High-Sensitivity CRP Levels In Women with Gestational Hypertension, Preeclampsia and in Normotensive Pregnant Women and Its Correlations

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Abstract

Introduction: Gestational hypertension is a less investigated hypertensive disorder of pregnancy than preeclampsia, but evidence exists of an unfavourable cardiovascular profile for women after such a pregnancy.

Aim: To determine serum high-sensitivity C-reactive protein (hs-CRP) levels in women with preeclampsia, gestational hypertension, and in normotensive pregnancy in order to assess the cardiovascular implications and to examine its correlations with some characteristics of women.

Materials and methods: Thirty-six women with gestational hypertension, thirty-seven with preeclampsia, and fifty maternal and gestational age-matched controls were included in a single-center prospective clinical-epidemiological study. Serum hs-CRP levels were determined using ELISA method.

Results: Significantly higher hs-CRP levels were found in the gestational hypertension group than in the controls (p=0.043), but not in the preeclampsia group (p=0.445). The levels between the two pathological groups did not differ significantly (p=0.247). Odds ratio for hs-CRP levels higher than the provided cut-off was 3.31 (95% CI 1.32–8.29) for the presence of gestational hypertension. In the normotensive pregnant women, the hs-CRP levels had a positive correlation with BSA, pre-pregnancy and current BMI, but such correlations were absent in the hypertensive groups. There were no correlations with the maternal or gestational age, current weight gain in any of the groups or with the highest detected blood pressure in the pathological groups. These levels did not differ according to gravidity, smoking status and smoking during pregnancy.

Conclusions: Elevation of hs-CRP was more pronounced in women with gestational hypertension than in women with preeclampsia, which could indicate a different pathophysiological mechanism and a higher cardiovascular risk for those women.

Keywords
biomarkers, cardiovascular risk, inflammation, pregnancy, women’s health
INTRODUCTION

High-sensitivity CRP is one of the most studied markers of inflammation. It was first discovered in 1930 and initially was thought to be a substance secreted by pneumococcal bacteria during the course of pneumonia. It was found later that it was a protein produced by the liver during the acute phase of infectious, inflammatory, and malignant processes as a non-specific response to tissue damage. It elevates rapidly after a pathological stimulus and has a relatively constant half-life as a result of which its circulating levels depend mainly on the synthesis rate. As early as the 1950s, reports started to emerge of elevated levels of CRP during myocardial infarction and in the 1990s and the following years, its higher levels, including those within the reference range, were found to be associated with a risk of cardiovascular and cerebrovascular events. Research in the field was amplified by the emergence of high-sensitivity assays. A study by Wang et al. encompassing over 53,000 people demonstrated that cumulative exposure to higher levels was a dose-dependent risk factor for the aforementioned diseases. Explanation was sought in the theory of atherosclerosis as an inflammatory process and the role of constant low-grade inflammation as an atherogenic factor.

In a statement from 2003, the American Heart Association and the Centres for Disease Control and Prevention designated hs-CRP as a reliable and readily available marker for risk stratification and established relative risk categories according to its levels (Class of recommendation IIa, Level of Evidence B). The European Society of Cardiology acknowledged in the current 2016 prevention guideline that the relative risk associated with hs-CRP levels is similar to the one associated with the classic cardiovascular risk factors, but did not advocate its use in risk stratification, as they doubted its added value to the endorsed SCORE system. However, they do not deny its use in specific scenarios and populations.

Hypertensive complications of pregnancy on the other hand emerged in the past decades as a risk factor for future cardiovascular events in women and are viewed by some authors as a failed cardiovascular "stress test" of the female organism that is a very early prodrome of unfavourable outcomes. In large cohort studies of women years after the target hypertensive pregnancy, there was a higher risk for arterial hypertension, type 2 diabetes mellitus, venous thromboembolism, dyslipidemia, coronary artery disease, stroke, heart failure, and cardiovascular mortality. Usually, the risk is proportionate to the severity of the disease and is reported to be more pronounced in preeclampsia than in gestational hypertension where investigations of both forms are available.

Although hypertensive complications of pregnancy are quite common and are associated with a high maternal and fetal mortality, their pathological mechanisms are still not completely understood. One of the culprit mechanisms is thought to be an underlying exaggerated inflammatory response of the maternal organism as a result of the improper placentation and the following placental ischemia.

Gestational hypertension is the least investigated of the two forms and is generally considered more benign, but it can progress to preeclampsia and eclampsia as well as lead to serious maternal and fetal complications in severe cases.

Based on the presented literature review, we suspect that a link between low-grade inflammation, as indicated by the hs-CRP levels, hypertensive disorders of pregnancy, and subsequent cardiovascular risk in women exists and aimed to investigate this problem in the present study.

AIM

To determine and compare high-sensitivity CRP levels in women with gestational hypertension, preeclampsia, and in normotensive pregnant women, establish correlations with characteristics of the women and investigate discriminative abilities of hs-CRP and odds ratio (OR) for the presence of the pathologies.

MATERIALS AND METHODS

A single-center prospective clinical-epidemiological study was performed at the Clinic of Cardiology at St George University Hospital in Plovdiv, Bulgaria between August 2018 and January 2020 and data for 123 pregnant women were analyzed. Thirty-seven of those women had preeclampsia, 36 had gestational hypertension, and 50 were normotensive pregnant controls. One-hundred and sixteen of the women had singleton pregnancies and nine had bigeminal pregnancies (4 in the preeclampsia group, 2 in gestational hypertension and 3 in the controls). The women were enrolled from the Clinic of Obstetrics and Gynecology at the same hospital and some of the controls were referred by local Obstetrics and Gynecology practices. The study was approved by the Ethics Committee of the Medical University of Plovdiv and all of the participants signed a written informed consent before participation. Current weight and height of the women were measured with standardized equipment at the Clinic of Obstetrics and Gynecology. Weight before the pregnancy was self-reported. Based on those values, body mass index (BMI) and body surface area (BSA; using DuBois & DuBois formula) were calculated. Women were diagnosed with preeclampsia if high blood pressure (office measured systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at least twice over the course of minimum 4 hours apart) was registered for the first time after gestational week 20 and also had proteinuria of ≥300 mg for 24 hours in at least one measurement. The women with gestational hypertension covered the same criteria for blood pressure, but registered proteinuria had to be less than 300 mg for 24 hours.

The participants were classified further as having early forms of the conditions if the hypertension was first regis-
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Statistical analysis

Data analysis was performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, SPSS Inc., Chicago, IL, USA) and MedCalc Version 14.8.1 (MedCalc Software, Mariakerke, Belgium). Continuous variables were tested for normality with Kolmogorov-Smirnov and Shapiro-Wilk tests. The Student's t-test, analysis of variance (ANOVA) test, and Bonferroni post hoc test were used to compare the continuous variables that had normal distribution more than two independent groups with homogeneity of variances. The continuous variables with non-normal distribution were compared with the Kruskal-Wallis test and the Mann-Whitney U test. The relationship between categorical variables in cross tables was analyzed using the χ² test and Fisher's exact test. Correlations analysis was performed using either Pearson's correlation coefficient or Spearman's rho according to the normality of the continuous variables. Receiver Operating Characteristics (ROC) curve analysis was carried out to determine discriminative abilities of hs-CRP. The optimal cut-off value was obtained from the Youden index \( \text{maximum (sensitivity + specificity−1)} \). Logistic regression was performed to explain the relationship between variables. Findings with \( p<0.05 \) were considered statistically significant.

RESULTS

Study population

The women in the study groups were maternal and gestational age matched and there was no statistical difference between the percentage of non-smokers and smokers and women smoking during the current pregnancy in the groups. The two pathological groups did not differ significantly for the presence of early and severe forms. BSA, pre-pregnancy and current BMI were significantly higher in the hypertensive women compared to controls, but there was no statistically significant difference in current weight gain between the groups. More primigravid women were in the gestational hypertension group than in the groups of the controls and fewer were pregnant with their second pregnancy in the gestational hypertension group than in the controls (Table 1).

High sensitivity CRP

Mean serum levels of hs-CRP were higher in the gestational hypertension group, compared to the controls \((6441.12±3124.17 \text{ ng/ml vs. } 5095.61±3086.67 \text{ ng/ml, } p=0.043)\), but there was no significant difference between the mean levels in the preeclampsia group and the controls, despite a tendency for higher levels in preeclampsia \((5581.02±3036.28 \text{ ng/ml vs. } 5095.61±3086.67 \text{ ng/ml, } p=0.445)\). The mean levels between the gestational hypertension group and the preeclampsia group did not differ significantly \((6441.12±3124.17 \text{ ng/ml vs. } 5581.02±3036.28 \text{ ng/ml, } p=0.247)\). There was borderline significant difference when comparing only the severe forms of gestational hypertension and preeclampsia together to the controls \((6453.0±2916.13 \text{ ng/ml vs. } 5095.61±3086.67 \text{ ng/ml, } p=0.063)\).

There was no significant difference between the hs-CRP levels in the women when divided into subgroups according to gravidity, smoking status and smoking during pregnancy (Table 2). Correlation analysis (Table 3) was conducted and a significant correlation between hs-CRP levels and certain characteristics of the women was found. In the whole study group, hs-CRP correlated positively with BMI before pregnancy, current BMI, and BSA of the women, but when analyzed separately into groups, these correlations were present only for the group of the controls and not in the gestational hypertension and the preeclampsia groups. There was no correlation between hs-CRP levels and maternal age, gestational age, weight gain and for the pathological groups with the maximum reported SBP or DBP.

ROC curve analysis was performed in order to assess the ability of hs-CRP to differentiate between the controls and the gestational hypertension group and it gave an area under the curve of 0.63, \( p=0.043 \) for levels higher than the
### Table 1. Characteristics of the study population

| Groups                  | Controls | Gestational hypertension | Pre-eclampsia |
|-------------------------|----------|---------------------------|---------------|
|                         | n        | X  | SD | n   | X    | SD | n   | X    | SD |
| Maternal age (years)    | 50       | 30.82a | 6.02 | 36  | 28.83a | 5.78 | 37  | 29.81a | 5.14 |
| Gestational age (weeks) | 50       | 34.08a | 5.23 | 36  | 33.71a | 4.08 | 37  | 33.24a | 3.74 |
| BMI before pregnancy (kg/m²) | 49   | 22.58a | 5.11 | 35  | 28.58b | 6.14 | 35  | 27.26b | 5.68 |
| BMI – current (kg/m²)   | 50       | 27.81a | 5.49 | 36  | 33.66b | 5.75 | 36  | 31.77b | 5.32 |
| Weight gain (kg)        | 49       | 14.05a | 6.18 | 35  | 13.69a | 6.54 | 36  | 12.94a | 7.51 |
| BSA (m²)                | 50       | 1.83a | 0.20 | 36  | 1.97b | 0.20 | 37  | 1.96b | 0.18 |

| Smoking                  | n % Sp  | n % Sp  | n % Sp |
|--------------------------|---------|---------|---------|
| Non smoker               | 13      | 26.0a   | 6.2     | 15  | 41.7a | 8.2  | 15  | 40.5a | 8.1   |
| Former smoker            | 10      | 20.0a   | 5.7     | 2   | 5.6a  | 3.8  | 3   | 8.1a  | 4.5   |
| Smoker                   | 27      | 54.0a   | 7.0     | 16  | 44.4a | 8.3  | 17  | 45.9a | 8.2   |
| Smoking during pregnancy | 14      | 51.9a   | 9.6     | 6   | 37.5a | 12.1 | 8   | 47.1a | 12.1  |

| Gravidity               | n      | X    | SD |
|-------------------------|--------|------|----|
| 1                       | 12     | 24.0a | 6.0 |
| 2                       | 22     | 44.0a | 7.0 |
| 3+                      | 16     | 32.0a | 6.6 |
| Early forms             | -      | -    | -  |
| Severe forms            | -      | -    | -  |

One lowercase letter indicates lack of statistical difference, while different lowercase letters indicate presence of statistical difference \((p <0.05)\).

### Table 2. Comparative analysis of hs-CRP levels and gravidity, smoking status of the women and smoking during pregnancy by groups

| Gravidity | n | X    | SD |
|-----------|---|------|----|
| Whole sample | 48 | 5640.71a | 3021.98 |
| Controls | 12 | 5547.21a | 3193.28 |
| GH | 20 | 6153.05a | 3150.62 |
| PE | 16 | 5070.41a | 2803.50 |
| GH + PE | 36 | 5671.88a | 3009.10 |

| Smoking status | n | X    | SD |
|----------------|---|------|----|
| Whole sample | 43 | 5904.23a | 2899.22 |
| Controls | 13 | 4647.84a | 2886.81 |
| GH | 15 | 6697.87a | 2865.14 |
| PE | 15 | 6199.47a | 2762.30 |
| GH + PE | 30 | 6448.67a | 2776.83 |

| Smoking during pregnancy | n | X    | SD |
|--------------------------|---|------|----|
| Whole sample | 32 | 5855.11 | 3554.49 |
| Controls | 13 | 5525.05 | 3587.92 |
| GH | 10 | 7338.62 | 3573.85 |
| PE | 9 | 4683.51 | 3287.44 |
| GH + PE | 19 | 6080.94 | 3611.73 |

GH: gestational hypertension; PE: preeclampsia; One lowercase letter indicates lack of statistical difference \((p<0.05)\). Subgroups with \(n<8\) were not analyzed due to lack of statistical representability.
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Table 3. Correlation coefficients between hs-CRP levels and certain characteristics of the women

| Characteristics  | All women | Controls | Gestational hypertension | Preeclampsia |
|------------------|-----------|----------|--------------------------|--------------|
| Maternal age     | −0.043    | 0.035    | −0.006                   | −0.081       |
| Gestational age  | 0.104     | 0.176    | 0.264                    | −0.112       |
| BMI before pregnancy | 0.270**     | 0.360*    | 0.273                    | 0.068        |
| Current BMI      | 0.325***   | 0.442**   | 0.326                    | 0.096        |
| BSA              | 0.280*     | 0.414**   | 0.164                    | 0.121        |
| Current weight gain | 0.122     | 0.125    | 0.118                    | 0.142        |
| Maximum SBP      | -         | -        | 0.089                    | 0.187        |
| Maximum DBP      | -         | -        | 0.181                    | 0.107        |

*p<0.05; **p<0.01; ***p<0.001

selected cut-off value of 5446 ng/ml with sensitivity of 72%, specificity of 56%, positive predictive value of 54%, and negative predictive value of 74% (Fig. 1). It could not differentiate between the controls and the preeclampsia group (AUC = 0.548, p=0.445) (Fig. 2).

Binary logistic regression was performed in order to quantify the role of hs-CRP as an indicator for gestational hypertension and the odds ratio (OR) was 3.31 (95% CI 1.32–8.29) for the presence of gestational hypertension in women with values higher than the cut-off of 5446 ng/ml.

DISCUSSION

Women in our pathological groups were statistically equivalent when it comes to severity and onset of the disease. Moreover, the criteria used for severity were the same in the gestational hypertension and the preeclampsia groups. All of the severe forms in gestational hypertension group were classified as such according to blood pressure values and one woman had both the blood pressure criterion and elevated ALT levels twice over the upper limit. In the preeclampsia group, all women with severe forms were according to blood pressure values and one woman was further classified in this groups due to having both AST and ALT significantly elevated. Truly severe forms of preeclampsia (such as HELLP syndrome, pulmonary edema and encephalopathy) were omitted for reasons given in the Materials and methods section. The hypertensive women as a result had homogenous characteristics as far as severity and onset were concerned and the only discriminator was the presence or lack of proteinuria of more than 300 mg for 24 hours. In this setting, the hs-CRP levels were statistically the same between the two pathologies, but only the gesta-

![Figure 1](image1.png) ROC curve for hs-CRP for differentiating between the controls and the gestational hypertension group with area under the curve 0.63, p=0.043.

![Figure 2](image2.png) ROC curve for hs-CRP for differentiating between the controls and the preeclampsia group with area under the curve 0.548, p=0.445.
tional hypertension group reached statistically significant difference for higher values in the preeclampsia group. These results imply a more marked inflammatory response in the women with pregnancy-induced hypertension without proteinuria and could support the hypothesis of the dominance of different etiological and pathophysiological mechanisms in the two hypertensive disorders, although they are often viewed as forms of the same disease.23

In a study by Jannesari et al.24, the authors did not find significantly different levels of serum hs-CRP between women with mild preeclampsia and controls and such difference was present only when comparing the severe forms to the controls. In another study by Fink et al.25 the presence of preeclampsia was not associated with higher hs-CRP levels. The explanations for the lack of significantly elevated hs-CRP in our preeclampsia group could be the prevalence of mild forms in it (64.9%). The small percentage of severe forms in our study group (36.1% in gestational hypertension and 35.1% in preeclampsia) reflects in fact the prevalence of those forms in a 1980-2010 cohort study conducted in the USA analyzing 120 million women who gave birth during this time period, in which the severe forms were 1.4% out of 3.8% (~ 36.8%) women with preeclampsia in 2010.26

There are fewer studies investigating gestational hypertension than studies investigating preeclampsia, yet we managed to identify a recent study by Rout et al. who also found elevated levels of hsCRP in the second and third trimester of women with gestational hypertension.27

ROC curve analysis in our study for the differentiation between gestational hypertension and normotensive pregnancies is with a slightly larger AUC of 0.63 (sensitivity 72% and specificity 56%), than the results of Jannesari et al.24, who reported an AUC of 0.61 for discriminating between preeclampsia and the controls with a sensitivity of 62.7% and specificity of 56%; but still AUC in the current study did not reach the threshold for satisfactory discriminative abilities of 0.7. Nonetheless, levels of hs-CRP higher than the estimated cut-off of 5446 ng/ml in our study were associated with a 3.31 higher chance for the presence of gestational hypertension compared to women below the cut-off value.

In our study, significant correlations between hs-CRP and the characteristics of the women existed only for the normotensive women, which could indicate that in the hypertensive groups, the levels were mostly determined by the presence of the pathology. Similarly to our findings, in other studies, hs-CRP levels were reported to be positively correlated with higher BMI in non-pregnant populations.28,29 Lack of significant change of hs-CRP for the duration of pregnancy was established by Watts et al. when sampling the same healthy gravid women twice after mid-pregnancy, which possibly is consistent with our findings of no correlation between hs-CRP levels and gestational age in any of the groups.30 Hs-CRP levels, which are known to be elevated with age, did not correlate with maternal age in our study population, which could be due to the fact that its levels are reported to be higher in populations older than 45 years, which are not represented in our study.31

Finally, evidence of higher hs-CRP levels in gestational hypertension, but not in preeclampsia in our study, could be in line with several large studies which confirmed a higher risk in women after gestational hypertension when compared to women who had preeclampsia for the development of a vast number of diseases, known to be associated with low-grade inflammation: arterial hypertension32, type 2 diabetes mellitus, hypercholesterolemia33, ischemic heart disease, myocardial infarction, death from myocardial infarction, heart failure, and chronic kidney disease34. This theory seems plausible as Brown et al. discovered elevated levels of hs-CRP in women years after a hypertensive pregnancy, even after adjustment for BMI and other cardiovascular risk factors.35

Limitations of the study

Relatively small sample size.

CONCLUSIONS

Hs-CRP levels were higher in gestational hypertension, but not in preeclampsia when compared to controls, possibly due to the presence of different underlying pathophysiological mechanisms in the two conditions. Discriminative abilities of hs-CRP for the presence of gestational hypertension are not satisfactory and therefore we do not advise its use as a screening test. Nonetheless, women with levels higher than the provided cut-off were 3.31 times more likely to have gestational hypertension. There was no correlation in either of the pathological groups with characteristics of the women. Since low-grade inflammation is now believed to be involved in the development of a large number of cardiovascular diseases, attention should be drawn to all women with hypertensive disorders of pregnancy, as the lack of proteinuria does not seem to indicate a more benign risk profile. In normotensive pregnant women on the other hand, hs-CRP levels correlated significantly and positively with BMI and BSA.

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Conflict of Interest

The authors declare that no competing interests exist.
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Высокочувствительный CRP у женщин с гестационной гипертензией, преэклампсией и при нормотензивной беременности и их корреляции

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Резюме

Введение: Гестационная гипертензия является менее изученной гипертонической патологией беременности, чем преэклампсия, но есть данные о неблагоприятном сердечно-сосудистом профиле у женщин после такой беременности.

Цель: Определить уровни сывороточного высокочувствительного С-реактивного белка (hs-CRP) у женщин с преэклампсией, гестационной гипертензией и нормальной беременностью, чтобы оценить сердечно-сосудистые эффекты и изучить корреляцию с некоторыми характеристиками женщин.

Материалы и методы: Тридцать шесть женщин с гестационной гипертензией, 37 женщин с преэклампсией и 50 здоровых женщин в качестве контрольной группы равного материнского и гестационного возраста были включены в эндоцентрическое проспективное клинико-эпидемиологическое исследование. Уровни hs-CRP в сыворотке определяли с помощью ELISA.

Результаты: Значительно более высокие уровни hs-CRP были обнаружены в группе гестационной гипертензии по сравнению с контрольной группой (p=0.043), но не в группе преэклампсии (p=0.445). Уровни детрепатологических групп достоверно не различались (p=0.247). Отношение вероятности для уровней hs-CRP выше порогового значения было 3.31 (95% ДИ 1.32–8.29) для гестационного диабета. Среди нормотензивных беременных уровень hs-CRP положительно коррелировал с площадью поверхности тела (ППТ), текущим ИМТ и ИМТ до беременности, но такие корреляции отсутствовали в группе гипертоников. Не было обнаружено корреляций с материнским и гестационным возрастом, прибавкой в весе в любой группе или с самым высоким измеренным артериальным давлением среди патологий. Эти уровни не различались в отношении беременности, статуса курения и курения во время беременности.

Заключение: Увеличение hs-CRP более выражено у женщин с гестационной гипертензией, чем у женщин с преэклампсией, что может быть индикатором другого патофизиологического механизма и более высокого сердечно-сосудистого риска для этих женщин.

Ключевые слова

биомаркеры, сердечно-сосудистый риск, воспаление, беременность, женское здоровье