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RISK FACTORS FOR THE DEVELOPMENT OF ENDOMETRIAL HYPERPLASTIC PROCESSES IN WOMEN WITH UTERINE FIBROIDS

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ABSTRACT

Despite the progress achieved in studying the etiopathogenesis, as well as in developing new diagnostic and therapeutic methods for endometrial hyperplastic processes (EHP), the problem of treating patients with this pathology still remains far from being fully resolved. This necessitates optimization of management strategies for patients with EHP during the menopausal transition period (MTP), which should be aimed not only at creating adequate comprehensive approaches for predicting the development and recurrence of endometrial hyperplasia (EH), but also at developing unified protocols for managing patients with this pathology.

Keywords: hyperestrogenism, proliferation, apoptosis.

ФАКТОРЫ РИСКА РАЗВИТИЯ ГИПЕРПЛАСТИЧЕСКИХ ПРОЦЕССОВ ЭНДОМЕТРИЯ У ЖЕНЩИН С МИОМОЙ МАТКИ

АННОТАЦИЯ

Несмотря на успехи, достигнутые в изучении этиопатогенеза, новых методов диагностики и терапии ГПЭ, проблема лечения больных с данной патологией до настоящего времени остается далекой от своего решения. Все это диктует необходимость оптимизации тактики ведения больных с ГПЭ в ПМП, которая должна быть направлена не только на создание адекватных комплексных подходов прогнозирования развития и рецидивирования ГЭ, но и разработки единых протоколов ведения больных с данной патологией.

Ключевые слова: гиперэстрогения, пролиферация, апоптоз.

Relevance

According to clinical statistics, in recent years there has been a progressive increase in the incidence of endometrial cancer. Approximately 150,000 new cases of uterine body cancer are diagnosed worldwide every year, and about 42,000 women die from this tumor annually. The peak incidence is observed at the age of 65–69 years and reaches 68.7 per 100,000 women. In 20–25% of patients, the disease is diagnosed during reproductive age, and in 5% of cases — in women younger than 40 years. Most morphologists, gynecologists, and oncologists consider endometrial cancer to be closely associated with endometrial hyperplastic processes (EHP).

Despite numerous studies, the molecular biological mechanisms underlying the development of endometrial hyperplasia (EH) remain incompletely understood. At present, there is no consensus regarding the key triggering pathogenetic factors of proliferative processes in the endometrium,

which leads to empirical therapeutic measures and the absence of a unified treatment strategy for EHP in women. This does not allow a significant reduction in the incidence of this pathology.
Currently, a close relationship between the reproductive and immune systems has been established [1]. According to several researchers, natural autoantibodies (auto-Abs), interacting with the body's own molecules, contribute to immune control and regulation of antigenic-molecular homeostasis and, together with macrophages, play a significant role in regulating apoptosis [3]. The use of multiparametric analysis of serum auto-Abs content, aimed at detecting secondary immunological changes, has expanded diagnostic capabilities and substantiated a differentiated approach to the treatment of pregnancy complications such as miscarriage, preeclampsia and eclampsia, and postpartum hemorrhage [2].
At present, there are no studies in the available global scientific literature assessing autoimmune parameters in patients with EHP. This dictates the need to investigate the autoimmune status in women with EH during the menopausal transition period in order to identify specific changes in regulatory auto-Abs levels and to apply them as biomolecular markers for predicting the development of EH, the risk of recurrence, and for implementing a differentiated treatment approach.
The problem of endometrial hyperplastic processes (EHP) during the menopausal transition period (MTP) remains one of the most relevant issues in gynecology due to the high prevalence of this pathology in women of this age group. Persistent interest in this issue is explained by the tendency of EHP toward a prolonged, recurrent course, the absence of specific pathognomonic symptoms, difficulties in differential diagnosis, and the complexity of choosing optimal treatment methods. According to clinical attendance data, the incidence of endometrial hyperplasia varies depending on its form and the woman's age from 10% to 30%, significantly increasing during periods of age-related hormonal restructuring [3].
From modern perspectives, EH is regarded as a polyetiological pathological process, the development and progression of which may be influenced by many diverse factors. The pathogenesis of EHP is characterized by a complex interaction of systemic processes (neuroendocrine, metabolic, and immune) and local changes (receptor status and genetic apparatus of endometrial cells), as well as the involvement of biologically active substances, growth factors, markers of proliferation and apoptosis, etc. Having different degrees of severity, EHP often becomes a favorable background for the development of precancer and subsequently endometrial cancer (EC) [4].
From current perspectives, endometrial hyperplasia is considered a polyetiological pathological process, whose development and progression may be facilitated by numerous causes. The main risk factors for endometrial hyperplastic processes and endometrial cancer include menstrual cycle disorders caused by anovulation, lipid metabolism disorders, prolongation of the reproductive period due to early menarche and late menopause, endocrine infertility, polycystic ovary syndrome, estrogen-secreting ovarian tumors, and others.
Endometrial hyperplastic processes remain of great scientific, medical, and social importance due to their frequency, reproductive dysfunction, and the lack of adequate treatment methods. Abnormal uterine bleeding, which is the most common clinical manifestation of EH, is the most frequent reason for visiting a gynecologist and ranks second among gynecological problems leading to hospitalization [6].
Treatment issues cover a wide range of conservative and surgical methods. However, in young women wishing to preserve reproductive function (in the absence of cellular atypia), conservative therapy remains relevant, with hormonal therapy playing a leading role. Therefore, hormonal influence on hyperplastic endometrium has not lost its clinical significance. Endometrial hyperplasia is known to be a consequence of absolute or relative hyperestrogenism and progesterone deficiency, which leads to excessive (uncontrolled) cell division and reduced apoptosis [5].
The classical therapy for endometrial hyperplasia, aimed at counteracting estrogen influence, is the administration of progestins. Progesterone has an antiproliferative effect on the mitotic

activity of endometrial cells. Progestins reduce the number of estrogen receptors and accelerate their catabolism by stimulating 17β-hydroxysteroid dehydrogenase and sulfotransferase, thereby reducing estrogen dominance in the hormonal background that leads to endometrial hyperplasia.
However, recent clinical trial reports have demonstrated side effects of these drugs during long-term use, associated with their androgenic activity: increased plasma insulin concentration, decreased serum HDL levels, increased LDL levels, vasoconstriction, blockade of nitric oxide synthase action, etc.
At present, based on the analysis of gynecological inpatient departments, it is important to develop principles for determining a medical strategy in the treatment of EH, especially regarding the choice of conservative treatment methods in women of reproductive age. In this direction, consideration of psychosomatic disorders appears promising, the frequency of which ranges from 30% to 57% among women seeking care in antenatal clinics.
Endometrial hyperplastic processes represent a large group of histological changes in endometrial glands and stroma, forming the basis for the development of neoplastic processes in the uterus. One of the most significant factors directly associated with the risk of this pathology is the perimenopausal period, when the frequency of hormone-dependent diseases increases.
Endometrial hyperplastic processes are among the most common causes of uterine bleeding and hospitalization. The issue of malignant transformation risk remains open. According to domestic and international studies, the risk of malignancy in different variants of EHP is determined by the morphological condition of the endometrium and depends primarily on the severity of cellular atypia, and to a lesser extent on age, ovarian status, concomitant endocrine disorders, and other factors [6]. It has been proven that histopathological and molecular changes reflect the potential risk of EH progressing to endometrial cancer.
The complexity of the etiopathogenesis of EHP creates significant difficulties in selecting treatment methods. This explains the lack of unified recommendations regarding the choice of medication, dosage, and optimal duration of therapy, which is often inadequate and results in EH recurrences [7]. Thus, despite progress achieved in the study of etiopathogenesis, new diagnostic and therapeutic methods, the problem of treating patients with this pathology still remains far from being solved. This dictates the need to optimize management tactics for patients with EHP during the menopausal transition period, aimed not only at creating comprehensive approaches for predicting EH development and recurrence, but also at developing unified protocols for managing such patients.

Endometrial hyperplastic processes: etiology and pathogenesis

Endometrial hyperplastic changes represent a serious problem in gynecology. These conditions belong to proliferative diseases that may contribute to the development of endometrial cancer if timely treatment is not provided. Modern data indicate an increasing incidence of endometrial cancer.
Endometrial hyperplastic processes occupy a significant place in the structure of gynecological diseases, occurring with a frequency ranging from 15% to 40%. Statistics show that depending on the form of the disease and the patient's age, the frequency of EHP ranges from 10% to 30%. According to studies, about half of all women in late reproductive age and perimenopause face this pathology. However, the risk of malignant transformation remains controversial. Studies show that in patients with recurrent forms of EHP, the probability of invasive uterine cancer development reaches 20–30% [8].
Approximately 150,000 new cases are recorded annually worldwide, with about 42,000 deaths. The highest incidence is observed in women aged 65–69 years, reaching 68.7 per 100,000 women. In reproductive age, the disease is detected in 20–25% of women, and in 5% — before the age of 40 [7]. The importance of the association between EHP and endometrial cancer is emphasized by leading specialists in morphology, gynecology, and oncology.
The World Health Organization classification introduced in 1994 and reaffirmed in 2003 divided endometrial hyperplasia into simple and complex without atypia, and simple and complex with atypia. In simple hyperplasia without atypia, glands of various sizes and shapes are present, some

with cystic dilatation. The glands are lined with cells in the proliferative phase of the cycle, with rare mitoses. The stroma contains a large number of cells. Such changes usually do not lead to cancer but end with cystic atrophy, where both epithelial and stromal cells undergo atrophy [9].

In 2014, taking into account a new binary classification system, WHO updated the classification of endometrial hyperplasia, which was confirmed in the 2020 revision. The current classification includes two categories:

1. **Endometrial hyperplasia without atypia** (synonym: benign endometrial hyperplasia), characterized by an increased gland-to-stroma ratio, tubular architecture, branching and/or cystically dilated glands resembling proliferative endometrium, and uniform nuclear distribution.
2. **Endometrioid intraepithelial neoplasia (EIN)** (synonym: atypical endometrial hyperplasia), characterized by gland crowding (more than 20 glands) and abnormal epithelial cytology distinct from adjacent glands.

The terms “simple” and “complex” hyperplasia have been excluded, and the term “EIN” is recommended to emphasize the association with endometrioid-type tumors rather than serous ones [10]. This classification was approved and recommended by international organizations such as the Royal College of Obstetricians and Gynaecologists (RCOG) in 2016 and the International Federation of Gynecology and Obstetrics (FIGO) in 2018 [9].

According to WHO 2014, EIN is included in the atypical hyperplasia group. In this review, the new classification is used; however, a significant part of the literature data refers to the older 1994 classification.

The WHO 1994 classification was based on studies of transformation of different hyperplasia types into adenocarcinoma. The risk is highest for atypical hyperplasia. Studies show that in 23–32% of women with atypical hyperplasia, endometrial cancer may develop, while other studies indicate malignancy in 52% of cases. In addition, a high percentage (23.9–27%) of atypical hyperplasia is accompanied by foci of adenocarcinoma [11].

For non-atypical hyperplasia, progression to atypical form occurs in 10.5%, while the risk of endometrial cancer is about 2% [13]. Recurrent hyperplasia increases the risk of invasive uterine cancer to 20–30%. Although the WHO 1994/2003 classification had advantages, it demonstrated low reproducibility, leading to the need for improved systems. Analysis shows that binary classification provides higher accuracy and reproducibility (10–52%) compared with WHO classification [12]. Some studies report that the binary system improves diagnostic reproducibility by 18%.

Endometrial hyperplasia is described as excessive proliferation of endometrial glands with irregular sizes and shapes. Unlike typical anovulatory changes, this disease is expressed through significant histological modifications. Hyperplasia is divided into two categories: polyclonal tissue responding to abnormal hormonal stimulation and monoclonal local proliferations with a high risk of malignant transformation [13].

Some studies suggest a possible association between human papillomavirus (HPV) and endometrial hyperplastic processes. While HPV’s role in cervical pathology is well known, data on its effect on the endometrium remain limited. The virus may contribute to cell cycle dysregulation and induce proliferative changes.

Risk factors include early menarche, delayed menopause, nulliparity, obesity, hyperlipidemia, insulin-dependent diabetes, menstrual disorders associated with anovulation, endocrine infertility, polycystic ovary syndrome, estrogen-producing ovarian tumors, and hormone therapy in postmenopause [14].

The main factor contributing to EH is hyperestrogenism, which may be absolute or relative. It can result from high-dose estrogen use, increased endometrial cell activity, imbalance in regulation and metabolism, increased endometrial sensitivity to estrogens, or prolonged estrogen use for therapeutic purposes.

It is important to note that free estrogens play the main role, as they have biological activity. Normally, up to 97% of sex steroids are bound to globulin, which regulates their activity.

Anovulation and other hormonal disorders may decrease globulin levels, increasing active estrogen and androgen fractions. The effect depends not only on estradiol levels but also on its free fraction [15].

Cytochrome P450 aromatase (CYP19A1) is a key enzyme in steroidogenesis, converting androgens into estrogens (androstenedione into estrone and testosterone into estradiol). Aromatase is expressed in granulosa cells, placental syncytiotrophoblast, Leydig cells, brain, adipocytes, and dermal fibroblasts. In premenopausal women, aromatase is mainly localized in ovarian granulosa cells, while after menopause the main source becomes adipose tissue. Although the aromatase gene is present in normal endometrial cells, its expression is usually absent [16].

Studies show that in women under 40, atypical endometrial hyperplasia and early endometrial cancer are detected in 5–25% of cases. Data from the National Cancer Institute indicate that endometrial cancer occurs in 7% of reproductive-age women. The number of atypical EH and EC cases in this group is increasing.

In the USA, insurance analysis over the last decade identified 4,007 cases of precancer and endometrial cancer in women under 45 years, averaging 400 cases per year. Early diagnosis allows fertility preservation when needed.

According to Ya.V. Bokhman, atypical hyperplasia progresses to invasive endometrial cancer in 50% of cases. Endometrial cancer is the most common malignancy of the female reproductive system in highly developed countries, second only to breast cancer, and more common than cervical cancer worldwide. Endometrioid adenocarcinomas account for 80% of uterine malignancies. Up to 417,000 new cases are diagnosed annually worldwide.

The cumulative risk has increased by 0.45 over the last ten years, reaching 2.35. The main factor is hyperestrogenism. Endometrial proliferation is closely linked to aromatase activation, leading to increased estrogen levels and receptor expression [15].

Some studies indicate heterogeneous distribution of steroid receptors depending on cycle phase. Data on receptor expression in EH remain controversial. Observations show estrogen receptor expression may be high or moderate in proliferative phase but decreases in hyperplasia. Progression of atypical changes is accompanied by decreased estrogen and progesterone receptor levels [16].

Activation of endometrial proliferation is closely linked to growth factors triggering intracellular signaling. Two main groups include insulin-like growth factors (IGF) and epidermal growth factors (EGF), as well as transforming growth factor alpha (TGF-α). Variable EGF expression with limited TGF activity is characteristic of atypical EH [17].

An imbalance between cell death and growth indicates the importance of these processes. Apoptosis cascades are regulated via TNF-α receptor family (TNFR1, TNFR2), FasR/APO-1 (CD95), and their ligands. Signaling through tumor suppressor genes and oncogenes (k-ras, beta-catenin) also affects progression [18].

Currently, metabolic-endocrine disorders are considered a major cause of EH development. Insufficient molecular biological data prevents a complete understanding of pathogenesis and primary causes, which remains important in clinical practice and reproductive medicine.

In reproductive and premenopausal periods, the most common endometrial pathology is endometrial polyps. These are exophytic benign glandular neoplasms originating from the basal layer. WHO defines an endometrial polyp as a nodular formation protruding above the endometrial surface, containing glandular and predominantly fibrous stroma with numerous thick-walled vessels [17].

Polyps arise due to proliferation of basal glandular epithelium. Morphological features include polypoid outgrowths on a stalk or broad base, composed of fibrous stroma and thick-walled vessels. Glands show irregular orientation and seemingly chaotic arrangement [18].

Modern research focuses on growth factors in myometrium and endometrium, influencing auto- and paracrine mechanisms of uterine tumor processes. The pathogenesis of uterine fibroids and

endometriosis is actively studied. Molecular biology, genetics, and clinical immunology have confirmed genetic, hormonal, and immune factors in fibroids and EH.
Regulation of endo- and myometrium involves not only hormones but also biologically active substances such as growth factors and cytokines [19]. Key roles include increased proliferative potential, reduced apoptosis, pathological neoangiogenesis, and increased IGF-1 expression [19]. Increased expression of these factors and receptors in fibroids, adenomyosis, and EH leads to pathological bleeding. Not only VEGF but also fibroblast growth factor, transforming beta growth factor, parathyroid hormone-related protein, and prolactin may play roles [17].
Uterine fibroids are common in women over 35, with frequency 25–50% [9]. They are hormone-dependent benign tumors formed by hypertrophy and proliferation of muscle and connective tissue [11]. Many authors note that fibroid formation occurs in late reproductive age, when somatic and gynecological diseases accumulate along with endometrial disorders [3].
Modern medicine is rethinking EH pathogenesis. Non-atypical EH is traditionally linked to hyperestrogenism, while atypical EH is associated with genetic mutations, and the role of estrogens remains under clarification. Non-atypical EH does not show mutations typical of endometrial adenocarcinoma. In EIN and endometrial cancer, mutations affect the same genes: PTEN inactivation in 44–63%, PAX2 in 71%, KRAS in 16%, and microsatellite instability in 20–25% [20].

Methods of diagnosis of endometrial hyperplastic processes

The complexity of early diagnosis of EHP and endometrial cancer remains a major issue, especially considering the increasing number of cases in reproductive-age women. Variability affects treatment quality and recurrence, reflecting the lack of objective, informative, and non-invasive diagnostic methods capable of accurately determining progression from benign to malignant stages. Literature reports that many endometrial cancer cases were misdiagnosed and treated as hyperplastic pathology, indicating an increase in incorrectly treated patients [14].
At the pre-hospital stage, ultrasound is the main diagnostic method for uterine cavity pathology. Key concepts include echogenicity and sound conductivity. Echogenicity refers to tissue ability to reflect ultrasound waves. Tissues may be anechoic, hypoechoic, isoechoic, hyperechoic, or highly hyperechoic. Myometrial echogenicity is considered medium [20].
Pelvic ultrasound is performed using transabdominal and transvaginal approaches, complementing each other. Before transvaginal ultrasound, bladder emptying is recommended.
In diagnosing endometrial conditions, assessment of the M-echo is important, evaluating size, shape, and structure. The maximum anteroposterior size is a key indicator.
A series of ultrasound studies has led to new approaches:

- Transvaginal echography is the first-line method due to high-frequency probes and better visualization, especially in obese patients (78–92% of patients with EHP have obesity).
- Direct ultrasound determination of structural changes is difficult due to morphological variability; histology is required for accurate diagnosis.
- The clinical value of ultrasound morphotyping is limited, since treatment decisions depend on histology.
- Endometrial polyps appear as well-defined, smooth-contoured formations in the uterine cavity, round/oval, with high echodensity.
- EH ultrasound signs include oval formations in the uterine echo area with increased anteroposterior size, homogeneous structure and high echogenicity (type 1), or thickened 4–7 mm smooth endometrial contours with decreased sound conductivity (type 2).

Ultrasound differences between morphotypes were described. Glandular-cystic polyps show multiple internal echo-negative signals with posterior acoustic enhancement. Glandular-fibrous polyps show homogeneous texture with linear echopositive inclusions and no enhancement. Fibrous polyps show increased echodensity and may produce acoustic shadowing. Adenomatous polyps show large size, homogeneous structure, echopositive and echonegative formations up to 5 mm, and acoustic enhancement. Glandular-cystic hyperplasia shows sponge-like structure with multiple small echo-negative inclusions, absent in atypical hyperplasia [21].

However, even high ultrasound accuracy does not exclude false results in 20–30% of cases [22].
Hysteroscopy, enabling diagnosis and treatment of cervical canal pathology, was first performed in 1896 by D. Pantaleoni. It evolved into the “gold standard” for intrauterine pathology. By 1925, Rubin adapted cystoscopy and introduced uterine distension media. Modern hysteroscopy is performed on an outpatient basis and is a key technology replacing inpatient treatment. Vaginoscopic technique is considered the standard approach [23].
Hysteroscopy is highly informative for endometrial assessment and uterine cavity pathology. Videohysteroscopy provides detailed visualization. In early proliferative phase, the endometrium is thin, transparent, pale pink to yellow-pink, 1–2 mm thick. Tubal ostia are visible as oval or slit-like openings [24].
In mid-late proliferative phase, the endometrium becomes bright pink, folded, thicker, with less visible gland openings. Vascular network becomes less visible. In early secretory phase, the endometrium is pale pink, velvety, 4–6 mm thick. Before menstruation, dark-burgundy detached endometrial layers hang freely, indicating menstrual shedding [25].
A major diagnostic method is aspiration (Pipelle) biopsy. It is safer than diagnostic curettage, which may traumatize malignant tissue and contribute to metastasis, and increases thromboembolic and bleeding risks.
Aspiration biopsy provides sufficient material for histology and reduces risks. Other methods are less used due to insufficient material and errors [17]. Aspiration biopsy is fast, minimally painful, low-trauma, does not require cervical dilation, and can be performed outpatient. Its main indication is screening for EH and endometrial cancer [17].
Pipelle is a disposable flexible plastic cylinder (3.1 mm diameter) with a piston creating negative pressure to aspirate endometrial tissue.
Modern technologies improve diagnostic quality. However, accurate differentiation of morphotypes remains debated [25].
Local estrogen synthesis and aromatase activity in the endometrium are important in understanding hyperplastic and malignant mechanisms. Aromatase converts androstenedione to estrone and testosterone to estradiol, increasing local estrogen levels and stimulating proliferation. Literature confirms that increased aromatase expression may contribute to EH and endometrial cancer, and aromatase inhibition may reduce proliferation stimulation [16].
Additionally, biomarkers such as CTEC and SLULT, PROK-1, integrins, and angiogenesis markers like VEGFR-2 are used for prognosis. These markers help assess angiogenesis and invasive tumor potential, contributing to targeted therapy development [17].

Modern methods of treatment of endometrial hyperplastic processes

Treatment is based on age, causes, disease features, symptoms, contraindications, tolerance to medications, and comorbid gynecological and extragenital conditions [14]. Hormonal therapy is the main approach and must be individualized. Ultrasound monitoring is recommended after 3 and 6 months.
If hyperplasia is associated with PCOS, wedge resection of ovaries may be considered, especially in recurrent hyperplasia threatening precancerous transformation [11].
In EH treatment, hormonal therapy is the initial focus. If ineffective or in perimenopausal age, hysterectomy may be considered [9]. Atypical EH often requires surgery; up to 85% of hysterectomies are performed for this indication.
Treatment strategy for atypical EH is determined by high malignancy risk and possible inadequate biopsy diagnosis [7]. Studies of removed uteri showed that 11% of endometrial cancer cases were initially diagnosed as hyperplasia after curettage, mostly atypical hyperplasia [8].
Nevertheless, conservative therapy remains important, especially for fertility preservation. Although 34% still require hysterectomy, two-thirds can avoid uterine removal [3].
Complex hyperplasia without atypia has a small malignancy risk (~3%), but hysterectomy is performed in 50% of cases. However, conservative therapy is effective in most patients [5].

For simple hyperplasia without atypia, hysterectomy is excessive. This condition is often a response to hormonal changes rather than true disease. Hormonal therapy is more appropriate [10].

The first stage often includes removal of abnormal tissue by curettage under hysteroscopic control. In premenopausal women, hormonal therapy aims to correct hyperestrogenism and anovulation and to stimulate cyclic secretory changes for normal cycle restoration [11].

In women wishing fertility preservation, treatment of bleeding due to simple EH is combined with endocrine infertility treatment [3].

Conservative therapy includes progestins, combined oral contraceptives (COCs), antigonadotropins, and GnRH agonists. Progestins remain most widely used [3].

Since the 1970s, high estrogen levels have been linked to increased endometrial cancer risk. Since the 1980s, progesterone and derivatives have been used to provide endometrial protection [8].

Estrogen receptors regulate the cell cycle in endometrial glands. Estrogens initiate the cycle, while progesterone blocks it. Synthetic progestins mimic progesterone. Dose selection is important, aiming to induce luteal-like changes. A sign of effective protection is withdrawal bleeding after 10–12 days of progestin use [9].

Progestins improve progesterone bioavailability. Progesterone metabolism involves reduction in GI tract and liver and hydroxylation. Modifications improve binding and allow lower doses [7,12,13].

Progestin effects depend on dose and regimen. Higher doses and continuous use lead to stromal decidualization and gland atrophy. Long-term monotherapy may cause significant side effects. Local administration is considered to reduce systemic effects and enhance local action [12].

COCs are effective for hormonal regulation in reproductive-age women without atypia. They reduce hyperandrogenism symptoms, menstrual blood loss, and dysmenorrhea [17]. They normalize cycle and reduce bleeding.

COCs are classified by ethinyl estradiol dose: high-dose (50 μg), low-dose (35 μg), microdose (<35 μg). For EH, low-dose and microdose monophasic COCs are used [19]. Microdose COCs are recommended in women >35 years due to reduced metabolic impact [20].

Progestins in COCs vary. Norgestimate, levonorgestrel, desogestrel, and gestodene are effective and require lower doses for secretory transformation [21].

COCs cause rapid regression of proliferative endometrium and induce secretory transformation. Vascular changes include suppression of spiral arteriole development and formation of capillary networks. These effects are linked to progestins [20].

COCs reduce endometrial cancer risk by 50%, also decreasing mortality [19].

Some progestins (e.g., gestodene) have weak anti-aldosterone effects, reducing estrogen-related side effects such as fluid retention, breast tenderness, and weight gain. This is important in overweight women and those with hypertension, where EH is common [15].

COCs affect folliculogenesis via hypothalamic-pituitary suppression, reducing gonadotropins. This is beneficial in PCOS patients, reducing hyperplasia risk. Prolonged regimens reduce LH and ovarian volume [16].

Prolonged COC regimens show higher effectiveness, restoring ovulation in many patients. Shortening pill-free intervals improves outcomes but may cause spotting, usually not preventing therapy continuation. Effectiveness is assessed after treatment. Morphological control is needed only in complex hyperplasia. Simple hyperplasia is monitored clinically by ultrasound and cycle assessment. Recurrence rates after COCs range from 7 to 16% [17].

Proper hormonal therapy selection helps avoid surgery and significantly reduces endometrial cancer risk, highlighting long-term protective effects.

Conclusions

Thus, despite progress in studying etiopathogenesis, diagnostic and therapeutic methods of endometrial hyperplastic processes, the problem of treating patients with this pathology remains far from being solved. This dictates the need to optimize management tactics for patients with

EHP during the menopausal transition period, aimed not only at creating comprehensive approaches to predicting the development and recurrence of EH, but also at developing unified protocols for managing such patients.

Local estrogen synthesis and aromatase activity in the endometrium represent important targets for research and clinical practice in gynecology, since their regulation may serve as a significant marker in preventing and treating hyperplastic diseases and endometrial cancer.

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