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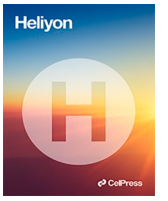

Matrix metalloproteinase-3 in preeclamptic and normotensive pregnancies complicated by foetal growth restriction

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ABSTRACT

The aim of the present study was to assess the interrelationships between the level of matrix metalloproteinase-3 in the blood serum of pregnant women and the occurrence of pregnancy complications in the form of foetal growth restriction, idiopathic or in the course of preeclampsia.
Methods: A total of 245 patients were included in the study. 65 of them are normotensive patients with idiopathic foetal growth restriction (FGR group). 115 women were diagnosed with severe preeclampsia. In the group of women with preeclampsia, there were 51 patients with adequate for gestational age foetal growth and 64 patients with the foetal growth restriction in the course of severe preeclampsia. The control group consisted of 65 healthy patients with normal pregnancy course, with no cardiovascular disorders at the present and in the history, normal blood pressure and normal intrauterine foetal growth. Matrix metalloproteinase-3 (MMP-3) in maternal circulation were determined by ELISA method.
Results: In our studies, we observed elevated levels of matrix metalloproteinase-3 in preeclamptic women with pregnancies complicated by FGR and significantly lower in the group of normotensive women with idiopathic FGR. The mean values of MMP-3 were 33.50 ± 65.74 ng/mL [Median (min-max) 19.19 (2.05–454.53)] in the Control group, 21.22 ± 23.28 ng/mL [Median (min-max) 16.39 (3.45–156.29)] in the FGR group, 35.96 ± 46.14 ng/mL [Median (min-max) 25.21 (4.16–253.05)] in the P group and 52.81 ± 61.61 ng/mL [Median (min-max) 32.83 (5.06–314.14)] in preeclamptic women with FGR (group PI) respectively.
The assessment of MMP-3 in the serum of women with pregnancies complicated by intrauterine foetal growth restriction with normal values of blood pressure and in the group of preeclamptic patients in relation to healthy pregnant women with uncomplicated pregnancies and in relation to preeclamptic patients with normal intrauterine foetal growth is the novelty of this study. Such a strict definition of each research group seems to allow for the assessment of each pregnancy complication separately.
Conclusion: It seems that higher levels of MMP-3 in preeclamptic women may suggest the need for observation towards the risk of lower birth weight of newborns. This necessitates further research and a better integration in the clinical practice.

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1. Introduction

Restricted intrauterine foetal growth (FGR) defined as the inability of the foetus to achieve its genetically determined growth potential remains a major challenge for modern obstetrics [1]. FGR both with and without accompanying preeclampsia has its consequences in increased mortality and perinatal morbidity [1–6]. In addition, we have more and more evidence of the adverse impact of this pregnancy complication on later periods of life of children born with FGR [1,7,8]. A more frequent occurrence of cardiovascular and metabolic diseases in adulthood in this group was observed [7,8]. Although we currently know several pathogenetic mechanisms that may lead to the development of both FGR and preeclampsia, the exact aetiology of these specific for human pregnancy diseases is not fully explained [6].

Numerous studies confirm the importance of abnormal transformation of the spiral arteries and disturbed placentation in the development of placental insufficiency and both above mentioned pregnancy complications, but there are still many questions about the mechanism initiating or triggering this pathological process [2,9,10]. Coexistence of two seemingly different syndromes, such as preeclampsia and FGR, suggest their common aetiology. However, these conditions are not always present together.

It has been suggested that metalloproteinases are enzymes that participate in the normal invasion of the extravillous trophoblast to the wall of the spiral arteries leading to the formation of an appropriate surface for maternal-foetal replacement and, consequently, to ensure proper oxygenation and nutrition of the foetus [2,9,10]. This is of key importance for a normal, uncomplicated course of pregnancy and foetal growth, adequate for gestational age.

Abnormal metalloproteinases activity is significantly related to abnormal transformation of the spiral arteries and placental development disorder, too shallow and superficial placentation [2,4,6]. Many available studies mainly concern MMP-2 and MMP-9, whereas we know little about the possible role of MMP-3 [11–13]. Matrix metalloproteinase-3 was detected in the epithelial cells of the amnion, syncytiotrophoblast cells and villi at all stages of pregnancy [14,15]. MMP-3 degrades collagen, proteoglycans, elastin, fibronectin, laminin and gelatin [16]. It is present in processes of tissue remodelling, trophoblast mobility, regulation of host response to intrauterine infections and angiogenesis processes [17,18]. In addition, it plays a role in the activation of other pro-metalloproteinases to the active forms of enzymes [13,16].

Reister et al. [9] found reduced expression of MMP-3 in close proximity to the spiral arteries in preeclamptic women, which could suggest a reduced invasiveness of trophoblast in these pregnant women. Merchant and Davidge [19] observed an increased spasm of blood vessels under the influence of metalloproteinases and the importance of serum levels of metalloproteinases in the process of relaxation of blood vessels. In her own research, Laskowska [11] observed significantly higher levels of MMP-3 in women with early preeclampsia, but not in preeclampsia with late onset, which may additionally suggest a relationship between MMP-3 and the severity of the disease, form of preeclampsia with maternal and placental features.

The above premises prompted us to undertake research into the meaning of matrix metalloproteinase-3 in the aetiopathogenesis of both these diseases. In order to investigate the nature of the disorders of each of these diseases individually and the special role of matrix metalloproteinase-3, we decided to undertake matrix metalloproteinase-3 studies in strictly homogeneous groups in which both these diseases occur as isolated disease syndromes compared to the group of patients where both syndromes occur together. The tests were also performed in relation to healthy patients with normal course of pregnancy and adequate intrauterine growth of the foetus.

The assessment of MMP-3 in the serum of women with pregnancy complicated by FGR with normal values of blood pressure and in the group of patients with FGR in the course of severe preeclampsia in relation to healthy pregnant women with uncomplicated pregnancy and in relation to preeclamptic patients with normal foetal growth is the novelty of this study. Such a strict definition of each research group seems to allow for the assessment of each pregnancy complication separately. It may allow for a better understanding of the pathogenic mechanisms that lead to these particular complications of pregnancy.

2. Methods

The aim of our study was to evaluate the potential relationship of circulating in the blood serum of matrix metalloproteinase −3 levels with FGR, both idiopathic and accompanying severe preeclampsia and with the development of severe preeclampsia without FGR. A total of 245 patients in 2nd and 3rd trimester of pregnancy were included in the study. 65 of them are normotensive patients with restricted foetal idiopathic growth (the FGR group). 115 women were diagnosed with severe preeclampsia. In the group of women with preeclampsia, there were 51 patients with adequate for gestational age foetal growth (the P group) and 64 patients with the foetal growth restriction in the course of severe preeclampsia (the PI group). In the preeclamptic women there were 10 patients with HELLP syndrome (9 women in the PI group and 1 woman in the P group) and 6 women with eclampsia (5 in the subgroup P and 1 in the PI subgroup). The control group consisted of 65 healthy patients with normal pregnancy course, with no cardiovascular disorders at the present and in the history, normal blood pressure and normal intrauterine foetal growth.

Informed consent was obtained from each woman for the participation in the study and for peripheral blood sampling. The protocol for the study was approved by the Bioethics Committee of the Medical University of Lublin (*KE-0254/51/2010*). All studies were performed in vitro and did not pose any threat to either the mother or the developing foetus.

Gestational age was established by first day of last menstrual period and confirmed by crown rump length measurements at ultrasound exam in first trimester of pregnancy.

Foetal biometry was based on ultrasonography and apart from the estimation of gestational age, it included the diagnosis of foetal growth restriction by monitoring foetal growth, development and wellbeing later in the second or third trimester of pregnancy. Foetal growth restriction (FGR) was classified as failure of the foetus to achieve its genetically determined growth potential assessed by means of ultrasonographic measurement when the weight of the foetus was below the 10th centile for gestational age with Doppler

abnormality (elevated pulsatility index (PI) in the uterine arteries and/or early diastolic notches, elevated PI in umbilical arteries, elevated head/abdomen ratio, and reduced AFI) [2,9,10,20–24]. The fetal measurements and Doppler studies were performed using curvilinear transabdominal probe upon routine conditions and guidelines. Biometry was performed by measuring the abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL). The fetal weight were calculated using the Hadlock curves [25]. The diagnosis was confirmed by the infant's weight at birth [22–24].

Severe preeclampsia was diagnosed using new diagnostic criteria by American College of Obstetricians and Gynaecologists – ACOG [26]. They were as follows: increased blood pressure >160 mmHg systolic and >110 mmHg diastolic on at least two occasions 6 h with significant proteinuria (>5 g in a 24-h urinary protein excretion) or when hypertension and proteinuria were associated with one or more of the following clinical manifestations such as renal abnormalities, haematological abnormalities (thrombocytopenia and microangiopathic haemolysis) or HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count and right-upper quadrant pain), or neurological symptoms (headache, visual disturbances and seizures) [26]. All preeclamptic patients and women with pregnancies complicated by FGR were admitted to the Department of Obstetrics and Perinatology of the Medical University Hospital in Lublin because of the symptoms of the disease and without signs of labour. All arterial blood pressure measurements in the control group and in the group of patients with isolated foetal FGR were normal and did not exceed 135/85 mmHg. None of the patients from any of these groups suffered from proteinuria [20].

The clinical data were ascertained prospectively and included maternal age, height, weight, gestational age, medical and obstetrical history, as well as maternal blood pressure and laboratory test values.

No participants smoked, used caffeine or alcohol, or had a history of endocrinological disease, diabetes, pre-pregnancy cardiovascular diseases, liver diseases, chronic renal diseases and chronic hypertension. Pregnant women with multiple pregnancies, premature rupture of membranes, chorioamnionitis, inflammatory features, connective tissue disease, presence of a congenital malformation or chromosomal abnormality in the foetus, recent cytomegalovirus infection were also excluded from this study [11,20].

The serum samples were collected according to a common standard operating procedure at our center. The venous blood was drawn by venipuncture in tubes without anticoagulant directly from the patient. Ten millilitres of blood were collected by venipuncture from each preeclamptic patient, women with pregnancies complicated by foetal growth restriction and from each woman from the control group before any drug administration and placed in sterile tubes at 4 °C and centrifuged at 1500×*g* for 15 min. Afterwards, the serum samples were stored at −70 °C until assayed. Maternal serum sampling for MMP-3 determination was performed following the diagnosis before treatment and before active phase of delivery. The levels of maternal serum matrix metalloproteinase-3 were determined using a specific and sensitive commercially available enzyme-linked immunosorbent assay (ELISA assay) according to the manufacturer's instructions (Bender MedSystem, Vienna, Austria). The minimum detectable level was 0.3 ng/mL with intra-assay 7.3% and interassay 8.8% precision rate. All measurements were performed blinded to the diagnosis.

Data were collected and analyzed using the statistical program Statistica 8.0 PL software (StatSoft, Inc., Tulsa, OK, USA). All data were described in terms of mean, median, standard deviation (SD), min-max. The chi square test or the Fisher exact test (two tailed), if appropriate, were applied for the categorical variables. Statistical significance was determined by using ANOVA to compare between four groups. A statistically significant effect in ANOVA was followed up with a follow-up post hoc test in order to assess which group is different from other groups. Data were also subjected to correlation analysis using the same software to determine Spearman "R"

Table 1
Characteristics of the groups studied women with pregnancies complicated by FGR with and without preeclampsia, preeclamptic women with normal foetal growth and control subjects.

	Control group (n = 65)	Group P (n = 51)	Group PI (n = 64)	Group FGR (n = 65)	Statistical analysis (p value)
Gravidity (Mean± SD) Mediana (Max-Min)	*1.41 ± 0.68 1 (1–5)*	*1.75 ± 1.08 1 (1–5)*	*1.83 ± 1.40 1 (1–4)*	*1,54 ± 0.85 1 (1–5)*	*p = 0.052105*
Parity (Mean± SD) Mediana (Max-Min)	*1.34 ± 0.55 1 (1–3)*	*1.57 ± 0.85 1 (4)*	*1.64 ± 1.35 1 (1–4)*	*1.43 ± 0.70 1 (1–5)*	*p = 0.171371*
Maternal age (years)	*29.21 ± 4.42*	*29.64 ± 6.26*	*29.94 ± 4.72*	*28.90 ± 4.70*	*p = 0.630112*
Height (cm)	*164.70 ± 5.54*	*164.19 ± 6.34*	*163.39 ± 5.60*	*156.12 ± 6.50*	*p = 0.444154*
Maternal weight (kg)	*78.26 ± 12.36*	*78.26 ± 12.36*	*78.61 ± 12.34*	*68.39 ± 11.21*	*p < 0.00001*[a]
BMI (kg/m^2)	*28.85 ± 4.35*	*32.20 ± 5.02*	*29.34 ± 4.14*	*25.13 ± 3.92*	*p < 0.00001*[a]
Systolic blood pressure (mmHg)	*113.56 ± 9.60*	*168.32 ± 17.812*	*168.21 ± 17.24*	*110.74 ± 12.02*	*p < 0.00001*[a]
Diastolic blood pressure (mmHg)	*72.24 ± 7.43*	*109.43 ± 10.83*	*111.12 ± 9.27*	*70.42 ± 9.05*	*p < 0.00001*[a]
Mean arterial blood pressure (mmHg)	*85.66 ± 8.17*	*129.03 ± 11.77*	*130.12 ± 10.93*	*83.85 ± 9.63*	*p < 0.00001*[a]
Age of pregnancy (weeks)	*38.13 ± 1.95*	*34.46 ± 4.68*	*33.34 ± 3.45*	*36.45 ± 2.30*	*p < 0.00001*[a]
Birth weight (g)	*3153.08 ± 579.61*	*2403.55 ± 1029.76*	*1601.84 ± 592.79*	*1907.71 ± 473.24*	*p < 0.00001*[a]

Data presented as a mean ± SD. Data presented as a mean ± SD, or as median and minimal and maximal value.
Groups of women studied.
Control group – healthy normotensive pregnant women.
P group – group of preeclamptic women with normal intrauterine foetal growth.
PI group - group of women with foetal growth restriction in the course of severe preeclampsia.
FGR group – group of normotensive women with pregnancies complicated by foetal growth restriction.
BMI - body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a] Statistical significance ($p < 0.05$).

values or Pearson's correlation coefficient. A statistical power analysis was within 4% with 95% confidence. A p-value of less than 0.05 was considered to be statistically significant.

3. Results

There were no statistically significant differences in parity, maternal age and height in patient profiles between the groups of women studied. Values of maternal BMI were lowest in the group of patients with normotensive pregnancies complicated by idiopathic foetal growth restriction and the highest in women with pregnancies complicated by preeclampsia without FGR. There were no differences in BMI between PI and Control groups and in maternal weight between both preeclamptic groups and healthy controls. None of the patients from the control group and from the FGR group suffered from proteinuria. Creatinine and urea levels were normal in all studied patients. Systolic and diastolic blood pressure and mean arterial blood pressure (MAP II) were significantly higher in both study groups of preeclamptic women than in the control group and in the pregnant patients with isolated growth restricted foetuses. Demographic and clinical data of the patients studied are given in Table 1.

The lower gestational age and birth weight of infants were observed in both groups of preeclamptic patients and in the group of normotensive women with pregnancies complicated by intrauterine growth restricted foetuses in comparison with the control subjects. Although there were no statistically significant differences in age of gestation at birth between both groups of preeclamptic patients, statistically significant lower birth weight of infants was observed in the PI group (1601.84 ± 592.79 g in the group PI versus 2403.55 ± 1029.76 g in the group P). The age of gestation at birth was lower in both preeclamptic groups of pregnant patients also in comparison with normotensive women with pregnancies complicated by isolated foetal growth restriction (the FGR group). However birth weight of infants in the group of patients with pregnancies complicated by isolated intrauterine foetal growth restriction (FGR group) was also lower than in the P group and in comparison with the control subjects. The mean birth weight of infants was 1907.71 ± 473.24 g in normotensive women with pregnancies complicated by FGR.

3.1. Serum levels of matrix metalloproteinase-3

MMP-3 serum levels were found to be elevated in patients with pregnancies complicated by intrauterine foetal growth restriction in the course of severe preeclampsia (the PI group) in comparison with pregnant women with preeclampsia and adequate intrauterine foetal growth (the P group), in comparison with healthy controls, and in comparison with normotensive women with pregnancies complicated by foetal growth restriction (the FGR group). Maternal serum levels of MMP-3 were decreased in normotensive pregnant

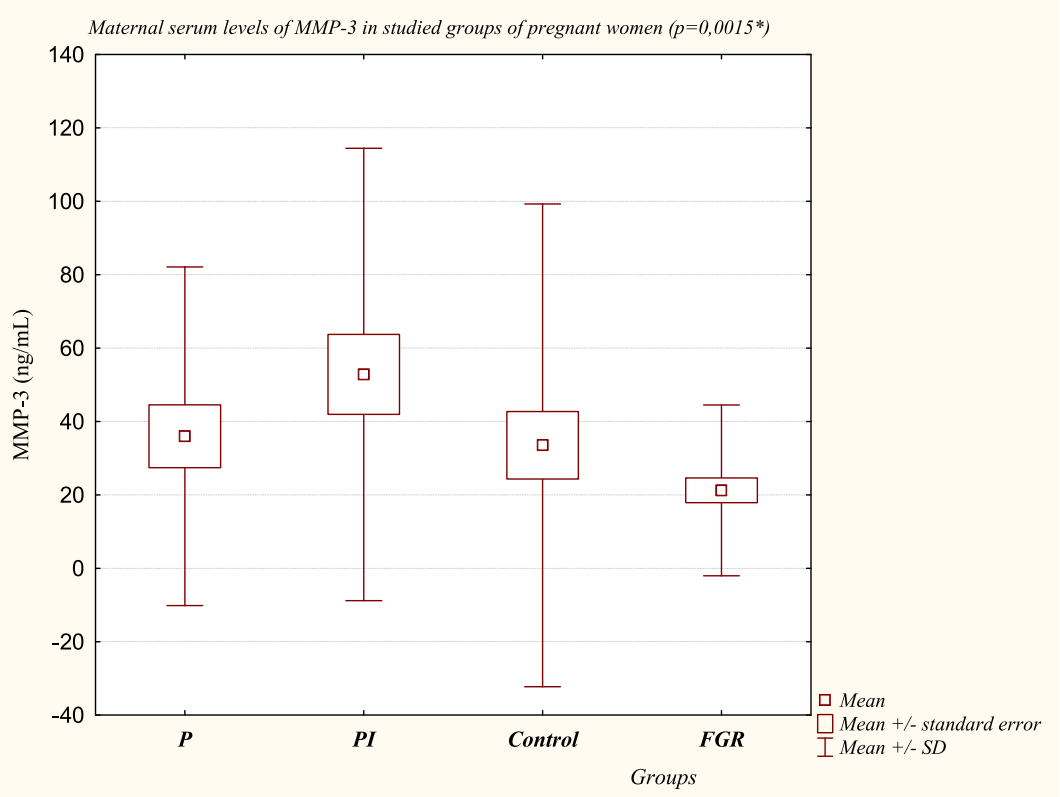

Fig. 1. Maternal serum levels of MMP-3 in studied groups of pregnant women (p = 0,0015*).

patients with pregnancies complicated by idiopathic intrauterine foetal growth restriction - the FGR group also compared with healthy controls and preeclamptic women without foetal growth restriction, but the differences were statistically significant only in comparison with women with pregnancies complicated by FGR in the course of severe preeclampsia (p = 0.0001268*).

Data are presented in Fig. 1 and Table 2.

The highest levels of MMP-3 were found in group PI. Furthermore, there were no statistically significant differences in levels of MMP-3 in the P group as compared with patients with isolated FGR and as compared with healthy controls.

MMP-3 serum levels were significantly different in pregnancies complicated by foetal growth restriction in the course of preeclampsia than in group of healthy normotensive women with idiopathic FGR and then in the group of preeclamptic women without FGR.

There were no statistically significant differences in MMP-3 levels in women with HELLP syndrome or patients with pregnancy complicated by eclampsia. The mean values of maternal serum MMP-3 in HELLP patients and women with eclampsia were 22.27 ± 8.19 ng/mL (the range of values from 14.29 to 37.12 ng/mL) and 38.94 ± 14.47 ng/mL (the range of values from 20.55 to 60.24 ng/L) respectively. But the small number of women in these subgroups of preeclamptic patients is important limitation of this analysis.

3.2. Correlation

There were no statistically significant correlations between maternal serum MMP-3 levels with maternal age, height, gravidity and parity as well as systolic, diastolic and mean arterial blood pressure in all the groups of pregnant women studied. In the present study negative correlation between serum MMP-3 levels and body mass index (BMI) in the group of normotensive patients with idiopathic intrauterine foetal growth restriction (the FGR group) (correlation index R = −0.446766, and p value p = 0.037117*) was observed. This association were not statistically significant in other groups.

There were negative correlations of serum MMP-3 levels with age of pregnancy and infant's birth weight in preeclamptic women with proper intrauterine foetal growth (correlation index R = −0.585651 and R = −0.580274, and p value p = 0.000845 × and p = 0.001208 × for age of pregnancy and infant's birth weight respectively for the P group). Those negative correlations were also found in normotensive patients with pregnancy complicated by isolated FGR without preeclampsia (correlation index R = −0.413409 and R = −0.301451 with p value p = 0.003873 × and p = 0.039478 × for age of pregnancy and infant's birth weight respectively). Above correlations were not statistically significant in the group of preeclamptic women with FGR and in healthy controls.

4. Discussion

There are no studies on maternal serum MMP-3 in pregnancies complicated by FGR with accompanying severe preeclampsia and without it. Therefore, the aim of the current study was to assess the relationship between MMP-3 levels in the blood serum of pregnant

Table 2
Maternal serum MMP-3 in pregnancies complicated by FGR with and without accompanying severe preeclampsia, in preeclamptic women with normal intrauterine foetal growth and in healthy controls.

	Matrix metalloproteinase-3 (MMP-3)
	Mean±SD
	Median (min-max)
The Control group (n = 65)	33.49 ± 65.74 ng/mL
	19.19 (2.05–454.53)
Statistical analysis Control/P	*p = 0.935656*
The P group (n = 51)	35.96 ± 46.14 ng/mL
	25.21 (4.16–253.05)
Statistical analysis Control/PI	***p = 0.015645***[a]
The PI group (n = 64)	52.81 ± 61.61 ng/mL
	32.83 (5.06–314.14)
The FGR group (n = 65)	21.22 ± 23.28 ng/mL
	16.39 (3.45–156.29)
Statistical analysis P/FGR	*p = 0,179,801*
Statistical analysis PI/FGR	***p = 0.0001268***[a]
Statistical analysis Control/FGR	***p = 0.224209***

Data presented as a mean ± SD, median and minimal and maximal value.
Groups of studied women.
Control group – healthy normotensive pregnant women.
P group – group of preeclamptic women with normal intrauterine foetal growth.
PI group - group of women with foetal growth restriction in the course of severe preeclampsia.
FGR group – group of normotensive women with pregnancies complicated by foetal growth restriction.
[a] Statistical significance (p < 0.05).

women and the occurrence of pregnancy complications such as intrauterine foetal growth restriction with and without accompanying preeclampsia. The novelty of this study is the determination of MMP-3 in maternal serum in patients with severe preeclampsia with and without FGR and in women with idiopathic FGR without preeclampsia compared to healthy pregnant women.

Our study revealed significantly higher concentrations of MMP-3 in maternal serum in pregnancies complicated by FGR in the course of severe preeclampsia as compared to women with severe preeclampsia and appropriate for gestational age foetal growth as well as in healthy pregnant women from the control group. Our results may suggest additional disturbances related to increased levels of MMP-3 observed in preeclamptic women with FGR. However, to our surprise, the levels of MMP-3 in women with idiopathic FGR without hypertension were lower compared to both groups of women with pregnancy complicated by severe preeclampsia and in comparison to the control group.

The results of the obtained studies may lead to the hypothesis that higher levels of MMP-3 correlate with the severity of preeclampsia, where the maternal form is accompanied by foetal form. Higher levels of MMP-3 appear to be a hallmark of FGR, but only in the course of preeclampsia, not the idiopathic form of FGR in normotensive pregnancies.

This data also seems to emphasize another mechanism or cause of FGR in women with normal blood pressure and in pregnant women with preeclampsia.

At the same time, the dissimilarity of instrumental mechanism or triggering preeclampsia with the foetus growth corresponding to the gestational age in relation to the preeclampsia additionally complicated by FGR, seems to be confirmed. The observed negative correlation between MMP-3 and BMI in FGR group of women with idiopathic FGR and negative correlation of MMP-3 with gestational age and birth weight of newborns in women with preeclampsia and adequate foetal growth and in the group of patients with isolated FGR, seems to suggest the presence of additional disorders which elevated MMP-3 levels observed in women with FGR during preeclampsia lead to.

Considering the statistically significant negative correlation of maternal MMP-3 levels with the level of nitric oxide synthase in women with normal blood pressure values and isolated FGR (correlation index $R = -0.310202$, and p value $p = 0.042926$ *) in previous Laskowska [20,27] studies it is likely that MMP-3 reduction in maternal serum reflects the attempt to compensate for existing disturbances in the production of nitric oxide in this group of pregnant women. At the same time, the negative correlation of the levels of metalloproteinase-3 with the birth weight of newborns observed in the FGR group seems to confirm this relationship. In addition, the negative correlation of serum MMP-3 levels with the age of pregnancy in this group of patients seems to suggest that this is a chronic, rather than acute or short-lived process.

In addition, elevated levels of MMP-3 in maternal serum in preeclamptic women with pregnancies complicated by FGR may be the cause of vascular endothelial dysfunction and impaired nitric oxide synthesis, which seems to be a possible mechanism underlying the development of FGR during preeclampsia. However, this study showed increased levels of MMP-3 only in patients with preeclampsia complicated by FGR (the PI group), but not in preeclampsia with normal intrauterine growth of the foetus (the P group).

The question remains, why these higher levels of MMP-3 occur only in the preeclampsia of FGR, but are not observed in preeclampsia without FGR. Different results obtained in both groups of patients with pregnancy complicated by preeclampsia with and without FGR seem to suggest a different mechanism or different severity of disease in preeclampsia with and without FGR. Therefore, speculation about the different role of MMP-3 in the pathogenesis of both forms of preeclampsia, i.e. the maternal form and the maternal-foetal form of the disease seem to justified.

Espino et al. [12] suggest the importance of abnormal concentrations of matrix metalloproteinase in the process of vascular endothelial cell damage and increased reactivity of blood vessels observed in preeclampsia [12]. In addition, these authors suggested the relationship of low placental concentrations of metalloproteinases with abnormal remodelling of the spiral arteries, which consequently leads to disturbances in blood flow between the placenta and the foetus. Anacker et al. [28] noted a weak expression of pro-metalloproteinase-3 in the decidua in the first and second trimester of pregnancy and its constant level in the third trimester of pregnancy. At the same time, they observed a significant increase in the expression of MMP-3 from the first to the second trimester of pregnancy with a reduction in the third trimester to the value at the beginning of pregnancy. The results of our research seem to confirm the importance of elevated MMP-3 levels in the development of FGR in the course of preeclampsia.

Decreased levels in patients with isolated FGR suggest a different mechanism of disorders leading to FGR in pregnant women with and without preeclampsia. The key question is whether it is possible to detect abnormalities earlier in pregnancy even before the onset of a clinically apparent phase of the disease and could it be used to prevent the occurrence of disorders and targeted therapy?

5. Limitations

Our study was done in a single center and it is of relatively small size. We also did not separate early-onset from late-onset patients in study cohorts for deeper analysis.

6. Conclusions

Elevated values of MMP-3 in maternal serum in pregnancy complicated by FGR during preeclampsia and reduced values in women with FGR without preeclampsia appear to indicate other mechanisms leading to the restriction of intrauterine growth in women with preeclampsia and in women without signs of preeclampsia. Different results in both groups of women with pregnancy complicated by preeclampsia (with and without FGR) suggest a different role of MMP3 in the development of both forms of preeclampsia. Elevated concentrations of MMP-3 in women with preeclampsia and FGR may be the resultant of the severity of the disease, the occurrence of severe preeclampsia with maternal-foetal symptoms.

Negative correlations of serum levels of MMP-3 with age at birth and birth weight of a newborn in women with preeclampsia with normal intrauterine foetal growth and in normotensive patients with isolated FGR without preeclampsia and lack of such dependences in women with preeclampsia and FGR, may lead to the intriguing hypothesis that higher levels of MMP-3 in preeclamptic may predict the risk of lower birth weight of newborns and earlier delivery.

An impact statement

What is already known on this subject?

FGR both with and without accompanying preeclampsia has its consequences in increased mortality and perinatal morbidity. Although we currently know several pathogenetic mechanisms that may lead to the development of both intrauterine foetal growth restriction and preeclampsia, the exact aetiology of these specific for human pregnancy diseases is not fully explained.

What do the results of this study add?

Elevated values of MMP-3 in maternal serum in pregnancy complicated by FGR during preeclampsia and reduced values in women with FGR without preeclampsia appear to indicate other mechanisms leading to the restriction of intrauterine growth in women with preeclampsia and in women without signs of preeclampsia. Elevated concentrations of MMP-3 in women with preeclampsia and FGR may be the resultant of the severity of the disease, the occurrence of severe preeclampsia with maternal-foetal symptoms.

What are the implications of these findings for clinical practice and/or further research?

Obtained results and observed correlations suggest that higher levels of MMP-3 in preeclamptic women with FGR may predict the risk of lower birth weight of newborns and earlier delivery.

Ethics approval and consent to participate

Informed written consent was obtained from each woman for the participation in the study and for peripheral blood sampling. The protocol for the study was approved by the Bioethics Committee of the Medical University of Lublin (KE-0254/51/2010). All studies were performed in vitro and did not pose any threat to either the mother or the developing foetus.

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Author contribution statement

Marzena Laskowska: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Elżbieta Szmit; Dominika Ledwich-Kibicka; Andrzej Wróbel; Weronika Dymara-Konopka: Analyzed and interpreted the data; Wrote the paper.

Data availability statement

The data that has been used is confidential.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

ACOG American College of Obstetricians and Gynaecologists – ACOG
AFI amniotic fluid index
BMI body mass index
Control group healthy normotensive pregnant women
ELISA the Enzyme Linked Immunosorbent Assay
FGR foetal growth restriction
FGR group group of normotensive women with pregnancies complicated by foetal growth restriction
HELLP syndrome haemolysis, elevated liver enzymes and low platelet count
MMP-2 matrix metalloproteinase −2
MMP-3 matrix metalloproteinase - 3
MMP-9 matrix metalloproteinase - 9
P group group of preeclamptic women with normal intrauterine foetal growth
PI pulsatility index

PI group group of women with foetal growth restriction in the course of severe preeclampsia
SD standard deviation

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