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Maternal serum matrix metalloproteinase 9 in pregnancies complicated by severe preeclampsia and/or intrauterine fetal growth restriction

Abstract

Objective: The aim of present study was to assess the maternal serum matrix metalloproteinase-9levels in pregnancies with intrauterine growth restriction (IUGR) in the presence or absence of preeclampsia and to compare the results with preeclamptic pregnant women with appropriate-for-gestational-age weight infants and healthy controls.

Patients and methods: The study was carried out on 243 pregnant women: 70 normotensive pregnant patients with pregnancy complicated by isolated IUGR (the iugr group) and 55patients with IUGR in the course of severe preeclampsia (the PI group), 63 preeclamptic patients with appropriate-for-gestational-age weight infants (the P group). The control group consisted of 55 healthy normotensive pregnant patients with singleton uncomplicated pregnancies (the C group). The maternal serum matrix metalloproteinase-9 (MMP-9) concentrations were determined using a sandwich enzyme-linked immunosorbent assays.

Results: The preeclamptic women with normal and growth restricted fetuses, and normotensive patients with pregnancy complicated by isolated IUGR revealed lower levels of maternal serum matrix metalloproteinase-9 in comparison with the control subjects. These differences were statistically significant only for normotensive women with pregnancy complicated by isolated IUGR (p=0.009827). The mean values of the MMP-9 levels in maternal serum were 1422.76±696.83ng/mL in the IUGR group, 1559.56±1108.06ng/mL in the P group, 1484.63±974.31ng/mL in the PI group compared with 1790.15±869.58ng/mL in the control

Conclusion: The results of the present study allow the conclusion that the decrease matrix metalloproteinase-9 levels may participate in the pathological processes underlying preeclampsia and intrauterine fetal growth restriction both in preeclamptic and particularly in normotensive pregnancies with idiopathic IUGR.

Keywords: severe preeclampsia, IUGR, matrix metalloproteinase-9 (MMP-9)

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Introduction

Preeclampsia is a human pregnancy specific disorder that manifests itself clinically as hypertension after 20 weeks of gestation with associated proteinuria or other multiorgan clinical symptoms such as impaired liver or renal function, thrombocytopenia, pulmonary oedema, or neurological disturbances and intrauterine fetal growth restriction (IUGR).[1,2] Although preeclampsia occurs in 5% to 10% of all pregnancies it remains one of the largest single causes of maternal and fetal morbidity and mortality.[1,2] Intrauterine growth restriction of the fetus (IUGR) affects approximately 8% of all pregnancies.[3] The exact aetiology of preeclampsia and IUGR remains mystery and currently delivery of the baby and placenta remains the only definitive treatment of these pregnancy disorders, but often resulting in prematurity.[1–3] It is generally accepted that shallow trophoblast invasion and defects in spiral artery remodeling are involved in aetiopathogenesis of preeclampsia and fetal growth restriction.[1–5] These processes are regulated by specific proteolytic enzymes, matrix metalloproteinases. Metalloproteinase-9 is one of gelatinases able to degrade type IV collagen.[6] Recent research presented that MMP-9 is involved in remodeling of the extracellular matrix and in spiral artery formation during placentation.[7–9] Furthermore MMP-9 initiates[10–11] the formation of new blood vessels[7] and increases endothelial cell survival.[12,13] The aim of present study was to assess the maternal serum matrix metalloproteinase-9 levels in pregnancies with intrauterine growth restriction (IUGR) in the presence or absence of preeclampsia and to compare the results with preeclamptic pregnant women with appropriate-for-gestational-age weight infants and healthy controls.

Patients and methods

All pregnant patients admitted to the Department of Obstetrics and Perinatology at Lublin University tertiary-level academic Hospital for further treatment and surveillance because of the symptoms of the preeclampsia and/or IUGR without any signs of labour, were offered participation in this study. Study population were included 4groups: women with pregnancies complicated by severe preeclampsia and appropriate intrauterine fetal growth (the P group), patients with pregnancies complicated by intrauterine fetal growth restriction in the course of severe preeclampsia (the PI group), normotensive pregnant women with isolated IUGR (the iugr group), and healthy normotensive pregnant women as the controls (the C group). According to American

College of Obstetricians and Gynecologistscriteria preeclampsia was diagnosed as hypertension in association with proteinuria. Hypertension was diagnosed as blood pressure greater than or equal to 140mmHg systolic or diastolic greater or equal to 90mmHg on two occasions at least 4hour in women who were normotensive before 20weeks of gestation. Diagnostic criteria for proteinuria were greater than or equal to 300mg protein loss in 24-hour urine collection.[14] Severe preeclampsia was defined as blood pressure 160/110mmHg confirmed within a short interval after 20weeks of gestation in a women with a previously normal blood pressure and when hypertension were associated with 1 or more of the following clinical manifestations: the new development of renal abnormalities, hematologic abnormalities (thrombocytopenia, microangiopathic hemolysis), or impaired liver function, or HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count, right-upper quadrant pain), or new-onset neurologic symptoms (headache, visual disturbances, seizures).[14] No women with pre-pregnancy hypertension or superimposed preeclampsia, were included in the present study. All preeclamptic women were normotensive 3months after delivery. All arterial blood pressure measurements in the control group and in the group of normotensive pregnant patients with isolated IUGR were normal and did not exceed 135/85 mmHg. None of the patients from these groups suffered from proteinuria.

Fetal biometry was based on non-invasive ultrasound method and included the estimation of gestational age in early gestation and diagnosis of fetal IUGR by monitoring fetal growth, development and well-being later in the second or third trimester of pregnancy. All pregnancies were dated according to last menstrual period and confirmed by first trimester crown-rump length measurement.[15,16] Intrauterine growth restricted fetuses (IUGR) diagnosed as the failure of a fetus to reach its full genetic growth potential and were classified as such according to ultrasonographic measurement[15] as the estimated fetal weight and abdominal circumference under the 10th percentile for a given gestational age according to reference ranges for Polish population.[16] Additionally, IUGR pregnancies were characterized by at least 1 of the disturbed placental functions and by an abnormal ultrasonographic examination (elevated pulsatility index [PI] in the uterine arteries and/or early diastolic notches, elevated PI in umbilical arteries, and elevated head/abdomen ratio, reduced AFI).[15,16] The diagnosis was confirmed by the infant's weight at birth.

The exclusion criteria were multiple pregnancies, the presence of a congenital malformations or chromosomal abnormalities in the fetus, recent cytomegalovirus infection or drug or alcohol abuse during pregnancy and any evidence of previous maternal medical illness. The study was accepted by the local Ethics Committee at the Medical University of Lublin, Poland. An informed consent was obtained from all patients included in the study. Demographic, clinical and obstetric variables were prospectively collected at the time of the patient's hospital admission and registered in a dedicated logbook. Five millilitres of blood were collected by venipuncture from each preeclamptic patient, from each patient with pregnancy complicated by isolated IUGR, and from each woman in the control group, placed in sterile tubes and centrifuged for 15min at 1500×g and the serum samples were stored at -70°C until assayed. The levels of maternal serum MMP-9 were determined using a sandwich ELISA assay according to the manufacturer's instructions (Bender MedSystem, Vienna, Austria for MMP-9). In the statistical analysis, results were expressed as mean±SD, or SEM or as median values and were statistically analyzed with the computer program "Statistica" using the Shapiro-Wilk test for the normally distributed data, and equality of variance by Levene test and, subsequently two-tailed t tests, or (in unequal variance) the Cochran-Cox test. The ANOVA and Kruskal-Wallis tests were used to test for differences among 4 independent groups. A statistically significant effect in ANOVA was followed up with follow-up post-hoc Tukey's test in order to assess which group is different from which other groups. A p-value of less than 0.05 was considered to be significant.

Results

The study was carried out on 243pregnant women:70normotensive pregnant patients with pregnancy complicated by isolated IUGR (the iugr group) and 55patients with IUGR in the course of severe preeclampsia (the PI group), 63 preeclamptic patients with appropriate-for-gestational-age weight infants (the P group). The control group consisted of 55 healthy normotensive pregnant patients with singleton uncomplicated pregnancies, without any renal, cardiac and vascular diseases and with normal laboratory tests and with appropriate-for-gestational-age weight infants (the C group). The general characteristics and obstetric history of the study groups are listed in Table 1. There were no statistically significant differences in gravidity, parity, maternal age and height in patient profiles between groups. Creatinine and urea levels were normal in all patients. Maternal weight, BMI and pre-pregnancy maternal weight were lower in the group of patients with pregnancy complicated by intrauterine fetal growth restriction than in the control group, and also in comparison with both groups of preeclamptic patients. The values of maternal weight and BMI were higher in group of preeclamptic patients without IUGR. Systolic and diastolic blood pressure and mean arterial blood pressure were significantly higher in the both study groups of preeclamptic pregnant women than in the control group and in the pregnant patients with isolated growth restricted fetuses. Lower gestational age and birth weight of infants were observed in the both groups of preeclamptic patients and in the group of normotensive women with pregnancy complicated by intrauterine growth restricted fetuses in comparison with the control subjects. The birth weight of infants was the lowest in the PI group. However, the birth weight of infants in the group of patients with pregnancy complicated by isolated IUGR was also lower than in the P group in spite of a higher age of gestation in the IUGR group. The mean weight of infants at birth were 2095.85±1009.87g in the P group, 1600.86±549.40g in patients with pregnancies complicated by IUGR in the course of preeclampsia, 1909.49±537.34g in women with idiopathic IUGR and 3090.94±487.88g in the healthy controls.

Table 2 displays the metalloproteinase 9levels in maternal serum samples in the both preeclamptic groups of studied women with and without IUGR (the P and PI groups), in the iugr group and in the healthy control group. The preeclamptic women with normal and growth restricted fetuses, and normotensive patients with pregnancy complicated by isolated IUGR revealed lower levels of maternal serum matrix metalloproteinase-9 in comparison with the control subjects. These differences were statistically significant only for normotensive women with pregnancy complicated by isolated IUGR (p=0.009827). The mean values of the MMP-9 levels in maternal serum were 1422.76±696.83ng/mL in the IUGR group, 1559.56±1108.06ng/mL in the P group, 1484.63±974.31ng/mL in the PI group compared with 1790.15±869.58ng/mL in the control group Figure 1.

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Table 1 Maternal study population - general characteristics and previous obstetric history

Data	Control Group C (n=55)	Group P (n=63)	Group PI (n=55)	Group IUGR (n=70)
Gravidity	1.5±0.8	1.7±1.0	1.7±0.9	1.6±1.0
Parity	1.4±0.6	1.4±0.7	1.5±0.8	1.5±0.8
Maternal age (years)	29.9±4.3	29.6±5.6	29.4±5.1	28.8±5.7
Maternal height (cm)	164.3±5.6	164.6±5.8	163.9±5.5	164.9±6.2
Maternal weight (kg)	79.66±11.73[h]	83.54±15.90[h]	79.03±13.30[h]	66.06±9.58[efg]
Maternal BMI (kg/m^2)	28.76±3.74[ch]	32.60±4.73[ah]	29.76±4.68[h]	24.50±3.71[efg]
Pre-pregnancy maternal weight (kg)	73.60±12.78[d]	65.98±13.30	62.01±7.35	53.75±6.35[a]
Systolic blood pressure (mmHg)	112.9±9.9[fg]	165.7±16.5[eh]	164.6±17.6[eh]	112.1±12.6[fg]
Diastolic blood pressure (mmHg)	72.1±7.8 [fg]	108.2±12.0[eh]	108.7±9.8[eh]	70.9±10.0[fg]
MAP II - mean arterial blood pressure (mmHg)	86.4±8.2[fg]	128.6±10.8[eh]	125.8±11.7 [eh]	84.8±9.6[fg]
Age of pregnancy at birth (weeks)	38.1±1.5[dfg]	33.4±4.8[eh]	33.3±3.1[eh]	36.1±2.5[abg]
Birth weight of infants (g)	3090.9±487.9[fgh]	2095.8±1009.9[ef]	1600.9±549.4[eg]	1909.5±537.3[be]

BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters);Values givens as mean±SD; *Statistical significance (p<0.05)
Groups of studied pregnant women:

i. C group - Healthy normotensive pregnant women;
ii. iugr group - Normotensive women with pregnancy complicated by IUGR;
iii. P group - Preeclamptic women without IUGR;
iv. PI group - Women with IUGR in the course of preeclampsia

a. ap<0.05 vs control group C,
b. bp<0.05 vs preeclamptic women with IUGR - group PI,
c. cp<0.05 vs preeclamptic women without IUGR - group P,
d. dp<0.05 vs isolated IUGR - group iugr,
e. ep<0.001 vs control group C,
f. fp<0.001 vs preeclamptic women with IUGR - group PI,
g. gp<0.001 vs preeclamptic women without IUGR - group P,
h. hp<0.0001 isolated IUGR - group iugr.

Table 2 Matrix metalloproteinase 9 levels in maternal serum samples in both preeclamptic groups of women, in normotensive pregnant patients with pregnancies complicated by IUGR and in healthy controls

	MMP-9 (ng/mL)
The C group (n=55)	1790.±869.58
Statistical analysis C-P	p=0.215854
The group P (n=63)	1559.56±1108.06
Statistical analysis P-PI	p=0.699085
Statistical analysis C-PI	p=0.085585
The group PI (n=55)	1484.63±974.31
Statistical analysis PI-IUGR	p=0.679918
The group IUGR (n=70)	1422.76±696.83
Statistical analysis C-IUGR	p=0.009827*
Statistical analysis IUGR-P	p=0.390753

Data presented as a mean±SD; *Statistical significance (p<0.05).
Groups of studied pregnant women:

i. C group - Healthy normotensive pregnant women;
ii. iugr group - Normotensive women with pregnancy complicated by isolated intrauterine growth restriction;
iii. P group - Preeclamptic women without IUGR;
iv. PI group - Women with IUGR in the course of preeclampsia.

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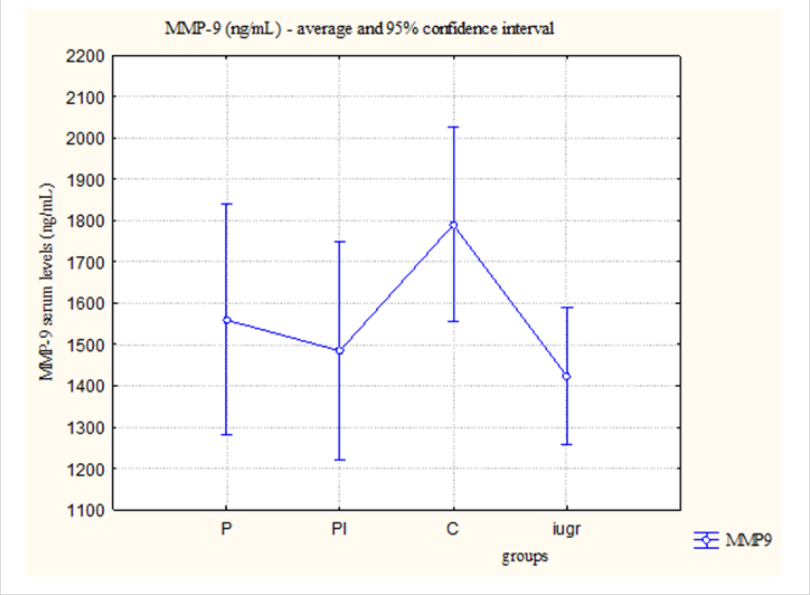

Figure 1 MMP-9 in maternal serum of pregnant women with severe preeclampsia and/or IUGR.

Discussion

The present study revealed lower levels of MMP-9 in maternal serum of women with normotensive pregnancies complicated by isolated intrauterine fetal growth restriction without preeclampsia and in both groups of preeclamptic patients with and without IUGR. But this difference was statistically significant only for normotensive pregnancies complicated by idiopathic isolated IUGR. Similar results of lower levels MMP-9 in maternal serum of preeclamptic women found Montagnana et al.[17] Moreover in their studies levels of MMP-9 were higher in pregnant women than in non-pregnant controls.[17] Coolman and colleagues,[8] presented that increased levels of MMP-9 in healthy pregnancies is crucial for the development of an appropriate maternal-fetal interface. It was also suggested that lower expression of MMP-9 leads to impaired angiogenesis and too shallow trophoblast invasion which results in higher resistance of very small blood vessels and decreased placental blood flow.[9] Also Tayebjee et al observed decreased values of MM-9 in pregnancies complicated by pregnancy hypertension.[18] The serum levels of MMP-9 in hypertensive pregnancies was similar to levels observed in non-pregnant women, but higher levels of MMP-9 were observed in normal pregnancies. Merchant et al.[19] observed lower placental MMP-9 expression also in pregnancies complicated by IUGR. Similar results decreased levels of MMP-9 in pregnancies complicated by preeclampsia showed Narumiya et al.[20] Moreover Shokry et al.,[9] observed absent or weak expression of metalloproteinase 9 in the preeclamptic placentas. By contrast Prochazka M et al reported no statistically significant differences in the levels of MMP-9 in any trimester of preeclamptic pregnancies when compared with healthy pregnant women.[21] Different results were also presented by Poon et al.,[22] who observed increased levels of MMP-9 in pregnancies complicated by preeclampsia.

Conclusion

The findings of the present study indicate that the decrease matrix metalloproteinase-9 levels may participate in the pathological processes underlying preeclampsia and intrauterine fetal growth restriction both in preeclamptic and particularly in normotensive pregnancies with idiopathic IUGR.

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None.

Conflict of interest

The author declares no conflict of interest.

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