C-Reactive Protein Level as an Inflammatory Marker in Patients with Preeclampsia

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Abstract

Objective: The objective of this study was to compare plasma concentrations of C-reactive protein between pregnant patients with preeclampsia and subjects with uncomplicated pregnancy.

Subjects and Methods: We conducted a case-control study of 60 nulliparous women without preexisting medical complications. In this study, 30 patients with preeclampsia and 30 women with uncomplicated pregnancy were enrolled. Maternal venous plasma samples were collected before delivery for estimation of C-reactive protein levels.

Results: The mean concentration of C-reactive protein was significantly higher in preeclamptic patients than in the control group. There was a significant positive correlation between C-reactive protein levels and both systolic and diastolic blood pressures. The receiver operator characteristics curve showed that the best cutoff value for C-reactive protein concentration for diagnosis of preeclampsia was 6mg/L.

Conclusion: C-reactive protein is significantly elevated during preeclampsia and is positively correlated with the severity of hypertension.

Key Words: Preeclampsia – Inflammation – C-reactive protein.

Introduction

PREECLAMPSIA complicates 3-7% of all pregnancies and continues to be a major contributor to maternal and neonatal morbidity and mortality [1,2]. A previous study [3] suggested that preeclampsia is not a different state of pregnancy but represents an extreme maternal response to pregnancy. Thus, preeclampsia is part of a more generalized intravascular inflammatory reaction, involving intravascular leukocytes and the clotting and complement systems. Preliminary studies showed significant differences in inflammatory cytokine levels between subjects with preeclampsia and those experiencing normal pregnancy [4,5].

C-reactive protein (CRP) is a sensitive marker of tissue damage and inflammation [6]. CRP is thus a potential marker of the inflammatory response characteristic of preeclampsia. Hepatic synthesis of CRP increases in response to IL-6 and TNF-α. These cytokines are implicated in the inflammatory response and in maternal endothelial activation in preeclampsia. The predictive role of CRP levels in pregnant women with preeclampsia is controversial [7-10].

The aim of this study was to determine whether CRP levels in preeclamptic subjects differed significantly from those of pregnant subjects without preeclampsia.

Patients and Methods

This was a case-control study of 60 women admitted to Ain Shams University Maternity Hospital. The study was approved by the Ethics Committee of Ain Shams University Maternity Hospital, Cairo, Egypt from March 2009 - June 2010 in accordance with local research governance requirements. Informed consent was obtained from each participant.

All pregnant participants were nulliparous, healthy women without known preexisting medical complications. Exclusion criteria included multiple gestation, prior preeclampsia, illicit drug use, and preexisting medical conditions such as diabetes, chronic hypertension, and renal disease.

The study included 30 patients with preeclampsia and 30 women with uncomplicated pregnancy serving as controls. Preeclampsia was diagnosed...
according to the definition of the International Society for the Study of Hypertension. Specifically, preeclampsia was defined as development of (1) hypertension with a diastolic blood pressure of 90mmHg on 2 or more occasions, measured at intervals of at least 4 hours; and (2) proteinuria, defined as a value of +1 on dipstick test on at least 2 midstream urine collections more than 4 hours apart or presence of 300mg protein per 2424 hours urine output. Preeclampsia was diagnosed if these signs developed after 20 weeks of gestation and decreased after delivery [11]. Gestational age was determined by a reliable date for the last menstrual period and/or a first trimester ultrasound evaluation (when available).

Maternal venous plasma samples (preserved with EDTA) were collected upon admission before delivery and before administration of any medications. Samples were aliquoted and stored at -70°C for later analysis. CRP was measured in duplicate by a high-sensitivity enzyme-linked immunoassay (ELISA) [11]. The sensitivity of the assay was 0.2ng/mL. Intra- and inter-assay variabilities were 3.9% and 7.4%, respectively. Other variables recorded were maternal age, body mass index (calculated as weight in kg/height in m$^2$), neonatal birth weight, and serum creatinine and uric acid levels.

A power analysis, based on previously reported differences in CRP levels in women with uncomplicated pregnancies and women with preeclampsia, suggested that a sample size of 26 participants per group would have 80% power to detect a 2-fold difference with an alpha of 0.05 [8].

Statistical analyses were performed using SPSS version 15.0. Unpaired Student's $t$-tests, chi-square tests, Fisher's exact probability tests, and Pearson's tests were used where appropriate. Significance was set at $p<0.05$.

Results

Demographic characteristics of each group are shown in Table (1). There were no significant differences in maternal age or body mass index between the preeclampsia and control groups. Mean gestational ages at delivery and neonatal birth weights were significantly lesser for women with preeclampsia than for women in the control group.

Women with preeclampsia had higher plasma uric acid concentrations than did those in the control group (7.4mg/dL±1.4mg/dL vs. 5.1mg/dL±1.1 mg/dL; $p<0.001$). The mean concentration of CRP was significantly higher in subjects with preeclampsia than in control subjects (9.1mg/L±1.8mg/L and 4.3mg/L±1.2mg/L respectively, $p<0.001$; Table 2).

We examined the relationship between CRP level and other variables among the preeclamptic patients. There was a significant positive correlation between serum CRP levels and both systolic blood pressures ($r=0.322$, $p<0.05$) and diastolic blood pressures ($r=0.454$, $p<0.05$).

A ROC curve was constructed for estimating the predictive value of serum CRP levels for diagnosis of preeclampsia (Fig. 1). The area under the curve (AUC) was 0.93 (95% CI, 0.882 to 1.003; $p<0.001$), indicating significant association and predictability. The best cutoff value of serum CRP levels for diagnosis of preeclampsia was 6mg/L (sensitivity, 93.3%; specificity, 93.3%; positive predictive value, 93.3%; negative predictive value, 93.3%; overall accuracy, 93.3%).

### Table (1): Demographic characteristics of experimental and control subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia group (n=30)</th>
<th>Control group (n=30)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>27.2±4.2</td>
<td>28.3±4.7</td>
<td>0.343</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>29.3±4.9</td>
<td>28.4±5.5</td>
<td>0.506</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>4 (13.3)</td>
<td>6 (20)</td>
<td>0.731</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>36.8±3.1</td>
<td>38.9±3.9</td>
<td>0.025*</td>
</tr>
<tr>
<td>Maternal systolic blood pressure (mmHg)</td>
<td>152.6±30.1</td>
<td>116.6±23.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Maternal diastolic blood pressure (mmHg)</td>
<td>95.4±22.3</td>
<td>73.4±28.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Neonatal birth weight (kg)</td>
<td>2.4±0.6</td>
<td>3.1±0.3</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

### Abbreviations: CRP, C-reactive protein.

* Values are given as mean ± SD or number (percentage).
* Statistically significant difference.

### Table (2): Creatinine, uric acid, and CRP levels in the experimental and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia group (n=30)</th>
<th>Control group (n=30)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.5±0.3</td>
<td>0.4±0.2</td>
<td>0.134</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.4±1.4</td>
<td>5.1±1.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>9.1±1.8</td>
<td>4.3±1.2</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

### Abbreviations: CRP, C-reactive protein

*Values are given as mean ± SD
*Statistically significant difference
Discussion

Our results showed that serum CRP is significantly higher in preeclamptic patients than in healthy pregnant women. In addition, there were significant positive correlations between serum CRP levels and both systolic and diastolic blood pressures.

Healthy human pregnancy requires adaptation of the maternal immune system in order simultaneously enable preservation of maternal immune competence and tolerance of the semiallogenic fetus. Shifts in both the adaptive and innate immune systems contribute to this process. Alterations in innate immunity include both cellular and soluble components, as reflected by elevated concentrations of acute phase proteins and increased numbers of monocytes and granulocytes [12]. Uterine natural killer cells play a primary role in both the local placental environment and in the broader maternal system [13]. The endothelial cell dysfunction evident in preeclampsia has long been thought to be a result of excessive immune activation [12].

Numerous studies have reported elevated CRP in women with preeclampsia, both prior to evident clinical symptoms and as long as 30 years postpartum [11,14-16]. In many studies, the association between elevated CRP and preeclampsia was significantly decreased or lost after adjusting for body mass index [8]. On the other hand, studies that controlled for body mass index obtained inconsistent results with regard to CRP and the risk of preeclampsia [14]. Importantly, elevated CRP concentration (4.9mg/L) in the first trimester has been associated with a 2.5-fold increased risk of preeclampsia among lean women. This relationship was absent among overweight and obese women [17].

As evidenced in our data, there is a significant increase in the circulating concentration of CRP in preeclamptic women compared to that in healthy pregnant women. In addition, we did not observe a relationship between CRP and body mass index, in contrast to the findings of other studies. However, this lack of an association may be the result of the timing of sample collection in our study (pre-delivery third trimester). In other studies, sample collection was completed during the first or second trimesters. Heterogeneity of study populations in developed and developing countries and differences in levels of chronic subclinical infection may also contribute to differences in inflammatory markers between studies [14,15,18,19]. There was no correlation between CRP levels and uric acid levels, suggesting that CRP levels are not directly related to the endothelial dysfunction observed in preeclampsia.

Plasma levels of CRP may be an important marker for differential diagnosis between transient hypertension and chronic hypertension. CRP levels were higher in pregnant patients with transient hypertension, preeclampsia, and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome than in pregnant patients with chronic hypertension and controls; this suggests that inflammation is a common cause of transient hypertension and preeclampsia [20].

Limitations of this study include the analysis of CRP in late pregnancy at the time of clinically recognizable preeclampsia and the differences in gestational age at delivery.

We conclude that the inflammatory marker CRP is significantly elevated during preeclampsia and positively correlated with the severity of hypertension. These data support the hypothesis that pregnancy is marked by activation of the innate immune system and that this activation is exaggerated in preeclampsia.

References


