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Endometrial Hyperplastic Processes, Pathogenesis and Modern Clinical Diagnostic Methods

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Abstract: Presents modern literature data on various aspects of the problem of endometrial hyperplastic processes. Some concepts of the development of this pathology are considered, information is provided on the risk of malignancy of various variants of endometrial hyperplastic processes and the main methods of treatment.

Keywords: endometrial hyperplasia, hyperestrogenism, chronic endometritis, methylation, progestogens.

Introduction:

Endometrial hyperplastic processes (EHP) are a very important, complex and multifaceted problem in practical gynecology. First of all, this is due to the fact that this pathology is one of the proliferative processes and, if left untreated for a long time, can become a background for the development of endometrial cancer.

According to clinical statistics, in recent years there has been a progressive increase in the incidence of endometrial cancer [13]. Every year, about 150,000 new cases of uterine cancer are diagnosed worldwide, and 42,000 women die from this tumor. The maximum incidence rate is observed in the age group of 65-69 years and is 68.7 cases per 100,000 women [13]. 20-25%

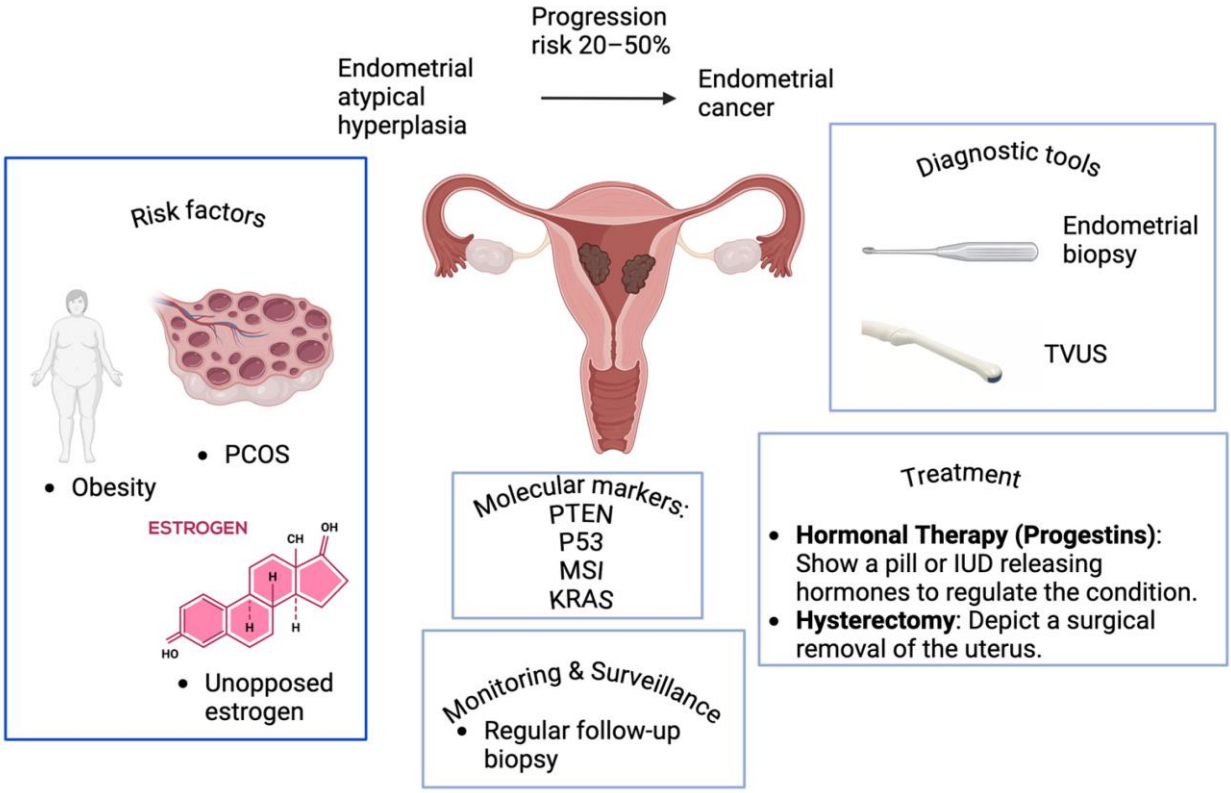
In 5% of cases, the disease is diagnosed in patients of reproductive age, and in 40% of cases, it is diagnosed in patients under 40 years of age.

Most morphologists, gynecologists, and oncologists consider endometrial cancer to be closely related to GPE.

In the structure of gynecological pathology, GPE occurs with a frequency of 15-40%. According to data on the incidence of GPE, the frequency of GPE varies from 10 to 30%, depending on its form and the age of the woman.

GPE is most often diagnosed between the ages of 45 and 55 [17]. According to some authors, GPE occurs in up to 50% of patients in the late reproductive and perimenopausal periods [24].

The question of the risk of developing malignant transformation of GPE remains open [21]. According to a number of studies, the degree of risk of malignancy of various variants of GPE is determined by the morphological state of the endometrium and depends primarily on the severity of cellular atypia and, to a lesser extent, on age, ovarian status, concomitant endocrine diseases and other factors [7, 12]. According to the WHO classification (1994), the following morphological forms of endometrial hyperplasia are distinguished [36, 40]: simple non-atypical endometrial hyperplasia; complex non-atypical endometrial hyperplasia; simple atypical endometrial hyperplasia; complex atypical endometrial hyperplasia; adenocarcinoma.



Simple endometrial hyperplasia is characterized by glands of various sizes and shapes, some of which have cystic dilatation. The mucous membrane of the glands corresponds to the proliferative phase of the cycle, although mitotic figures are very rare. The stroma is rich in cells. Such changes rarely become cancerous and often end with cystic atrophy, in which the epithelium and stroma are atrophic [7, 11, 14, 36].

In complex hyperplasia, the number and size of the glands increase. The characteristic features of complex hyperplasia are the convolutions and the close arrangement of the glands. Their lining is multi-row, multilayered, more pronounced than in simple hyperplasia, but the smooth contours of the gland lumens are preserved. There is no cellular atypia. However, malignancy is observed in more than 4% of cases [7, 11, 14, 36].

Research methods and materials:

In atypical hyperplasia, in addition to the changes described above, irregular internal contours of the glandular lining are detected. Stratification is highly developed, which is accompanied by the appearance of a scalloped silhouette of the lining. The pronounced atypia of epithelial cells is complemented by the loss of polar arrangement of cells, hyperchromatosis of some nuclei, prominent nucleoli, and an increase in the cytoplasmic ratio. Very large epithelial cells and mitotic figures are found [13, 21]. In endometrial scrapings, it is difficult to distinguish atypical hyperplasia from well-differentiated adenocarcinoma [15].

According to a number of authors, approximately 23-32% of patients with atypical hyperplasia develop endometrial cancer [2, 7, 12]. According to other studies, atypical hyperplasia undergoes malignant transformation in almost 52% of cases [32]. In addition, a high frequency of foci of atypical hyperplasia and adenocarcinoma has been noted - 23.9-27% [31]. The risk of transformation of typical hyperplasia into atypical hyperplasia is 10.5%, and endometrial cancer is 2% [32]. Invasive cancer of the uterine body is observed in 20-30% of cases with recurrent endometrial hyperplasia [4].

Some authors combine simple and complex hyperplasia without atypia into one category - “hyperplasia”, and for atypical hyperplasia and adenocarcinoma they use the term “endometrial neoplasia” [35, 40].

The term "hyperplasia" refers to an increase in the number of cells, intracellular structures, and intercellular formations as a result of increased organ function or pathological neoplasm of tissues.

Endometrial hyperplasia is an abnormal proliferation of endometrial glands with irregular shape and size.

This pathology differs from typical manifestations of anovulation primarily in the degree and extent of histological changes in the endometrium [14].

Risk factors for the development of EHP include early menarche, late menopause, nulliparity, obesity, hyperlipidemia, non-insulin-dependent diabetes mellitus, menstrual irregularities due to anovulation, endocrine infertility, polycystic ovary syndrome, estrogen-producing hormonal tumors, and postmenopause [13, 28, 39].

One of the prerequisites for the development of GPE is relative or absolute hyperestrogenism. Hyperestrogenism occurs as a result of non-cyclic synthesis of estrogens in the ovaries; impaired regulation of estrogen secretion and their metabolism; increased sensitivity of endometrial receptors with normal or low secretion of estrogens; long-term treatment with high doses of estrogens [11, 12, 15, 29].

In patients with hormone-dependent tumors, the most pronounced disorders are observed in three homeostatic systems: reproductive, energy, and adaptive [15]. If the body weight does not exceed 23 kg above the norm, the risk of uterine cancer

3 times, and more than 23 kg - 10 times [13]. Adipose tissue becomes a source of endogenous estrone formation due to the aromatization of its precursor androstenedione, secreted by the adrenal glands, which leads to an increase in the estrogen pool in the body. Interacts with estrone receptors in target tissues (endometrium, mammary glands, colon)

It is mainly observed in menopausal patients. The source of chronic hyperestrogenism in the reproductive and perimenopausal periods is the follicular apparatus and hyperplastic stroma (theca tissue) of the ovaries [15].

According to modern understanding, hormones do not directly cause tumorigenic transformation of cells, since they do not change the basic structure of DNA [15]. At the same time, they create conditions in which the likelihood of cancer development increases under the influence of a real carcinogenic factor. There are at least three such conditions: an increase in the pool of proliferating cells, a weakening of antitumor immunity, and a decrease in the ability to repair DNA.

In most patients, GPE is not an independent disease, but a morphological sign of hyperestrogenism as a result of a benign tumor or early ovarian cancer. The occurrence of atypical hyperplasia and endometrial cancer in young women can be considered as a late complication of untreated polycystic ovary syndrome [5].

The presence of an active uterine estrogen receptor apparatus can lead to endometrial hyperplasia in conditions of relatively low estrogen levels [10].

However, research data on the possibility of developing endometrial hyperplasia in the absence of hormonal disorders suggest the existence of other mechanisms of endometrial hyperplasia formation associated with local disruption of the regulation of cell proliferation and local changes in tissue metabolism [23].

In addition to estrogens, activators of endometrial proliferative activity

are growth factors and proliferation markers required for genomic DNA replication [1 , 7 , 8].

In addition to systemic changes, adequate response of the endometrium to hormonal influences is of great importance in the formation of GPE. The role of disorders in the interaction of hormonal receptors in the development of GPE, which is modulated by specific cytoplasmic and nuclear

receptors, is widely discussed in the literature. These disorders in GPE may be associated with a deficiency of progesterone receptors in the cellular elements of the uterine mucosa [4, 11, 20, 21].

One of the key genetic abnormalities required for tumor development is the inactivation of tumor suppressor genes. Tumor suppressor and repair genes can be inactivated as a result of their structural damage (deletion and/or mutation) or functional damage (abnormal methylation) [22].

Methylation is a reversible covalent modification of DNA in which the cytosine residue in the CG dinucleotide is methylated at the N5 position of the pyrimidine ring. Methylation of cytosine residues is carried out by DNA methyltransferase enzymes, which transfer the methyl group of S-adenosyl methionine. This modification is the only chemical modification of DNA that is permitted under physiological conditions and

DNA is stably maintained over a number of cell divisions, provided by a whole family of methyltransferases.

Given that the nucleotide sequence of DNA does not change during methylation, this process

is a reversible phenomenon, unlike true DNA mutations, by the action of demethylating agents or enzymes [22, 30].

One of the most common and early mechanisms of tumor suppressor gene inactivation is the methylation of CpG islands in the promoter and regulatory regions of these genes. Abnormal methylation of CpG islands leads to the suppression of the function of tumor suppressor genes, the gene sequence is not changed, but it stops functioning [22, 27].

Studies have shown that recurrent endometrial hyperplasia and atypical hyperplasia have an increased frequency of methylation of hMLH1, RASSF1A genes [22, 26, 34, 38, 41] and a high frequency of methylation of p16, PTEN, RASSF1, 2, 3, 32, 32, RASSF1, 37, 38].

a) There is an opinion that GPE can be genetically determined. Glycoprotein

b) The GP-IIIa gene is expressed in two allelic forms - PL-AI and PL-AII. Therefore, each

c) a person can be a carrier of any form of the gene - homozygous (AIAI, AIIAII) or

d) the genotype can contain two alleles (AIAII) at the same time - heterozygous. The frequency of the AIAI genotype in the population

e) The incidence of AIAII is 73.1%, AIAII - 24.8%, and AIIAII homozygotes reaches 2.1% [6].

The frequency of GPIIIa glycoprotein gene polymorphism in the presence of GPE, according to a number of studies, is as follows [6]: homozygotes of the PL-AI allele in women with glandular hyperplasia of the endometrium are 90.6%, with typical hyperplasia - 90.9%. In the group of patients with glandular hyperplasia of the endometrium, the carriage of the PL-AII allele was 9.4%, with atypical hyperplasia - 9%, which differs from the average population data. It is clear that the AI allele of the GP-IIIa gene determines the genetic predisposition to active implantation, and the carriage of the AII allele of the GP-IIIa gene can be considered as a genetic factor that prevents the development of GPE.

One of the important links in the etiopathogenesis of GPE is chronic endometritis [19]. In chronic endometritis, not only the proliferation of endometrial cells but also apoptosis increases,

The balance between these processes maintains tissue homeostasis. Tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF-β), produced by macrophages, play a major role in the mechanisms of apoptosis in chronic endometritis.

Development of pathological proliferation or atrophy of the endometrium in chronic endometritis possible when the balance between the opposing processes of proliferation and apoptosis is disrupted (especially against the background of viral infection) [19].

Diagnosis of GPE does not present any difficulties, but there are several controversial points. Recognition of pathological processes of the endometrium before the appearance of clinical symptoms is possible with color

It is possible with transvaginal echographic scanning in combination with Doppler mapping. There is a clear correlation between the thickness of the endometrium measured by ultrasound and the presence of endometrial pathology. The endometrium is assessed according to the results of a single linear measurement on the 5th-7th day of the menstrual cycle. An increase in the anteroposterior size of the M-echo to 7-9 mm in the entire or local area is considered pathological. The threshold for normal endometrial thickness in postmenopause is 5 mm [5, 11,16, 18]. If the true anteroposterior size is not determined, if there is deformation in the uterine cavity or if it is not possible to measure the thickness of the endometrium, the accuracy of detecting endometrial pathology decreases [18]. Cytological examination of aspirate from the uterine cavity is of high diagnostic value, but is not sufficient for a reliable diagnosis [5, 14, 16]. In cases of multiple localization of the pathological process in the uterine mucosa or the simultaneous presence of various types of endometrial hyperplasia, it is advisable to conduct a separate diagnostic curettage of the uterus under hysteroscopy with subsequent morphological examination of the diagnosis [5, 7, 14, 18]. However, curettage of the uterus does not always allow a complete study of the entire endometrium, since areas with cellular atypia may not reach the morphologist. In addition, the absence of histological signs of atypical hyperplasia or adenocarcinoma does not exclude the presence of a malignant process in the uterus if the clinical symptoms of the disease persist.

Results :

There are different types of endometrial pathology, and their differential diagnosis can be very difficult. An important factor in the diagnosis of GPE remains the high qualification of the pathologist.

Analysis of the literature shows that today various approaches are used in the treatment of GPE: removal of pathologically altered endometrium, hormonal therapy and surgical treatment. However, the lack of a single, generally accepted classification of GPE hinders a clear understanding of this pathological process and often leads to disagreements between clinicians and morphologists, which affects the choice of tactics for managing patients with GPE.

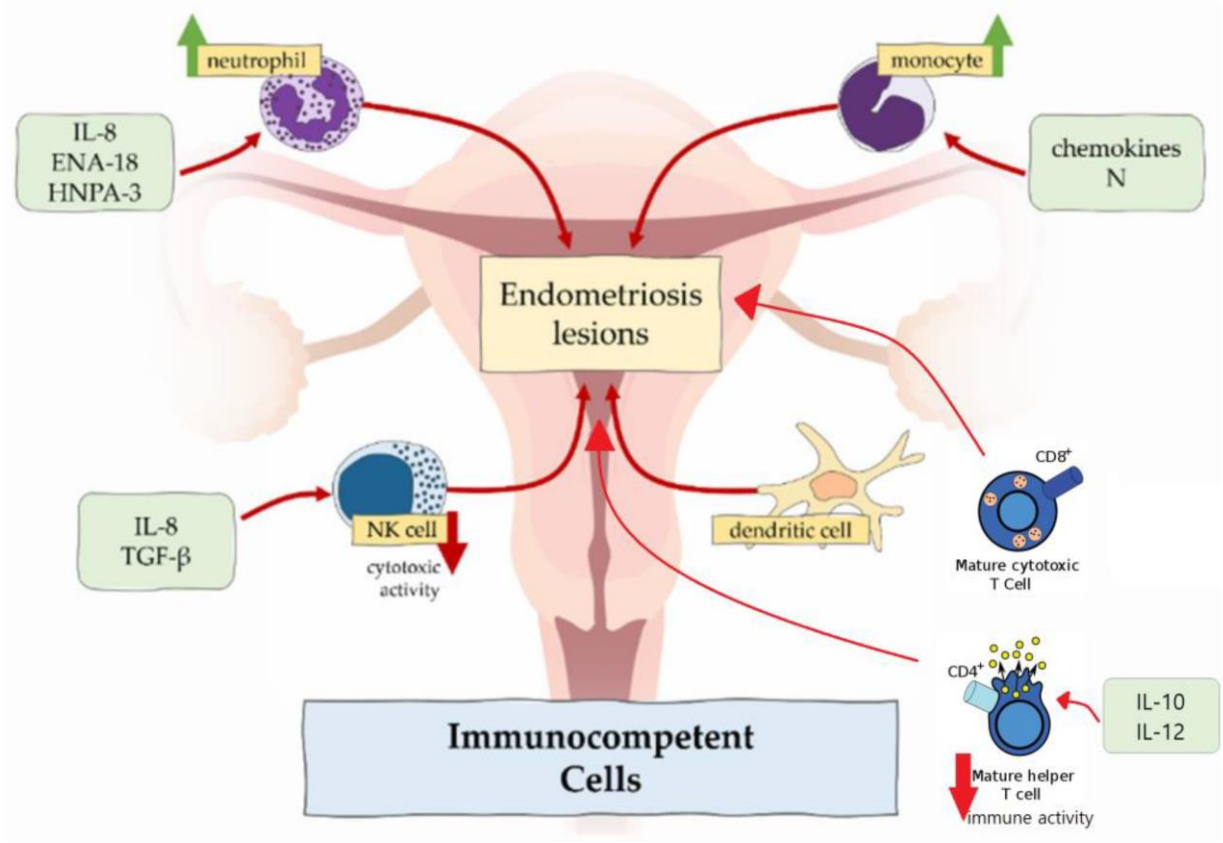
In the presence of GPE, treatment tactics are developed after morphological examination of the diagnosis and depend on the patient's age, the presence of concomitant gynecological pathology and extragenital diseases. One of the most common methods of treating GPE without atypia remains hormonal therapy.

The effectiveness of hormonal methods for the treatment of GPE without atypia, according to a number of studies, is low - 42% [9]. According to other data, only 26% of women who received hormonal treatment had a recurrence of GPE [11]. Several groups of drugs are used to treat GPE.

The ability of progestogens to induce endometrial regression has been demonstrated in numerous studies [5, 33]. One component of the therapeutic effect of progestogens may be the induction of apoptosis activity, which explains the significant reduction in glandular apparatus during successful treatment.

secretory changes in the endometrium and suppression of ovulation. Synthetic progestogens actively bind to estrogen and progesterone receptors in target organ tissues, i.e. have a direct antiestrogenic and antiprogesterone effect.

Dydrogesterone is a highly selective progestogen that binds specifically to the progesterone receptor. Biochemical studies [20] have shown that dydrogesterone has the highest binding energy for the progesterone receptor and the lowest binding energy (or does not bind at all) for other types of steroid receptors. In this regard, the clinical use of dydrogesterone is not only of therapeutic importance, but also practically does not cause side effects.



For the treatment of GPE, dydrogesterone is prescribed 10 mg 2 times a day for 6-12 months continuously. An important advantage of the drug dydrogesterone is the possibility of its use in the presence of GPE in patients with impaired endometrial receptor activity.

Discussions :

Progestins can be used in all forms of EHP. The morphological conclusion changes the choice of progestogen and the method of its administration. For atypical endometrial hyperplasia, medroxyprogesterone acetate (Depo-Provera) is prescribed, the dose and regimen are selected individually. The main effect of antiprogestins (gestrinone) is to affect the hypothalamic-pituitary system - suppressing the release of gonadotropins and slightly inhibiting their synthesis [11, 18]. Gonadotropin-releasing hormone agonists are successfully used as monotherapy for GPE. These drugs, acting on the pituitary-ovarian-endometrial system, cause temporary and reversible amenorrhea ("pseudomenopause") [11, 16, 20]. In addition, the drugs have an antiproliferative effect on endometrial cells by binding to specific receptors with high affinity for gonadotropin-releasing hormones.

Combined oral contraceptives (COCs) are the drugs of choice for the treatment of EHP in the reproductive period. The therapeutic effect of COCs is due to their ability to inhibit regression and early changes in endometrial glands, decidual changes in the stroma, and the development of spiral arterioles. The optimal course is 6-12 cycles of taking the drug according to the standard regimen (21 days, with a 7-day break).

GPE is a polyetiological disease, in its development not only

hormonal disorders, but also infectious and traumatic factors play an important role. In this regard, issues related to the treatment of chronic endometritis are widely discussed in the literature [20]. The first stage of complex treatment of chronic endometritis is aimed at eliminating the causative agent of the inflammatory process and reducing the activity of the viral infection. For this purpose, antibacterial and antiviral drugs are traditionally used in combination with immunostimulants.

Conclusion : The second stage of treatment of chronic endometritis is aimed at restoring the morphofunctional potential of tissues and eliminating metabolic disorders, the consequences of hypoxia, as well as restoring hemodynamics and the activity of the uterine receptor apparatus. For this purpose, actovegin is most often administered intramuscularly at 5 ml for 7-10 days, then switched to oral form at 1 tablet 3 times a day for 14-25 days. The antihypoxic effect begins to manifest itself 10-30 minutes after parenteral administration and reaches a maximum on average after 3 hours. Actovegin can also be administered intravenously at a dose of 5-10 ml for 3-5 days.

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