

### Hyperplastic Processes of the Endometrium: Issues of Ethiopathogenesis, Clinic, Diagnosis, Treatment

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#### ABSTRACT

Hyperplastic processes of the endometrium remain one of the most urgent problems of modern gynecology due to the steady increase in the incidence of endometrial cancer. Endometrial hyperplasia (EH) is a non-physiological proliferation of the endometrium, accompanied by a structural reorganization of the glandular and, to a lesser extent, stromal component of the endometrium against the background of excessive estrogen influence.

Currently, the following classification of changes in the endometrium is used (WHO, 1994):

- atypical GE (AGE) - proliferation of endometrial glands with signs of cytological atypia: - simple AGE; - complex, or complex AGE (adenomatosis with atypia). Separately, endometrial polyps (PE) are isolated.

Simple GE without atypia corresponds to glandular cystic hyperplasia in the previous classification. In this condition, the glands are enlarged, they can form cysts, there is practically no tortuosity, the number of glands is increased, but they do not form clusters, there is no cellular atypia. Complex, or complex HE without atypia corresponds to AGE I degree - it differs from simple HE in structural restructuring and proliferation of epithelial glands. Simple AGE corresponds to AGE of the II degree and is characterized by a pronounced proliferation of the glandular epithelium in the absence of signs of cellular and nuclear polymorphism; complex, or complex AGE is similar to grade III AGE, has signs of cellular and nuclear polymorphism along with disorganization of the epithelium of the endometrial glands. Etiology and pathogenesis

Pathological proliferation of endometrial cells can cause:

- dishormonal disorders (violation of the ratio between the content of progesterone and estrogen). The immediate cause of HE is absolute or relative hyperestrogenism, which occurs with ovulation disorders (anovulation, monophasic cycles). This pathology is more often observed in the pubertal and premenopausal periods, somewhat less often in women of reproductive age with unstable regulation of the functions of the reproductive system. A special role in the genesis of hyperestrogenism is assigned to excessive extragonadal production of estrogens (in adipose tissue). Hyperplastic processes in the endometrium are often observed in polycystic ovaries, namely in the secondary form of this pathology, which occurs in connection with dysfunctions of the hypothalamic structures and is accompanied by obesity;
- traumatic cell damage resulting in the formation of infiltrates consisting of macrophages, leukocytes, lymphocytes, etc., induce factors that stimulate the growth of the stroma, and proteolytic enzymes that destroy the extracellular matrix;
- inflammatory diseases that inhibit apoptosis, which accelerates the transformation of damaged cells. Based on the analysis of a large clinical material, a hypothesis was proposed about the mechanisms of the occurrence of endometrial hyperplastic processes in postmenopausal women.

After the onset of menopause, regular atrophic processes occur in the genital organs, while the biological barriers that prevent the penetration of the infectious agent into the uterine cavity are violated. As a result, chronic endometritis of infectious etiology may occur, especially in women who have suffered from prolonged or chronic inflammatory processes of the genital organs. Further development of infectious inflammation in the uterine cavity can take place in two ways. The first way is a destructive purulent inflammatory process, with pyometra often developing; the second is a long-term productive inflammatory process with degenerative-proliferative changes, disorders of mitosis processes in endometrial cells.

**Clinical picture** The clinical picture of GE is characterized by the so-called dysfunctional (anovulatory) uterine bleeding, which occurs, as a rule, after a delay in menstruation. Bleeding is usually prolonged with moderate blood loss or profuse profuse bleeding. The intensive nature of bleeding is often observed during anovulatory cycles during puberty (juvenile uterine bleeding), but can also be in women of reproductive and elderly age. Sometimes intermenstrual bleeding occurs. Endometrial hyperplasia is usually accompanied by infertility, the main cause of which is anovulation. In some patients, GE occurs with mild symptoms or asymptotically. As a combined pathology, uterine myoma, PE, adenomyosis, and mastopathy are often noted.

**Diagnosis** Ultrasound examination of the pelvic organs (outside of bleeding) is of great informative value. An increase in M-echo is the main prognostic marker of endometrial pathology. In menstruating women, the value of this indicator is determined by the phase of the menstrual cycle and normally reaches maximum values in the late stage of secretion - the peak of secretory transformations in the mucous membrane of the uterine body - 16 mm. GE is characterized by an increase in the echogram of the endometrium up to 2-3 cm. Recognition of GE is important for choosing a method of treatment and prevention of endometrial cancer. For the purpose of diagnosis, diagnostic curettage of the mucous membrane of the body of the uterus and subsequent histological examination of the material obtained are widely used. Endometrial scraping is recommended on the eve of the expected menstruation or at the very beginning of the appearance of spotting. In this case, it is necessary to remove the entire mucous membrane, including the area of the uterine fundus and uterine tubal angles, where foci of adenomatosis and polyps are often located. The practice of recent years shows a significant diagnostic value of

hysteroscopy. The method allows to detect GE in the form of a thickened, unevenly folded surface of the endometrium of a pale pink or red color. With focal HE, such changes are observed in the form of local foci. In polypoid GE, protrusions of the thickened endometrium fill the uterine cavity. The removed mucosa is sent for histological examination with an accompanying form, where information about the patient (age, complaints, main symptoms, nature of the menstrual cycle, duration of the disease, clinical diagnosis) is briefly stated, which helps the morphologist to correctly assess the histological data. Histological examination is the most reliable method for diagnosing HE and determining the nature of this pathology. During histological and histochemical studies, the activity of GE is also determined by the degree of mitotic activity of cells, the content of nucleic acids, and other parameters. Repeated curettage of the mucous membrane of the uterine body should be performed according to indications reasonably argued in each specific case (for example, control diagnostic curettage after completing a course of hormone therapy for adenomatosis and adenomatous polyps in women of reproductive age, recurrent bleeding in postmenopausal women, etc.). To control treatment, as well as in the order of screening examination of women (medical examination), a cytological method is used to study the contents of the uterus obtained by aspiration. Aspiration is carried out in the second half of the menstrual cycle in compliance with the rules of asepsis. If actively proliferating cells in the glandular complexes are found in the aspirate, then these findings indicate HE. However, the aspiration-cytological method does not give a clear idea of the nature of GE. Therefore, it is used mainly for the purpose of selecting patients for a more detailed study. Treatment

Treatment of HE is carried out taking into account numerous factors - the age of the patient, the causes of HE and the nature of this pathology, clinical manifestations, contraindications to a particular treatment method, tolerance of medications, concomitant extragenital and gynecological diseases. In the absence of contraindications to hormone therapy in patients of reproductive age with HE without atypia, it is possible to use combined oral contraceptives (CPC) - monophasic, with an estradiol content of 0.05 mg. Combined oral contraceptives are prescribed in a cyclic mode (21 days with a 7-day break) for at least 6 months. Progestins (dydrogesterone, less often natural micronized progesterone) are prescribed for patients with simple HE. The dosage regimen depends on the age of the patient. In the reproductive period - from the 16th to the 25th day of the menstrual cycle (10 mg of dydrogesterone 2 times a day or 200-300 mg of natural micronized progesterone 2 times a day). In premenopausal age - from the 5th to the 25th day of the menstrual cycle. Under the influence of gestagens in the endometrium, sequential inhibition of proliferative activity, secretory transformation of the mucosa, decidual reaction of the stroma occur, and with further use, atrophic changes in the glands and stroma.

The choice of drug depends on the age of the patient and the morphological state of the endometrium. In recent years, the possibility of using levonorgestrel contained in the intrauterine system for the treatment of uterine bleeding has been discussed. The mechanism for reducing menstrual blood loss is due to atrophy of the endometrium, a decrease in its vascularization, a decrease in the level of prostaglandins and inhibition of fibrinolytic activity. The use of a contraceptive hormonal agent is especially indicated for the category of women who raise the issue of contraception or, due to the state of homeostasis, need to minimize the systemic effects of progestins. Agonists of gonadotropic releasing hormones (aGnRH). Buserelin-long FS competitively binds to the receptors of the anterior pituitary gland, causing a short-term increase in the level of sex hormones in the blood plasma, then the drug leads to a complete reversible blockade of the gonadotropic function of the pituitary gland, thus inhibiting the release of luteinizing and follicle-stimulating hormones. As a result, suppression of the synthesis of sex hormones in the ovaries is observed, which is manifested by a decrease in the concentration of estradiol in the blood to a level corresponding to oophorectomy or postmenopause. The

concentration of estradiol remains low during the entire period of treatment, which leads to inhibition of growth and regression of hormone-dependent tumors. Buserelin-long FS provides a stable therapeutic effect with a single intramuscular injection once every 28 days at a dosage of 3.75 mg. The recommended duration of treatment is up to 6 months. In case of AGE in reproductive age, it is recommended to use Buserelin-long FS for 6 months, it is possible to prescribe medroxyprogesterone acetate 100 mg 3 times a week for 6 months in a continuous mode or 17-OPK at a dose of 250 mg 3 times a week in a continuous mode. With AGE in premenopause, surgical treatment is indicated - hysterectomy. However, in severe concomitant pathology, contraindications to surgery, it is possible to use intrauterine intervention - ablation or resection of the endometrium. At the same time, most researchers consider the onset of the uterine form of amenorrhea to be the criterion for the effectiveness of endosurgical treatment.

The use of Buserelin-long FS in preoperative hormonal preparation before endometrial ablation greatly facilitates the technique of the operation and improves its long-term results. Given the high responsibility for the life and health of the patient, organ-preserving treatment of patients with AHE should be performed in specialized oncological institutions and ensured by strict dynamic control. Endometrial polyps. Endometrial polyps are local benign tumors originating from the basal layer of the endometrium.

It is customary to distinguish the following forms of PE:

- 1) glandular, originating from the basal layer; consist of stroma and glands, the lumen of which can be expanded (glandular cystic PE);
- 2) glandular-fibrous PE, consisting of connective tissue stroma and a limited number of glands;
- 3) fibrous PE - connective tissue formations, which are often collagenized; glands are very few or absent.

Unlike GE, the estrogen dependence of polyps is questioned. In women of reproductive age, PE usually have a glandular structure. Fibrous PE are much less common, predominantly in older women. The issue of PE malignancy has not been clearly resolved. Glandular and glandular-fibrous PE are extremely rarely malignant, but can serve as a favorable background for the development of endometrial cancer. The clinical picture, despite the variety of forms of PE, has been studied quite fully. In most cases (12–56%), they are asymptomatic and are a diagnostic finding during screening ultrasound examination of the pelvic organs, but at the same time they occupy a leading place among the causes of postmenopausal uterine bleeding. The clinical manifestations of postmenopausal PE are usually bleeding (spotting to profuse). Large endometrial polyps may be accompanied by cramping pains in the lower abdomen. The question of the necessity and expediency of hormone therapy after polypectomy is still controversial. The type of hormonal therapy, the duration of treatment depend on the age of the patient, the morphological structure of the polyp, the nature of the comorbidity. At the same time, long-term hormonal therapy, given its side effects, is unacceptable for many patients. In the treatment of patients with PE, the same hormonal preparations are used as in other types of hyperplastic processes of the endometrium (CHC, progestins, aGnRH Buserelin-long FS). Prevention of endometrial hyperplastic processes - the use of PDA, timely treatment of the causes of anovulation and its clinical manifestations.

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