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ORIGINAL ARTICLE

# ASSOCIATION BETWEEN SERUM MATRIX METALLOPROTEINASE-2 LEVELS AND MEAN DOPPLER PULSATILITY INDEX OF UTERINE ARTERIES IN PATIENTS WITH PREECLAMPSIA

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***Abstract. Background:*** *Matrix metalloproteinase-2 (MMP-2) is an enzye from the gelatinases family involved mainly in collagen degradation. It is also known as a key regulator of normal vascular remodelling during a healthy pregnancy. Failure of regulation of MMP-2 has been associated with abnormal vasodilation, placentation, uterine expansion and development of preeclampsia (PE). Aims: (1) determine serum MMP-2 levels in women with PE and healthy pregnancy, (2) evaluate mean uterine arteries Doppler pulsatility index (UtA PI) and (3) investigate the a possible association between these parameters.* ***Materials and methods:*** *This was a case-control study. Fifty-five women with PE (mean age 24.9 ± 6 years) and a control group of 35 women with normal pregnancies (mean age 24.7 ± 5.4 years) were examined. An enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of MMP-2. Mean UtA PI were evaluated by Doppler velocimetry.* ***Results:*** *Serum MMP-2 levels in preeclampsia were significantly higher than in women with normal pregnancy 11.7 (9.1÷15.5) vs. 7.7 ng/ml (6.5÷13.4) (p = 0.016). Mean UtA PI was significantly higher in preeclampsia than in healthy pregnant women: 1.12 (0.82÷1.5) vs. 0.75 (0.69÷0.85); (p = 0.024). MMP-2 correlated with UtA PI (r = 0.214; p = 0.043). Cut-off value at 14 ng/ml for MMP-2 was found to discriminate between PE and healthy pregnancy.* ***Conclusion:*** *Our data showed an association between serum MMP-2 and Mean UtA PI. We suggest that MMP-2 could have a potential imply on maternal uterine arteries' structure, favoring their constriction, increased resistance and abnormal uterine vascular remodeling. Further studies are warranted to clarify whether determination of MMP-2 cut-off value might contribute in the diagnosic work-out strategy for PE.*

***Key words:*** *matrix metalloproteinase-2, preeclampsia, uterine Doppler pulsatility index*

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## INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder of pregnancy, defined by the occurrence of new-onset hypertension (140/90 mm Hg) and either proteinuria (0.3 g in a 24 h urine sample) or end-organ dysfunction developing later than 20 weeks of gestation [1]. It is a major cause of maternal and perinatal morbidity and mortality [2]. According to the current understandings preeclampsia is a systemic disease with generalized endothelial cells injury/dysfunction and multi-organ involvement [3]. However, it has not been thoroughly explored.

Type IV collagen (CIV) is a major structural component of the vascular basement membrane [4]. Alterations in the uterine spiral arteries' CIV structure have been observed in women with preeclampsia [5]. Matrix metalloproteinases (MMPs) are important regulators of extracellular matrix (ECM) remodelling. It is well known that dysregulation of the MMPs expression/activity leads to structural collagen damage [6, 7]. It has been hypothesised that in preeclampsia, these mechanisms play a key role in the altered uterine and vascular CIV turnover characterised by abnormal vasodilation, placentation and development of generalized vascular damage [8, 9].

MMP-2 is known as an enzyme originating from the family of the gelatinases matrix metalloproteinases, which are associated with efficient degradation of CIV [10]. It has been postulated that control of expression and regulation of MMP-2 may play a crucial role in normal and complicated pregnancy.

Doppler uterine artery pulsatility index (UtA PI) is used to assess vascular resistance by measuring the velocity of blood flow in the uterine arteries. Thus it can detect utero-placental insufficiency (mainly in the second trimester) before any clinical manifestations and thus identify women at increased risk of developing complicated pregnancies [11]. Elevated Doppler UtA PIs have been associated with the development of PE and adverse events during pregnancy [12]. The use of UtA PI to predict PE has been extensively studied in the second and first trimesters of pregnancy. Abnormal placental function, which characterizes PE, is associated with increased blood flow resistance in the utero-placental circulation. This is evidenced by ultrasound with increased UtA PI [13]. However, there are no data in the literature on a parallel examination of serum MMP-2 concentrations and uterine Doppler ultrasound measurements in preeclampsia.

## AIM

This study aimed to: (1) determine serum MMP-2 levels in women with preeclampsia (PE) and healthy pregnancy, (2) evaluate mean uterine arteries Doppler pulsatility index (UtA PI), and (3) investigate the existence of a possible association between these parameters.

## MATERIALS AND METHODS

### *Subjects*

This was a case-control study. The study was part of a university scientific project, approved by the Ethics Committee of Medical University – Pleven (N1/2020). All participants signed informed consent. Study procedures followed all guidelines for ethical standards of the local committee on human experimentation as well as the Helsinki Declaration of 1975, as revised in 2000. All patients were inpatients of the Clinic of Obstetrics and Gynaecology, University Hospital "Georgi Stranski" Pleven. Sera of subjects were taken from October 2020 to March 2021. The study group consisted of 55 women with preeclampsia, with mean age of 24.9 ± 6 years and a control group of 35 women with normal pregnancies with a mean age of 24.7 ± 5.4 years.

The inclusion criteria were: pregnant women with clinical symptoms and laboratory criteria for preeclampsia (2018 European Society of Cardiology Guideline for the management of cardiovascular diseases during pregnancy was used for the diagnostic criteria of preeclampsia: gestational hypertension with significant proteinuria > 300 mg/24 h urine collection or the extrapolated amount from a timed collection) [14]; maintaining a current diet and exercise during the study; signed informed consent to participate in the study; dysfunction of maternal organ such as: HELLP syndrome, renal failure, neurological involvement, hepatic involvement and foetal growth retardation. Exclusion criteria were as follows: diabetes mellitus, kidney and heart disease, signs of chorioamnionitis, presence of a foetus with a chromosomal abnormality.

### *Laboratory investigations*

Enzyme-linked immunosorbent assay (ELISA) was used for determination of MMP-2 levels. MMP-2 was measured in serum samples using ELISA kit (Total MMP-2 Quantikine ELISA Kit, R&D Systems) and according to the manufacturer's instructions.

### *Doppler ultrasound of uterine arteries*

Doppler ultrasound of uterine arteries was performed by a single operator. Flow velocity waveforms of the uterine arteries were performed by ultrasound using an AB 2-7 MHz convex abdominal probe. The mean pulsatility index (PI) was calculated. An abnormal Doppler of uterine artery was diagnosed if the mean PI exceeded the 95th percentile for each gestational age [15].

### *Statistical analyses*

The following computer programs were used to analyse the research data: Excel (Microsoft Corporation, Redmond, WA), SPSS and Statgraphics Plus (Manugistics, Rockville, MD) for Windows. Tables, graphs, numerical values (share indicators and correlations) were used to describe all results. The level of significance was determined as $p < 0.05$. The tests used to check the normality of distribution and equality of variances were Stnd. Skewness and Stnd. Kurtosis. To find significant differences between groups Student's t-test and ANOVA with mean ± SD were used in cases with normal distribution (LSD, Tukey HSD, Scheffe, Bonferroni, Newman-Keuls, Duncan). $\chi^2$ and K-W H-test with median (M) value were used in cases with skewed distribution, together with first and third quartile Q1 and Q3; (twenty-fifth and seventy-fifth percentile P25 and 75P). Pearson type of correlation was used. To check the existence of significant relationship between MMP-2 and UtA PI, linear regression analysis was carried out. All the linear regression assumptions were checked.

## RESULTS

The clinical data of the women with preeclampsia and healthy pregnant women are presented in Table 1.

Serum MMP-2 levels in preeclampsia were significantly higher than in women with normal pregnancy 11.7 (9.1÷15.5) vs. 7.7 ng/ml (6.5÷13.4) (KW = 5.782; p = 0.016) (Table 2, Figure 1). Mean UtA PI was significantly higher in preeclampsia than in healthy pregnant women: 1.12 (0.82÷1.5) vs. 0.75 (0.69÷0.85); (KW = 5.868; p = 0.024) (Table 2). MMP-2 correlated with Mean UtA PI (r = 0.214; p = 0.043). Linear regression analysis was performed, which confirmed the existence of significant relationship between MMP-2 and UtA at 95% confident interval (r = 0.214; p = 0.043) (Figure 2). Cut-off value at 14 ng/ml for MMP-2 was found to discriminate between PE and healthy pregnancy.

**Table 1.** Clinical data of women with preeclampsia and healthy pregnant women

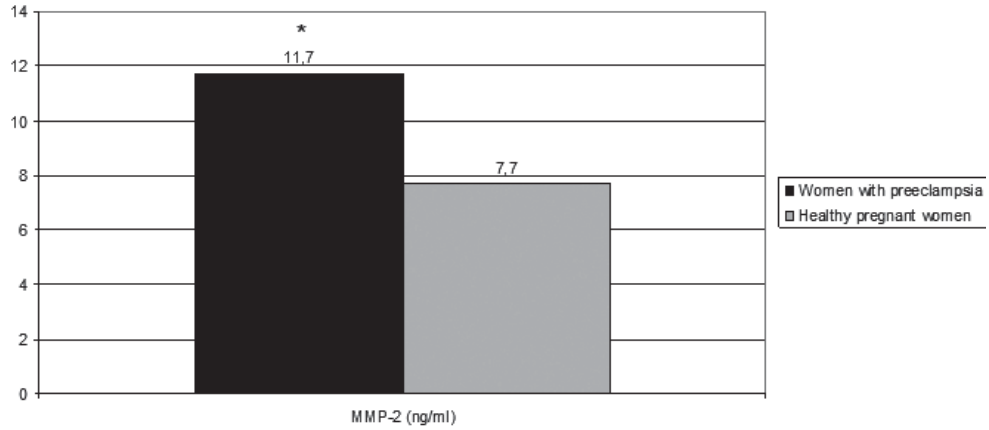
| | Normal pregnant women | Preeclampsia | p |
|---|---|---|---|
| Maternal age | 24.7 ± 5.4 | 24.9 ± 6 | p > 0.05 |
| BMI | 26.7 ± 4.2 | 34 ± 7.3* | p = 0.001* |
| Gravida | 2(2) ** | 2(2)** | |
| Parity | 1(2) ** | 1(2) ** | |
| SBP (mm Hg) | 116.1 ± 9.55 | 157.8 ± 22* | p = 0.001* |
| DBP (mm Hg) | 75.3 ± 7.76 | 100.5 ± 10* | p = 0.001* |
| Past history of PE | 0/35 | 23/55 | |
| Family history of AH | 1/35 | 26/55 | |
| AH before pregnancy | 0/35 | 15/55 | |
| PP | 40.8 ± 7.32 | 57.3 ± 16.1* | p = 0.001* |
| MAP | 88.8 ± 7.69 | 119.7 ± 13.1* | p = 0.001* |
| Urea | 2.96 ± 0.78 | 3.75 ± 1.63* | p = 0.01* |
| Creatinine | 75.78 ± 14.45 | 73.33 ± 15.33 | p > 0.05 |
| Uric acid | 205.6 ± 40.2 | 326.8 ± 105.93* | p = 0.001* |
| Total protein | 68.89 ± 3.16 | 58.71 ± 8.78* | p < 0.01* |
| Albumin | 37.31 ± 2.78 | 31.67 ± 4.98* | p < 0.01* |
| ASAT | 8.43 ± 2.33 | 20.67 ± 7.82* | p < 0.01* |
| ALAT | 9.83 ± 2.50 | 27.76 ± 8.25* | p < 0.01* |
| LDH | 369 ± 70.78 | 435.25 ± 80.74* | p = 0.04* |
| PLT | 237.26 ± 61.12 | 228.74 ± 88.53 | p > 0.05 |
| CPK | 83.1 ± 23.77 | 130.5 ± 46.8* | p < 0.05* |
| Number | (n = 35) | (n = 55) | |

**Abbreviations:** BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; PE – preeclampsia; AH – arterial hypertension; PI – pulsatility index; PP – pulse pressure; MAP – mean arterial pressure; ASAT – aspartate aminotransferase; ALAT – alanine aminotransferase; LDH – lactate dehydrogenase; PLT – platelets; CPK – creatine phosphokinase; *Data are shown as the mean ± SD; **Data are expressed as median, p < 0.05

**Table 2.** Serum MMP-2 levels and Mean UtA PI in preeclampsia and healthy pregnant women

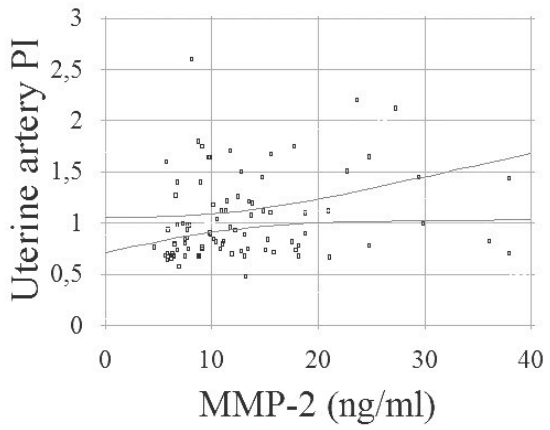
| | Normal pregnant women | Preeclampsia | p |
|---|---|---|---|
| MMP-2 (ng/ml) | 7.7 (6.5÷13.4) | 11.7 (9.1÷15.5) | p = 0.016 |
| Mean UtA PI | 0.75 (0.69÷0.85) | 1.12 (0.82÷1.5) | p = 0.024 |
| Number | (n = 35) | (n = 55) | |

**Abbreviations:** MMP-2 – matrix metalloproteinase-2; Mean UtA PI – mean uterine arteries Doppler pulsatility index. Data are expressed as median (interquartile range), p < 0.05




Serum MMP-2 levels in preeclampsia were statistically significantly higher than in women with normal pregnancy (KW = 5.782; p = 0.016)

**Fig. 1.** Serum MMP-2 levels in preeclampsia and healthy pregnant women




There is a statistically significant relationship between MMP-2 and UtA PI at 95% confidence interval (r = 0.214; p = 0.043)

**Fig. 2.** Linear regression analysis, describing the relationship between MMP-2 and UtA PI

## DISCUSSION

The fine balance between MMPs and their tissue inhibitors plays a crucial role in the process of vascular remodelling. MMP-2 is known as an important regulator of physiological uterine vascular remodelling during normal pregnancy. It has been estimated that dysregulation of MMP-2 is associated with abnormal vasodilation and placentation in preeclampsia. There is evidence that MMP-2 is increased in preeclampsia and an imbalance between MMP-2 and its natural tissue inhibitor (TIMP-2) can occur [16, 17, 18]. The following research data describe studies measuring levels of MMP-2 in samples of patients with different hypertensive disorders of pregnancy:

Laskowska (2017) investigated maternal serum matrix metalloproteinases-2, -3, -9, and -13 levels in early- and late-onset preeclampsia and uncomplicated pregnancies. Maternal serum MMP-2 levels were significantly higher than those in the controls in both the groups of preeclamptic women. A major conclusion of this study was that higher levels of MMP-2 and MMP-13 and lower levels of MMP-9 were possibly associated with both early and late-onset severe preeclampsia [19].

The circulating plasma MMP-2 and -9 levels, TIMP-1 and TIMP-2 in women who subsequently develop preeclampsia, were explored by Myers et al. (2005) via zymography and Western blot. The study was focused on women whose pregnancies were subsequently complicated by preeclampsia. The investigators took samples from a control group including normal pregnant women at 22 and 26 weeks and at delivery or diagnosis. They reported an imbalance in the MMP-2/TIMP-1 ratio at all three gestational time points in patients who subsequently developed preeclampsia [20].

Palei et al. (2012) found that pregnant women with preeclampsia had significantly higher plasma MMP-2 and TIMP-2 concentrations than healthy pregnant, although the MMP-2/TIMP-2 ratios were similar. In addition, plasma MMP-2 levels and MMP-2/TIMP-2 ratios in pregnant women with gestational hypertension were significantly elevated as compared with healthy pregnancies [21].

The study conducted by Montagnana et al. (2009) explored via ELISA MMP-2, -9 and their inhibitors TIMP-1 and -2 in preeclamptic, normotensive pregnant and non-pregnant women [22]. MMP-2 levels were found to be increased in PE compared with both non-pregnant and physiologic pregnant women.

Narumiya et al. (2001) investigated plasma MMP-2/MMP-9 levels in women with preeclampsia by zymographic analysis and compared them to those of women with uncomplicated pregnancies. The authors reported that plasma MMP-2 levels were significantly higher in women with preeclampsia as compared with women with uncomplicated pregnancies [23].

The physiological uterine spiral arteries remodelling during normal implantation is essential for successful pregnancy [24]. The balance between MMPs and TIMPs plays an important role in normal remodelling of uterine arteries in pregnancy and it may represent means by which vasodilatation is maintained in later pregnancy [25]. Failure of the physiological conversion of the spiral arteries can cause a number of complications, including intrauterine growth restriction and preeclampsia.

Of note, MMP-2 is associated with ECM remodelling and trophoblast invasion in the spiral arteries in both healthy and complicated pregnancy. Gelatinase MMP-2 is responsible for the breakdown of collagen type IV, a major component of the basement membrane [26]. There is evidence that plasma MMPs may lead to modification of vasoactive peptides and activated MMP-2 may increase vasoconstriction and reduce vasodilatation in PE [27]. Elevated net MMP-2 levels in PE may contribute to endothelial cell activation, increased vascular MMP-2 expression, endothelin-1 cleavage and vasoconstriction with increased transmural pressure [28]. As a result, vascular reactivity is impaired and these processes lead to abnormal vascular remodelling. Hence, increased MMP-2 levels may contribute to vascular dysfunction, secondary to hypertension-related mechanical stress on the vessel wall [29].

In our study, serum MMP-2 levels in women with preeclampsia were significantly higher than in women with normal pregnancies. Our findings are consistent with the above mentioned studies showing higher MMP-2 levels in preeclamptic patients compared with healthy pregnant women [19, 20, 21, 22, 23]. In addition, we found that MMP-2 levels correlated with the mean Doppler pulsatility index of the uterine arteries. This evidence implicates a possible role of MMP-2 in the pathogenesis of preeclampsia through the process of altered uterine arteries' remodelling. Based on the literature reports [27, 28, 29] that activated MMP-2 can increase vasoconstrictor levels and decrease vasodilator levels, we suggest that our results could be related to possible endothelial dysfunction of the uterine arteries. These processes might favour vasoconstriction, increased vascular resistance and abnormal uterine vascular remodelling. Hence, they could contribute to the development of placental ischemia, which may lead to hypertension of pregnancy and further development of preeclampsia. Taken together, these factors play a key role in the pathogenic mechanisms of preeclampsia. Our finding was also supported by linear regression analysis which verified the relationship between MMP-2 and mean UtA PI, an indicator of increased vascular resistance.

The present findings are in agreement with previous reports, which hypothesized that measurement of serum MMP-2 might help in the diagnostic process of PE [19, 20, 21, 22, 23]. Furthermore, the results obtained from our research demonstrated for the first time that cut-off value at 14 ng/ml for MMP-2 discriminates between PE and healthy pregnancy.

We suggest that determination of serum MMP-2 levels above this cut-off point indicates a category of typically positive patients who might require additional diagnostic tests, because they could be at higher risk for development of preeclampsia. Larger and longitudinal investigations are needed to assess whether determination of serum MMP-2 levels can be helpful in the diagnostic process of preeclampsia.

In the current study, the source of serum MMP-2 was not defined. We measured the net serum concentration of MMP-2, so we could not estimate what proportion of it has been released exactly by the pre-eclamptic endothelial cells of uterine arteries. Other tissues as placenta or uterus might also be suggested as a potential origin of MMP-2 secretion. Our results confirmed the increased MMP-2 levels in PE. Moreover, for the first time in preeclampsia patients, evidence was found indicating an association between MMP-2 and mean UtA PI. The reported association suggests an interplay between MMP-2 and maternal uterine arteries. What is the mechanism of interaction between MMP-2 and uterine vasculature in preeclampsia is a question of a great importance. Further studies with serial measurements and more specific methods like Western blots, gelatine zymography and immunohistochemical analysis would allow for a more precise assessment of the MMP-2 impact on maternal uterine arteries and may help to elucidate its role in the pathogenesis of preeclampsia.

## CONCLUSION

We demonstrated for the first time that a MMP-2 cut-off above 14 ng/ml could provide better discrimination of PE patients from healthy pregnancy. Our study also gives arguments for a possible MMP-2 imply on maternal uterine arteries' structure in PE, favoring their constriction, increased resistance and abnormal uterine vascular remodeling. All the mentioned processes take part in the central pathways in the etiology of preeclampsia. Considering that, we suggest that MMP-2 might be involved in the mechanisms of abnormal uterine vasculature remodelling and might probably contribute to the diagnosic work-out strategies for preeclampsia.

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