# 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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**Short communication**

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# Abstract

Background 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.

Methods 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.

Conclusions The serum levels of MMP-9, MMP-2/TIMP-2 and TIMP-1 on different time points during normal pregnancy are poorly studied. 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.

# Methods And Results

The study was conducted in Oulu University Hospital at 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). | | | | | |

# Concluding Remarks

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 [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]. However, 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 and our relatively small material may not reflect the activity on these markers on gravid reproductive tract tissues. Future studies are needed.

# Abbreviations

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

# Declarations


### Acknowledgements

Not applicable


### Ethics approval and consent to participate

The Ethical Committee of Norther Ostrobothnia Hospital has approved this study and written informed consent was obtained from all patients. Samples were taken in accordance with the Helsinki Declaration.

### Consent for publication

Not applicable

### Availability of supporting data

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

### Competing interest

Authors declare no competing interest.

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### Authors`contributions

ATM designed the 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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### Declarations

Ethical Committee of Oulu University Hospital has approved this study. Before participation, informed consent was taken from all patients. All authors agree for sending this manuscript to “Reproductive Biology and Endocrinology”. Availability to all data and materials are obtained on request. We have no competing interests, University of Oulu funded the laboratory costs. Anne Talvensaari-Mattila and Markku Santala analysed and collected the material and Ritva Nissi wrote the article.

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