

# The role of metalloproteinases in endometrial remodelling during menstrual cycle

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## ABSTRACT

Endometrium is the only tissue in the human body subject to cyclic transformations under the influence of ovarian steroid hormones. As estradiol and progesterone balance throughout the physiological menstrual cycle changes, so does the expression of metalloproteinases (MMPs). These endopeptidases are responsible for keeping the balance between the process of synthesis and degradation of extracellular matrix proteins. Thus, MMPs take part in sustaining physiological stability of the endometrium. A number of MMPs found in the endometrial tissue and their activity is related to menstrual cycle phase. This paper is an up-to-date review of literature of Medline database. The search was conducted for key words including “matrix metalloproteinases”, “MMPs”, “TIMPs” and “tissue inhibitors of metalloproteinases”. Over 1092 publications regarding interdependence and interplay between ovarian hormones and the role of various MMPs and their inhibitors in normal endometrial remodelling and in pathological conditions were analysed and critically reviewed.

**Key words:** extracellular matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), endometrium, bleeding

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## INTRODUCTION

Endometrium is the only tissue in the female body subject to constant cyclic transformations. The function of hormones, especially estradiol and progesterone, is crucial for the proper course of such cyclic transformations. Changes in hormone excretion directly influence the release and activity of both metalloproteinases (MMPs, matrix metalloproteinases) as well as their tissue inhibitors (TIMPs).

MMPs are vital for the maintenance of physiological haemostasis, angiogenesis and proper endometrium development [1]. Its bioactivity regulates proliferation, endometrial cells' differentiation and decidual transformation. Some MMPs are involved in the activation of apoptosis and thus the onset of menstrual bleeding [2].

Expression of various MMPs in female endometrium is different throughout the menstrual cycle. Most MMPs yield maximal expression around menstruation time while in proliferative or secretive phase they remain undetectable. Expression of some other MMPs in turn remains constant throughout the whole menstrual cycle [3]. The course of endometrial transformation, proliferation, secretional changes,

exfoliation and finally re-growth, as well as coordination of such processes is directly dependent on MMPs and their inhibitors. A dozen different MMPs are involved and their expression is strongly influenced by sex hormones.

Yet, the interactions between the sex hormones and the activity of individual MMPs remain not well understood since most of the studies concern a pathophysiological role of MMPs while their regulating role in a normal tissue is rarely investigated. This review attempts to collect and summarize the results of studies that assess the endometrial changes in MMPs' expression in a physiological hormonal cycle and in some selected pathological conditions of female reproductive organs.

## METHODOLOGY

A Medline search for the following MeSH terms and key words was performed on January 31<sup>st</sup> 2017: “MMPs”, “matrix metalloproteinases”, “TIMPs” and “tissue inhibitors of metalloproteinases”. From over 1092 publications we selected those that concerned the interdependence of ovarian hormones on various MMPs and their inhibi-

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tors in normal endometrial remodelling or in pathological states. Such works were analysed and critically reviewed. MMPs are widely described in various fields of medicine, but surprisingly enough only a few studies assessed their role in endometrium shedding and remodelling. A more detailed cross-check for MeSH terms: "MMPs expression", "genetic factors" and "epigenetic factors" revealed 197 publications that investigated regulatory mechanisms responsible for changes in cellular membrane and extracellular matrix. Data here was analysed with a particular emphasis on processes occurring in female reproductive organs — both healthy and in pathological conditions.

### **The structure and function of matrix metalloproteinases and their tissue inhibitors**

MMPs are a group of enzymatic proteins with a proteolytic activity and they derive from endopeptidase family. In their structure they have a signal peptide responsible for a molecular transport through endoplasmic reticulum and a catalytic domain with a zinc molecule ( $Zn^{2+}$ ). This domain is responsible for functional proteolytic capacity of the enzyme [4].

Transcription genes regulate MMPs activity by three means: intracellular production of proenzymes, enzyme excretion and its extracellular activation.

Genes responsible for MMPs synthesis are regulated by many factors including steroid hormones, growth factors, cytokines and oncogenes [5]. It has been demonstrated that secretion of MMP-1, MMP-3 and MMP-9 is stimulated by  $TNF-\beta$  and interleukin-1. In contrast, MMP-2 is independent of such cytokines [6, 7].

MMPs are activated in tissue by proteases including plasmin, MMP-3 and MT-MMPs (membrane-type metalloproteinases) [8]. Proteolytic activity of MMPs depends on the type of tissue, local pH and the activity of MMP inhibitors and serine proteases [9].

In mature tissues MMPs have usually low concentrations. Their production and expression is increased during tissue reorganisation, inflammation or during a healing process. Most MMPs are activated outside of the cell by other active MMPs or by serine proteases except MMP-11, -14 and -28, which can be activated on the inside of the cell [10].

MMPs play an important role in the pathogenesis of diseases associated with structural changes of tissues. The term "metalloproteinases-dependent diseases" is used in various fields to describe such diseases including: multiple sclerosis, diabetes mellitus, ovarian and breast cancer or endometriosis, all of which share the pathomechanism that involves a deregulation of MMPs balance [11].

The activity of MMPs is also regulated by their tissue inhibitors (TIMP-1 to TIMP-4). It has been shown that they not only regulate MMPs activity, but also play an important

role in neoplasm growth stimulation, angiogenesis and apoptosis. Research on their function and their collateral interactions with MMPs is still on-going.

The molecule of TIMP is built out of two domains that form a complex of low molecular weight and small size. TIMPs have an inherent ability to bind to the active centre of a MMP molecule. The attachment of TIMP's N-terminal domain to the catalytic site of MMP disables the MMP's activity [12]. TIMPs inhibit both: the active forms of MMPs and their proenzymes, which translates to a better regulation of extracellular matrix. Their activity ensures balance between the processes of matrix synthesis and degradation [13].

The two major MMP inhibitors are TIMP-1 and TIMP-2. TIMP-1 is a glycoprotein with a molecular weight of 28 kDa and may be produced by most types of cells. TIMP-2 in turn is a soluble protein of 21 kDa synthesised by fibroblasts and endothelial cells only. TIMP-1 has a stronger affinity to MMP-9, whereas TIMP-2 exhibits selective affinity to MMP-2. TIMP-1 binds with inactive MMP-1, -2, -3, -9 while TIMP-2 binds with active forms of these MMPs, and also with an inactive form of MMP-2 [12]. An imbalance between active forms of enzymes and their inhibitors leads to connective tissue degradation.

### **Phases of reproductive cycle**

The occurrence of menstrual bleeding is normally caused by the decrease of circulating steroid hormones as their synthesis in the ovaries drops. In vitro studies show an important role that estradiol and progesterone have in determining the correlation between expression and inhibition of metalloproteinases' activity that happens mainly in tissues where collagen fibres were disrupted [3]. It has been reported that estradiol enhances the inhibitory effect of progesterone on both release and activity of collagenase [14].

Immunocytochemistry studies have shown that a physiological decrease in progesterone production or cessation of its administration in patients increase production and activity of some metalloproteinases, but has no influence on the expression of their inhibitors [15]. As a result metalloproteinases and their tissue inhibitors get out of balance. The predominance of active MMPs induces the degradation of collagen, which is closely connected with the beginning of menstrual bleeding [16].

The constriction of spiral arteries induced by prostaglandins causes regional endometrial ischemia and eventually arterial wall damage, which results in blood leakage and exfoliation of functional endometrial layer. This process starts right after the secretory phase and is induced by an active proteolysis process regulated by MMPs activity [17]. High expression of MMPs in the superficial surface of endometrium indicates their initiating role in the degradation of arterial wall during menstrual bleeding. Estradiol in contrast

**Table 1.** Expression of chosen MMPs and TIMPs in various menstrual cycle phases and their localisation in endometrium. According to Freitas S. (1999), Kokorine I. (1996), Marbaix E. (1996)

Premenstrual and menstrual phase	MMP-1 (stroma) MMP-3 (arteries, late secretory phase only, decreases along with menstrual bleeding) MMP-7 (epithelium, late secretory phase) MMP-8 (stroma) MMP-9 (stroma, early secretory phase only) MMP-10 (menstrual phase only) MMP-12 (stroma)
Proliferatory phase	MMP-7 (epithelium) MMP-11 (stroma) MMP-26 (epithelium)
Doesn't change during the menstrual cycle	MMP-2 (stroma, arteries, late secretory phase) MMP-19 (stroma, vascular endothelial and smooth muscle cells) TIMP-1 (stroma, arteries) TIMP-2 (stroma, arteries)

controls the structural changes of endometrium, especially its growth that begins just after menstrual bleeding. It drives the endometrial cell proliferation and angiogenesis.

Maintaining the balance between proteases and their inhibitors expression may play a fundamental role in cases of acyclic bleeding caused by numerous reasons including hormonal therapy or administration of contraception [2]. Paradoxically, MMPs also play a role in stopping of menstrual bleeding by influencing function of platelets. It has been shown that MMP-1, MMP-2, MMP-9 and MT1-MMP increase aggregation of platelets [18].

Expression of selected MMPs in relation to menstrual cycle phases and the area of MMPs activity is shown in Table 1.

### Collagenase (MMP-1)

The expression of MMP-1 in the stroma is increased during the primary menstrual bleeding period and is inversely related to sex steroid concentration and their receptors in epithelial cells. This applies especially to progesterone since the inhibitory effect of estradiol on MMP-1 expression remains quite weak. It was shown that stromal cells were stimulated to synthesize more MMP-1 in the setting of low steroid hormones concentration or scarce steroid receptors on the epithelial cell surface. This paracrine effect is mediated by interleukin-1 $\alpha$  and by tumour necrosis factor- $\alpha$ . Depending on the cycle phase, the expression of MMP-1 is restricted to superficial foci of stromal cells or extended towards the entire functional layer and correlates both with the disruption of fibrillary matrix and with menstrual bleeding [19].

### Stromelysin (MMP-3, MMP-10)

MMP-3 shows intensive expression in the stroma directly prior to menstruation (26<sup>th</sup>–28<sup>th</sup> day of the cycle). During the menstruation MMP-3 can be observed in the arteries. It degrades collagen type IV found in the basal lamina and

is expressed in the place of endometrial detachment so it may be lost with it [3]. This way the concentration decreases along with menstrual bleeding [20]. MMP-10 in turn expression was identified in stromal cells only during the menstrual phase of the reproductive cycle [21].

### Gelatinases (MMP-2, MMP-9)

MMP-2 is present in endometrium throughout the whole menstrual cycle playing a role in endometrium stabilisation [22]. High expression is observed mainly in arteries in late secretory phase and in menstrual phase and is negatively correlated with progesterone concentration [20]. A decrease in its concentration provokes a cyclic endometrial breakdown and onset of menstruation [23]. In vitro studies have shown that both MMP-2 synthesis and expression (smooth muscle cells of umbilical artery and coronal arteries) depends on 17 $\beta$ -estradiol concentration. At low concentrations MMP-2 prevents arteriosclerotic activity but its high concentration promotes vessel injury. This effect is inhibited by tamoxifen — an estrogen receptor inhibitor. It seems that a similar activity might also influence endometrial vessels [24]. This may be the reason why in patients receiving tamoxifen we often see thick endometrium with multiple vacuoles. MMP-2 also has a vasoconstrictive effect through its contribution to endothelin — a peptide important for maintenance of vascular homeostasis [25]. Recently it was confirmed that MMP-2 activity is increased in patients with cervical cancer [26].

A correlation between MMP-2 concentration and steroid hormones in serum and peritoneal fluid in women with endometriosis has been found. High concentration of estradiol up-regulates MMP-2 while progesterone decreases its activity.

MMP-9 expression in arterioles and stroma is cycle-phase dependent [7]. MMP-9 substrates are mainly elastin and collagen IV which is a major component of basal membranes. It

has been concluded that progesterone inhibits MMP-9 expression and increases TIMP-1 and TIMP-2 expression. The results of one study indicate that proMMP-9 is activated by MMP-26, which may influence endometrial tissue turnover [13]. Endometrial explant culture has shown that addition of estradiol and progesterone did not consistently affect total MMP-9 release but visibly reduced proMMP-9 [7]. This observation may indicate the potential role of hormones in regulation and cessation of menstrual bleeding. The mechanism of progesterone influence on MMP-9 expression is unknown. It has been observed that glandular MMP-9 production increases with a progesterone increase and is maintained when progesterone concentration decreases like before menstruation [7]. This observation may suggest the involvement of other mechanisms in regulation of MMP-9 levels. MMP-9 is highly expressed in endometrial glandules and endometrial stromal cells in women with levonorgestrel-containing intrauterine system [27]. Interestingly, MMP-9 expression is not detected after the 20<sup>th</sup> day of cycle [28]. Stettner et al. have shown that MMP-9 may play an important role in the invasiveness, progression and formation of metastases in several types of malignant gynaecological tumours [11].

#### **Collagenase (MMP-8) and metalloelastase (MMP-12)**

The expression of mRNAs for MMP-8 and MMP-12 was shown only during menstrual phase of the cycle and was correlated with the infiltration of functional layer by transient immune cells and induced by inflammatory cytokines [1].

#### **Matrilysins (MMP-7 and MMP-26)**

Matrilysins are the only metalloproteinases with their respective mRNAs localized in the epithelium [29]. MMP-7 is involved in the degradation of matrix components (i.e. fibronectin and gelatine), adhesive molecules (i.e. E-cadherin and pro-alpha defensin) and in the process of apoptosis. These changes are followed by the shedding of the functional layer of the endometrium and onset of menstruation [22]. It has been demonstrated that progesterone treatment can suppress directly or indirectly the MMP-7 gene and protein expression [30]. MMP-7 may also play a role in the pathogenesis of endometriosis since MMP-7 expression levels in the endometrial epithelial cells of patients with deep infiltrating endometriosis are significantly higher compared to less severe disease [31]. Cervical cancer cells are capable of producing large quantities of MMP-7 [26].

The other matrilysin — MMP-26 is structurally similar to MMP-7 but has a different biological function. Most probably it takes part in cellular proliferation, development of endometrial glands, growth of stroma and angiogenesis in preovulatory phase [32]. MMP-26 expression in the endo-

metrium is detected mainly in proliferative phase. During secretory phase of the endometrial cycle MMP-26 expression is low and in contrast to MMP-7 it does not increase with the decrease of progesterone concentrations [1]. The above-mentioned enzymes are probably not involved in endometrial cells apoptosis and endometrium exfoliation. MMP activity is controlled by the expression of their respective genes. Some recent publications investigate the role of epigenetic factors in the development of several pathological conditions like cancer and immune disorders [33].

#### **Tissue inhibitors (TIMPs)**

During early and mid-follicular phase the expression of TIMP-1 is predominantly found in the arterioles and capillaries while in the early luteal phase in smooth muscle of spiral arteries as well. During menstruation TIMP-1 activity is abundant in arterioles so to separate necrotic tissue from non-necrotic endometrium. The expression of TIMPs in the first days of the cycle indicates their involvement in limiting the process of tissue exfoliation and the forthcoming endometrium regeneration. Endometrial arterioles have strong expression of TIMP-1, whereas the expression of this enzyme in glands and stroma throughout the menstrual cycle and in the beginning of the cycle is similar [20]. Maintaining an appropriate balance between MMPs and TIMPs activities is important also for normal trophoblast implantation in physiological pregnancy [34].

#### **Membrane-type MMPs**

MT2-, 3-, 4- and 5-MMP expression, which is minimal during menstrual bleeding and maximal in early proliferation phase, advocates for its role in angiogenesis and endometrial reconstruction [35].

#### **MMP-19 (RASI 1)**

MMP-19 expression was found throughout the whole menstrual cycle and its vital role in angiogenesis has been well documented. The process of creating new vessels is closely related to normal endometrial cyclic changes [1].

#### **SUMMARY**

Various MMPs can be found in different parts of endometrium and their concentrations are cycle dependent. MMPs with the highest stromal and peri-arterial activity during menstrual bleeding are: MMP-1, MMP-3, MMP-8, MMP-9, and MMP-12. The highest expression of MMP-7, MMP-11 and MMP-26 in proliferative endometrium indicates their possible role in endometrial reconstruction and regeneration. Their expression is directly and indirectly dependent on progesterone and estradiol concentrations. MMP-2, MMP-19, TIMP-1, TIMP-2 and MT-MMP are expressed throughout the whole menstrual cycle and this observation indicates

their possible role in physiological endometrial stabilization. Knowledge of MMPs sites of synthesis, their role in cyclic endometrial transformation and the factors activating and inhibiting their expression allows a far better understanding of both physiological and pathological conditions such as endometriosis or dysfunctional uterine bleeding. Further investigation of MMPs and TIMPs interactions with the genetic and epigenetic factors that influence signalling pathways may allow to develop new drugs that would precisely and more effectively treat women affected by the before-mentioned conditions.

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### Conflict of interest

All authors report no conflict of interest concerning presented paper.

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