

## REVIEW ARTICLE

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## Molecular characterization of the endometrium as a fertility-determining factor

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### Abstract

**Background:** Structural transformation of the endometrium during the menstrual cycle is a genetically determined process and is provided by complex molecular-biological interactions aimed at the onset and development of pregnancy. Sex steroid hormones play a key role in endometrial morphogenesis, which mediate or directly affect angiogenesis and immunogenesis.

**Conclusions:** The primary function of the endometrium is to provide an immuno-privileged site for embryo implantation and to provide a nurturing environment for the fetus during pregnancy. The cyclic differentiation of the endometrium depends on the actions of steroid hormones that act through specific down – stream mechanisms involving complex molecular signaling. The endometrium undergoes repetitive episodes of proliferation, secretion, and menstruation, up to 400 times during a woman's life, without apparent signs of aging. The human endometrium undergoes complex and dynamic changes during the menstrual cycle. Thus, the combination of molecular, endocrine, biochemical, immunological factors leads to a complete transformation of the endometrium during the menstrual cycle. Secretory transformation of the endometrium with an appropriate ratio and distribution of estrogen and progesterone receptor expression, complete angiogenesis and immunological balance determine implantation, placentation and pregnancy development.

**Key words:** menstrual cycle, endometrium, angiogenesis, immunogenesis.

### Cite this article

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### Introduction

The endometrium has been an interest for scientists for decades, but its functional activity has yet to be discovered. In the endometrium, complex molecular interactions of biologically active substances take place in order to create optimal conditions for fulfilling its important function, implantation of the embryo and pregnancy development [1, 2, 3]. With the modernization of medicine, subsequently, the knowledge about the structure and functional activity of the endometrium has been detailed and extended. Proliferative and secretory transformation of the endometrium during the menstrual cycle is a genetically determined process based on the balance of the interaction of steroidogenesis, angiogenesis and immunogenesis in the endometrium, starting from the intrauterine development of the fetus [3-6].

### Ontogeny of the endometrium

Uterine embryo development begins in the fetus at 8–9 weeks of age. The glandular component of the endometrium comes from the mucosal epithelium of the Muller canals, the cells of the adjacent mesenchyme serve as a source of

endometrial stroma and uterine muscle layer. At the beginning of the development, the endometrium is represented by a small cylindrical epithelium, however, as the gestational age advances, the height of the endometrium increases, and from 18 weeks the formation of the first endometrial glands takes place. From 20 weeks of gestation, the active growth of the uterus is observed, which is associated with the development of receptors and the sensitivity of the organ to the mother's sex hormones, especially estrogens. From 24 weeks of pregnancy, the first signs of subnuclear vacuolization are observed in the endometrial epithelium, and the endometrium acquires the characteristics of a secretory tissue. Signs of well-defined secretion in the endometrium and endocervical epithelium are observed from the 28th week with a peak up to 35–36 weeks of gestation, when the placenta secretes estrogen and progesterone maximally [1, 7].

The endometrium, regardless of age, has a thickness of 0.5 to 1.5 mm, contains a significant number of cells (lymphocytes, fibroblasts, plasmocytes) and a small number of fibers. In the neonatal period, the glandular component of the endometrium is represented by glandular "divers", and only from the first year of life, the glands acquire the characteris-

tics of a typical structure and their number increases. Until puberty, a significant growth and branching of the glands is observed without increasing the thickness of the endometrium [1, 8].

### Menstrual cycle in the endometrium

With the onset of puberty, in the endometrium there is a cyclical cascade, complex of molecular and neuroimmunoenocrine interactions under the control of the hypothalamus-pituitary-ovarian axis, which leads to the appearance of the genetically determined menstrual cycle. The endometrium is a complex and interconnected system consisting of glandular epithelium, stroma and vascular component [9].

From the early stage of the proliferation phase to the late stage of the phase of secretion the gland epithelium and stromal cells are characterized by heterogeneity, which provides the processes of cell transformation. With the beginning of the proliferation phase, endometrial reepithelization begins from the process of migration of epithelial cells from the growing glands to the beginning of proliferative activity of stromal and epithelial cells. This process fully covers the entire wound surface of the uterus, and there is a rapid restoration of the functional layer [9-12].

The use of scanning electron microscopy of the menstrual endometrium showed that epithelial cells arise from stromal mesenchymal cells in desquamated areas, and not only from epithelial glands, which suggests reprogramming of endometrial stromal cells even in the phase of menstrual decay [13, 14]. In this case, mesenchymal cells change their characteristics and become epithelial cells, this process is known as the mesenchymal-epithelial transition (MET). Evidence for this hypothesis was obtained in an experiment in mice using the cytoskeleton protein pancytokeratin and the vimentin stromal cell marker. Significant changes in MET were detected in endometrial cells 24 hours after progesterone withdrawal [15, 16]. It was demonstrated the activation of proliferation processes in areas of damaged endometrial stroma under the influence of cytokeratin and osteopontin, similar to the MET process [16]. Therefore, it can be assumed that the basal layer of the endometrium promotes reepithelization of the desquamated surface.

There is a reverse MET process – the epithelial-mesenchymal transition (EMT), which is necessary for wound healing and the development of fibrosis [17]. The role of EMT in the endometrium remains unclear, but it is likely that the balance of EMT and MET is of great importance for the processes of full repair of the endometrium in the desquamation phase. Strict control of these factors in the endometrium enables the tissue to heal without scarring [18].

### Vascular remodeling and angiogenesis

Within the myometrium, the arcuate arteries arise from the uterine and ovarian arteries, which in turn give rise to radial arteries. After crossing the endometrial – myometrial junction, they branch to form the basal (anastomosing) and spiral (terminal) arteries. The former supply the basal layer and the latter the functional layer of the endometrium.

Branching of the spiral arteries occurs throughout the functional layer. Just below the surface they break up into a prominent subepithelial plexus, which drains into venous sinuses. Each spiral arteriole supplies tissue with an approximate endometrial surface area of 4 – 9 mm [19, 20].

Unlike other vascular beds, the endometrial vasculature undergoes cycles of growth and regression during the menstrual cycle [21]. The proliferative phase growth in endometrial thickness is accompanied by growth of the vascular tree [22]. By the middle of the late proliferative phase the sprouting terminal branches of the spiral arteries become somewhat coiled. By the middle of the secretory phase the spiral arteries ascend from the basal to the functional layer [20, 22].

There are two main mechanisms for the formation of new blood vessels: vasculogenesis, *de novo* development of vessels and angiogenesis, the creation of new microvessels from pre-existing vessels. Angiogenesis may occur by sprouting/branching or elongation, in addition, circulating endothelial cell progenitors may be incorporated into existing vasculature to contribute to these processes. For perfusion of growing tissue, adequate angiogenesis is required. Angiogenesis is thought to occur in three phases of the menstrual cycle: during menses, when vascular repair is occurring, during the proliferative phase, coinciding with the estrogen-driven rapid tissue growth, and during the secretory phase, associated with the elaboration of the spiral arterioles. Angiogenesis normally involves endothelial cell activation, degradation and breakdown of the basal lamina, migration and proliferation of the endothelial cells, fusion of sprouts, and tube formation. By the 5–6th day of the menstrual cycle, estradiol synthesis is increasing by growing follicles, which directly stimulates endometrial neovascularization by expression of angiopoietin-2 (Ang-2) in the endothelium. Estrogen does not significantly affect endometrial repair in the early stage of the proliferation phase. However, during the middle and late stages of the proliferation phase, when the main mechanism of angiogenesis is an increase in vessel length, estrogen, together with VEGF (vascular endothelial growth factor), synthesized by stromal cells, provides estrogen-dependent regeneration and increased vascular permeability [21, 23, 24]. In an experiment on animals undergoing ovariectomy, three peaks of the effect of VEGF on the endometrium were shown: in the early stage of the proliferation phase on the surface epithelium, in the middle stage of the proliferation phase on stromal fibroblasts and during the late stage of the secretion phase on the glandular component [23]. The significance of the vascular component in endometrial regeneration has been confirmed by studies of stromal growth factor (SDF-1) via pro-fibrotic CXCR4 or pro-regenerative CXCR7 receptors. Stromal growth factor (SDF-1) is present in all phases of the menstrual cycle, and CXCR4 expression is expressed in the early proliferative phase in both epithelial and endothelial cells [25].

The physiologic consequences of angiogenesis are reflected in changes in endometrial blood flow. By measuring the clearance of radioactive xenon gas, highest endometrial perfusion was reported between days 10 and 12 and days 21

and 26 of the cycle. Microvascular perfusion has been assessed by laser Doppler flowmetry with transvaginal placement of a fiberoptic probe into the uterine cavity. With use of this technique, endometrial perfusion was found to be highest during the proliferative phase and the early secretory phase, not too dissimilar from the finding based on xenon clearance. Uterine blood flow is greatest in the fundus, and higher flow rates are associated with better outcomes in assisted reproduction. Notably, diminished uterine blood flow has not been found in the perimenstrual period, but these methods cannot easily identify localized areas of vasoconstriction [26].

### Immunology of the endometrium

The uterus is an immunologically privileged organ: it can accommodate tissue invasion by immunologically semiforeign placental cells, yet maintain mucosal immune defenses against ascending foreign organisms, and provide a system to efficiently clear the endometrial detritus that results from menstruation. Remarkably, the endometrium also uses mechanisms of acute inflammation during normal, hormonally regulated physiologic processes, including menstruation and embryo implantation. These acute inflammatory episodes are quickly resolved, avoiding the consequence of scarring and dysfunction. Despite the description of critical active processes to resolve inflammation in other tissues and the clear relevance to endometrial physiology and pathophysiology, mechanisms that resolve endometrial remain largely unstudied [27-29].

The complex requirements of uterine immunity and tolerance use overlapping and redundant mechanisms dependent on both innate and adaptive branches of the immune system. The onset and development of pregnancy is inextricably linked with the presence of physiological and pathological inflammatory-immune reactions in the endometrium and directly in the nidation zone [30-32]. One of the important features of a woman's reproductive tract is the constancy of the physiological microbial population and the prevention of inflammatory reactions [33]. Endometrial immune processes, as with other uterine functions, but unlike those for other mucosal immune sites, are markedly influenced by cyclic and pregnancy-specific changes in sex steroid concentrations and possibly by human chorionic gonadotropin [34, 35].

The endometrium is populated by bone-marrow derived immune cells, as well as endometrial epithelial and stromal cells that demonstrate immune functions [36]. As is the case for many epithelial cells, endometrial epithelium express members of the Toll-like receptor family (TLR2 to 6, 9, and 10), which detect pathogen products and trigger a cellular response to these "foreign" molecules, including peptidoglycans from Gram positive bacteria (TLR2), lipopolysaccharide from Gram negative bacteria (TLR4), and unmethylated CpG islands found in bacterial DNA (TLR9) [33]. The endometrium also produces host defense molecules, defensins, as well as cytokines and chemokines. Uterine lymphoid and myeloid cells play roles in tissue defense, immune modulation, angiogenesis, and tissue remodeling [37-39]. These

cells are present in the fallopian tubes, uterus, and cervix, with the fallopian tubes and uterus containing a higher proportion of leukocytes than the cervix and vagina [40].

The endometrial innate and adaptive immune systems are regulated by steroid hormones. For example, progesterone induces a local Th2-type cytokine response in the uterus, which includes an increase in IL-4, IL-5, and IL-15 and downregulation of the IL-13 receptor  $\alpha 2$ , which is a negative regulator of the anti-inflammatory cytokine, IL-13, and powerful inhibitor of the Th2 response [35, 41, 42]. The Th2 response is believed to counter proinflammatory processes in the endometrium that could lead to rejection of the embryo. Steroid hormone-directed alterations in endometrial chemokine production influence the trafficking of blood leukocytes in the reproductive tract. Further, actions of progesterone are important in the overall immune suppressive phenotype adopted by the receptive endometrium [33, 43].

During the secretory phase, there is a profound recruitment of leukocytes into the endometrium starting in the perivascular locations around spiral arterioles and glandular epithelium [44]. The progesterone-induced alteration in endometrial cytokine/chemokine production contributes to this recruitment [40]. Cytokines IL-1, IL-11, IL-15, LIF, and TGF- $\beta$  regulate trafficking of leukocytes to the endometrium [44, 45]. IL-15 recruits NK cells into the endometrium, and IL-15 knockout mice lack NK cells. Locally acting prostaglandins (PG), including PGE along with VEGF, modulate vascular permeability [46-49]. Cyclooxygenase-2 (COX-2), a rate limiting enzyme that regulates the biosynthesis of PGE<sub>2</sub>, is critical to implantation in the mouse, and in animal models, PG are required for initiation and maintenance of decidualization. Blockade of COX-2 prevents decidualization in mice and clearly plays a role in endometrial function surrounding pregnancy, with reduced COX-2 associated with implantation failure [50-52].

The immune component of the mucous membrane of the female genital tract in different parts of the genital tract is represented by the predominant population of T cells, macrophages / dendritic cells, natural killer cells (NK), neutrophils and mast cells [33, 37]. Macrophages (CD68), plasmacytes (syndicans) and B cells are present in the endometrium at all stages of the menstrual cycle in small quantities. Also during the proliferative phase, syndicans induce angiogenesis [53, 54]. The basal layer of the endometrium contains true lymphoid follicles formed from germinal centers, the bright centers of which consist of B cells surrounded by T cells and an external halo of macrophages (CD14). In the late stage of the proliferation phase and in the phase of secretion, lymphoid follicles increase in size, with B cells expressing CD19 and T cells expressing almost exclusively CD8 and extremely rare CD4 [44].

In the functional layer of the endometrium of the proliferation phase, there are predominantly cytotoxic T-lymphocytes (CD8 +), which have increased cytolytic activity compared to the secretory phase of the cycle. Moreover, the suppression of the cytolytic activity of CD8 + is noted only in the secretory endometrium and fallopian tubes, in contrast to the cervix. The content of the number of cytotoxic

T-lymphocytes (CD8 +) and T-helpers (CD4 +) in the normal endometrium is up to 10 cells in the field of view, B-lymphocytes (CD20 +) up to 3 cells in the field of view [44]. An increase in the number of cells of cytotoxic T-lymphocytes, B-lymphocytes and the presence of plasmocytes (CD138 +) indicates the presence of chronic endometritis [46]. The process of decidualization of the endometrial stroma is characterized by a limiting effect on inflammatory processes in the functional layer, while the basal layer remains intact, which is crucial for effective reparative processes of the endometrium. In addition, progesterone blocks the activation of metalloproteinases (MMP) during the secretory phase of the cycle [55, 56].

The immunological cell composition of the endometrial secretory phase is represented by NK cells that express surface receptors CD56 +, CD16 +, CD3 + and are phenotypically different from peripheral blood NK cells. An increase in CD56 + during the middle stage of the secretion phase with predominantly periglandular and perivascular localization is associated with maintaining the immune tolerance of the mother's body to the onset and developing pregnancy [44, 56]. By the end of the secretion phase in the endometrium, the population of neutrophilic leukocytes increases significantly (up to 7–15%), which contain high levels of MMP for initiating endometrial decay. White blood cells do not have estrogen and progesterone receptors and penetrate the endometrium by chemotaxis in response to physiological and pathological inflammatory reactions in the tissue [44]. A feature of neutrophils in this period is resistance to apoptosis and hypoxia under the influence of inflammatory mediators, which enhances tissue damage [45, 46].

Progesterone, in addition to secretory transformations of the endometrium, also affects the contractility of the myometrium. A decrease in progesterone receptors expression in the late stage of the secretion phase leads to activation of the myometrium and an increase in contractile activity in the menstrual phase, while the level of progesterone in the blood serum does not correlate with the concentration of progesterone in the myometrium [12, 27, 28]. In the desquamation phase, an excessive or prolonged inflammatory response can lead to significant tissue damage and polymenorrhea, while the level of tumor necrosis factor and pro-inflammatory cytokines increases, and expression of cyclooxygenase-2 (COX-2) mRNA also increases [31]. 36 hours after the onset of menstruation in the endometrium, reparative processes begin. Thus, the combination of molecular, endocrine, biochemical, immunological factors leads to a complete transformation of the endometrium during the menstrual cycle.

An immunotolerance maternal immune response is essential for the acquisition of endometrial receptivity and the success of pregnancy [57]. Factors that support a more suppressed immune environment, including the recruitment of T regulatory cells (Tregs) and a shunting away from a pro-inflammatory, Th1/Th17 responses are central to our understanding of infertility and pregnancy loss associated with various inflammatory conditions.

## Conclusions

The human endometrium undergoes complex and dynamic changes during the menstrual cycle. Thus, the combination of molecular, endocrine, biochemical, immunological factors leads to a complete transformation of the endometrium during the menstrual cycle. Secretory transformation of the endometrium with an appropriate ratio and distribution of estrogen and progesterone receptor expression, complete angiogenesis and immunological balance determine implantation, placentation and pregnancy development.

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#### Authors' contributions

MB designed the trial and drafted the first manuscript. NC interpreted the data. VF revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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#### Ethics approval and consent to participate

No approval was required for this review study.

#### Conflict of Interests

No competing interests were disclosed.