr urine collection or one dipstick measurement of  $\geq 1+$ ) according to the Committee of Terminology of ACOG definition (9). Severe preeclampsia was diagnosed on the basis of diastolic blood pressure  $\geq 110$  mmHg or a significant proteinuria (dip stick measurement of  $\geq 2+$ ) or the presence of severity evidence such as headache, visual disturbances, upper abdominal pain, oliguria, convulsion, elevated serum creatinine, thrombocytopenia, marked liver enzyme elevation, or pulmonary edema. Inclusion criteria for preeclamptic group were: primigravida who visited hospital during gestation weeks 28-40, absence of labor contractions, and premature rupture of membranes, or clinical chorioamnionitis. None of the patients included had underlying diabetes, renal diseases, chronic hypertension, or symptomatic infectious diseases, systemic lupus erythematosus, or another chronic disease which were excluded during routine interviews, clinical investigations, and laboratory tests. The pregnant women were not given corticosteroids at least 7 days prior to inclusion in the study.

Normal pregnant women had no hypertension, proteinuria, and edema. All normal pregnant women were singleton primigravidas monitored at the Department of Obstetrics and Gynecology of our hospital with gestational age 28–40 weeks, no chronic medical disorders and not in labor. They were normotensive and had normal blood pressures throughout gestation. Patients with a history of diabetes, renal disease, hypertension, other cardiovascular illness, and symptomatic infectious diseases were excluded.

The population consisted of 40 women with normal pregnancy, 37 women with mild preeclampsia, and 38 women with severe preeclampsia. Three groups were similar in age and body weight (mild preeclampsia group with a mean age of  $27.4 \pm 6.4$  years, severe preeclampsia with an age of  $26.1 \pm 5.8$  years and pregnant control group having an age of  $24.6 \pm 4.2$  years).

Blood samples were collected through an indwelling ante-cubital venous catheter at admission to the hospital, at least 6 h before delivery and before magnesium sulphate application. None of the participants were in labor at the time of sample

collection. In addition, none of the patients or control subjects was treated with any antihypertensive or other medications and none of them was in active labor before and/or at the blood collection time. Collected blood samples were centrifuged at 1500 g for 10 min and stored at -20 °C until assayed for hsCRP.

In all patients and normal pregnant women, serum hsCRP level was measured with immunoturbidometric assay (Diagnostica kit, Germany). The lowest limit of detection was 0.1 mg/l. The maximum inter- and intra-assay coefficients of variation for the range of concentrations evaluated were 3.5% for hsCRP. The results were expressed as mean  $\pm$  S.D. and analyzed by an independent samples t-test. All statistical analyses were carried out using SPSS 11.0 software package from SPSS Inc., Chicago, USA. The level of significance was set at  $p < 0.05$ .

## Results

This study included 40 normal pregnant women and 75 pregnant women with preeclampsia (37 cases of mild preeclampsia and 38 cases of severe preeclampsia). Table 1 lists the clinical characteristics

of the three study groups.

There was no difference in the mean gestational age at venipuncture and the birth weight between normal pregnant and mild preeclamptic women. However, the mean gestational age at delivery ( $p < 0.001$ ) and the birth weight ( $p < 0.05$ ) were significantly lower in the group with severe preeclampsia than in normal pregnant women.

Table 2 shows the laboratory characteristics of patients with preeclampsia.

There was no statistically significant difference in BUN, bilirubin, creatinine, blood glucose, uric acid, Hb, hematocrit, and platelet between mild and severe preeclampsia, while AST, ALT, and urine protein were significantly different between two groups ( $p < 0.05$ ).

In addition, hsCRP was detected in all specimens. There was a significant difference in the mean hsCRP between normal pregnant women and mild preeclamptic women ( $6.7 \pm 2$  mg/l vs  $9.2 \pm 7.1$  mg/l,  $p < 0.05$ ). Patients with severe preeclampsia had a significantly higher mean plasma levels ( $12.8 \pm 7.3$  mg/l) than normal pregnant ( $6.7 \pm 2$  mg/l) and mild preeclamptic women ( $9.2 \pm 7.1$  mg/l) ( $p < 0.05$ ) (Table 1).

**Table 1. Clinical characteristics of the study population. Data are presented as mean  $\pm$  standard deviation (SD)**

Group	Normal pregnant (n = 40)	Mild preeclampsia (n = 37)	p	Severe preeclampsia (n = 38)	Pa	Pb
Age (years)	24.6 $\pm$ 4.2	27.4 $\pm$ 6.4	NS	26.1 $\pm$ 5.8	NS	NS
Gestational age at blood sampling (weeks)	37.1 $\pm$ 2	35.7 $\pm$ 4	NS	32.7 $\pm$ 5.6	0.02*	<0.001*
Body weight	71.4 $\pm$ 10.4	77 $\pm$ 12.5	NS	71.1 $\pm$ 11.4	NS	NS
Birth weight (kg)	2.6 $\pm$ 0.7	2.3 $\pm$ 0.68	NS	2.1 $\pm$ 0.97	NS	<0.05*
<b>Blood pressure (mmHg)</b>						
Systolic	111 $\pm$ 14	149.1 $\pm$ 15	<0.001*	154.7 $\pm$ 19.7	NS	<0.001
diastolic	63 $\pm$ 12	92 $\pm$ 12	<0.001*	107.6 $\pm$ 14.8	<0.001*	<0.001*
hsCRP(mg/l)	6.7 $\pm$ 2.0	9.2 $\pm$ 7.1	<0.05*	12.8 $\pm$ 7.3	<0.05*	<0.05*

P, comparison between normal pregnant and mild preeclampsia; Pa, comparison between women with mild and severe preeclampsia; Pb, normal pregnant and severe preeclampsia women

\* Statistically significant,  $p < 0.05$ ; NS, non-significant

**Table 2. Laboratory findings of the study population. Data are presented as mean  $\pm$  standard deviation (SD)**

Group	Mild preeclampsia (n = 37)	Severe preeclampsia (n = 38)	P
<b>BUN (mg/dl)</b>	25.0 $\pm$ 14	25.7 $\pm$ 12	NS
<b>Bil T.(mg/dl)</b>	0.7 $\pm$ 0.20	0.87 $\pm$ 0.45	NS
<b>Bil D.(mg/dl)</b>	0.26 $\pm$ 0.11	0.31 $\pm$ 0.17	NS
<b>Creatinine (mg/dl)</b>	0.62 $\pm$ 0.18	0.72 $\pm$ 0.24	NS
<b>Blood glucose (mg/dl)</b>	83.2 $\pm$ 15.5	88.0 $\pm$ 20.3	NS
<b>Uric acid (mg/dl)</b>	5.81 $\pm$ 1.37	6.29 $\pm$ 1.54	NS
<b>Hb (g/dl)</b>	11.92 $\pm$ 1.39	12.47 $\pm$ 1.61	NS
<b>Hematocrit (%)</b>	37.00 $\pm$ 3.93	38.16 $\pm$ 5.31	NS
<b>Platlete</b>	208217 $\pm$ 95180	191120 $\pm$ 142383	NS
<b>AST (U/L)</b>	22.26 $\pm$ 10.63	36.92 $\pm$ 28.57	<0.05*
<b>ALT (U/L)</b>	18.39 $\pm$ 7.09	31.24 $\pm$ 25.28	<0.05*
<b>Urine Protein (gr/l)</b>	1.10 $\pm$ 1.96	2.26 $\pm$ 2.60	<0.05*

P, comparison between mild preeclampsia and severe preeclampsia

\* Statistically significant,  $p < 0.05$ ; NS, non-significant

## Discussion

Endothelial cell damage or activation and hypercoagulation are associated with preeclampsia (10, 11) and there is increasing evidence that preeclampsia is a systemic inflammatory disease (11). Some studies have shown that markers of inflammation or endothelial activation have important roles in preeclampsia. CRP is responsible for the clearance of membranes and nuclear (7, 11, 12) antigens and acts as a scavenger (13).

Some reports have shown that elevated CRP levels during first trimester of pregnancy are indicative of preeclampsia (14) and to be an independent predictor of preeclampsia (15), but another study reported that serum levels of CRP at 23-25 weeks of gestation were similar in pregnant women who subsequently developed preeclampsia and in women without complications of pregnancy (16).

Although normal pregnancy is associated with increased pro-inflammatory markers, it has been suggested the cause of serum hsCRP elevation in the preeclamptic women may be as a result of reduced plasma volume in these patients (11, 13). The relationship of CRP levels and preeclampsia has already been studied and higher concentration of CRP has been reported during preeclampsia (7, 17). It has also been shown that women with a history of preeclampsia had increased CRP levels (18).

In our study, levels of hsCRP were found to be significantly higher in women with mild and severe preeclampsia than in normotensive women with similar chronological age.

Belo et al found significantly higher levels of CRP in preeclampsia but statistical significance was lost after adjustment for maternal weight (19). Üstün et al showed that level of CRP to be significantly higher in women with mild and severe preeclampsia than in normal pregnant women with similar chronological age, gestational age, and body mass index (20). There are also few studies concerning CRP levels due to severity of preeclampsia (21). In these studies, it has been shown that CRP levels were positively related to the degree of blood pressure elevation. In our study, we found significantly higher levels of hsCRP in severe preeclampsia than mild preeclampsia.

## Conclusion

We have determined the serum concentration of hsCRP in normal pregnancy and preeclampsia. In addition, hsCRP are elevated in severe preeclampsia compared with mild preeclampsia and normal pregnancy and may be useful in predicting the severity of preeclampsia. The clinical validity of the monitoring of hsCRP needs to be established in further longitudinal studies.

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