REVIEW

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INFLUENCE OF MICROBIAL COLONIZATION OF THE ENDOMETRY ON ITS FUNCTION AND DEVELOPMENT OF HYPERPROLIFERATIVE CONDITIONS

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Abstract. The article provides an overview of literary sources that describe research on the microbiome of the endometrium in women of reproductive age. Thus, in many works, data is given indicating that the uterine cavity is not sterile. Various microorganisms can be found on the surface of the endometrium. So far, there is not enough research on microorganisms that can be considered a normal microbiome of the endometrium and its influence on the function and development of hyperproliferative processes of the endometrium in women. Many studies have proven the undoubted role of the uterine microbiome in the development of endometrial hyperplasia and other proliferative diseases. The cited studies indicate that 60 % of examined women with signs of microbial colonization caused by an infection of viral, bacterial, or fungal origin developed endometrial dysfunction, which led to the development of hyperproliferative processes. The study of the microbiocenosis of the uterine cavity in patients of reproductive age with various types of endometrial pathology indicates the role of certain pathogenic microflora in their occurrence. In all cases of atypical proliferation of the endometrium, an increase in the number of anaerobes up to 30 % was found among all isolated microorganisms, in particular, anaerobic bacteria of the genus Bacteroides spp. Representatives of the Enterobacteriaceae family (E. coli) and Gram-positive cocci (staphylococci and streptococci) prevailed among the aerobic flora. The largest spectrum of isolated microorganisms was found in patients with endometrial polyps. Studies of the immune system of the endometrium, which is formed to a greater extent due to the microbiome and directly participates in the cyclic changes of the endometrium, which are necessary for its physiological function during reproduction, are also presented. The immune system of the endometrium participates in the cyclic changes of the endometrium necessary for its physiological function in the process of reproduction. A proven factor is cells of the immune system and proper remodeling of spiral arteries, NK (neutrophil killer), T-lymphocytes and antigen-presenting cells (APC – antigen-presenting cell). A very important factor in the interaction between the gut microbiome and the immune system is the gut mucosa, and from this it can be inferred that similar connections may exist for the endometrium and its microbiome. Further studies of the state of the microbiome of the uterine cavity will allow adding information about its participation in functional processes and the pathogenesis of the development of hyperproliferative endometrial conditions.

KEY WORDS*: *endometrial hyperplasia, proliferative processes, endometrial microbiome, microbial colonization of uterus, the immune system of the endomet

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INTRODUCTION

Microbial colonization is significantly involved in the physiological functions of many organs, and changes in the microbiome can be accompanied by the development of various pathologies. In modern literature, there is a large number of publications and evidence that change the old opinion about the sterile environment of the uterine cavity. Microbial colonization of the endometrium and its metabolic activity is involved in various processes in the endometrium, important for the functioning of the endometrium and possibly for the normal development of pregnancy [1, 2]. Recent studies have investigated the relationship between the presence of bacteria in the uterus, the proliferative processes of the uterus, and reproductive difficulties and pregnancy complications [3, 4]. Most of the works are devoted to the relationship between the microbiome of the uterus and its influence on the immune system of the endometrium, which is an important factor in its proper function [5, 6]. It has been proven that bacteria can also affect the morphology of cells and tissue of the endometrium, and protect against the penetration and reproduction of pathogenic types of microorganisms. This makes the microbiome of the endometrium essential for the regeneration of the endometrium in the proliferative phase and the subsequent susceptibility of the endometrium to embryo implantation, as well as to the development of hyperproliferative processes [5, 7]. There are still few studies evaluating the influence of the endometrial microbiome on the development of endometrial hyperplasia, and there is very little useful information on the microbial colonization of the mucous membranes and their functions.

THE AIM OF THE STUDY

A literature review to study the impact of changes in the endometrial microbiome on its function and the development of endometrial hyperproliferative processes in women.

MATERIALS AND METHODS

Literature sources and patent search materials were used. Methods are applied: information-search, bibliographic, comparative analysis.

RESULTS AND THEIR DISCUSSION

At the general level, there is a certain relationship between microbes and humans, which is called symbiosis. A constant supply of nutrients is important for microbes, and the host uses the contribution of microbes for a number of physiological processes – homeostasis of epithelial cells, the function of the mucous membrane and a natural barrier against colonization by pathogenic bacteria.

Bacterial colonization also plays a significant role in modeling host immunity. Metagenomic analysis gave rise to extensive studies of natural colonization of the human body and demonstrated the presence of microbes in such cavities of the woman's body, which were initially considered completely sterile, until convincing evidence of colonization of the uterine mucosa in the absence of inflammation and other pathological changes was proven. The presence of microbes was often not noticed, or their presence was not paid attention to, because there were no effective methods of obtaining biological material from the uterus and preventing its contamination with the external environment. The frontier of research in this field has been the obtaining of samples and the technology to prove and identify all microorganisms present. Currently, there is a growing number of studies that provide important information about the endometrial microbiome [8–10].

A condition for a safe symbiosis between a host and a bacterium is the definition of a space for their growth – a niche – and compliance with a certain defined limit of their persistence. The penetration of microorganisms into host tissues must be limited in some way to prevent the transition from the saprophytic or opportunistic state of microorganisms to the development of an inflammatory reaction [11]. Three types of immunological barrier necessary for this homeostasis have been described:

− the anatomical layer of the endometrium, which prevents the penetration of bacteria;

− state of the immune system;

− protection mediators limiting direct contact between bacteria and epithelium;

− quick elimination of bacteria that penetrate through the barrier.

− In endometrium, all these requirements are currently met [12]. The undamaged

secretory endometrium is an anatomical barrier firmly connected to the myometrium for the penetration of bacteria into the underlying layers of the uterus.

Endometrium and endometrial fluid (EF – endometrial fluid) contain molecules of antimicrobial peptides (AMP – antimicrobial peptides). Their levels fluctuate during the menstrual cycle. One of the AMPs is an inhibitor of leukocyte secretion of proteases, which have a bactericidal effect on gram-negative bacteria (Escherichia coli) and gram-positive bacteria, such as (Staphylococcus aureus)[13–15].

Lymphocytes are present in the endometrium at all stages of the menstrual cycle, which can quickly respond to the invasion of microorganisms. Thus, the endometrium is a safe niche for symbiotic bacteria similar to the intestinal mucosa.

Standard studies used to identify the presence of bacteria in the uterine cavity are culture methods on specific media, which are mainly used in the diagnosis of inflammation.

However, for the qualitative and quantitative characterization of all types of bacteria in the microbiome, one culture method is not sufficient. This is due to the fact that the samples are most often dominated by aerobic microflora, which gives rapid growth, in contrast to those types of bacteria that grow slowly, which requires specific conditions for their cultivation. Molecular genetic methods gave a new impetus to the identification of various bacteria of the uterine cavity. Mitchell et al. [14] examined endometrial fluid samples by quantitative polymerase chain reaction (PCR) for the presence of 12 species of bacteria and demonstrated differences in their representation in the vaginal environment and endometrium. The presence of bacteria was detected in 95 % of the tested samples. Atopobium vaginae was more often detected in the vagina. Lactobacillus iners were present in the endometrial fluid. Further studies used FISH methods (fluorescent in-situ hybridization) or sequencing of the characteristic hypervariable region of 16S ribosomal RNA for certain species of bacteria [8].

Decidualization and transformation of the endometrium are influenced not only by cyclic changes of ovarian steroids, but also by cells and agents involved in the receptive state – the window of implantation, which is largely provided by the immune system. There are significant changes in endometrial stromal fibroblasts and epithelial cells, the cellular cytoskeleton changes and is modified with the construction of the plasma membrane. Changes in adhesion molecules – integrins and L-selectin ligands were proven (L-selectin ligands are present in the endometrial epithelium, L-selectin receptors are involved in blastocyst invasion and trophoblast formation). Analysis of the proteome of intrauterine secretion provides important information [5]. Already at this stage, disorders can arise that lead to abnormal vascularization of the placenta and subsequent pregnancy complications, preeclampsia and fetal growth restriction. Thus, the endometrium plays a key role for physiological placentation and the physiological course of pregnancy. The microbiome and its products can thus participate in the implantation and placentation of the embryo [4].

The immune system of the endometrium participates in the cyclic changes of the endometrium, which are necessary for its physiological function in the process of reproduction [15]. The proven factor is the cells of the immune system and the correct remodeling of spiral arteries, NK (neutrophil killer), T-lymphocytes and antigen-presenting cells (APC – antigen-presenting cells). A very important factor in the interaction between the gut microbiome and the immune system is the intestinal mucosa [16, 17], and possible analogous connections for the endometrium and its microbiome can be deduced from them.

Endometrial killer neutrophils (eNK) make up the majority of the immune system cells present in the endometrium - approximately 70 %. Phenotypically and functionally, eNK differ from natural killer cells of peripheral blood, decidual natural killer cells (DNA) [18]. The endometrium is dominated by eNK cells that do not produce cytolytic cytokines, only a very small proportion represents NK cells that destroy infected cells. DNA cells produce a large number of cytokines – for example, interleukin 10 (IL-10), tumor necrosis factor alpha (TNF-α), which can be involved in the initial implantation and formation of the placenta. eNK and DNA, as well as intestinal

NK cells, which are constantly exposed to the intestinal microbiome, differ from pbNK cells in that they do not produce cytotoxic perforins and other cytotoxic substances [19]. In particular, APC cells (antigen presenting cells). Macrophages and dendritic cells (DC - dendritic cells) make up approximately 10–20 % of endometrial leukocytes. ARS integrate individual stimuli, including microbial ones, and are key to initiating an adequate immune system response. During the menstrual cycle, the number of macrophages increases and reaches a peak at the end of the secretory phase. By producing LIF (leukemia inhibitor factor), they participate in the fucosylation of surface structures important for the establishment of the trophoderm, and thus for the receptivity of the endometrium. Macrophages present in the intestinal mucosa and exposed to the gut microbiome also differ in many functional parameters from peripheral blood macrophages. This was proven by a significant decrease in their ability to initiate an inflammatory reaction [20–22].

T cells represent another important cell fraction of the immune system present in the endometrium. Outside of pregnancy, they are stored in the deeper layers of the endometrium for the formation of the placenta shortly after implantation. There is also evidence that the microbiome influences the «tuning» of certain groups of T cells. One of the known vectors between the microbiome and T-lymphocytes of the host is polysaccharide A (PSA), obtained from the capsule of Bacteroides fragilis [23]. An important role is played by T-regulatory cells of the mucous membrane, which are involved in maintaining the homeostasis of the microbiome and increasing the tolerance of the local immune system. T-regulatory cells of the intestinal mucosa are activated by many commensals – for example, Lactobacillus, Bacteroides, Flexistipes, Clostridium. A similar mechanism can also be used to program the immune system of the endometrium in connection with implantation and placentation of the embryo [24].

Cytokines and chemokines produced by the immune system and endometrial cells are an important factor in the physiology of the menstrual cycle and the development of endometrial hyperplasia. In the second phase of the menstrual cycle, the number of pro-inflammatory Th1 cytokines IL-6, IL-8 and TNF-α increases, which lead to the activation of cells of the immune system and possibly participate in the secretory transformation of the endometrium. Chemokine CCL2 is also an important factor produced by endometrial stromal cells that attracts monocytes, T cells, and endometrial dendritic cells. Secretion of CCL2 has also been demonstrated in decidual cells obtained in the first trimester of pregnancy, where it ensures a local balance of T cells and dendritic cells [25, 26].

The microbiome has been shown to be an important factor in establishing baseline CCL2 production and induction of plasmacytoid dendritic cell homeostasis [22]. Mechanisms of innate and adaptive immunity are involved in maintaining the physiological balance between the presence of the microbiome and the activity of the immune system. It is necessary to maintain the border with the physiological microbiome and effectively eliminate pathogens [27]. The innate immune system includes PRR receptors (pattern recognition receptors), which are able to recognize characteristic features of microbes, pathogens – PAMPs (pathogen-associated molecular). PAMPs are most often cell wall molecules – lipopeptides, proteoglycans or lipopolysaccharides. PAMPs are derived from microorganisms and thus cause inflammation in response to infections. One well-known PAMP is lipopolysaccharide (LPS), which is found on the outer cell wall of gram-negative bacteria. DAMPs originate from host cells, including tumor cells, dead or dying cells, or products released from cells in response to signals such as hypoxia. Because DAMPs originate from host materials, they cause so-called sterile inflammatory responses. DAMPs are often generated or exposed in environments of trauma, ischemia, or tissue damage and do not require the presence of a pathogenic infection [27–29].

These environments are created in situations such as myocardial infarction, cancer, autoimmune diseases, and atherosclerosis. Toll-like receptors (TLRs), NOD-like receptors (NLRs) and C-type lectin receptors such as selectins, collectins and proteoglycans belong to the most famous PRRs [26]. TLR activation induces nuclear factor kappa-B, which initiates a cascade of inflammatory responses. PPDs form the first

line against STDs (sexually transmitted diseases) and other pathogens that can enter the uterus from the vaginal environment. Epithelial and stromal cells of the endometrium express numerous TLRs and other PRRs in contact, thus, with PAMPs can initiate an intense inflammatory process [27]. It has been shown that NLR and TLR are involved in the regulation of the microbiome and endometrium in the periconceptional period [26–29]. New discoveries in this area can contribute to improving the results of treatment of proliferative processes of the endometrium, as well as fertility disorders.

Stable colonization of commensal bacteria protects the host from pathogens because the physiological microbiome is better adapted to its niche than invasive pathogens. Commensal bacteria in their environment competitively reduce the amount of nutrients for pathogens, their mutual symbiosis prevents the penetration of pathogens into their niche. Commensal bacteria also stimulate TLRs and contribute to their ability to respond to PAMP possible pathogens [27]. By a similar mechanism, the endometrium can protect its microbiome. Another very important factor of protection is the layer of epithelial cells and its strength. An intact epithelium prevents the penetration of bacteria into the mucosal stroma and their contact with the immune system. Drawing an analogy with the intestinal microbiome, in which the microbiome affects the structure and differentiation of the intestinal epithelium, it can be assumed that the microbiome in the endometrium may also play an important role in supporting endometrial regeneration and the development of endometrial hyperplasia [24]. But this question needs more careful research. The main factor in the development of hyperplastic processes of the endometrium is disturbances in the hypothalamic-pituitary-ovarian system, which lead to absolute or relative hyperestrogeny and insufficient progesterone influence [4].

Proliferative changes persist in the endometrium, which, with long-term estrogen stimulation, acquire the character of hyperplasia. Also, endometrial hyperplasia can be the cause of the development of endometrial cancer, which is the most common gynecological malignancy [2,23–25]. In 20–25 % of cases, endometrial hyperplasia with atypia is the basis for the formation of malignant endometrial tumors, therefore, the study of all possible factors influencing the induction of endometrial proliferation is an urgent goal of modern research [5].

While estrogen stimulation is considered the main etiological risk factor for the development of endometrial hyperplasia, immunosuppression and infection may also be involved in the development of this condition [7,26–28].

It is believed that immune disorders that can lead to endometrial hyperplasia are caused by viral and bacterial infectious agents in more than 60 % of cases [8, 29].

The study of the microbiocenosis of the uterine cavity in patients of reproductive age with various types of endometrial pathology indicates the role of certain pathogenic microflora in their occurrence. In all cases of non-atypical proliferation of the endometrium, an increase in the number of anaerobes up to 30 % was found among all isolated microorganisms, in particular, anaerobic bacteria of the genus Bacteroides spp. Representatives of the Enterobacteriaceae family (E. coli) and Gram-positive cocci (staphylococci and streptococci) prevailed among the aerobic flora. Patients with endometrial polyps showed the largest spectrum of isolated microorganisms [2, 9].

CONCLUSION

Numerous studies testify to the important role of chronic persistence of infection in the development of endometrial hyperproliferative processes [2, 15].

It is believed that immune disorders that can lead to endometrial hyperplasia are caused by viral and bacterial infectious agents in more than 60 % of cases [16].

Proliferation always exists in the foci of inflammation as a protective compensatory mechanism that works until the complete destruction or eradication of the pathogenic agent. It has been proven that in the conditions of a long-term chronic inflammatory process, the cell-genetic apparatus is exhausted, which leads to atypia and malignancy [17, 18].

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ВПЛИВ МІКРОБНОЇ КОЛОНІЗАЦІЇ ЕНДОМЕТРІЯ НА ЙОГО ФУНКЦІЮ І РОЗВИТОК ГІПЕРПРОЛІФЕРАТИВНИХ СТАНІВ

A – концепція та дизайн дослідження; B – збір даних; C – аналіз та інтерпретація даних; D – написання статті; E – редагування статті;F – остаточне затвердження статті

Анотація. У статті наведено огляд літературних джерел, в яких викладені дослідження мікробіому ендометрію у жінок репродуктивного віку. Так, в багатьох роботах наведені дані, що вказують на те, що порожнина матки не є стерильною. На поверхні ендометрію можуть знаходитися різноманітні мікроорганізми. Поки що не має достатньо досліджень, щодо мікроорганізмів, які можна вважати нормальним мікробіомом ендометрію і його впливу на функцію та розвиток гіперпроліферативних процесів ендометрію у жінок. Багатьма дослідженнями доведено безсумнівну роль мікробіому матки на розвиток гіперплазії ендометрію й інших проліферативних захворювань. Приведені дослідження вказують, що у 60 % обстежених жінок з ознаками мікробної колонізації, викликаною інфекцією вірусного, бактеріального або грибкового походження, спостерігався розвиток дисфункції ендометрію, що призводив до розвитку гіперпроліферативних процесів. Вивчення мікробіоценозу порожнини матки у пацієнток репродуктивного віку з різними видами патології ендометрію вказує на роль певної патогенної мікрофлори в їх виникненні. У всіх випадках нетипової проліферації ендометрію виявлено збільшення кількості анаеробів до 30 % серед усіх виділених мікроорганізмів, зокрема анаеробних бактерій роду Bacteroides spp. Серед аеробної флори переважали представники родини Enterobacteriaceae (E. coli) та грампозитивні коки (стафілококи та стрептококи). У пацієнток з поліпами ендометрію виявлено найбільший спектр ізольованих мікроорганізмів. Також приведені дослідження імунної системи ендометрію, що формується більшою мірою за рахунок мікробіому і бере безпосередню участь в циклічних змінах ендометрію, що необхідні для його фізіологічної

функції в процесі відтворення. Імунна система ендометрія бере участь у циклічних змінах ендометрію, необхідних для його фізіологічної функції в процесі репродукції. Доведеним фактором є клітини імунної системи та правильне ремоделювання спіральних артерій, NK (нейтрофільний кілер), Т-лімфоцити та антигенпрезентуючі клітини (APC – antigen-presenting cell). Дуже важливим фактором у взаємодії між мікробіомом кишківника та імунною системою є слизова оболонка кишківника, і з неї можна зробити висновок про можливі аналогічні зв'язки для ендометрію та його мікробіому. Подальші дослідження стану мікробіому порожнини матки, дозволять доповнити інформацію щодо його участі в функціональних процесах та патогенезі розвитку гіперпроліферативних станів ендометрію.

КЛЮЧОВІ СЛОВА: *гіперплазія ендометрія, проліферативні процеси, мікробіом ендометрія, мікробна колонізація матки, імунна система ендометрія*

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