Impact of changes in the vaginal microbiome and chronic endometritis on the initiation of hyperplastic processes of the endometrium in women

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Abstract: the article presents a review of the literature, which examines the impact of changes in the vaginal microbiome and chronic endometritis on the development of hyperplastic processes of the endometrium in women. Many studies have proven the undoubted role of these factors in the development of endometrial hyperplastic processes, such as atypical hyperplasia and endometrial polyposis. Chronic endometritis, on the background of which there was a course of endometrial hyperplasia, in 95.1% of women studied was caused by an infection of viral, bacterial or fungal origin. Numerous studies indicate the important role of chronic persistent infection in the development of hyperproliferative processes of the endometrium. The largest role in the pathological process is probably played by bacteria of the genus Gardnerella viridans as well as gram-positive cocci (Streptococcus). Herpes simplex virus, cytomegalovirus, human papilloma virus and pathogenic fungi represented by the genus Candida also influence the occurrence of this process. Further studies of the pathological action of these microorganisms will achieve greater accuracy in the diagnosis of hyperplastic processes of the endometrium.

Key words: chronic endometritis, diagnosis, endometrial hyperplasia, infections, microbiota

Introduction
Endometrial hyperplasia is a benign pathology characterized by changes in the morphological structure of the endometrium in the form of excessive proliferation of glandular and, to a lesser extent, stromal components. According to the bulletin of the National Cancer Registry of Ukraine № 21 for 2018-2019, uterine cancer is characterized by a slight increase in both morbidity and mortality. The incidence of endometrial hyperplasia increases with age and is 133 cases per 100,000 patient-years. Endometrial hyperplasia is rare in women under 30 years of age and peaks at 50 to 54 years of age (McCluggage, Singh & Gilks, 2022). In 2014, the WHO modified the 1994 edition, leaving only 2 categories: (1) hyperplasia without atypia and (2) hyperplasia with atypia: atypical hyperplasia or intraepithelial endometrial neoplasia (IEN) (Kurman, Kaminski, & Norris, 1985; Raglan et al., 2019). In fact, up to 60% of patients with IES already have invasive endometrial cancer or will develop it in the future. Hyperplasia without atypia rarely progresses to endometrial cancer (1–3%) and is not characterized by such genetic mutations as the variant with atypia (Kurman et al., 1985; Vereshchagina, 2020).

The main factor in the development of endometrial hyperplastic processes is disorders in the hypothalamic-pituitary-ovarian system, which lead to absolute or relative hyperestrogenism and insufficiency of progesterone effects (Chaika,
Yaremchuk, & Karetna, 2017). In the endometrium, proliferative changes persist, which with long-term estrogenic stimulation acquire the character of hyperplasia. Endometrial hyperplasia can also be the cause of endometrial cancer, which is the most common gynecological malignancy (Armstrong et al., 2012; Eddib, Allaf, Lee, & Yeh, 2012; Kurman et al., 1985; Hui et al., 2021). In 20–25% of cases, endometrial hyperplasia with atypia is the basis for the formation of malignant endometrial tumors, so the study of all possible factors influencing the induction of endometrial proliferation is an urgent goal of modern research (Armstrong et al., 2012). While estrogen stimulation is considered a major etiological risk factor for endometrial hyperplasia, immunosuppression and infection may also be involved (Auclair et al., 2019; Eppele et al., 2008; Ricci et al., 2002; Sobczuk, & Sobczuk, 2017). It is believed that immune disorders, which can lead to endometrial hyperplasia, in more than 60% of cases are caused by viral and bacterial infectious agents (Allhorn et al., 2008; Bespoiasnaia, 1998; Tatarchuk et al., 2021).

Aim

Literature review to study the effect of changes in the microbiome of the vagina and chronic endometritis on the development of endometrial hyperplasia in women.

Materials and methods

References and materials of patent search are used. Methods used: information retrieval, bibliographic, comparative analysis.

Results and discussion

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 endometrial proliferation, an increase in the number of anaerobes to 30% was found among all isolated microorganisms, in particular anaerobic bacteria of the genus Bacteroides spp. The aerobic flora was dominated by members of the family Enterobacteriaceae (E. coli) and gram-positive cocci (staphylococci and streptococci). The largest spectrum of isolated microorganisms was demonstrated by patients with endometrial polyps (Akmetova, Belokrinitskaya, & Chartorizhskaya, 2009; Zhang et al., 2021; Walther-António et al, 2016).

Many studies indicate differences in the profile of the microbiome in women with endometrial polyps and chronic endometritis. An increase in the levels of Lactobacillus, Gardnerella, Bifidobacterium, Streptococcus and Alteromonas was found in these groups, compared with healthy patients. The hypothesis that the presence of a large number of lactobacilli indicates a violation of the cervical barrier in these pathological conditions (Dobbs, & McCluggage, 2007; Horban et al., 2019; Kelly, Peric et al., 2019; Nikitina et al., 2021).

Comparing the microbiomes of healthy women and patients with chronic endometritis and endometrial polyps. The authors (Garcia-Grau, Simon, & Moreno, 2019) showed such insights a significant increase in the taxa Lactobacillus (groups EP / CE and EP: 33.21% and 38.64%) and Desulfosporosinus (5.41% and 4.23%) in comparison with the control group (Fig. 1).

Fig.1 Relative number (percentage) of the 10 most common bacterial types (A) or genera (B) in 30 intrauterine microbiomes of healthy women (group H (I)), patients with endometrial polyp with (group EP / CE (I)) and without chronic endometritis (Group EP [I]), based on highly productive sequencing of 16S rRNA (Garcia-Grau et al., 2019).
Candida albicans has also been identified in studies of cervical mucus in patients with endometrial hyperplasia, which may promote proliferation because it develops against a background of reduced immunity, suppresses cellular and humoral immunity, and has the ability to bind estrogen, increasing tissue estrogen (Fang et al., 2016). Among viral infections, herpes simplex virus (HSV) and cytomegalovirus (CMV) play a significant role in the development of endometrial hyperplastic processes. In women with polyps of the uterine body, the presence of CMV in the uterine cavity was detected in 54.84 ± 6.32% of cases, in women with atypical endometrial hyperplasia - in 38.33 ± 6.28% of cases. Serum Ig G-Ab and Ig M-Ab levels to CMV clearly depend on the degree of antigen expression in endometrial tissue. HSV-2 antigens were detected in 22.58 ± 5.31% of women with uterine polyps and in 8.33 ± 3.57% of patients with atypical endometrial hyperplasia with elevated levels of specific serum antibodies to HSV-2.

This indicates a clear association between the target tissue viral infection (hyperproliferatively altered endometrium) and the determination of a positive level of peripheral blood immunoglobulin, which may be a reliable marker of chronic persistence of viral infection in women (Khanina, 2013; Nicolae, Preda, & Nogales, 2011).

Inflammatory viral diseases inhibit apoptosis, which allows viruses to complete the cycle of replication to cell death and accelerate the transformation of damaged cells (Gorban et al., 2020).

Numerous studies indicate the important role of chronic persistence of infection in the development of hyperproliferative processes of the endometrium (Khaskhachykh, Potapov, & Kukina, 2019).

It is believed that immune disorders, which can lead to endometrial hyperplasia, in more than 60% of cases are caused by viral and bacterial infectious agents (Haskhachih & Potapov, 2018; Nikitina et al., 2021; Sobczuk, Wrona, & Pertysiński, 2007).

Proliferation always exists in the foci of inflammation as a protective compensatory mechanism that acts until the complete destruction or eradication of the pathogen. It is proved that in the conditions of long-term chronic inflammatory process there is a depletion of the cellular-genetic apparatus, which leads to atypia and malignancy (Gromova & Afanasyeva, 2012).

Causes of infection of the mucous membrane of the uterus with subsequent provocation of the inflammatory process and its chronicity can be septic complications, birth trauma, manual revision of the uterine cavity and manual removal of manure, abortion, diagnostic scraping, hysterosalpingography, ie any intrauterine manipulation at promiscuity (Gromova et al., 2014).

Given the prevalence of endometrial hyperplastic processes in postmenopausal women, it is possible to assume that the cause is chronic inflammation of infectious etiology, which develops due to the violation of biological barriers. Infectious inflammation occurs in the form of a productive process with degenerative-proliferative changes and disruption of the processes of mitotic division of endometrial cells (The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia, 2015; Fallahi et al., 2017). Chronic endometritis, on the background of which the course of GPE occurred, in 95.1% of the studied women was caused by an infection of viral, bacterial or fungal origin (Goncharenko et al., 2013). It was found that more often than other cervical mucus, which was taken for analysis in all subjects without exception, contained human papilloma virus, cytomegalovirus, fungal infection caused by Candida albicans, and mixed infection (viral and bacterial at the same time). Viral infection was prevalent in women with atypical forms of hyperplastic processes (Chaplin, Rebrikov, & Boldyreva, 2015; Pelzer et al., 2018; Podolskyi, Lisyana, & Ponomaryova, 2017; Shalepo, Mikhaylenko, & Savicheva, 2016), due to the strong correlation between viral tissue infection, primarily human papilloma virus, and the presence of genetically transformed cells, confirmed by a number of studies, including that indicating tissue changes in estrogen-sensitive areas caused by the papilloma virus. Candida albicans was a fairly frequent “companion” of chronic endometritis in the studied women, which can also contribute to the development of GPE, because, firstly, it develops by existing already reduced immunity, and secondly, suppresses cellular and humoral immunity; in ad-
dition, it has the ability to bind estrogen, thereby increasing the estrogenic saturation of the tissue (Saprykina, Dobrokhotova, & Litvinova, 2011; Andrews et al., 2006; Cicinelli et al., 2014; Chaplin et al., 2017; The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia. 2015; Pelzer et al., 2018; Shalepo, Mikhaylenko, & Savicheva, 2016).

Conclusions
As a result of the study, it was found that changes in the vaginal microbiome and chronic inflammation affect the occurrence of endometrial hyperplasia. The largest role in the pathological process is probably played by bacteria of the genus Gardnerella viridans as well as gram-positive cocci (Streptococcus). Herpes simplex virus, cytomegalovirus, human papilloma virus and pathogenic fungi represented by the genus Candida also influence the occurrence of this process. Further studies of the pathological action of these microorganisms will achieve greater accuracy in the diagnosis of endometrial hyperplasia.

The influence of the presence of chronic endometritis in the initialization of endometrial hyperplasia in 95.1% is proved. The final proof of the role of pathogenic microflora as an etiological factor of hyperplastic processes of the uterine epithelium will prevent these diseases, or conduct etiotropic treatment in the early stages of their development.

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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

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Вплив мікробіому піхви та хронічного ендометриту на ініціалізацію гіперпластичних процесів ендометрію у жінок

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Анотація: у статті представлено огляд літератури, в якій досліджується вплив змін вагінального мікробіому та хронічного ендометриту на розвиток гіперпластичних процесів ендометрію у жінок. Багато досліджень довели безсумнівну роль цих факторів у розвитку гіперпластичних процесів ендометрію, таких як атипова гіперплазія та поліпоз ендометрію. Хронічний ендометрит, на тлі якого спостерігався перебіг гіперплазії ендометрію, у 95,1% досліджуваних жінок був викликаний інфекцією вірусного, бактеріального або грибкового походження. Численні дослідження вказують на важливу роль хронічної персистуючої інфекції у розвитку гіперпроліферативних процесів ендометрію. Найбільшу роль у патологічному процесі, ймовірно, відіграють бактерії роду Gardnerella viridans, а також грампозитивні коки (Streptococcus). На протікання цього процесу впливають також вірус простого герпесу, цитомегаловірус, вірус папіломи людини та патогенні гриби роду Candida. Подальші дослідження патологічної дії цих мікроорганізмів дозволять досягти більшої точності в діагностиці гіперпластичних процесів ендометрію.

Ключові слова: хронічний ендометрит, діагностика, гіперплазія ендометрію, інфекції, мікробіота.