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ENDOMETRIAL HYPERPLASIA: YESTERDAY AND TODAY

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Resume. In the future, it is advisable to expand the understanding of the role of biomarkers in the diagnosis and dynamic monitoring of profile patients, to determine the optimal duration of treatment and possible timing of the resumption of menopausal hormone therapy after an episode of GE. It is also necessary to assess the impact of weight loss, including after bariatric surgery, and lifestyle changes on the frequency of relapses of the disease and the possibility of regression of hyperplasia.

Keywords. Women, endometrium, reproductive, hyperplasia,adenomyos.

Hyperplastic processes of the endometrium are one of the most common gynecological pathologies [1]. According to O. Ozdegirmenci et al., about 200,000 new cases of endometrial hyperplasia (GE) are registered annually in developed countries [2]. However, scientists believe that these indicators are significantly underestimated due to the lack of unified approaches to the statistical accounting of diseases.

According to the classification of the World Health Organization (WHO), proposed in 1994 and revised in 2003, there are four types of GE [3]: simple and complex with or without atypia. It should be noted that the classification has found wide application in clinical practice, but it is not without significant drawbacks. First of all, this is due to the significant variability of histological conclusions – depending on the experience of the pathologist, his subjective attitudes when analyzing histological material [3].

K.H. Allison et al. [4] found that when analyzing histological sections by several pathologists, the frequency of coincidence of diagnoses in the absence of endometrial hyperplasia is 90.3%, with simple hyperplasia – 31.1%, with complex hyperplasia – 51.1%, with atypical – 49.8%, with endometrial cancer – 57.5%. There was no unity among histologists regarding the presence/absence of an endometrial polyp ($p < 0.0001$). These data have become one of the prerequisites for improving diagnostic criteria and classification of endometrial hyperplastic processes. In 2000, G.L. Mutter et al. A two-level classification of GE has been proposed, in which benign and atypical hyperplasia (endometrial intraepithelial neoplasia (EIN)) is distinguished [5]. This modernization of the classification was supported by the European Working Group of Experts [6], and in 2014, WHO experts made appropriate changes to the classification of tumors of female reproductive organs [7], having previously corrected the terminology and approved the term "endometrioid intraepithelial neoplasia". The new name made

it possible to emphasize the connection of EIN with endometrioid-type carcinomas and non-cancerous cancers.

In contrast to the 1994 classification, the new classification has a number of clinical and pathological advantages, especially in terms of reproducibility of diagnostic results. So, J. Ordi et al. 198 tissue samples were examined and a conclusion was made in accordance with the four- and two-level classification [8]. When using the old classification, full agreement on the diagnosis was achieved only in 28% of cases, the new one – in 39-59%.

According to clinical data, 40% of patients with EIN develop endometrial cancer within a year after diagnosis [9, 10]. Such high figures can be explained by the fact that at the time of the initial histological conclusion, cancer cells were already in the endometrium, but did not get into the studied sample. In other cases, the risk of developing endometrial cancer in subsequent years increased by 45 times (compared with the control group) [9].

The new classification allows not only to make a more accurate and reproducible pathomorphological conclusion [8], but also to predict the risk of malignancy (Table 1). More objective data from genetic and immunohistochemical (IHC) studies can be added to the microscopic criteria [11].

The new classification began to gain popularity and worldwide recognition only in recent years, due to the lack of standardized approaches to the management of patients within the new diagnostic criteria and the peculiarities of gynecological practice in the regions.

It should be noted that experts of the American College of Obstetricians and Gynecologists (ACOG) recommend using the term "endometrioid intraepithelial neoplasia" rather than "atypical hyperplasia", although the results of later studies have proved that with atypical hyperplasia and EIN, the probability of malignancy during the year is comparable [12]. In 2016 recommendations for the management of patients with endometrial hyperplastic processes of the Royal College of Obstetricians and Gynecologists of Great Britain (Royal College of Obstetricians and Gynaecologists – RCOG) were published for the first time [13]. According to the document, the terms "atypical endometrial hyperplasia" and "endometrioid intraepithelial neoplasia" are recognized as interchangeable. In addition, it offers algorithms for the management of such patients.

Benign endometrial hyperplasia. Endometrial hyperplasia is the result of prolonged exposure to excessive estrogen levels on the endometrium. At the beginning, the process is reversible, histologically, an indistinct enlargement of the glands is determined against the background of a normal proliferative endometrium. This form of endometrial alteration is called "proliferative endometrium with disorders" [14]. It does not belong to the forms of glandular

hyperplasia. Changes occur throughout the endometrium, while the ratio of the volume of the "gland – stroma" does not change significantly.

The main morphological signs of proliferative endometrium with disorders are considered to be the presence of proliferative glands with mitotic activity and cystic enlargement of the glands, as well as pseudo-order of the arrangement of nuclei, tubal metaplasia of the epithelium. Clinically, this disorder corresponds to anovulation, and during curettage, a non-sterile scraping of the endometrium is determined.

Due to the longer-term effect of estrogens, which is not replaced by the effect of progesterone, benign endometrial hyperplasia (active phase) develops against the background of proliferative endometrium with disorders. There is a non-constant density of the location of the glands throughout the volume. Endometrial foci appear in which the volume of the glands exceeds the volume of the stroma, which distinguishes benign endometrial hyperplasia from proliferative endometrium with disorders. In the future, in the absence of compensatory effects of progesterone, the number of glands and stroma volume increase, cystic glands appear, tubal metaplasia develops, fibrin thrombi forms in small vessels, and stroma destruction and reactive epithelial changes occur in adjacent areas [1,4]. With a small magnification, the endometrium appears to be fairly homogeneous, but with an average increase, the frequency of detection of cysts and the degree of convergence of the glands vary from one field of view to another. This combination of the apparent uniformity of the endometrium at low magnification and its absence in individual fields of vision is regarded as an important diagnostic sign and has been called "regular/irregular endometrium". A distinctive feature of benign endometrial hyperplasia is the identity of cytological signs in areas of the endometrium with a discharged and close arrangement of glands [1,4].

The endometrium reacts to changes in the hormonal background even with benign hyperplasia. Consequently, morphological changes reflecting dynamic hormonal fluctuations arising under the influence of both endogenous and exogenous iatrogenic factors can be observed in GE.

With a gradual reduction in the amount of estrogens, the mitotic activity of the epithelium in the glands decreases. With a rapid decrease in their concentration, stroma destruction develops with hemorrhagic infiltration. Such changes can be identified by a pathologist. In conclusion, they are referred to as "benign endometrial hyperplasia in the depletion phase."

Termination of the stimulating effect of estrogens leads to apoptosis of stromal and epithelial cells of the endometrium and, as a consequence, widespread destruction of the stroma and rejection of the endometrium. Clinically, this is manifested by massive uterine bleeding, most

often developing after a delay in menstruation. Morphological signs of hyperplastic endometrium in a state of rejection are pronounced necrobiotic changes in the stroma, the presence of characteristic fibrin thrombi, indeterminate structure of the glands, low/absent mitotic activity of the epithelium, the presence of glands with secretory epithelium, decidu-like reaction in the stroma [35].

When analyzing histological material, it is difficult to determine what preceded this condition – normal or pathologically altered endometrium.

In some cases, after prolonged exposure to estrogens on the endometrium, delayed ovulation or the introduction of progesterone from the outside occurs. This causes typical progesterone-dependent morphological changes, including secretory changes in the glandular epithelium and decidu-like rearrangement of stromal elements. Mitotic activity is practically absent. In the pathomorphological description of such an endometrium, the term "benign endometrial hyperplasia with additional effects of progesterone" is used.

According to the RCOG recommendations [34], after histological confirmation of the diagnosis of "benign endometrial hyperplasia", risk factors are assessed. In their absence, you can limit yourself to dynamic observation and a control biopsy after six months. In the presence of risk factors, such as obesity, infertility, anovulatory conditions, taking tamoxifen, oral progestins (PP) are prescribed in a continuous mode or an intrauterine system containing levonorgestrel (LNG-IUD). LNG-IUD is the first line of therapy due to a more pronounced antiproliferative effect. This can be explained by the fact that when using the intrauterine system, the local increase in levonorgestrel concentration in the endometrium is more significant [33].

According to the results of meta-analysis, LNH-IUD, compared with PP, more effectively suppresses proliferative activity in the endometrium after three, six, 12 and 24 months of treatment. The relative risk (RR) at 95% confidence interval (CI) was 2,30 (1,39–3,82), 3,16 (1,84–5,45), 5,73 (2,67–12,33) and 7.46 (2.55–21.78), respectively. Patients who used LNH-IUD were less likely to notice irregular blood discharge and side effects of therapy (evidence level A), and also needed hysterectomy (HR 0.26 (95% CI 0.15–0.45) [29,31].

Progestins in a continuous mode (medroxyprogesterone 10-20 mg / day or norethisterone 10-15 mg / day) should be prescribed to patients who are contraindicated with LNG-IUD or who refuse to use it (evidence level B). Prescribing progestins in a cyclic mode is not recommended due to lower efficacy compared to their use in a continuous mode and the use of LNG-IUD (evidence level A) [28,30].

The duration of treatment with LNH-IUD should be six months (evidence level B). With good tolerance and the need for contraception, it can be extended up to five years.

The endometrial condition is assessed at intervals of six months. The observation continues until two negative endometrial samples are obtained (evidence level D). Patients should be informed about the symptoms of GE and the need to immediately contact a gynecologist if they appear. For women at risk for relapse of the disease (for example, with a body mass index of more than 35 kg/m^2), in addition to two biopsies with an interval of six months, it is recommended to conduct an annual examination of endometrial biopsies (evidence level D). The duration of observation for each patient is set individually, taking into account the clinical picture and risk factors.

Radical surgical treatment, according to the above recommendations, is offered to patients who do not need to preserve fertility in the following cases: detection of atypical hyperplasia during the follow-up period; absence of regression against the background of hormone therapy conducted for 12 months; recurrence of endometrial hyperplasia at the end of the course of hormone therapy; persistent uterine bleeding against the background of therapy; refusal of the patient from medication therapy.

In the postmenopausal period, laparoscopic hysterectomy with bilateral salpingo-oovariectomy is considered optimal. In premenopause, the issue of ovarian removal is decided individually in each case. Tubectomy can be recommended to all patients, as it reduces the risk of malignant neoplasms of the ovaries. In our opinion, vaginal hysterectomy may be considered as an alternative [25,27].

Endometrial ablation is not recommended, since its implementation does not guarantee the radical removal of the endometrium, and the emerging intrauterine synechiae make it difficult to assess the condition of the uterine cavity.

Atypical endometrial hyperplasia. Endometrioid intraepithelial neoplasia is a monoclonal noninvasive genetically modified neoplasm that develops focally from glandular cells. Unlike benign hyperplasia, this is a precancerous process that can acquire a malignant phenotype with additional genetic damage and turn into endometrioid adenocarcinoma (type 1). EIN is characterized by a focal change in the glands. The size of the focus should be at least 1 mm in diameter. If the focus is less than 1 mm, diagnosis is impossible [24,26]. The pathologist should give only a descriptive conclusion and recommend a second examination of the endometrium in three to six months. The diagnosis of EIN is possible only if there are two key signs: a decrease in stroma by less than 45% and atypia of the epithelium. In the future, the background endometrium can be replaced by neoplastic glands, the process becomes diffuse.

With EIN, the meaning of the term "atypia" differs from the generally accepted one (polymorphism, hyperchromatism of nuclei, etc.). This refers to any cytological differences

between the epithelium of the glands of the neoplastic focus and the epithelium of the glands of the endometrial background. The background, in turn, may reflect any benign changes in the epithelium caused by hyperestrogenism, not compensated by the effects of progesterone.

Traditional approaches to diagnosis often do not allow to determine the transition of a hyperplastic process to a neoplastic one, therefore, diagnostic criteria for EIN have been developed based on computer morphometry [15, 16,18]. With EIN, hysterectomy with or without salpingo-ovariectomy is recognized as the first line of therapy (evidence level B). Laparoscopic and vaginal access is considered preferable (evidence level B). The advantages of urgent intraoperative histological examination or simultaneous lymphadenectomy have not been proven (evidence level C). Endometrial ablation in EIN, as well as in benign hyperplasia, is not recommended.

Conservative treatment is possible only if it is necessary to preserve the ability to procreate at a young age and in the absence of risk factors [7,8,13]. The decision on the use of organ-preserving tactics should be made collectively and based on serious arguments. When prescribing hormonal treatment, the patient should be examined for the presence of endometrial or ovarian cancer [4,6].

LNG-IUD is recommended as the first line of drug therapy, and PP is the second [2,3,5]. As a result of the treatment, in 75% of cases, a complete response to therapy with regression of EIN will be obtained. However, 35% of these patients may relapse [10,12,14]. A quarter of the patients will not respond to such therapy, and in the first three years of follow-up they will be diagnosed with the persistence / progression of the disease. If the follow–up is prolonged to six years, their percentage will increase to 51%, and after seven years - to 72% [1,9,11]. Therefore, upon completion of treatment and implementation of reproductive tasks, patients with EIN are shown to perform a hysterectomy. The frequency of live births in women with EIN who are actively planning pregnancy is high and can reach 73% [17,19,22].

To assess the potential of the endometrium for malignancy, it is possible to conduct an IHC study. In particular, the study of such markers as PTEN, p53, beta-catechin, Bcl-2, COX-2, p27, p21, MLH-1, -2 and -6, survivin, p16, expression of estrogen and progesterone receptors (ER-alpha, ER-beta, PR).

According to the British recommendations, when prescribing hormonal treatment, a control examination of the endometrium should be carried out twice with an interval of three months. If signs of progression or persistence of EIN are detected, at least one of the samples shows a hysterectomy. In case of receiving two negative samples, the endometrial examination should be carried out once every six months or a year. ACOG (2015) experts point out that to date, the

optimal duration and regimen of therapy, as well as the timing and frequency of follow-up observations, have not been determined. However, according to available data, the frequency of EIN regression with systemic administration of progestins is 69% (95% CI), with local use – 90% (95% CI) [20, 21,23].

Conclusion. The new classification of endometrial hyperplastic processes approved in 2014 by WHO allows solving a number of important clinical tasks. However, its widespread use is hindered by one unresolved problem – the improvement and refinement of algorithms for the management of patients. In 2016, RNCOS experts proposed basic protocols for the management of women with benign and atypical endometrial hyperplasia.

In the future, it is advisable to expand the understanding of the role of biomarkers in the diagnosis and dynamic monitoring of profile patients, to determine the optimal duration of treatment and possible timing of the resumption of menopausal hormone therapy after an episode of GE. It is also necessary to assess the impact of weight loss, including after bariatric surgery, and lifestyle changes on the frequency of relapses of the disease and the possibility of regression of hyperplasia.

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