The Serum Levels of Circulating Matrix Metalloproteinase MMP-9, MMP-2/TIMP-2 Complex and TIMP-1 do not Change Significantly During Normal Pregnancy.

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Research note

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Abstract

Objective: Matrix metalloproteinases (MMPs) are important regulators of vascular and uterine remodeling. Normal pregnancy is associated with increased MMP activity. Measurements of the plasma levels on MMPs have not been consistent between studies in complicated pregnancies. We have examined MMP-9, MMP-2 and their respective tissue inhibitors TIMP-1 and TIMP-2 in different time points in the sera of 13 women with normal pregnancy.

Results: The serum levels of MMP-9 and TIMP-1 were stable throughout pregnancy. The level of MMP-2/TIMP-2 complex was slightly increased after week 15 without statistical significance. The serum levels of MMP-9, MMP-2/TIMP-2 and TIMP-1 on different time points during normal pregnancy are poorly studied and further measurements of the plasma levels of MMPs and the correlation with MMP levels in the placenta and other maternal tissues are needed.

Introduction

Matrix Metalloproteinases (MMPs) consists of a large family of at least 28 proteolytic enzymes. MMPs are structurally related, zinc-dependent endopeptidases, which hydrolyze extracellular matrix components collagen being a main substrate. MMPs involves processes like embryogenesis and implantation, wound healing, inflammatory states, tumor metastasis, angiogenesis and various other pathological conditions. MMPs can be inactivated through tissue inhibitors of metalloproteinases (TIMPs) [1].

The gelatinases MMP-2 and MMP-9 are especially involved in successful cytotrophoblast invasion in early pregnancy as they are considered key enzymes of degradation of basement membrane. Transcription and secretion are thought to increase in preparation for labor, resulting in cervical ripening, and dilation and subsequent rupture of the fetal membranes [2].

The amount and activity of MMP-2 and MMP-9 are increased in the aorta of normal pregnant rats, supporting a role of MMPs in pregnancy-associated vascular remodeling [3]. MMP-9 knockout mice show a phenotype mimicking preeclampsia [4]. Measurements of the plasma levels of MMPs have not been consistent in preeclampsia: some studies show an increase in serum levels of MMP-2 and MMP-9, whereas some studies show a decreased MMP-9 level [1]. Serum levels of MMP-2, MMP-9 and their inhibitors do not differ between pregnant woman with glucose intolerance as compared to healthy controls [5]. Serum imbalances between matrix metalloproteinases and their inhibitors have been detected in preterm labor [6]. The aim of the study was to investigate concentrations of circulating MMP-9, MMP-2/TIMP-2 complex and TIMP-1 during normal pregnancy.

Main Text

The study was conducted in Oulu University Hospital in the department of Obstetrics and Gynecology. 13 patients were enrolled in this study. The patients who participate the study come to their first visit to maternity clinic in pregnancy week 10. They are also followed in weeks 15-16, 26-28 and 36-37. In every

visit blood samples were taken to assess matrix metalloproteinases. The method for analysis is described in detail our previous publication [2].

Patients median age was 31 (23-40). As shown on Table 1, median MMP-9 levels were 19 ng/ml on week 10, 15 ng/ml on week 15-16, 14 ng/ml on week 26-28 as well as week 36-37. For MMP-9, no marked changes were observed. For TIMP-1 median values were 212 ng/ml on week 10, 240 ng/ml on week 15-16, 209 ng/ml on week 26-28 and 196 ng/ml on week 36-37. For MMP-2/ TIMP-2 complex, the values were 199 ng/ml on week 10, 191 ng/ml on week 15-16, 204 ng/ml on week 26-28 and 233 ng/ml on week 36-37.

Table 1
Comparison of TIMP-1, MMP-2/TIMP2 and MMP-9 in maternal serum

Protein	n	Pregnancy week 10 (n=18)	Pregnancy weeks 15-16 (n=31)	Pregnancy weeks 26-28 (n=27)	Pregnancy weeks 36-37 (n=24)
TIMP-1	33	212 (204-313)	240 (164-288)	208 (151-269)	196 (85-291)
MMP-2-TIMP-2	33	199 (106-269)	191 (89-235)	204 (102-246)	233 (110-329)
MMP-9	34	19 (14-26)	15 (8-26)	14 (6-42)	14 (8-64)
Results are expressed as median (range) (ng/ml).					

Conclusion

Our results show no marked changes when measured MMP-9, TIMP-1 and MMP-2/TIMP-2 serum levels on different time points during normal pregnancy. The levels of MMP-2/TIMP-2 complex increased from pregnancy weeks 15-16 forward but the difference is not statistically significant. An increased TIMP-2 level on women with a history of recurrent pregnancy loss has been observed [6]. Few studies have investigated MMPs or TIMPs in maternal serum. Lakowska [7] reported that decreased MMP-9 levels may be involved on pathological processes during pregnancy such as intrauterine growth restriction (IUGR) and preeclampsia, but the results are not matched on pregnancy week. On the other hand, during pregnancy the blood volume increases so that may mix the results. Several different tissues contribute to systemic levels of serum markers and local expression levels are likely to vary. Our observations may suggest that cytokine changes during pregnancy are not always reflected in maternal circulation which is in line with data from animal models indicating that that alterations in cytokine profiles are strictly compartmentalized and independently regulated [1]. Matrix metalloproteinases participate embryo

implantation, trophoblast invasion, and placentation in early gestation and later in gestation in cervical dilatation and fetal-maternal membrane lysis and have critical roles on various stages of pregnancy [1].

Limitations

There are only few studies how serum levels of matrix metalloproteinases and their tissue inhibitors change during normal pregnancy. The contribution of reproductive tract tissue to serum levels of MMPs and TIMPs during pregnancy is unknown. The main limitation in this study is our small sample size, which may not reflect the activity on these markers on gravid reproductive tract tissues very well. Future studies are needed.

Abbreviations

MMPs	matrix metalloproteinases
MMP-9	matrix metalloproteinase 9
MMP-2	matrix metalloproteinase 2
TIMP-1	issue inhibitor of matrix metalloproteinase 1
TIMP-2	tissue inhibitor of matrix metalloproteinase 2
IUGR	intrauterine growth restriction

Declarations

Ethics approval and consent to participate

The Ethical Committee of North Ostrobothnia´s Hospital (PPSHP, 3358298) has approved this study. Samples were taken in accordance with the Helsinki Declaration. Before participation, informed consent was taken from all patients.

Consent for publication

Written informed consent was obtained

Availability of supporting data

All data generated in the present study is available from the authors on reasonable request.

Competing interest

Authors declare no competing interest.

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Authors`contributions

ATM designed study, MS conducted the research and RN analyzed the data and wrote the article. All authors read and approved the final manuscript.

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