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The Role Of Matrix Metalloproteinases (MMPS) In The Female Reproductive System - Review Article

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ABSTRACT

Matrix metalloproteinases comprise of several endopeptidases which have certain roles in physiological and pathological processes within various body parts. It has been suggested that their role is very important in endometriosis, recurrent implant failure, infertility and even gynecological malignancies. Therefore, we searched Pubmed in order to summarize already known data upon MMPs within female genital tract and 48 articles were included. It seems that matrix metalloproteinases might have role in the treatment of endometriosis and recurrent implantation failure as well as they could serve as markers in women with gynecological malignancies. However, there is a wide heterogeneity among so far published studies and results, and also among applied techniques. Further research of the role of specific MMPs is needed to verify the results.

Keywords: matrix metalloproteinases; endopeptidases; markers; female reproductive system; gynecological health

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INTRODUCTION

Matrix metalloproteinases (MMPs) are a group of endopeptidases that are involved in numerous developmental and disease-related processes. They are a part of physiological and pathological tissue remodeling processes, such as bone development, vascular remodeling, wound healing and cancer, inflammation etc. [1]. In humans, the group of MMPs comprises of 28 enzymes divided into six groups, based on their substrate specificities. These are: collagenases (MMP-1, 8, and 13), gelatinases (MMP-2 and 9), stromelysins (MMP-3, 10, and 11), matrilysins (MMP-7), metalloelastase (MMP-12), and membrane type-MMPs. Their activity is regulated by several groups of inhibitors, such as tissue inhibitors of metalloproteinases (TIMP). TIMP family comprises of four members. For physiologic tissue function, it is important that the activity of TIMP and MMPs is balanced [2, 3].

In the last few years, the activity of MMPs' has been investigated in various conditions. The aim of this article was to give an overview of MMPs' role in physiological and pathological conditions of the female reproductive system.

MATERIALS AND METHODS

Pubmed we searched in order to summarize already known data upon MMPs within female genital tract and 48 articles were included.

DISCUSSION

Physiological conditions of the female reproductive system

Menstrual cycle

MMPs have important role in haemostasis, development of blood vessels and endometrium. They are crucial for regular endometrial changes during menstrual cycle-proliferation, secretion, exfoliation and re-epithelisation [4,5]. Changes in the secretion of estradiol and progesteron directly influence activity of MMPs [6].

The expression of MMP 8 and MMP 12 in the endometrium was first reported by Goffin et al. [7], using reverse transcription-polymerase reaction. Their expression during the menstrual phase coincides with infiltration of inflammatory cells, particularly neutrophils, eosinophils, and macrophages, that are known to produce these enzymes [8].

The highest stromal and peri-arterial activity during menstrual bleeding is governed by MMP-1, MMP-3, MMP-8, MMP-9, and MMP-12. Expression of MMP-1, -2, -3, -7 and -9, and TIMP-1 and -2 produced by endometral cells is proven by use of immunocytochemistry [9,10] and in situ hybridization [10,11]. MMPs' activity in both stromal and vascular compartments at the beginning of menstruation indicates that bleeding results from degradation of both stromal components and vascular walls.

It has been shown that the expression of TIMPs is elevated in the first days of menstrual bleeding, which suggests TIMP involvement in limiting the process of tissue exfoliation and the forthcoming endometrium regeneration [6].

This expression and functions of MMPs and TIMPs in vascular structures is also found in other phases of menstrual cycle where they exhibit opposite functions. It seems that increased expression of MMP-2 and MMP-9 in the endometrial vessels during the proliferative and secretary periods is associated with vascular growth and angiogenesis. Conversely, expression of MMP-3 (stromelysin-1) in the vessels situated in the superficial endometrial layer during menstruation suggests that this metalloproteinase initiates vascular wall damage during menstrual breakdown. Finally, the finding of strong expression of TIMP-1 and TIMP-2 in the vessels during the menstruation where they separate necrotic from non-necrotic areas, might suggest that they reduce tissue damage and allow regeneration of endometrium [12].

Pregnancy

MMPs play an important role in early pregnancy by controlling endometrial cells' differentiation and decidual transformation, the key factors for implantation and development of placenta [4,5]. Unlike other adult tissues where the expression of MMPs is very low, their activity is significantly pronounced during the processes of active tissue remodeling. Results from the literature obtained in a mouse model implicate activity of MMP-3, TIMP-1, and MMP-10 during uterine extracellular matrix (ECM) remodeling[13].Proteolytic abilities of MMPs are regulated by gene transcription, zymogen activation, and specific inhibition by physiologic tissue inhibitors (TIMPs). Therefore, MMP inhibitors show potential as useful blockers of endometrial remodeling and bleeding [14, 15]. Also, some results from the literature implicate that MMP-9 gene polymorphism is associated with increased lumbopelvic pain-intensity during pregnancy, due to tissue remodelling mechanism [16].

Non-complicated vaginal delivery and lowered uterus

Matrix metalloproteinase 9 (MMP-9) is considered as a key vaginal elastase. High activity of MMP-9 in swabs of vaginal epithelial cells in first trimester of pregnancy correlates with non-complicated vaginal delivery, as shown by Oliphant et al. [17].Also, MMP-9 activity has been shown to increase postpartum. The same authors have shown that women with higher activity of MMP-9 postpartum experience better recovery and more acute vaginal angulation relative to the levator plate, when compared with women with lower activity of MMP-9 during pregnancy and postpartum, who experienced complicated delivery and did not fully recover vaginal angulation [18].

Pathological conditions of the female reproductive system

Preterm birth

The association of MMP and/or TIMP gene polymorphism and pregnancy complications regarding spontaneous preterm birth[19-21] and preterm premature rupture of membranes[19, 22]has also been investigated in the literature. It seems that gene polymorphism for MMP-9 increases the risk for preterm birth, as shown by different authors[21, 22]. Frey et al.[19] have found that genetic variations in genome regions for MMP-1 and MMP-2 increase the risk for preterm birth earlier than 34 weeks. On the contrary, Pereza et al.[20] have not found enough evidence that gene polymorphisms for MMP-1 and MMP-9 is correlated with spontaneous preterm birth, while Erzincan et al. [23]have not find a correlation of MMP-2 level in second-trimester amniotic fluid with adverse pregnancy outcomes.

Recurrent implantation failure

Many studies have investigated the role of matrix metalloproteinases in embryo implantation, but the exact roles and levels of activity of MMPs in each step of embryo implantation are not yet known. Embryo implantation consist of three steps, apposition, adhesion of the blastocyst to the endometrial epithelium, and invasion of the endometrium by trophoblast cells. It is still unknown which MMP is the most important for this process.

The best-studied MMP in embryo implantation is MMP-9. Vu et al.[24] have shown that MMP-9 is a key regulator of invasive mechanism of cytotropfoblast cells in vitro. During the invasive process, trophoblast cells secrete many proMMPs, mainly proMMP-2 and proMMP-9 and thus enable migration through matrix environment. In response, decidual cells produce high amount of TIMPs to inhibit MMP activity. Specific MMP/TIMP balance is very important for controlling the invasion and successful implantation[25].

Since recurrent implantation failure (RIF) is one of the major causes of infertility in assisted reproduction treatment (ART), few studies have focused on the MMPs role in ART and their relation with RIF. The results from Pereza et al.[26] implicate that gene polymorphism for MMP-2 and MMP-9 might be associated with idiopathic recurrent spontaneous abortions. On the contrary, Singh et al.[27] have not found a correlation of maternal gene polymorphism for MMP-9 and idiopathic recurrent spontaneous abortions. Yoshii et al.[28] have shown elevated levels of activity of the gelatinases MMP-2 and MMP-9 in the uterine flushing fluid of women with RIF, relative to fertile women. They have proven that reducing MMPs activity by the use of antibiotics and corticosteroids can improve implantation in RIF women. Similar results have been presented

byInagaki et al.[29], who have shown significantly higher activity of MMP-2 and MMP-9 in women with RIF relative to control group. On the contrary, Konac et al.[30] have observed a significant decrease in the endometrial expression of MMP-2 and TIMP-3 during the late secretary phase in women with RIF and unexplained infertility in regard to fertile women.

Endometriosis

MMPs activity is considered to be crucial in early stages of endometriosis development. Results from the literature implicate that MMP-9 is very important for development of endometriosis[31-34]. Its levels and activity have been increased in this condition, particularly at advanced stages of the disease[35]. Liu et al.[34] have found that MMP-9 concentrations are higher in the plasma and peritoneal fluids of patients with endometriosis than in those of healthy women. Yang et al.[33] suggested that MMP-9 could be involved in the tissue growth and breakdown cycle that occurs during endometriosis, enabling the migration and dissemination of endometrial cells outside the uterus.

On the contrary, Syzmanowski et al.[36] did not find any statistical difference in endometrial expression of MMP-2, MMP-9, TIMP-1, and TGF-β2 between women with endometriosis and without visible signs of this illness.

Infections of the female reproductive system

Intrauterine infection during pregnancy initiates inflammatory process. This activates MMPs which can cause premature labor, as shown by Goldenberg et al.[37]. Literature results show that the levels of MMP-3 and MMP-9 are elevated in amniotic fluid and fetal membranes[38, 39], and the levels of MMP-2 and MMP-3 in placenta are higher in women delivering preterm birth[40].Also, Singh et al.[41] have shown that Chlamydia trachomatis-infected females which have had recurrent spontaneous abortions have significant up regulation of MMP-2/MMP-9 and decreased TIMP-1/TIMP-3.

Some authors have investigated the expression of different MMPs in Fallopian tubes (FT) during infection with Neisseria gonorrhoeae. Juica NE et al.[42] have noticed a significant increase of MMP-8 expression, while the expression of MMP-3, MMP-8, MMP-9 and TIMP-1 was not significantly changed. On the contrary, Rodas et al.[43] have noticed significantly increased levels of secreted MMP-9 in FT epithelial cells, during gonococcal infection.

Endometrial and ovarian tumors

Several MMPs have been investigated in patophysiology of endometrial and ovarian tumors[44, 45], since it is known that these enzymes degrade extracellular matrix components which serve as a barrier in tumor metastasis, together with the basement membrane. It is known that matrix metalloproteinases have important roles in invasion and angiogenesis of different types of tumors, such as lung cancer, bladder cancer, laryngeal cancer, oral cancer or breast cancer[46-49].

There are some articles in the literature which have observed the expression of MMP-2 in ovarian cancer, using immunohistochemistry or *in situ* hibridization[50, 51]. The evidence have pointed out that the expression of MMP-2 in cancer cells is associated with significant reduction in overall survival rate, while the expression of MMP-2 in stromal cells has no impact on survival of patients with ovarian cancer[52].

Although there are some limitations among results from different studies, these results point out the potential of evaluating MMP-2 expression in cancer cells for therapeutic or prognostic purpose or assessment of the disease spread.

CONCLUSION

Elucidating the role of specific MMPs in different physiological and pathological conditions of female reproductive system could lead to numerous health benefits. Inhibition or limitation of their activity in certain pathological conditions may be adequate therapy, for example in endometriosis or recurrent implantation

failure. Some MMPs show potential as cancer markers which could be applied in prognostic and therapeutic purposes in women with gynecological malignancies.

REFERENCES

[1] Nagase H Visse, R., Murphy, G.Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res. 2006; 69:562-573.

[2] Kleine DE, Stetler-Stevenson W.G.Structural biochemistry and activation of matrix metalloproteases. Curr Opin Cell Biol. 1993, 5:891-897.

[3] Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003;92(8):827-839.

[4] Werb Z. ECM and cell surface proteolysis: regulating cellular ecology. Cell. 1997; 91:439–442.

[5] Henriet P, Cornet PB, Lemoine P, Galant C, Singer CF, Courtoy PJ, Eeckhout Y, Marbaix E. Circulating ovarian steroids and endometrial matrix metalloproteinases (MMPs). Ann N Y Acad Sci. 2002; 955: 119 - 138.

[6] Grzechocińska B, Dąbrowski F, Cyganek A, Panek G, Wielgoś M. The role of metalloproteinases in endometrial remodelling during menstrual cycle. Ginekol Pol. 2017;88(6):337-342.

[7] Goffin F, Munaut C, Frankenne F, Perrier D'Hauterive S, Béliard A, Fridman V, Nervo P, Colige A, Foidart JM. Expression pattern of metalloproteinases and tissue inhibitors of matrix-metalloproteinases in cycling human endometrium. Biol Reprod. 2003;69(3):976-84.

[8] Salamonsen LA, Lathbury LJ. Endometrial leukocytes and menstruation. Hum Reprod Update. 2000; 6:16–27.

[9] Martelli M, Campana A and Bischof P. Secretion of matrix metalloproteinases by human endometrial cells in vitro. J Reprod Fertil. 1993; 98:67–76.

[10] Rodgers WH, Osteen KG, Matrisiann LM, Navre M, Giudice LC , Gorstein F. Expression and localization of matrilysin, a matrix metalloproteinase, in human endometrium during the reproductive cycle Am J Obstet Gynecol.1993; 168: 253–260.

[11] Hampton AL, Salamonsen LA (1994). Expression of messenger ribonucleic acid encoding matrix metalloproteinases and their tissue inhibitors is related to menstruation. J Endocrinol. 1994:141:1-3.

[12] Freitas S, Meduri G, Le Nestour E, Bausero P and Perrot-Applanat M. Expression of metalloproteinases and their inhibitors in blood vessels in human endometrium Biol Reprod.1999; 61(4):1070–1082.

[13] Lombardi A, Makieva S, Rinaldi SF, Arcuri F, Petraglia F, Norman JE. Expression of Matrix Metalloproteinases in the Mouse Uterus and Human Myometrium During Pregnancy, Labor, and Preterm Labor. Reprod Sci. 2018;25(6):938-949.

[14] Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem. 1999;274:21491–21494.

[15] Gomez DE, Alonso DF, Yoshiji H, Thorgeirsson UP. Tissue inhibitors of metalloproteinases: structure, regulation and biological functions. Eur J Cell Biol. 1997;74:111–122.

[16] Mahmood AK, Moen A, Stafne SN, Robinson HS, Vøllestad NK, Salvesen KÅ, Mørkved S, Gjerstad J. The MMP9 rs17576 A>G polymorphism is associated with increased lumbopelvic pain-intensity in pregnant women. Scand J Pain. 2018;18(1):93-98.

[17] Oliphant S, Canavan T, Palcsey Stacy, Meyn L, Moalli P. Pregnancy and parturition negatively impact vaginal angle and alter expression of vaginal MMP-9. Am J Obstet Gynecol. 2018; 218: ex-x.ex.

[18] Oliphant S, Nygaard NE, Zong W, Canavan TP, Moalli PA. Maternal adaptations in preparation for parturition predict uncomplicated spontaneous delivery outcome. Am J Obstet Gynecol. 2014; 211: 630.

[19] Frey HA, Stout MJ, Pearson LN, Tuuli MG, Cahill AG, Strauss 3rd RF, Gomez IM, Parry S, Allsworth JE, Macones GA. Genetic variation associated with preterm birth in African-American women. Am J Obstet Gynecol Scand. 2016; 215:235.

[20] Pereza N, Plesa I, Peterlin A, Jan Z, Tul N, Kapovic M, Ostojic S, Peterlin B. Functional polymorphisms of matrix metalloproteinases 1 and 9 genes in women with spontaneous preterm birth. Dis Markers. 2014; 171036.

[21] Jones NM, Holzman C, Tian Y, Witkin SS, Genc M, Friderici K, Fisher R, Sezen D, Babula O, Jernigan KA, Chung K, Wirth J. Innate immune system gene polymorphisms in maternal and child genotype and risk of preterm delivery. J Matern Fetal Neonatal Med. 2012; 25:240-247.

[22] Fang X, Li H, Diao Y, Shan R, Dong J, Li H, Ma Q, Hou Y, Kong B, Cui J. Polymorphisms in the MTHRF, VDR, MMP-9 and IL-genes and the risk of premature rupture of membranes. Gynecol Obstet Investig. 2010; 70: 206-214.

[23] Erzincan SG, Varol FG, Inan C, Sayin NC. Relationship between second-trimester amniotic fluid levels of Prokineticin-1 and Matrix Metalloproteinase-2 with adverse pregnancy outcome. Placenta. 2018;62:25-27.
[24] Vu TH, Shipley JM, Bergers G, Berger JE, Helms JA, Hanahan D, Shapiro SD, Senior RM, Werb Z. MMP-9/gelatinase B is a key regulator of growth plate angiogenesis and apoptosis of hypertrophic chondrocytes. Cell. 1998;93(3):411-22.
[25] Cohen M, Meisser A, Haenggeli L, Bischof P. Involvement of MAPK pathway in TNF-alpha-induced MMP-9 expression in human trophoblastic cells. Mol Hum Reprod. 2006;12(4):225-32.
[26] Pereza N, Ostojic S, Volk M, Kapovic M, Peterlin B. Matrix metalloproteinases 1, 2, 3 and 9 functional single-nucleotide polymorphisms in idiopathic recurrent spontaneous abortion. Reprod Biomed Online. 2012; 24: 567-575.
[27] Singh K, Nair RR, Khanna A. Functional SNP-1562C/T in the promoter region of MMP9 and recurrent early pregnancy loss. Reprod Biomed Online. 2016; 24:61-65.
[28] Yoshii N, Hamatani T, Inagaki N, Hosaka T, Inoue O, Yamada M, Machiya R, Yoshimura Y, Odawara Y. Successful implantation after reducing matrix metalloproteinase activity in the uterine cavity. Reprod Biol Endocrinol. 2013;11:37.
[29] Inagaki N, Stern C, McBain J, Lopata A, Kornman L, Wilkinson D. Analysis of intra-uterine cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed embryo transfer. Hum Reprod. 2003;18(3):608-15.
[30] Konac E, Alp E, Onen HI, Korucuoglu U, Biri AA, Menevse S. Endometrial mRNA expression of matrix metalloproteinases, their tissue inhibitors and cell adhesion molecules in unexplained infertility and implantation failure patients. Reprod Biomed Online. 2009;19(3):391-7.
[31] Sillem M, Prifti S, Neher M, Runnebaum B. Extracellular matrix remodelling in the endometrium and its possible relevance to the pathogenesis of endometriosis. Hum Reprod Update. 1998; 4(5):730– 5.
[32] Liu H, Wang J, Wang H, Tang N, Li Y, Zhang Y, et al. Correlation between matrix metalloproteinase-9 and endometriosis. IntJ Clin ExpPathol. 2015; 8(10):13399–404.
[33] Yang M, Jiang C, Chen H, Nian Y, Bai Z, Ha C. The involvement of osteopontin and matrix metalloproteinase- 9 in the migration of endometrial epithelial cells in patients with endometriosis. Reproductive biology and endocrinology: RB&E. 2015; 13:95.
[34] Liu H, Wang J, Wang H, Tang N, Li Y, Zhang Y, et al. The plasma and peritoneal fluid concentrations of matrix metalloproteinase-9 are elevated in patients with endometriosis. Ann Clin Biochem. 2016; 53:599–605.
[35] Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nature medicine. 2015; 21(8):938–45.
[36] Szymanowski K, Mikołajczyk M, Wirstlein P, Dera-Szymanowska A. Matrix metalloproteinase-2 (MMP-2), MMP-9, tissue inhibitor of matrix metalloproteinases (TIMP-1) and transforming growth factor-b2 (TGF-b2) expression in eutopic endometrium of women with peritoneal endometriosis. Ann Agric Environ Med. 2016; 23(4): 649–653.
[37] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
[38] Maymon E, Romero R, Pacora P, Gervasi MT, Gomez R. Evidence of in vivo differential bioavailability of the active forms of matrix metalloproteinases 9 and 2 in parturition, spontaneous rupture of membranes, and intraamniotic infection. Am J Obstet Gynecol. 2000;183(4):887-894.
[39] Fortunato SJ, Menon R, Lombardi SJ. Stromelysins in placental membranes and amniotic fluid with premature rupture of membranes. Obstet Gynecol. 1999;94(3):435-440.
[40] Sundrani D, Chavan-Gautam P, Pisal H, Mehendale S, Joshi S. Matrix metalloproteinases-2, -3 and tissue inhibitors of metalloproteinases-1, -2 in placentas from preterm pregnancies and their association with one-carbon metabolites. Reproduction. 2013;145(4):401-410.
[41] Singh N, Prasad P, Das B, Rastogi S. Involvement of matrix metalloproteinases and their inhibitors in endometrial extracellular matrix turnover in Chlamydia trachomatis-infected recurrent spontaneous aborters. Pathog Dis. 2017;75(1).
[42] Juica NE, Rodas PI, Solar P, Borda P, Vargas R, Muñoz C, Paredes R, Christodoulides M, Velasquez LA. Neisseria gonorrhoeae Challenge Increases Matrix Metalloproteinase-8 Expression in Fallopian Tube Explants.Front Cell Infect Microbiol. 2017;7:399.
[43] Rodas PI, Perez D, Jaffret C, Gonzalez Y, Carreño C, Tapia C, et al. Modified profile of matrix metalloproteinase-2 and -9 production by human fallopian tube epithelial cells indection in vitro with Neisseria gonorrhoeae. J Infect Dis. 2017; 215:452–455.

[44] Fu Z, Xu S, Xu Y, et al. The expression of tumor-derived and stromal-derived matrix metalloproteinase 2 predicted prognosis of ovarian cancer. Int J Gynecol Cancer. 2015;25:356–62.
[45] Cymbaluk-Ploska A, Chudecka-Glaz A, Pius-Sadowska E, et al. Clinical importance of serum HE4 and MMP2 levels in endometrial cancer patients. Onco Targets Ther. 2017;10:3169–75.
[46] Liu RR, Li MD, Li T, et al. Matrix metalloproteinase 2 (MMP2) protein expression and laryngeal cancer prognosis: a meta analysis. Int J Clin Exp Med. 2015;8:2261–6.
[47] Chen Y, Wang X, Chen G, et al. The impact of matrix metalloproteinase 2 on prognosis and clinicopathology of breast cancer patients: a systematic meta-analysis. PLoS One. 2015;10:e0121404.
[48] Cao C, Xu N, Zheng X, et al. Elevated expression of MMP-2 and TIMP-2 cooperatively correlates with risk of lung cancer. Oncotarget. 2017;8:80560–7.
[49] Ikebe T, Shinohara M, Takeuchi H, et al. Gelatinolytic activity of matrix metalloproteinase in tumor tissues correlates with the invasiveness of oral cancer. Clin Exp Metastasis. 1999;17:315–23.
[50] Davidson B, Goldberg I, Berner A, Nesland JM, Givant-Horwitz V, Bryne M, Risberg B, Kristensen GB, Tropé CG, Kopolovic J, Reich R. Expression of membrane-type 1, 2, and 3 matrix metalloproteinases messenger RNA in ovarian carcinoma cells in serous effusions. Am J Clin Pathol. 2001;115(4):517-24.
[51] Davidson B, Goldberg I, Gotlieb WH, Kopolovic J, Ben-Baruch G, Nesland JM, Berner A, Bryne M, Reich R. High levels of MMP-2, MMP-9, MT1-MMP and TIMP-2 mRNA correlate with poor survival in ovarian carcinoma. Clin Exp Metastasis. 1999;17(10):799-808.
[52] Ziyi F, Sujuan X, Ye X, Jiehua M, Jingyun L, Pengfei X. The expression of Tumor-Derived and Stromal-Derived Matrix Metalloproteinase 2 Predicted Prognosis of Ovarian Cancer. Int J Gynecol Cancer. 2015;25: 356-362.