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*Original article*

# LEVELS OF C-REACTIVE PROTEIN IN PREDICTION OF PREECLAMPSIA

**Todorovska Irena[1], Dabeski Drage[1], Simeonova Krstevska Slagjana[1], Tanturovski Mile[1], Jovanovska Viktorija[1], Kondova Topuzovska Irena[2]**

[1]University Clinic for Gynecology and Obstetrics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia
[2]University Clinic for Infectious Diseases and Febrile Conditions, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia
*e-mail: tirenat1501@gmail.com*

## Abstract

Preeclampsia is a hypertensive disorder that occurs in 4-5% of pregnant women and is the cause of significant maternal and fetal morbidity and mortality. C-reactive protein is considered a sensitive inflammatory marker and its values increase in response to inflammation that occurs during tissue injury. The level of C-reactive protein increases, correlating with the severity of the clinical picture of preeclampsia.

To determine the level of C-reactive protein in patients with preeclampsia and the correlation of the value with the severity of the clinical picture of preeclampsia.

This study included 25 patients with a moderate form of preeclampsia, 25 patients with severe preeclampsia and 30 patients without symptoms, with normal pregnancy. All women were in the third trimester of pregnancy, hospitalized at the University Clinic for Gynecology and Obstetrics, Skopje, in the Department of preeclampsia, intrauterine growth retardation and premature births. Patients were examined in the period from 01.10.2022 to 10.04.2023. The severity of preeclampsia was determined by blood pressure, 24-hour proteinuria, and laboratory tests characteristic of preeclampsia.

The results obtained showed that increased CRP levels were statistically significant ($p<0.001$) in the serum of patients with moderately severe form of preeclampsia (group A) (mean value 8.4 mg/L; 6.1-11.3 mg/L) and severe preeclampsia (group B) (mean value 30.2 mg/L; 13-54 mg/L) in correlation with the control group (group C) (mean value 2.5 mg/L; 0.2-4.5 mg/L). There was a significant correlation between serum CRP levels and systolic blood pressure ($p<0.001$) and proteinuria ($p<0.001$).

High levels of serum CRP correlate with the severity of the clinical picture of preeclampsia.

**Keywords**: CRP, Preeclampsia, blood pressure

## Introduction

Hypertensive disorders in pregnancy and their associated feto-maternal complications are a leading condition that results in increased feto-maternal morbidity and mortality. Epidemiological studies indicate an increased incidence of hypertensive disorders in pregnancy. Worldwide, over 50,000 deaths per year caused by hypertensive disorders are registered[1,2].

Despite the progress of medicine, prediction and prevention of hypertensive disorders are elusive for most obstetricians and complications in pregnancy cannot be avoided. There are several factors such as hypoxia, angiogenic factors, impaired immunity, inflammatory cascade that are involved in the occurrence of hypertensive disorders in pregnancy and its complications[3].

C-reactive protein is a sensitive marker of inflammation, and may be a potential marker in determining the increased inflammatory response characteristic of preeclampsia. Hepatic synthesis of C-reactive protein increases in response to inflammatory cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor alpha, which are responsible for the inflammatory response and maternal endothelial activation in preeclampsia[1,3].

According to the American College of Obstetricians and Gynecologists (ACOG), gestational hypertension and preeclampsia take precedence over other hypertensive disorders of pregnancy[1]. As the condition worsens, eclampsia develops when convulsions occur or may manifest as hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Eclampsia and HELLP syndrome are associated with severe complications such as cerebral hemorrhage, liver hemorrhage, pulmonary edema, and renal failure[2,4,6].

Insufficient adaptation of maternal immune responses and defective trophoblast invasion are hypothesized to participate in the etiology of preeclampsia. Thus, an excessive maternal inflammatory response against foreign fetal antigens occurs and triggers a chain of events that include the release of proinflammatory cytokines into the systemic circulation, defective spiral artery remodeling, abnormal trophoblastic invasion, and placental infarcts that lead to poor fetal outcome[4,6].

Hypertensive disorders in pregnancy often culminate in unfavorable obstetric and neonatal outcomes, therefore early detection and effective management are required. The aim of this study was to investigate and detect the role of C-reactive protein as a prognostic marker of hypertensive disorders in pregnancy and the associated feto-maternal outcome.

## Material and methods

This study included 25 patients with moderate preeclampsia, 25 patients with severe preeclampsia and 30 patients without symptoms, with normal pregnancy. All women were in the third trimester of pregnancy, hospitalized at the University Clinic for Gynecology and Obstetrics, Skopje, in the Department of preeclampsia, intrauterine growth retardation and premature births. Patients were examined in the period from 01.10.2022 to 10.04.2023. The study included 50 patients with preeclampsia divided into two groups: moderately severe form of preeclampsia (25 patients), severe form of preeclampsia (25 patients) and 30 female patients as a control group.

Patients with preeclampsia were >28 weeks of gestation. On admission, the level of C-reactive protein was determined. The control group included 30 healthy pregnant women, in the second trimester of pregnancy, from 22-26 weeks of gestation, mobilized by the Outpatient Polyclinic Department at PHI University Clinic for Gynecology and Obstetrics. Eclampsia was determined by blood pressure, 24-hour proteinuria, and angiogenic factors.

The form of preeclampsia was determined according to ACOG criteria. Preeclampsia is defined as hypertension occurring after 20 weeks of gestation with systole pressure >140 mmHg and diastole >90 mmHg, proteinuria ≥300 mg in urine during 24 hours or qualitative with a positive result in urine sediment[1].

Severe preeclampsia is defined as presence of hypertension ≥160 mmHg/110 mmHg; significant proteinuria ≥2+, visual disturbances, headache, epigastric pain, oliguria, convulsions,

thrombocytopenia, increased liver enzymes, increased serum creatinine levels and pulmonary edema[2,7].

The concentration of CRP was determined by immunoturbidimetric method at 522 nm, on biochemical analyzer Cobas Integra 400 plus, Roshe Diagnostic, Germany. Human CRP agglutinates latex particles are coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically at 522 nm. Measuring range of the test is 0.1-20 mg/L (0.952-190 mmol/L). The lowest detection level is 0.1 mg/L (0.952 nmol/L).

Upon admission of patients with preeclampsia, obstetric and laboratory tests were made, measurement of vital parameters, and appropriate antihypertensive therapy was prescribed according to the protocol of the Department. Statistical analysis was performed with Chi square test and Student's t-test.

## Results

In this study, all patients from the three groups (control group, moderate and severe preeclampsia) were comparable for age and parity (25.6±9.4 years of the control group; 26.7±2.1 years of patients with moderate preeclampsia; 30.5±4.3 years of patients with severe preeclampsia).

The results obtained showed that the increased CRP levels were statistically significant ($p<0.001$) in the serum of patients with moderately severe form of preeclampsia (group A) (mean value 8.4 mg/L; 6.1-11.3 mg/L) and severe form of preeclampsia (group B) (mean value 30.2 mg/L; 13-54 mg/L) in correlation with the control group (group C) (mean level 2.5 mg/L; 0.2-4.5 mg/L) (Table 1). There was a significant correlation between serum CRP levels and systolic blood pressure ($p<0.001$) and proteinuria ($p<0.001$). Patients with higher levels of total CRP had increased values of systolic and diastolic blood pressure (Table 2).

**Table 1.** CRP level in the three analyzed groups

| | Normal level of hsCRP, N (%) | Increased level of hsCRP, N (%) | P-values |
|---|---|---|---|
| Control group | 25 (83.33%) | 5 (16,67%) | |
| Medium PE | 7 (28%) | 18 (72%) | |
| Severe PE | 3 (12%) | 22 (88%) | |
| | | | <0.01 |

**Table 2.** Values of blood pressure and proteinuria in the three groups of patients

| | Blood pressure | Proteinuria | P-values |
|---|---|---|---|
| Control group | 110/60-120/70 mmHg | 0.4-0.8g/24h | |
| Medium PE | 140/80-150/90 mmHg | 1.0-2.2g/24h | |
| Severe PE | 160/100-180/120 mmHg | 2.5-11.0g/24h | |
| | | | <0,01 |

**Table 3.** Mode of delivery in patients with normal and increased hsCRP level

| Mode of delivery | Normal level of hsCRP, N (%) | Increased level of hsCRP, N (%) | P-values |
|---|---|---|---|
| Vaginal delivery | 30 (75%) | 10 (25%) | |
| Cesarean section | 12 (34.29%) | 23 (65.71%) | |
| Instrumental delivery | 1 (20%) | 4 (80%) | |
| | | | <0.01 |

There was no maternal mortality and extreme prematurity of the fetuses. Patients with higher total CRP levels had a higher incidence of severe preeclampsia or eclampsia and higher maternal and neonatal complications (prematurity) (Table 3). These patients had a higher rate of cesarean termination (65.71%) and feto-maternal complications.

**Discussion**

In this study, the level of hsCRP in third-trimester pregnant women was significantly higher in preeclamptic women than normotensives, which showed an increased inflammatory response in these patients. This is in correlation with other studies[9,10]. The highest levels of hsCRP were obtained in patients with a severe preeclampsia. However, 20% (10 of 50) of patients with moderate and severe preeclampsia in our cohort had normal levels of hsCRP and 16.67% of the control group had higher hsCRP levels and they never developed preeclampsia. Therefore, the predictive ability of CRP is limited, but it can be helpful in combination with additional markers. In a study that followed 394 women, first-trimester maternal serum hsCRP levels were found to be significantly higher in preeclamptic women[12], but only 41.4% of the women with high CRP developed preeclampsia. Montagna *et al*. reported a significantly higher level of CRP in patients with severe PE, but the level of CRP was not different significantly between severe and mild form of PE[8]. According to their study, procalcitonin values were more clinically useful and relevant in comparison to CRP values.

In a study from Denmark[13] on a cohort of 174 pregnant women, acute phase reactants were analyzed. They found that plasma ferritin and albumin levels reflected higher inflammation in preeclampsia compared to healthy pregnancies. The hsCRP level and albumin had the most predictive value in identifying the preeclamptic from healthy pregnancies and preterm from term preeclampsia cases.

Some studies indicate that preeclampsia is not only associated with higher rate of morbidity and mortality, but also it is considered as a risk factor for vascular disease both for mother and child. Current strategies are not sufficient to prevent the complications of preeclampsia[2].

There was a positive correlation between blood pressure and hsCRP level. The study showed that higher hsCRP levels were associated with a more severe form of preeclampsia. In the interest of a mother's health, the number of caesarean sections has increased in order to end the pregnancy faster and improve the condition of the mother after the end of the pregnancy. Since more severe forms of preeclampsia occur at a lower gestational week, a premature fetus is obtained whose condition is worsened due to the mother's worsening condition[1,3].

Limitation of this study is the small sample size. In order to assess the true prognostic value of hsCRP, a larger sample size is needed as well as adding more inflammatory markers to reach better diagnostic performances.

**Conclusion**

High levels of third-trimester maternal serum CRP correlate with the severity of the clinical picture of preeclampsia. Also, increased total CRP levels in maternal serum lead more often to surgical termination of pregnancy in patients with preeclampsia. Patients with increased total CRP levels have a worse feto-maternal outcome, and therefore it can be used as a prognostic biomarker in the identification of high-risk cases before the appearance of preeclampsia complications.

*Conflict of interest statement*. None declared.

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