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NURKHANOVA NILUFAR ODIL KIZI

Modern views on the problem of endometrial hyperplasia in women of the perimenopausal period

(Monograph)

Bukhara – 2026

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The monograph is addressed to obstetricians and gynecologists, a wide range of practicing physicians, as well as students and residents of medical universities and technical schools.

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Annotation

The monograph presents the mechanisms of endometrial hyperplasia development, which is one of the urgent problems of modern gynecology, identifies risk factors, causes of occurrence and recurrence of this pathology in women during the perimenopausal transition period, and also describes diagnostic methods and early markers, in addition, a differentiated approach to the management and treatment of women with hyperplasia is presented. Globally, in the structure of gynecological diseases in women of perimenopausal age, benign endometrial processes account for 60-70%, therefore, predicting, early diagnosis, and treatment of endometrial proliferative processes, which serve as a prerequisite for the development of endometrial cancer, is one of the preventive measures for this disease. It should be emphasized that the frequency of endometrial hyperplasia increases due to hormonal restructuring in the perimenopausal period of women aged 45-55 and ranges from 25-40%. The formation of this pathology in patients of late reproductive and transitional age occurs due to persistent hyperestrogenemia and a decrease in progesterone production. As is known, endometrial hyperplasia can be a cause not only of abnormal uterine bleeding (ABB), which reduces the quality of life, but also a significant risk factor for endometrial malignant transformation.

The author provides detailed information on risk factors for endometrial hyperplasia, such as weight gain, insulin resistance, hormonal imbalance in the body, vitamin D deficiency, and disruption of systemic and local immunity.

Annotatsiya

Monografiyada zamonaviy ginekologiyaning dolzarb muammolaridan biri bo‘lgan endometriy giperplaziyasining rivojlanish mexanizmlari, xavf omillari, perimenopauzal o‘tish davridagi ayollarda ushbu patologiyaning paydo bo‘lishi va qaytalanish sabablari aniqlangan, shuningdek, tashxislash usullari va erta markerlari tavsiflangan, bundan tashqari, giperplaziyali ayollarni olib borish va davolashning differensial taktikasi taqdim etilgan. Dunyoda perimenopauza yoshidagi ayollarda ginekologik kasalliklar tarkibida endometriyning xavfsiz jarayonlari 60-70% ni tashkil qiladi, shu munosabat bilan endometriy saratonining rivojlanishi uchun zamin bo‘lib xizmat qiladigan endometriy proliferativ jarayonlarini bashorat qilish, erta tashxislash va davolash ushbu kasallikning oldini olish choralaridan biri hisoblanadi. Shuni ta’kidlash kerakki, endometriy giperplaziyasining uchrash chastotasi 45-55 yoshdagi ayollar hayotining perimenopauzal davrida gormonal o‘zgarishlar tufayli 25-40% ni tashkil qiladi. Kechki reproduktiv va o‘tish yoshidagi bemorlarda ushbu patologiyaning shakllanishi turg‘un giperestrogeniya va progesteron ishlab chiqarishning pasayishi tufayli yuzaga keladi. Ma’lumki, endometriy giperplaziyasi nafaqat hayot sifatini pasaytiradigan anomal bachadondan qon ketishiga (BBA) sabab bo‘lishi, balki endometriyning xavfli transformatsiyasi uchun muhim xavf omili bo‘lishi mumkin.

Muallif tomonidan endometriy giperplaziyasi rivojlanishida tana vaznining ortishi, insulinga rezistentlik, organizmda gormonal disbalans, D vitamini yetishmovchiligi, tizimli va mahalliy immunitetning buzilishi kabi xavf omillari haqida batafsil ma’lumotlar keltirilgan.

Аннотация

В монографии представлены механизмы развития гиперплазии эндометрия, являющегося одной из актуальных проблем современной гинекологии, выявлены факторы риска, причины возникновения и рецидивирования данной патологии у женщин период перименопаузального перехода, а также описаны методы диагностики и ранние маркёры, кроме этого представлена дифференцированная тактика ведения и лечения женщин с гиперплазией. Во всем мире в структуре гинекологических заболеваний у женщин в перименопаузальном возрасте доброкачественные процессы эндометрия составляет 60-70%, в связи с чем прогнозирование, ранняя диагностика и лечение пролиферативных процессов эндометрия, служащих предпосылкой для развития рака эндометрия, является одним из профилактических мероприятий данного заболевания. Необходимо акцентировать, что частота встречаемости гиперплазии эндометрия увеличивается за счет гормональных перестроек в перименопаузальном периоде жизни женщин от 45-55 лет, составляя от 25-40%. Формирование данной патологии в позднем репродуктивном и переходном возрасте у пациенток происходит за счет стойкой гиперэстрогении и снижения продукции прогестерона. Как известно, гиперплазия эндометрия может стать не только причиной аномальных маточных кровотечений (АМК), снижающих качество жизни, но и весомым фактором риска злокачественной трансформации эндометрия.

Автор приводит подробную информацию о факторах риска развития гиперплазии эндометрия, таких как увеличение массы тела, инсулинорезистентность, гормональный дисбаланс в организме, дефицит витамина D, нарушение системного и локального иммунитета.

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LIST OF CONVENTIONAL SYMBOLS

GPE - hyperplastic processes of the endometrium

GE - endometrial hyperplasia

PGE - pathological endometrial hyperplasia

ER - endometrial cancer

AUB - abnormal uterine bleeding

BS - pain syndrome

IUD - intrauterine device

HRT - hormone replacement therapy

IR injection contraception

KS-climacteric syndrome

OC - oral contraception

PP - perimenopausal period

CS-cytokine status

HEBA - endometrial hyperplasia without atypia

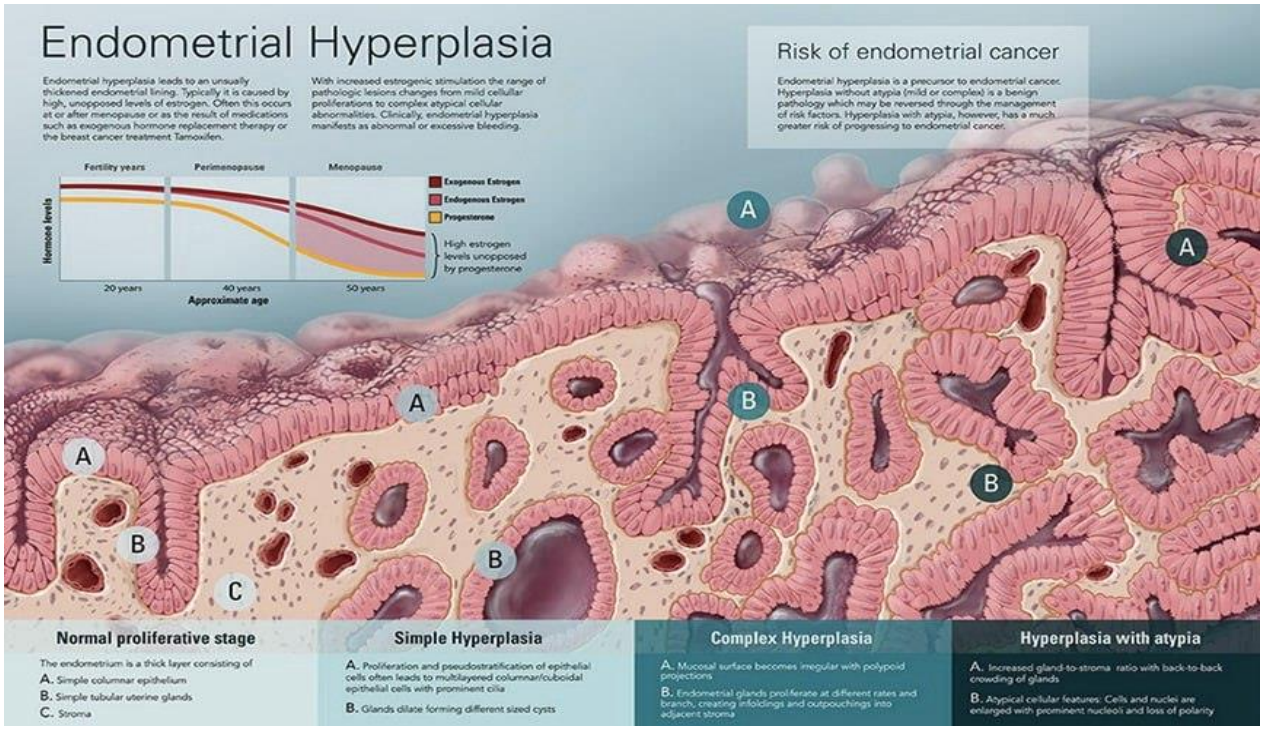
Ultrasound - ultrasound examination

LNG - levonorgestrel

CHAPTER I. CURRENT CONCEPTS OF ENDOMETRIAL HYPERPLASTIC PROCESSES IN THE PERIMENOPAUSAL PERIOD (LITERATURE REVIEW)

Endometrial hyperplasia is a significant medical problem requiring the close attention of gynecologists. This condition, characterized by abnormal growth of uterine tissue, can eventually develop into cancer if not treated promptly. [2; p. 13-14, 6;71-75, 14;42-47, 40;35-40] .

Endometrial hyperplasia (EH) is a pathological condition characterized by abnormal proliferation of the glands and stroma of the endometrium. The main characteristic feature of this disease is the proliferation of the inner layer of the uterus - the endometrium, which leads to thickening and an increase in its volume [44; p. 380-381 , 46; 68-77, 50;15-20, 89; p.20-27, 99; 345-349].



In the structure of gynecological diseases, benign endometrial processes in women in peri- and postmenopause account for 60-70%. Considering that this age period is the peak of endometrial cancer incidence, effective early diagnosis and treatment of proliferative processes of the endometrium, which serve as a

prerequisite for the occurrence of a malignant process, is one of the main preventive measures for this disease [1; p. 91–106 , 5; 4-13 , 9;9-10, 70;368, 78; 57-66].

Hyperplasia caused by dysfunction of cells is a precancerous condition; in some cases it is asymptomatic and its presence can be detected only after a diagnostic examination. However, most often, endometrial hyperplasia is externally manifested by hormonal cycle disorders [17; p. 66-92 , 26; 304 , 39; 127-128, 84]

Many women during menopause may develop endometrial hyperplasia even with normal hormone levels. This is due to disruptions in intracellular processes and changes in receptors. The disease can progress in different ways: either through the proliferation of normal cells due to elevated estrogen levels or through the growth of abnormal cells. Therefore, endometrial hyperplasia and cancer cannot be considered stages of the same disease. It is important to understand that these conditions have different causes and require different treatment approaches.

§1.1 . Etiology and pathogenesis of endometrial hyperplasia

Asymptomatic endometrial hyperplasia carries its own dangers. The absence of discomfort does not preclude the development of serious complications, including endometrial cancer. Long-term untreated disease can negatively impact reproductive function and even lead to endometrial cancer. [86; p. 25, 130; p. 160-1175].

In recent years, there has been an alarming trend towards an increase in the number of cases of endometrial cancer. About 150,000 new cases of this disease are diagnosed annually, and more than 42,000 women die from it. Women aged 55-65 years are most at risk. However, endometrial cancer is increasingly diagnosed in younger women, including those of reproductive age. According to most experts, endometrial cancer is closely related to a previous condition - endometrial hyperplasia. EHP is a fairly common pathology in gynecology, occurring in 15-40% of patients. It is especially often diagnosed in women closer to menopause, reaching 50% of cases. [42; p. 28-31 , 53;13-16, 72;40-42, 90; 565-570 , 97; 33-38] .

Estrogens play a key role in regulating the menstrual cycle by stimulating the growth of the uterine lining (the endometrium). With prolonged exposure to these

hormones, whether natural (due to hormonal imbalances) or artificial (due to hormonal medications), the normal process of endometrial growth can develop into a pathological condition called hyperplasia, characterized by excessive cellular proliferation. Endometrial hyperplasia is an abnormal proliferation of both the glandular and stromal components of the endometrium, accompanied by a disruption of their normal histological organization. Unlike physiological endometrial hypertrophy, hyperplasia is characterized by specific cytoarchitectonic changes that indicate a pathological process.

There are two types of classification of endometrial hyperplasia. They are based on the analysis of several factors: the thickness of the inner uterine lining, the number and structure of glands, and the cytological characteristics of the glandular epithelium. The first type of classification uses more general terms, such as "cystic hyperplasia," "adenomatous hyperplasia," and "atypical adenomatous hyperplasia." These terms describe how much the glands and cells have changed compared to the norm. The more changes, the higher the risk of developing cancer. According to the classification adopted by the international community of gynecologists and pathologists, hyperplasia is divided into several types. This allows for a more accurate determination of the likelihood of a benign process turning malignant. A distinction is made between simple hyperplasia, complex hyperplasia without signs of malignant changes, and atypical hyperplasia, which is characterized by the presence of cells with deviations from the norm and is considered a precancerous condition. [22; p. 28–32. , 107 ; p. 399-404 , 113;259-268] .

According to research, from 23 to 32% of women with atypical endometrial hyperplasia face the risk of developing uterine cancer. (Ashrafyan L.A., Kisilev V.I. 2008, M.I. Davydova et al. 2005 G) According to other studies, the risk of malignancy (transformation into cancer) of atypical hyperplasia is about 52%. (Liu F. C. 2007) The risk of transformation of recurrent hyperplasia into uterine cancer is 20-30%.

Scientists from the Royal College of Obstetricians and Gynaecologists note that studies conducted in the United States, Canada, and China have shown that

endometrial hyperplasia without atypia (EHBA) does not always progress to cancer. Over 25 years, this risk is less than 5%. Moreover, in many cases, EHBA resolves spontaneously without treatment within a few years. In routine practice in our country, gynecologists are guided by the 2018 "Standards for the Diagnosis and Treatment of Gynecological Diseases in Medical Institutions of the Healthcare System of the Republic of Uzbekistan."

Risk factors for the development of endometrial hyperplasia include early onset of menstruation, no history of pregnancy or childbirth, late menopause, hormonal imbalance, obesity, polycystic ovary syndrome, and estrogen. secreting ovarian tumors, taking hormonal drugs during menopause [12; p. 291 , 23;23, 33;220–269, 62; 40-56, 106;p.35] .

Simple endometrial hyperplasia is characterized by excessive proliferation of glandular elements and endometrial stroma, which distinguishes it from the physiological cystic involution typical of the perimenopausal period. Although the risk of malignancy in simple hyperplasia is relatively low, it is considered a potential precancerous marker requiring dynamic monitoring and, in some cases, specific treatment.

Complex endometrial hyperplasia is an abnormal proliferation of glandular cells without stromal proliferation. According to many authors, adenomatous hyperplasia is a true precancerous condition that can be diagnosed histologically even in the presence of small lesions against a background of normal endometrium.

Atypical hyperplasia is characterized by pathological changes in endometrial cells, which significantly increases the risk of malignancy. The risk of developing endometrial cancer with this pathology ranges from 20 to 30%. [30; p. 56-61, 35; 138, 51; 70-74, 59; 166-167, 96; p. 1191–1197].

Traditionally, the pathogenesis of endometrial hyperplasia has been associated with hormonal imbalances. However, modern scientific evidence suggests a more complex picture. Even with normal hormonal levels, pathological changes in the endometrium can develop. Advances in molecular biology, genetics, and immunology have identified numerous interacting factors that influence

endometrial growth and regulation. Regulation of endometrial cell growth is a complex process involving not only female sex hormones but also numerous other biologically active substances. These include growth factors, cytokines, lipid breakdown products (arachidonic acid metabolites), and components of the immune system. Research has shown that an imbalance between cell proliferation and programmed cell death plays a key role in the development of various diseases associated with abnormal tissue growth. Increased resistance of endometrial cells to programmed death (apoptosis) contributes to their excessive proliferation and accumulation of abnormal cells, which underlies the development of tumor processes in the endometrium [16; p. 21-27 , 18; 55-78, 25; 37-40, 32; 45-46, 80; 306-310] .

High expression of estrogen receptors in the endometrium creates conditions for the development of endometrial hyperplasia at relatively low levels of circulating estrogens. This process is caused by local disturbances in the regulation of cell proliferation and metabolic changes in the endometrium [66; p. 62-66 , 92 ; p. 621-629, 100; 135-136].

A study by Yu.E. Dobrokhotova and L.V. Saprikina (2021) identified the following risk factors for the development of endometrial hyperplasia (EH): hereditary predisposition (34.62%), intrauterine disorders, pathological conditions that arose in adolescence, irregular periods or other deviations in the menstrual cycle (46.92%) leading to reproductive dysfunction (20%), which leads to gynecological diseases and surgical interventions.

Modern medicine views endometrial hyperplasia as the result of several factors. Numerous studies confirm that one of the main factors contributing to the development of this disease is elevated levels of female sex hormones (estrogens) in a woman's body [66; pp. 62-66 , 92 ; pp. 621-629] .

Scientific studies confirm that long-term use of synthetic estrogens, including drugs such as tamoxifen, can stimulate excessive proliferation of endometrial cells (hyperplasia) and, in some cases, contribute to the development of cancer [95; 435-442, 105 ;137–150].

Chronic endometritis disrupts the natural mechanism of endometrial cell renewal, whereby cell division and death are balanced. This imbalance, caused by chronic inflammation, leads to the development of pathological changes in the endometrium and, consequently, endometrial hyperplasia. Chronic endometrial inflammation is associated with an imbalance between cell death (apoptosis) and cell division. Macrophages play a key role in this process, releasing tumor necrosis factors and transforming growth factor. These substances promote both endometrial cell death and their uncontrolled proliferation. Depending on which process predominates, either pathological proliferation or endometrial atrophy develops [109; p. 1146-1149, 120;64] .

Although elevated estrogen levels are the primary cause of endometrial hyperplasia, other factors such as a weakened immune system (e.g., in kidney transplant patients) and infections may also contribute to the development of this condition. Studies have shown that women who have undergone a kidney transplant are twice as likely to experience abnormal uterine bleeding associated with endometrial hyperplasia compared to women without a transplant [4; p. 113-119, 34; 33-42, 43; 50-58, 94; p. 327-330].

Current knowledge about the immune system in women with reproductive organ tumors is insufficient and contradictory. This creates difficulties in assessing the body's immune response to the tumor and selecting the most effective treatment methods. To optimize therapeutic approaches and develop new preventive strategies, additional research is needed to understand the immunological aspects of the development of these diseases [29; pp. 35-40 , 58; 46-47].

Despite the numerous scientific studies conducted on this pathology, the molecular biological mechanisms of its development and its influence on the increased risk of malignancy of the process, issues of prognosis, early diagnosis and treatment of its subclinical forms still remain not fully understood and scientifically substantiated.

§ 1.2. Determination of risk factors and preclinical diagnosis of endometrial hyperplasia

One of the main challenges in modern medicine remains the search for reliable ways to predict who will develop endometrial hyperplasia and, more importantly, its malignant form. Scientists are striving to develop systems that would help identify groups of women at increased risk. As noted by Klinyshkova T.V., Tuchaninov D.V., and Frolova N.B. (2020), in order to select the optimal treatment for each patient with endometrial hyperplasia, it is necessary to accurately assess their individual risk. However, despite numerous studies in this area, a unified and universal risk assessment system has yet to be developed, and existing approaches often contradict each other.

Many researchers believe that the main causes of endometrial hyperplasia in women during menopause include diabetes mellitus, obesity, certain health conditions, and the use of hormonal medications. One of the most significant factors associated with the development of endometrial hyperplasia and its progression to endometrial cancer is a woman's lack of childbirth. Research shows that women who have given birth are less likely to develop endometrial cancer. For example, a study by Raglan O. and colleagues (2019) found that the risk of developing endometrial cancer is lower in women who have given birth than in those who have not. These findings are a consequence of hormonal changes in the body during pregnancy, specifically increased progesterone levels.

In recent years, endometrial hormonal resistance has been considered one of the key links in the pathogenesis of endometrial hyperplasia, especially in patients with obesity and insulin resistance. Hormonal resistance refers to the decrease in the biological response of endometrial tissue to physiological and therapeutic concentrations of steroid hormones, primarily progesterone, despite its adequate or elevated levels in the systemic bloodstream.

Obesity is accompanied by pronounced endocrine-metabolic changes that contribute to the formation of endometrial hormonal resistance. Fat tissue, acting as an active endocrine organ, enhances the peripheral aromatization of androgens into

estrogens, leading to chronic hyperestrogenism. Prolonged exposure to estrogens without adequate progesterone counteraction causes persistent proliferative activity of the endometrium and depletion of the progesterone signal cascade.

Insulin resistance and accompanying hyperinsulinemia play an independent role in the disruption of endometrial hormonal sensitivity. Increased insulin levels reduce the synthesis of sex hormone-binding globulin (SHBG), which increases the concentration of free, biologically active estrogens. Simultaneously, insulin and insulin-like growth factor-1 (IGF-1) directly stimulate endometrial cell proliferation through the activation of tyrosine kinase-type receptors and intracellular signaling pathways PI3K/Akt/mTOR and MAPK, competing with progesterone-dependent differentiation mechanisms.

At the molecular level, in patients with obesity and insulin resistance, a decrease in the expression of progesterone receptors (PR), especially the isoform PR-B responsible for the antiproliferative effect of progesterone, is observed. Disruption of the PR-A/PR-B ratio, epigenetic changes, and inflammatory microenvironment of the endometrium lead to weakening of stroma decidualization and decreased apoptotic activity, forming the progesterone resistance phenomenon.

An additional pathogenetic factor is chronic low-intensity inflammation, characteristic of obesity. Increased production of adipokines (leptin, resistin) and pro-inflammatory cytokines (TNF-α, IL-6) disrupts steroid signaling and enhances the expression of proliferative and anti-apoptotic factors in the endometrium. Under conditions of insulin resistance, these changes become persistent and maintain the pathological proliferative phenotype of endometrial tissue.

The clinical manifestation of endometrial hormonal resistance in patients with obesity and insulin resistance is a decrease in the effectiveness of progestin therapy, a high frequency of endometrial hyperplasia relapses, and the need for repeated treatment courses or surgical interventions. Thus, obesity and insulin resistance form an interconnected pathogenetic complex, leading to a disruption of endometrial hormonal regulation and resistance to standard treatment methods.

Considering the above, studying the mechanisms of endometrial hormonal resistance in the context of metabolic disorders presents a promising direction for developing personalized diagnostic and therapeutic approaches to endometrial hyperplasia.

Many studies indicate a close link between endometrial hyperplasia and endocrine disorders. Women with elevated blood insulin levels, insulin resistance, impaired glucose tolerance, diabetes mellitus, and excess body weight are at higher risk of developing this disease. [48; p. 380, 63; 8-18, 88 ; p. 195-198] .

An analysis of risk factors for endometrial diseases conducted by Akhmetova et al. in 2006 revealed a close association between endometrial pathologies and a number of somatic diseases. Specifically, it was noted that women with endometrial diseases are significantly more likely to suffer from obesity, nodular goiter, type 2 diabetes, and hypertension.

A 2011 study by Korneva and colleagues found the following trends among perimenopausal women:

- **High levels of metabolic disorders:** Most women (71.8%) in this age group demonstrated increased glucose sensitivity and insulin resistance.
- **The problem of excess weight:** A significant proportion of the study participants (66%) were overweight.

From the above data it is clear that endocrine and metabolic disorders are one of the main background conditions for the development of proliferative diseases of the endometrium and a manifestation of hormonal imbalance.

Overweight and obesity are significant risk factors for endometrial cancer. This is primarily because adipose tissue in overweight women actively produces female sex hormones (estrogens). Elevated estrogen levels stimulate the growth of endometrial cells and can lead to the development of malignant tumors. Furthermore, obesity is associated with impaired carbohydrate metabolism (elevated insulin levels) and chronic inflammation, which also contribute to the development of cancer.

IN A study by Kacalska-Janssen et al. (2013) established a statistically significant link between insulin resistance and premenopausal age in women. The authors demonstrated a correlation between the hyperglycemic response to the oral glucose tolerance test and endometrial pathology.

Numerous studies, including the work of D.I. Baburin and T.E. Kolesova (2017), as well as a meta-analysis by K.K. Tsilidis (2015), demonstrate a statistically significant association between diabetes mellitus and an increased risk of endometrial cancer. The risk of developing this disease in women with diabetes increases almost twofold. The mechanism of this phenomenon is associated with hyperinsulinemia, characteristic of type 2 diabetes mellitus. It is believed that insulin can have a direct mitogenic effect on endometrial cells or indirectly contribute to the development of cancer by increasing estrogen levels. Obesity, insulin resistance, and diabetes mellitus were often combined with hypertension in perimenopausal women, and late menopause in this category of patients occurred in 40-50% of cases. [7; pp. 27-33, 36; 44-48, 55; 125, 85; 52-55].

The research results indicate a close relationship between hyperplastic processes and endometrial cancer with endocrine disorders (hyperestrogenemia), metabolic syndrome (obesity, diabetes mellitus, hypertension) and the patient's reproductive history.

Unfortunately, there are currently no objective preclinical markers that accurately correlate the dynamics of endometrial hyperplasia and predict the likelihood of its malignancy. Based on clinically significant risk factors, tailoring individualized management, treatment, and follow-up strategies is a promising approach for increasing the effectiveness of endometrial hyperplasia therapy and improving the lifestyle of perimenopausal women.

§ 1.3. Early diagnosis of endometrial hyperplasia: markers and prognosis.

According to the latest statistics, the incidence of endometrial cancer in Uzbekistan has increased by 11.6% over the past five years. This trend is consistent with the global pattern of increasing incidence of this type of cancer. There is a direct

link between endometrial hyperplasia and the risk of developing endometrioid adenocarcinoma, especially its recurrent form, but data on its prevalence are extremely scarce, since there is no official registration of this insidious pathology, although assessment of the incidence of HE plays an important role not only in the aspect of tactics for managing uterine bleeding associated with women in the perimenopausal period, but also for the purpose of preventing the development of endometrial cancer. Proliferative processes in the endometrium are considered a precancerous condition with varying degrees of probability of malignancy [11; pp. 25-32, 15; 333-338, 81; 65-71].

The incidence of malignancy for GE without atypia is up to 1-3%, while for women with atypical hyperplasia and endothelial intraepithelial neoplasia it is more than 30% (SobczukK 2017, Selenium S. Et . al . 2020). This close relationship and the steady increase in the incidence of GE and endometrial cancer dictates the need for specialists and scientists to search for effective markers for preclinical diagnosis and prognosis of this serious pathology in patients of late reproductive age.

The first step in diagnosing endometrial diseases is usually a transvaginal ultrasound. If the findings are inconclusive, hysterosalpingography or uterine lavage may be performed to confirm the diagnosis. The most accurate results are achieved by combining hysteroscopy with separate diagnostic endometrial curettage. The final diagnosis is confirmed by histological examination of the endometrium.

One of the characteristic signs of endometrial hyperplasia is anovulatory uterine bleeding. This manifests itself as irregular menstrual periods, which begin with a delay and can last significantly longer than usual, accompanied by both moderate and heavy blood loss [8; pp. 188-192, 49; 78-82].

Pelvic ultrasound plays a crucial role in the prediction and early detection of endometrial hyperplasia, especially its complicated forms. This method allows for the assessment of the endometrium and is one of the most informative markers for determining the further course of the disease. Transvaginal ultrasound is a modern, safe, and informative method for assessing the endometrium and identifying various pathological processes, including hyperplasia. The most accurate results can be

obtained by performing the examination on days 5-7 of the menstrual cycle in menopausal women. Normally, the endometrial thickness during this period should not exceed 5-7 millimeters. If this value is lower, the likelihood of endometrial hyperplasia is extremely low. On ultrasound, hyperplastic endometrium has a diffuse, heterogeneous echo pattern. This can be manifested by the presence of ECHO positive and ECHO negative inclusions, the absence of a line of closure of the mucous membrane of the uterine cavity and its uneven contour, as well as an unclear border “endometrium-myometrium” [20; p. 178-180, 57; 192, 61; 225, 64; 89-93, 83; [205-213]

In women with active endometrial glandular hyperplasia, ultrasound reveals a significantly thicker uterine lining than normal. It can increase by 5-12 millimeters per week. Before the onset of menstruation, it can reach 16-30 millimeters. Despite this thickness, the uterine lining appears normal mid-cycle on ultrasound. That is, it consists of three layers. However, it is dominated by dark areas, indicating that the upper layer of the lining has grown more than necessary.

In inactive glandular hyperplasia, the uterine lining appears uniform, without obvious changes, as if in the early phase of the menstrual cycle. The tissue is of medium to high density, closely following the shape of the uterus. In glandular cystic hyperplasia, areas of the lining are visible that do not fill with fluid during the procedure, forming so-called "filling defects." The shape of the uterus usually remains unchanged, but characteristic cavities appear on its surface.

Perimenopausal women typically experience a disruption in endometrial echogenicity relative to the menstrual cycle phase. The optimal time for an ultrasound examination is immediately after menstruation, when a thin M-echo indicates complete shedding of the functional layer of the endometrium. An increase in the anteroposterior diameter of the M-echo, both diffuse and focal, should be considered a pathological sign. It should be emphasized that differential diagnosis of glandular and atypical endometrial hyperplasia using ultrasound is generally difficult.

Assessing blood flow in the spiral arteries using Doppler ultrasound is a promising method for the early diagnosis of endometrial hyperplasia. Patients with this condition exhibit increased blood flow in these vessels, which may indicate the onset of proliferative processes in the endometrium. The absence of such blood flow in the M-echo projection in healthy women indicates a normal endometrium.

Modern diagnostics of endometrial hyperplasia (EE) requires the integration of morphological and molecular research methods, among which immunohistochemistry (IH) occupies one of the key positions. The limited possibilities of routine histological analysis, especially in differentiating endometrial hyperplasia without atypia, atypical hyperplasia, and endometrial intraepithelial neoplasia (EIN), necessitate the use of additional objective criteria that allow for increased accuracy in diagnosing and prognostically assessing the disease.

Immunohistochemical methods are based on the identification of tissue-specific expression of hormone receptors, proliferation markers, apoptosis, and molecular signaling pathways involved in the pathogenesis of endometrial hyperplastic processes. The use of IGC allows for a quantitative and qualitative assessment of the biological behavior of endometrial tissue and the identification of early signs of adverse transformation.

One of the key areas of IGC diagnostics in GE is assessing the expression of estrogen (ER) and progesterone receptors (PR). It has been established that endometrial hyperplasia without atypia is characterized by high ER expression and preserved PR expression, while in atypical hyperplasia and EIN, there is a decrease or heterogeneity of PR expression, especially the PR-B isoform. The imbalance between ER and PR reflects hormonal regulation disorders and is an important predictor of progestin therapy effectiveness.

Cell proliferation markers, primarily Ki-67, are widely used to assess the proliferative activity of the endometrium. An elevated Ki-67 index correlates with the severity of hyperplastic changes and the risk of the process progressing. In atypical GE, the proliferative activity is generally moderate and uniform, while in

atypical forms, a marked and focal increase in Ki-67 expression is observed, especially in the glandular epithelium.

Determining the expression of PTEN tumor suppressor has significant diagnostic and differential diagnostic significance. The loss or decrease in PTEN expression is an early molecular event in the development of endometrial neoplasia and is characteristic of EIN and high-risk forms of GE. In contrast, with simple endometrial hyperplasia, PTEN expression is typically preserved, allowing for the use of this marker to differentiate between benign and precancerous processes.

Additional information about the biological potential for endometrial hyperplasia is provided by apoptosis and cell cycle markers such as p53, Bcl-2, and Bax. Anomalous expression of p53, although relatively rare in HE, may indicate a high risk of malignancy and requires caution regarding the hidden malignant process. Elevated expression of the antiapoptotic protein Bcl-2 in combination with a decrease in Bax reflects the suppression of programmed cell death and contributes to the persistence of hyperplastic changes.

In recent years, increasing attention has been paid to IGC assessment of PI3K/Akt/mTOR signaling pathway components, as well as insulin receptors and insulin-like growth factor (IGF-1R), especially in patients with obesity and insulin resistance. The activation of these pathways is associated with the progression of endometrial hyperplasia and the formation of hormonal resistance, which emphasizes the importance of IGC not only in diagnosis but also in the pathogenetic stratification of patients.

Endometrial pathologies in perimenopausal women often remain asymptomatic, complicating early diagnosis. However, the risk of malignancy increases significantly, especially in the presence of abnormal uterine bleeding and recurrences. Endometrial hyperplasia with atypia can be diagnosed using ultrasound. Absence of blood flow in the uterine lining on ultrasound is generally considered normal in menopausal women. Therefore, the detection of blood flow in this area may be a sign of pathological changes, such as endometrial hyperplasia with atypia. Ultrasound and histology are different diagnostic methods, each with their own

limitations. In the case of endometrial pathology and small fibroids, ultrasound can detect the presence of a lesion but cannot always determine its exact nature. Histology, in turn, provides an accurate morphological diagnosis based on the examination of tissue obtained during a biopsy. [21; p.57-65, 73;243, 98; p.851-856, 104;235].

Histological confirmation of endometrial hyperplasia (EH) is a key step in the diagnosis of endometrial cancer. Endometrial biopsy, performed according to clearly defined algorithms, allows for an accurate diagnosis and the determination of treatment strategies. Women over 40 years of age and with a body mass index of 30 or higher are at risk and are recommended to undergo a more thorough examination [41; p. 68-72, 68; p. 59-61, 108; p. 241-245].

An endometrial biopsy performed under hysteroscopy is especially important for patients undergoing the procedure on an outpatient basis. This method allows for accurate sampling and excludes the possibility of endometrial cancer or other dangerous changes. This allows the physician to select the most effective treatment for each individual patient. Given that the diagnostic accuracy of hysteroscopy alone is insufficient for the prognosis and early diagnosis of endometrial cancer, a targeted endometrial biopsy is essential when ultrasound findings are suspicious.

Cytological examination of uterine contents obtained by aspiration in the second phase of the menstrual cycle is a valuable tool both for monitoring the treatment of gynecological diseases and for screening endometrial pathologies. Detection of signs of active proliferation in the glandular structures of the endometrium serves as an indicator of hyperplastic processes. However, given the limited information content of the cytological method in the differential diagnosis of various types of hyperplasia, its main purpose is to identify patients requiring in-depth histological examination to clarify the diagnosis and determine management tactics [13; p. 105-108, 52; 567-570, 74; 39-42, 102; p. 1-9, 111; 1476-1478].

The endometrium is a dynamic tissue that constantly changes throughout the menstrual cycle under the influence of hormones. Any disruption to this hormonal

regulation can lead to abnormal growth of the endometrium and, consequently, to various pathologies.

Absolute or relative hyperestrogenism is a pathogenetic factor in the development of endometrial hyperplasia. Microscopically, disruption of the endometrium's architecture is observed, manifested by diffuse proliferation of glands and stroma and loss of the clear boundary between the basal and functional layers.

Endometrial glandular cystic hyperplasia is a condition in which the glands of the uterine lining grow and change shape, becoming tubular, cystic, or branched. Long-term exposure to the female hormone estrogen without the counteraction of progesterone leads to the formation of cysts in the glands, changes in their structure, and the appearance of clots in small vessels. Tissue destruction and changes in the epithelial cells around the glands occur. Microscopic examination reveals uneven gland growth: in some areas, there are many glands located close to each other, while in others, there are fewer and more widely spaced. Uneven glandular growth is an important sign that helps assess the severity of the condition and the likelihood of developing endometrial cancer. [45; p. 105-115, 79; 37-40, 93; p. 258–63, 101; 1006–1026].

After a comprehensive examination and establishment of a clinical and morphological diagnosis, it will be necessary to address issues of therapy, assess the effectiveness of treatment and select the optimal gynecological tactics for managing perimenopausal women.

§ 1.4. Tactics of management and treatment of women with proliferative processes in the perimenopausal period

Treatment of endometrial proliferative processes in women is aimed at solving several key problems depending on the patient's age:

- **Stopping bleeding:** This is a priority, especially if there is heavy or prolonged bleeding associated with these processes.

- **Restoring the menstrual cycle:** In women of reproductive age, the main goal is often to restore the normal menstrual cycle.
- **Achieving endometrial atrophy:** In older women, the goal of treatment is to create conditions for the reduction and thinning of the uterine lining (endometrium), which reduces the risk of complications.
- **Prevention of relapse:** All treatment methods involve measures aimed at preventing the recurrence of pathological changes in the endometrium.

In essence, treatment is selected individually, taking into account the woman's age, the nature of the disease, the presence of concomitant diseases and other factors, and is aimed at eliminating symptoms, preventing complications and improving the patient's quality of life [47; p. 78, 56; 256, 110;p.52, 119;379-382, 123; 232–240].

Modern treatment of endometrial hyperplasia is multifaceted and depends on the individual characteristics of each patient.

Existing methods of treating GE can be divided into several groups:

- **Curettage of the uterine cavity:** involves the removal of altered endometrial tissue.
- **Hormonal therapy:** aimed at regulating hormonal levels.
- **Surgical treatment:** In some cases, more radical intervention may be required.

The choice of treatment method is determined in a comprehensive manner:

- **The results of histological examination** allow us to accurately determine the type and extent of changes in the endometrium.
- **Patient age:** Younger women may require different approaches than menopausal women.
- **Concomitant diseases:** both gynecological and general.

It is important to note that treatment for GE always begins with a thorough diagnosis and is selected individually for each patient [31; p. 26, 115; p. 245-247, 124;273-279, 128; 1459–1465].

Hormone therapy remains the primary treatment for endometrial hyperplasia without atypia. Research shows that the rate of endometrial tissue growth is directly

related to the dosage and duration of estrogen administration. Although high free estrogen levels increase the risk of these processes, combined estrogen and progesterone therapy during menopausal hormone therapy has become the standard treatment for women with this condition.

To protect the endometrium from excessive growth under the influence of estrogens, it is necessary to select the correct hormonal drugs.

- **The choice of hormonal medications and their dosage are very important.** Optimal effects are achieved with continuous use of certain combinations of estrogens and progestins.
- **Not all progestogens are equally effective.** Normethyltestosterone derivatives are better for endometrial protection; they are more effective than pregnane or microdose progesterone.
- **Microdose progesterone and dydrogesterone are recommended as first-line treatments** for hormone replacement therapy (HRT), but their effectiveness may be lower than that of other drugs.
- **It is important for women to understand that the correct use of hormonal drugs** requires strict adherence to the doctor's recommendations regarding dosage and duration of use.

According to some studies, hormonal therapy for endometrial hyperplasia without atypia can be effective in 42% of cases [19; p. 768, 60; 18, 77; 98, 114 ; p. 89-97 , 127; 6].

Hormonal drugs, particularly progestogens, play an important role in the treatment of endometrial hyperplasia. Numerous studies have confirmed their effectiveness in reducing pathological growths of the endometrium. This effect is achieved due to the ability of progestogens to stimulate programmed cell death of the endometrium (apoptosis), which leads to a reduction in the glandular component [24; p. 59-63 , 54; 496-501 , 118; p. 443-448 , 126; 121-124].

Dydrogesterone is a highly selective progestogen that specifically binds to progesterone receptors and has few side effects. Dydrogesterone is prescribed for the treatment of endometriosis at a dosage of 10 mg twice daily continuously for 6-

12 months. The effectiveness of therapy is monitored by ultrasound with M-echo determination of endometrial thickness. Duphaston has no estrogenic, androgenic, or corticoid activity and exhibits antiestrogenic activity only in certain target tissues, including the endometrium. This hormonal drug offers the following advantages:

- **Safe for the cardiovascular system:** does not affect blood clotting, fat, sugar and insulin levels, or water-salt balance.
- **High efficiency:** the drug actively binds to progesterone receptors, which is especially important for problems with endometrial sensitivity to progesterone [87; p. 78-79, 125; p. 375–378].

Gonadotropin-releasing hormone agonists are considered a promising agent for the independent treatment of endometrial hyperplasia. Their mechanism of action is based on the ability to suppress the proliferation of endometrial cells by interacting with special receptors sensitive to hormones that stimulate the production of germ cells [27; p. 11-24 , 65; 61-62 , 82; 59-63 , 116;r. 205] .

The Mirena intrauterine device, which contains the hormone levonorgestrel, has become a popular treatment for various gynecological conditions. Its effectiveness is due to the high concentration of the hormone in the uterine lining, which is hundreds of times higher than that found with hormonal pills. Mirena has a comprehensive effect on the woman's body: it reduces endometrial blood flow, lowers prostaglandin levels (substances that cause inflammation and pain), and inhibits fibrinolysis (the process of dissolving blood clots). Thanks to these mechanisms, Mirena not only reliably prevents pregnancy for 5 years but also helps treat a number of gynecological conditions.

A study conducted by Tkachenko and Sviridova in 2019 found that in 95.4% of cases of patients with various forms of endometrial hyperplasia after six months of therapy with a levonorgestrel-releasing intrauterine system (LNG-IUS), repeated histological analysis did not reveal signs of pathological endometrial proliferation [75; pp. 40-44].

The main indicators of success of conservative treatment are: the disappearance of clinical manifestations of the disease, prevention of recurrence of

symptoms, and normalization of the menstrual cycle. Despite this, none of the existing conservative methods are aimed at eliminating the underlying cause of the disease. Moreover, there is a risk of progression of the pathological process, which may require surgical treatment.

If conservative treatment of endometrial hyperplasia does not provide positive results, or if there is a high risk of developing cancer, the only effective method is a two-stage surgical procedure. Endometrial ablation is the initial stage of surgical treatment, which uses two main methods: destruction of the endometrium with electrodes or its excision with an electrical loop. However, if, after ablation, a woman develops endometrial hyperplasia again, especially in combination with uterine fibroids or adenomyosis (in the period before and during menopause), then a more radical operation is often necessary – removal of the uterus (hysterectomy) [28; pp. 28-31 , 67; 248, 121 ; pp. 382-386].

A key aspect of endometrial neoplasia prevention is normalizing a woman's hormonal balance. To prevent the disease from developing, it is necessary to address the causes of excessive endometrial growth. Endometrial neoplasia prevention is aimed at reducing the risk of developing endometrial tumors by correcting risk factors.

A key aspect of endometrial cancer prevention is secondary prevention, which involves timely diagnosis and treatment of precancerous conditions. Regular screening using transvaginal ultrasound, as well as targeted clinical examinations for at-risk groups, are the most effective measures for achieving this goal.

Thus, given the deteriorating gynecological health of women, the most promising areas are early diagnosis, prevention, and treatment of conditions that lead to the development of pathological endometrial hyperplasia in women during the critical perimenopausal period. Early prognosis and subclinical diagnosis of this pathology are crucial for reducing oncological problems in women of late reproductive age in the Republic of Uzbekistan.

Based on the above data, despite the high recurrence rate of GE, the problem of identifying factors predicting treatment efficacy and the likelihood of recurrence

remains unresolved. The lack of reliable diagnostic criteria for GE recurrence and its development into PGE, as well as predictors of its progression to endometrioid adenocarcinoma, justifies the need for monitoring the effectiveness of long-term hormone therapy, morphological examination, and the selection of appropriate patient management strategies to prevent adverse outcomes.

CHAPTER II. CLINICAL AND LABORATORY CHARACTERISTICS OF EXAMINED WOMEN WITH ENDOMETRIAL HYPERPLASIA

§2.1. Health status of the contingent and determination of risk factors for the development of hyperplastic processes in women in the perimenopausal period of life.

Endometrial hyperplasia is a pathological process characterized by abnormal proliferation of the endometrial glands and stroma. This endometrial pathology, lacking specific pathognomonic symptoms, complicates differential diagnosis, thereby increasing the risk of malignancy. Benign endometrial lesions account for 50-60% of gynecological diseases in perimenopausal women.

The age of the study participants ranged from 45 to 55 years, averaging approximately 49±2 years. There were no statistically significant differences in mean age between the main and control groups ($p > 0.05$).

Women's employment and education can also characterize the examined patients. An analysis of their place of employment revealed that the majority of women were temporarily unemployed (35%) or housewives (15%). The remaining patients were manual workers (29.8%) and mental workers (21.4%). Of these, in the control group, 18.1% were temporarily unemployed, 9.1% were housewives, 10.2% were manual workers, and 9.1% were mental workers. In the main group, this indicator was distributed as follows: temporarily unemployed (17.4%), housewives (6.3%), manual workers (19.6%), and mental workers (12.3%) (Fig. 2.1.1).

As can be seen from the above, no obvious differences were found between the groups by type of employment, only in the main group there were almost 2 times more female manual workers.

Furthermore, examining the medical histories of women in the study groups, we determined that 71% of patients in the control group were married, compared to 58.2% in the study group. Single women accounted for 6% and 8.1%, respectively, and 23% of the control group and 33.7% of the study group were divorced. As can be seen from the above data, a significant difference of 9.3% between divorced

women was found in the study group, suggesting that this aspect can be considered a risk factor for the development of perimenopausal AUB.

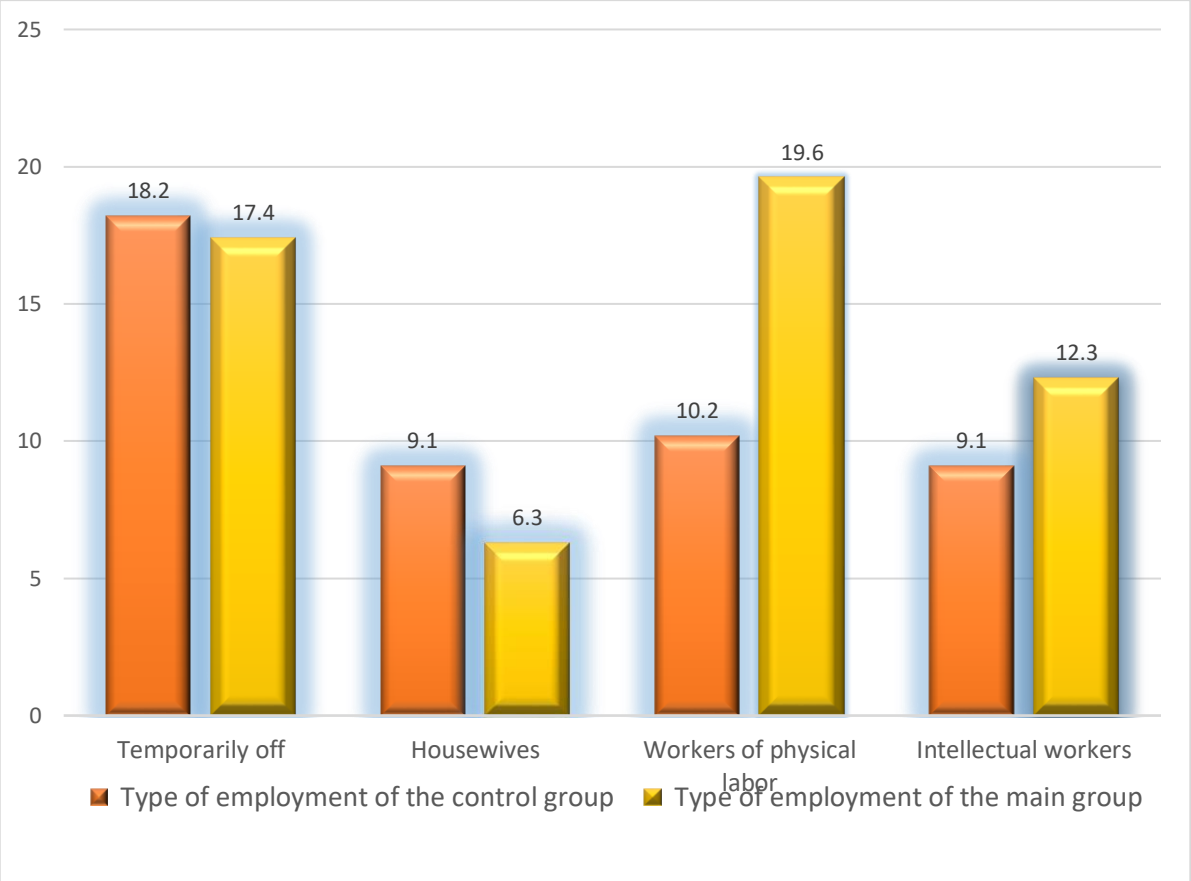


Figure 2.1.1. Type of employment of women in the study groups (%)

Furthermore, as a result of examining women in the selected groups, we found that the nature of menstrual function in both groups did not differ significantly. The average age of menarche in the main group was ±14.0 and ±14.5 years, in the control group ±13.2 years (p> 0.05). The duration of the menstrual cycle ranged from 25 to 32 days, on average, it was 28-30 days in the main group, and 26-27 days in the control group (> 0.05). The duration of bloody discharge did not differ significantly in the main study groups, amounting to 8.2 ± 0.5 and 8.6 ± 0.6 days, and blood loss was assessed as significantly heavy in all cases. Pain at the onset of menstruation also affects the quality of life in the perimenopausal period, which was assessed based on the severity of pain.

As can be seen from the table below, the survey of women in the control group revealed that the severity of pain was grade I in 6 patients (14.3%), grade II in 3 (7.1%), and grade III in 1 (2.3%). In the main group with GE, the following picture

was observed: these indicators were distributed in the following order: 9 (25%), 6 (16.6%), and 5 (13.8%), respectively. In the group with recurrent PGE, the figures were 10 (29.4%), 6 (17.6%), and 8 (23.52%). The data are presented in Table 2.1.1.

Table 2.1.1.

Assessment of pain severity in comparative groups

Severity of dysmenorrhea	I - group , (control group), n = 36		II - group, main (women with GE), n = 40		Group III , main group (women with GE with transition to PGE), n = 38	
	ABS	%	ABS	%	ABS	%
Grade I (mild pain)	4	11.1	6	15	5	13.2
Grade II (menstruation with severe pain)	2	5.56	9	22.5	10	26.3
Grade III (severe pain)	1	2.78	3	7.5	4	10.5

Based on this, it can be concluded that in the third group, the indicators were compared; the severity of symptoms of dysmenorrhea increased exponentially compared to the control group.

Since previous gynecological diseases have a direct impact on the development of AMC, we decided to study them. The data concerning this nosology are reflected in Table 2. 1.2.

Table 2.1.2.

Gynecological diseases identified in the comparative groups, n=114, abs (%)

Diseases/interventions	I - group , (control group), n = 36		II - group, main (women with GE), n = 40		III group , main, (women with GE with transition to PGE), n = 38	
	abs.	%	abs.	%	abs.	%
Endometritis	1	2.78	1	2.5	2	5.26
Ovarian cyst	-	-	1	2.5	2	5.26
Adenomyosis	-	-	4	10	6	15.8
Myoma	2	5.56	7	17.5	9	23.7
Adnexitis	1	2.78	1	2.5	1	2.63
Colpitis	2	5.56	2	5	3	7.9
Endocervicitis	3	8.33	5	12.5	9	23.7
TORCH infection	1	2.78	2	5	2	5.2 6
Mastopathy	1	2.78	2	5	2	5.26
Infertility	1	2.78	3	7.5	2	5.26
Genital surgeries	1	2.78	3	7.5	2	5.26
Erosion of the cervical spine	2	5.56	3	7.5	4	10.5
DEK sh/m	1	2.78	1	2.5	2	5.26
Result	18	50	37	92.5	47	130.6

As can be seen from the table below, all gynecological pathologies and interventions were significantly more common in the third study group. Inflammatory diseases of the genital organs were particularly prevalent in this regard, accounting for 19.4% in Group I , 22.5%, and 39.5% in Groups II and III , respectively.

We know from numerous recent sources that BMI (body mass index) directly influences the course of many diseases, including BMD. For this reason, we included this criterion in our study, calculated using the Quetelet formula (kg/m2) = weight (kg) : height2 (m2) . The data are shown in Figure 2. 1.2.

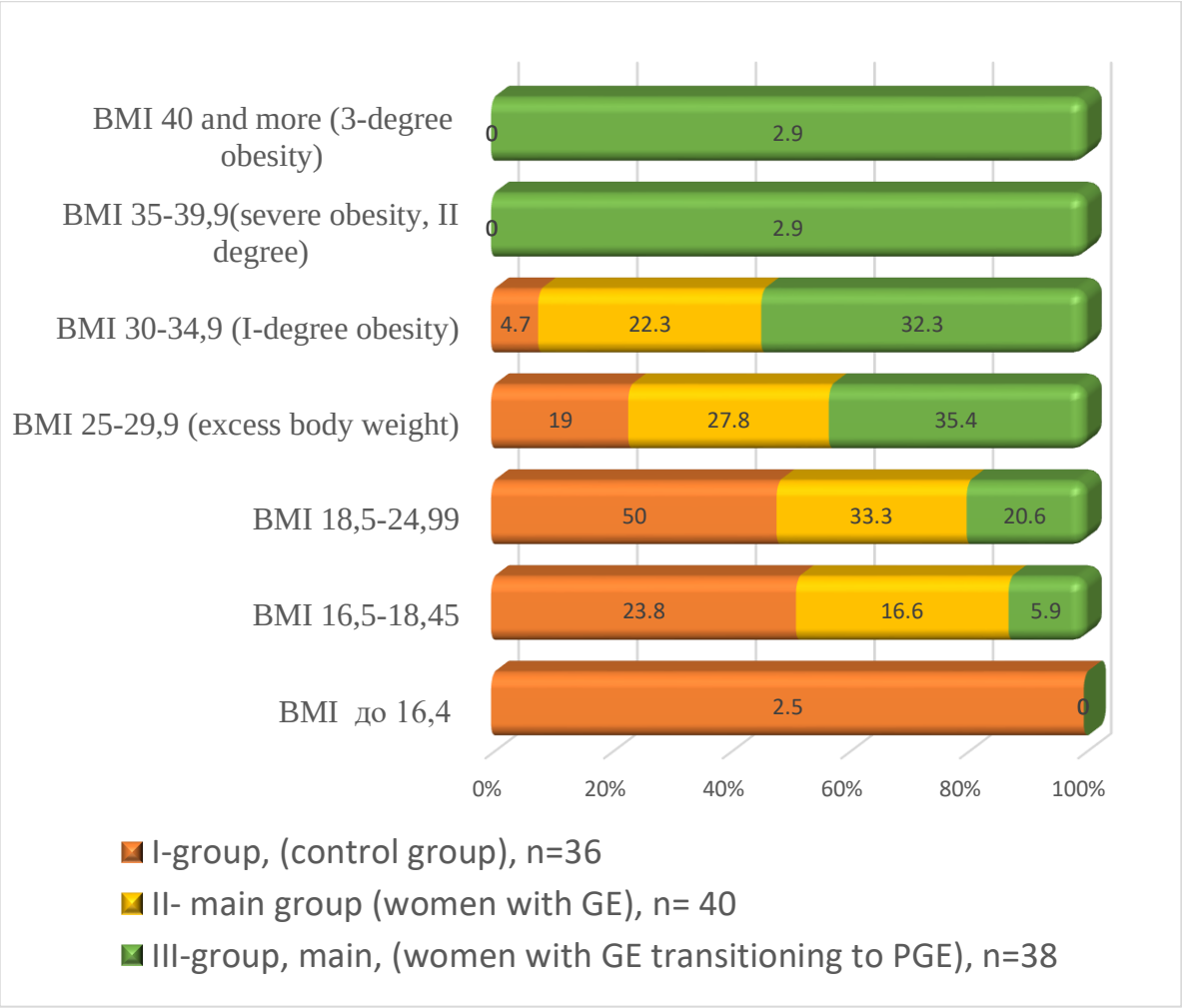


Figure 2.1.2. Comparative BMI indicators for the study groups, n=114 (%)

Based on the data in the figure, it can be concluded that in the two main groups of patients, the prevalence of overweight and obesity was significantly higher than in the control group, which was 27.8% and 22.3% in Group II and 35.4% and 38.1% in Group III , respectively (Fig. 2.1.2). Therefore, we considered this criterion to be a risk factor for the development of PGE, mainly prevalent in the structure of perimenopausal AUB.

Since somatic pathology has an impact and is considered a risk factor for aggravating or provoking perimenopausal AUB, its study is no less valuable. Systematizing the pathologies encountered in the study groups, we found that gastrointestinal tract diseases, endocrine system diseases, and varicose veins were diagnosed more frequently than other premorbid conditions, but iron deficiency

anemia of varying degrees was the most common. The data are presented in Table 2. 1.3.

Table 2.1.3.

Somatic status of the examined women, n=114 (%)

Nosology	**I-group (control group), n=36**		**II- group, main (women with GE), n= 40**		**Group III, main group (women with GE with transition to PGE), n=38**	
	avs	**%**	**avs**	**%**	**avs**	**%**
Diffuse goiter	8	22,2	12	30	14	36.8
Diabetes mellitus	-	-	4	10	6	15.8
Cardiovascular diseases	-	-	1	2.5	2	5.3
Hypertension (HT)	1	2.8	3	7.5	2	5.3
Varicose veins	3	8.3	10	25	7	18.4
Chronic gastritis	2	5.6	2	5	4	10.5
Calculous cholecystitis	2	5,6	5	12.5	4	10.5
Chronic cholecystitis	3	2.8	5	12.5	7	18.4
Urinary tract diseases	2	5.6	3	7.5	6	15.8
Anemia (IDA)	21	58.3	37	92.5	38	10 0
Neurosis	2	5.6	4	10	6	15.8

A comparative analysis shows that extragenital pathology is detected 5 times more often in women in the main group than in women in the control group, which once again proves that extragenital pathology affects the gynecological condition of patients.

All women in the groups underwent a full planned examination: clinical and laboratory tests, including blood tests, biochemical analysis, hormone analysis, and determination of immune status – cytokines, tumor markers.

It is known that women's health, specifically their somatic and gynecological health, directly influences the occurrence of AUB during the perimenopausal period. Therefore, we studied the nature of somatic pathologies based on the medical histories of the women studied. Analysis of this parameter revealed that, of all chronic pathologies, anemia of varying degrees ranks first, with its severity and incidence significantly exceeding the control group by 1.5 times in both comparison groups. In the control group, anemia of varying degrees was detected in 21 patients, while in the second group with GE, it was 37, and in the third group with RGE, this figure was 38. All data are presented in Figure 2.1.3.

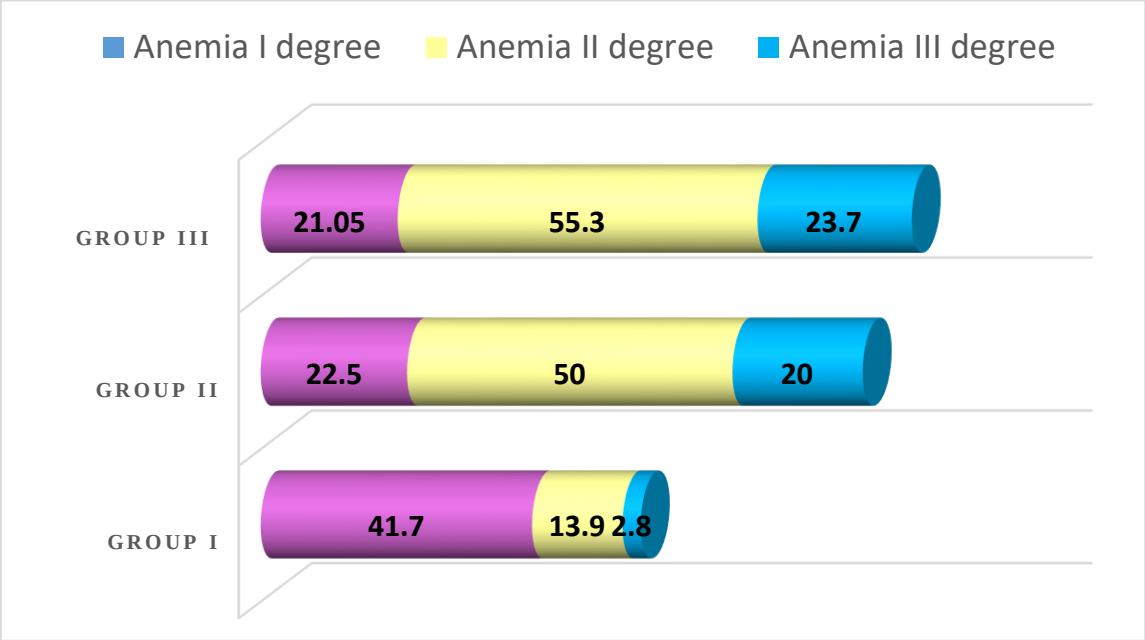


Figure 2.1.3. Comparative indicators of anemia in the study groups.

As can be seen from the above data, anemia of grades II and III was most pronounced in the main groups compared to the control group.

In addition, when analyzing other somatic pathologies by system, it was revealed that pathologies of the endocrine system and gastrointestinal tract were more common than pathologies of other systems.

The next step is occupied by pathologies of blood vessels. In this case, in the control group, endocrine system diseases were detected in 12 patients (33.3%), 32 (80%) in the second group, and 30 (78.9%) in the third group. Gastrointestinal diseases were found in 7 patients (19.4%) of the first group, 12 in the second (30%),

and 15 patients in the third group (39.5%), and pathologies of the circulatory and nervous systems were found in 2 (5.5%), 4 (10%), 6 (15.8%) and 3 (8.3%), 10 (25%), 7 (18.4%), respectively, in the groups. Pathology of the urinary system was encountered in all groups in the following ratio: 4 (11.1%), 5 (12.5%), and 7 (18.4%). The data are shown in Figure 2.4.

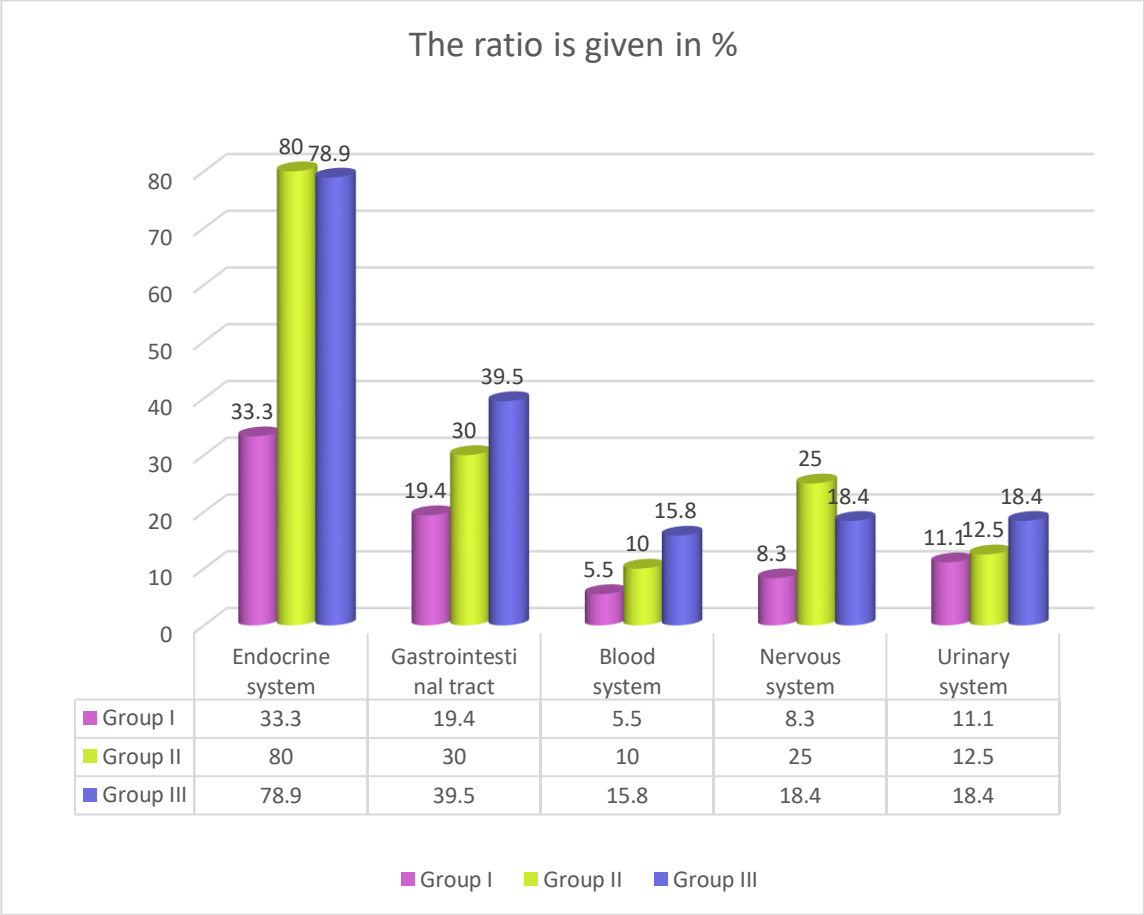


Figure 2.1.4. Comparative indicators of somatic pathologies by systems in the study groups.

The incidence of endocrine pathologies was significantly higher than in the control group in both clinical groups. The high incidence of these pathologies in the study groups allowed us to classify them as a risk group for the development of endometrial pathologies and their progression—ER.

The next criterion examined in the patients' medical histories was the contraceptive methods used, as they also have a direct impact on changes in the patients' hormonal levels and their effect on proliferative processes in the

endometrium. The obtained anamnestic data by type of contraceptive method used are presented in Table 2.1.4 below.

Table 2.1.4.

Comparative indicators of used methods of contraception in the study groups, n = 114

Methods of contraception	**I-group (control group), n=36**		**II- group, main (women with GE), n= 40**		**Group III, main group (women with GE with transition to PGE), n=38**	
	ABS	**%**	**ABS**	**%**	**ABS**	**%**
Biological	9	25	7	17.5	8	21.05
Navy	14	38.9	22	55.0	21	55.2
OK	4	11.1	3	7.5	2	5.26
DHS	9	25	8	20.0	7	18.4

Based on the table data, it can be concluded that, in most cases, 55% of patients in all groups used an IUD, followed by the DHS method, followed by biological contraception; these methods showed almost no significant differences across all comparison groups. A significant difference was found in the third group compared to the control group. Hormonal methods (OCs) had the lowest percentage (7.9%).

The next study outcome was an analysis of reproductive function in the study groups. Across all groups, there were 241 pregnancies, distributed among the groups as follows: 87, 80, and 74, respectively. Of these, 83 in the control group delivered, 16 by cesarean section, and 71 by cesarean section. In the second study group, women with GE Of the 80 pregnancies, birth occurred in 63 cases, 17 by cesarean section, and through the pelvis. Naturalis 46. In the third group of 74 cases, delivery occurred in 61 cases, by cesarean section in 16 cases and via pelvis naturalis in 45 cases. Abortions were distributed into groups 3, 7, and 8, respectively. Non-viable

pregnancies were distributed into groups 1, 7, and 3, respectively. Habitual miscarriage occurred in the two main groups in a ratio of 3 and 2 cases. From the anamnesis, it was revealed that infertility occurred in 1 (2.3%), 2 (5.5%), and 4 (11.7%) cases. The data are presented in Table 2.1.5.

Table 2.1.5.

Comparative data on obstetric and gynecological anamnesis indicators in the examined groups n = 114 (%)

	I-group (control group), n=36		**II- group, main (women with GE), n= 40**		**Group III, main group (women with GE with transition to PGE), n=38**	
	abs.	%	abs.	%	abs.	%
Infertility	1	2.8	2	5	4	10.5
Number of pregnancies	87	-	80	-	74	-
Births, total number	83	95.4	63	78.7	55	74.3
C-section	12	14.4	17	27	20	36.4
Childbirth through the pelvis naturalis	71	85.5	46	73	35	63.6
Abortions	2	2.29	7	8.75	8	10.8
Miscarriage	1	1.14	4	5.0	5	6.7
Habitual miscarriage	-	-	1	1.2	2	2.7
Non-viable pregnancy	1	1.14	3	3.8	3	4.1
Ectopic pregnancy	-	-	2	2.5	1	1.4

Based on the table data, it can be concluded that all pregnancy complications were almost twice as common in the second and third groups compared to the control group. The rate of cesarean section delivery was twice as high in the study groups compared to the control group, at 6.8% and 12.6%, respectively. The rate of abortions and miscarriages was significantly higher than in the control group. This suggests that the number of births, miscarriages, and gynecological interventions, such as

operative deliveries and abortions, directly influences the occurrence of perimenopausal AUB. Based on these data, they can be considered a risk factor for the development of perimenopausal AUB.

According to our data, the reproductive potential of patients in the study groups had a direct impact on the condition of the endometrium later in life. When studying this indicator, we found that women in the groups became pregnant up to six times, of which three to four resulted in births. The remaining one to two cases were non-viable pregnancies or abortions (Table 2.1.6).

Table 2.1.6.

Comparative indicators of reproductive potential in women of the study groups, n = 114

Pregnancy date	**Groups**					
	I-group (control) group), n= 87		**II- group, main (women with GE), n= 80**		**Group III, main group (women with GE with transition to PGE), n=74**	
	ABS	**%**	**ABS**	**%**	**ABS**	**%**
1 pregnancy	**5**	**5.7**	**7**	**8.7**	**6**	**8.1**
2 pregnancies	**43**	**49.4**	**38**	**47.5**	**39**	**52.7**
3 pregnancies	**22**	**25.2**	**26**	**32.5**	**24**	**32.4**
4 pregnancies	**12**	**13.7**	**6**	**7.5**	**4**	**5.4**
5 pregnancies	**-**	**-**	**2**	**2.5**	**1**	**1.35**
6 pregnancies	**-**	**-**	**1**	**1.25**	**1**	**1.35**

When comparing the number of third, fourth, and fifth pregnancies in the control group, it was significantly lower than in the two main groups; no sixth pregnancies were detected. Comparing the two main groups, it can be concluded that

the second main group, compared to the third group, had a higher number of third and fourth pregnancies and births than the third group.

Thus, the risk factors for the development of AUB in the perimenopausal period caused by the disruption of proliferative processes in the endometrium may be: the premorbid background of women, especially inflammatory diseases of the pelvic organs, anemia of varying severity, as the main factor of hemic hypoxia and circulatory disorders in these organs, partly unprecedented rates of increase in obesity and a steady trend towards "rejuvenation" of this endocrine pathology, disruption of the ovarian-menstrual cycle in reproductive age, incorrect use of contraceptive methods, especially the IUD, which is a source of vertical infection of the pelvic organs, and surgical interventions during childbirth.

§2.2. Comparative indicators of clinical and laboratory data of patients with GPE in the perimenopausal period.

Endometrial hyperplasia is a pressing issue in modern gynecology due to its high prevalence among patients entering the premenopausal period. Of particular interest is the fact that this condition tends to be long-lasting and recurrent, with no identical pathognomonic symptoms or treatment methods. As we know, the development of endometrial adenocarcinoma is associated with endometrial hyperplasia, although data on the prevalence of endometrial hyperplasia are not published, which may be due to the lack of official registration of the disease.

The purpose of this section was to identify predictors for the early detection of AMC caused by GE in premenopausal age, for timely diagnosis with subsequent correction and development of prevention methods.

Ovarian decline, also known as menopause, is an expected and crucial episode in every woman's life, often after age 45. During this period, a woman's ovarian production of the youth hormone begins to slow. - estrogens , namely the active fraction of estradiol, which is transferred to progesterone with a simultaneous decrease in its fertile activity.

In hyperplasia, the endometrium is affected by only one steroid—estradiol, in normal or hyperconcentrations. This is because the follicle that forms is not a healthy one, but a persistent and rarely atretic one, which contains more estrogen than a normal follicle. With persistent progesterone deficiency, a pathological focus develops in the endometrium. Proliferation does not progress to the secretory stage, and hyperplasia develops . This is because elevated FSH concentrations, in response to age-related estrogen decline, do not produce such high levels of LH, which is responsible for ovulation and subsequent production of the normal amount of progesterone necessary for secretory transformation. When collecting the anamnesis, our patients began to complain of menstrual cycle irregularities in the form of metrorrhaggia (acyclic bleeding) several years before the episode of abnormal bleeding. However, women often consulted a specialist for cases of severe vaginal bleeding. Our study results showed that, in the late reproductive period, FSH blood levels were high compared to the control group, although in both groups they were higher than the norm for the active reproductive period, indicating the women's transition to the perimenopausal period. Estradiol concentrations were also within the reference range but higher than in the control group. Most interestingly, progesterone levels were low in both the control and treatment groups, leading to the development of endometrial hyperplasia against the background of progesterone deficiency. Moreover, it was impossible to establish the exact date of the onset of the pathological process (hyperplasia), as the women presented to us after the onset of abnormal bleeding; i.e., a period of delayed menstruation was followed by heavy bleeding, which bothered them for 30-35 days, and in some cases, for 7-10 days. Of the 78 patients, only 4 (5.1%) had menorrhagia, and these patients presented to the hospital due to heavy uterine bleeding, although they had not yet experienced cycle irregularities. In our patients with perimenopausal EHP, E2 was 1.5 times higher than in the control group, but there was a significant decrease in progesterone by 2-2.5 times or more, which intensified the pathological transition from the proliferative phase to the secretory phase. Furthermore, elevated FSH gonadotropin levels further aggravated the transition, which failed to simultaneously increase LH production.

In the main group (78 patients) there were 74 (94.9%) patients with GPE in the perimenopausal period, i.e. before the onset of menopause, and only 4 (5.1%) patients with menopause. Globally, hypertensive encephalopathy (HPE) is a common gynecological condition, and women primarily seek medical attention for abnormal uterine bleeding. This was also observed in our study, where 67 (85.9%) of 78 patients registered for HPE presented with bleeding, and 11 (14.1%) had menorrhagia. Several hormones are altered in this condition, including FSH and LH.

Of the steroid hormones, the active fraction of estrogens—estradiol and progesterone—was studied. All 114 patients, as previously indicated, were divided into 3 groups: the control group (n = 36 patients with normal PP), and the 2nd group (n = 36 patients with normal PP). n = 40 with primary diagnosis of GE and the age of patients ranged from 45 to 51.7 years, 3rd group n = 38 women with recurrent GE, their age was 49.5 years (from 43-52 years).

All 114 women, both healthy and with EHP: 36 patients in Group 1 with a physiological perimenopausal period and 78 patients with EHP, of whom 38 (48.7%) had a recurrent process, had their hormonal status checked in the morning using the IHL method (Table 3.2.1) on an empty stomach. Considering that most of them had an acyclic menstrual cycle, we checked hormones the following day. In those with a normal cycle, which only 7 (6.1%) in the main group had, we collected blood on days 3-5 of the cycle. Considering that dyshormonal imbalances in monocyclic hyperplastic processes can be accompanied by a persistent progesterone deficiency, we decided to also check progesterone levels in the blood on days 21-23 of the cycle if the values were low.

Table 2.2.1.

Comparative data on hormonal status in the study groups of women in the perimenopausal period, n = 114

Hormonal indicators	**Reference fluctuations**	**Control group 1 (n= 36)**	**Main 2nd group (n= 40)**	**Main 3rd group (n= 38)**

FSH, mlU/ml Fol.phase 3.2-15 mIU/L Ovulation phase 7.5-20 mIU/L Lute phase 1.3-11 mIU/L Menopause: 18-150 U/L	3.9-21.8	11.8±0.59	24.95±0.56 ***	29.0±0.87 *** ^
LH, mlU/ml, Fol.phase 1.2-12.5 mIU / L Ovulation phase 12-82 mIU/L Lute phase 0.4-19 mIU/L	13.4-19.9	14.6±0.79	28.8±0.61 **	33.4±0.78 *** ^
LH/FSH		1.24±0.04	1.16±0.03 *	1.172±0.03 *
Estradiol, E pg/ml Fall phase 28.1-178.1 Lutein phase-33.6-250.9 pg/ml Menopause-18.4-64.0	44.6-98.5	101.4±2.46	129.4±9.77 *	154.8±16.0 ** ^
Progesterone, ng/ml F.f.-0.2-1.4 L.f.4.0-25.0 Menopause-0.1-1.0	0.64-0.81	4.48±0.49	2.41±0.27 **	1.98±0.22 *** ^

Note: * – differences are significant compared to the data of the control group (* – p <0.05, ** – p <0.01, *** – p <0.001), ^ – differences are significant compared to the data of the 2nd group (^ – p <0.05).

When analyzing the endocrine state of patients of perimenopausal age, which included patients of the premenopausal and menopausal periods, both the central and peripheral (gonadal) links of the reproductive system were studied; radioimmune blood tests (venous) were performed on the day of admission to the hospital during an anovulatory cycle or on days 3-5 or 21-23 of a regular cycle.

Hormonal testing was preceded by mandatory separate diagnostic curettage, followed by histological verification. We were unable to compare the histological results with those of the control group, as they included women without hyperplastic processes or abnormal uterine bleeding.

Considering that women of active reproductive age are characterized by low FSH values, in comparison with premenopausal and menopausal women. According to the literature, FSH before menopause is almost ten times lower, which was also observed in our studies: whereas in healthy women this hormone amounted to an average of 11.8 ± 0.59 IU / ml, and almost 2.11 and 2.45 times higher in the two main groups 24.95 ± 0.56 IU / ml and 29.0 ± 0.87 IU / ml. The reference range of

FSH in the norm was 3.9-21.8, in our healthy women out of 11.8 ± 0.59, 31 were normal and did not go beyond the normative data (3.2-15 mIU / ml). An interesting fact is that the FSH level was lower in obese women with active physical activity, where in the main group, in patients with a high BMI (these were office workers or women who led an active lifestyle - were manual workers, partly engaged in physical education), the FSH indicator was lower than in other patients with EHP. In the three corresponding groups, in each group there were overweight women - 11 (30.5%) in the control group, 1-a main group - 7 (17.5%) overweight and 11 (27.5%) with obesity of 1-2 degrees, in the 2nd main group 6 (15.7%) - overweight, 1-2 degrees - in 9 (23.6%). An interesting fact is that in these patients, even in the relatively healthy control group, the blood estradiol levels were high compared to other patients without overweight or obesity, and on ultrasound, the thickness of the median M-echo was over 11-15 mm, even on the 6th-9th days of bleeding.

LH is responsible for egg maturation and ovulation. In healthy premenopausal women, LH levels were 15.0 mlU/ml, within the normal range of 14.6 ± 0.79 mlU/ml. If this level was above 20 mlU/ml or more, we considered the woman to have entered premenopause, which is what we observed in our studies.

In the two main groups, LH was also high compared to the control group and amounted to 28.8±0.61 and 33.4±0.78 mlU/ml, and if we compare the increase in two gonadotropic hormones, the concentration of FSH is still 1.92 and 2.2 times higher than LH, which is why the concentration of progesterone in the blood is low, especially in the two main groups, which amounted to 2.41±0.27 pg/ml and 1.98±0.22 pg/ml in groups II and III , respectively, since LH is responsible for ovulation and progesterone growth.

Estradiol, a hormone produced by the ovaries, is normally present in the blood. Its concentration increases during follicle growth and peaks just before egg release, after which it decreases. In our study, estrogen levels were higher than in the control group, amounting to 101.4±2.46 pg/ml in Group 1 , 129.4±9.77 pg/ml, and 154.8±16.0 pg/ml in Groups 2 and 3 , respectively. Despite the relative increase in FSH, estradiol concentrations were relatively elevated in the study group. This is

explained by the fact that with age, along with follicle depletion, the number of gonadotropin receptors also decreases, a finding reflected in our studies. In our opinion, the relatively high content of estradiol and constant progesterone deficiency led to the pathological transformation of endometrium proliferation into hyperplasia, which echoes the data of a number of authors [12,64,100,112].

During premenopause, a woman's production of the steroid hormones estradiol and progesterone begins to decline, and in response, gonadotropic hormones, especially FSH, begin to increase in the hypothalamic-pituitary system via a feedback loop. Literature data indicate that their ratio during the reproductive period is 1-1.5 in favor of LH, while during menopause this ratio should be within the range of 0.5-0.75, but in favor of FSH. However, since our women were mainly in the premenopausal period, this indicator was 1.16 ± 0.03 and 1.172 ± 0.03. It should be remembered that a decrease in this indicator indicates a pronounced hormonal imbalance, with pronounced signs of pathological menopause, which has not yet been particularly observed in our patients.

Considering that hormonal levels influence behavior, emotional state, appearance, and overall health, a separate uterine curettage (D&C) was performed during diagnosis and subsequent treatment planning.

In our studies, high FSH concentrations were accompanied by a relative decrease in estradiol concentrations, but progesterone concentrations were low in almost all samples. Therefore, the RIAG in patients admitted with AUB was measured after curettage of the uterine cavity on days 3-5 of the reference cycle, as 84% of the patients had anovulatory cycles, which is typical of hyperplastic processes.

Gonadotropic hormone levels showed a positive and negative correlation, as estradiol levels were significantly elevated in most patients. Ultrasound data revealed ovarian atrophy, localized multifollicular changes, and antral follicles numbering up to 5-8 in each ovary.

Progesterone levels were abnormally low, as LH did not significantly increase due to high FSH. They ranged from 0.84±0.03 pg/ml in the control group to

0.87±0.02 pg/ml in the two treatment groups. This low level of fluctuation exacerbated the development of endometrial hyperplasia. In women in the control group, progesterone levels were nearly 1.85 and 2.26 times higher, respectively, compared to those in the two treatment groups. It was the progesterone deficiency that contributed to the development of pathological endometrium and halted the transition of proliferation to the secretory stage.

Understanding the hormone levels in patients with EHP, especially those in perimenopause, allowed us to correct hormonal imbalances by prescribing progestogens. By prioritizing progestogens, we were able to normalize progesterone deficiency specifically in endometrial hyperplasia, when the proliferative phase partially fails to transition to the secretory phase and worsens the irregular cycle, especially AUB, although this was not our goal.

Perimenopausal age is associated with a risk of increased cancer risk. We tested our patients for the CA-125 and CA-15-3 tumor markers to rule out ovarian and breast cancer, determine their sensitivity for endometrial pathology, and monitor treatment effectiveness. The data are shown in Figure 2.2.1.

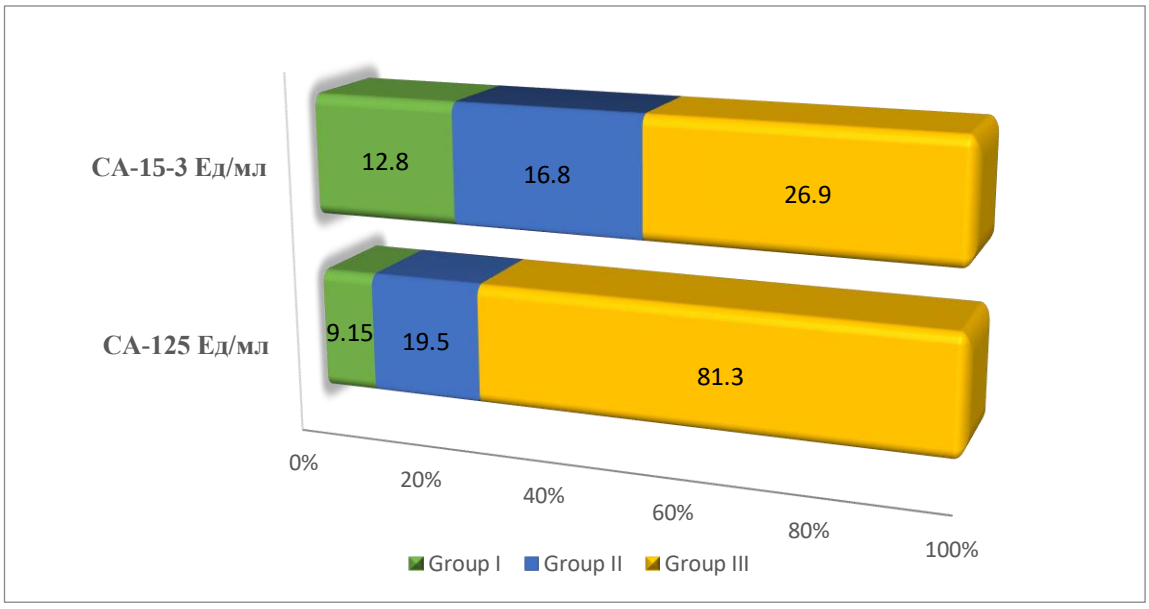


Figure 2. 2 .1. Comparative data of tumor markers in the study groups of women, n = 114

As can be seen from the above figure, the fluctuations of the CA-125 indicator were 9.15±0.55 U/ml in group I , 19.5±1.63 U/ml and 81.3±8.63 U/ml in groups II

and III , respectively. In patients of groups I and II , these indicators were within the normal range, and in patients of the recurrent group III, in 29 (76.3%) patients, they reached very high values.

The CA-15-3 tumor marker titer fluctuated within the normal range in the three study groups, amounting to 12.8±0.75 U /ml, 16.8±1.17 U/ml, and 26.9±2.22 U/ml. However, these indicators were higher in women with endometrial pathology than in healthy women of the same age.

From the data obtained, it can be concluded that the tumor marker C A-125 is an early marker of recurrent forms of PGE.

Thus, it should be noted that endometrial hyperplasia (EHP) is one of the most common causes of uterine bleeding in women aged 45-55 years and their hospitalization. Another reason for the close attention to EHP is the potential for malignant transformation, as atypical hyperplasia progresses to invasive cancer in up to 50% of cases. The aforementioned risk of malignancy in glandular hyperplasia and endometrial polyposis occurs at 4-5% and can reach up to 10% in peri- and postmenopause.

Summarizing the data of this section, it should be noted that hormonal disorders in the perimenopausal age in patients with EHP have multidirectional changes, but it is still necessary to take into account that high levels of gonadotropic hormones do not They always reduce primarily estrogen concentrations (estradiol fractions), and the pathological process arises not only as a result of hormonal imbalances but also against the background of severe inflammatory processes in the biliary tract, especially with a recurrent course. It should also be noted that hyperestrogenism is particularly severe in women with endocrine-metabolic disorders, particularly in women with metabolic disorders where excess adipose tissue, especially in the abdominal phenotype, disrupts estrogen aromatization, leading to relative hyperestrogenism.

§ 2.3. Spectrum of hemogram and vitamin D abnormalities in hyperthyroidism

In this subchapter of the dissertation, we considered it appropriate to present materials on the study, analysis, and evaluation of peripheral blood parameters in perimenopausal women (hemograms) and, from biochemical parameters, the concentration of vitamin D in the blood serum was determined. These parameters were studied comparatively in both patients with EHP and in the control group. The obtained complete blood count results are presented in the table below (Table 2.3.1).

Table 2.3. 1 .

Comparative indices of peripheral blood (hemograms) in patients of the study groups, n = 114.

Indicators	Reference data	Control group , n = 36	1st main , n = 40	2nd main group, n = 38
Erythrocytes, 10^{12} /l	3.9-4.7	3.69±0.07	2.85±0.09 *	2.89±0.11 *
Hemoglobin, g/l	120.0-140.0	119.1±1.98	77.7±2.67*	79.9±2.54*
Color indicator	0.85-1.05	0.86±0.01	0.83±0.02	0.81±0.01
Hematocrit, %	32-45%	32.7±0.65	24.7±0.82*	25.0±0.79*
Platelets,	240-320	270.4±5.26	229.9±2.48*	233.05±1.59*
Leukocytes, 10^{9} /l	4.0-9.0	4.98±0.11	5.78±0.26*	5.89 ±0.2 7 *
Neutrophils p/y, %	1-6%	1.11±0.05	3.30±0.38***	3.105±0.30***
Neutrophils, s/o, %	47-72%	62.75±1.10	63.4±1.06	65.0±0.88
Eosinophils,%	0.5-5%	1.06±0.05	1.38±0.17	1.24±0.07
Lymphocytes, %	19-37%	27.0±0.55	26.3±0.96	26.2±0.32

Monocytes, %	3-11%	5.03±0.24	5.81±0.62*	5.45±0.37
ESR, mm/h	2-15	9.81±0.67	12.0±1.003*	12.2±0.64*

Note: * – differences are significant compared to the data of the control group (* – p <0.05, ** – p <0.01, *** – p <0.001).

As can be seen from the obtained data, in all the studied groups, a decrease in the content of red blood cells and hemoglobin was noted in comparison with the reference values , but a significant decrease was noted in patients with EHP. A decrease in red blood cells was observed in relation to the control group, amounting to 3.69 , while in the two main groups it was 2.85 and 2.89, which proved to be reliable, respectively, and hemoglobin levels were 119.1 g/L, 77.7 g/L, and 79.9 g/L, representing a 40% decrease in percentage terms and also proved to be reliable. Accordingly, the color index of the blood was reduced, varying within the range of 0.81-0.86, which indicated that most of our patients had anemia of varying severity as a background condition for the development of hemic hypoxia leading to dysfunction of the pelvic organs. As can be seen from the data in the table below, it should be noted that the color index and vitamin D levels were dependent on each other in opposite directions - with hypochromic anemia, the vitamin D level decreased sharply, i.e., patients with EHPE initially had low levels of this vitamin, but women in the control group, who did not have dyshormonal disorders, also showed a vitamin deficiency, but in less severe numbers. Based on this, it should be noted that low color index values are directly proportional to decreased vitamin D levels in the blood . All the obtained data and their correlations must be considered when choosing a combination therapy, taking into account the degree of anemia and vitamin D deficiency.

All data from the red portion of the formed elements of a complete blood count allow us to predict the development of proliferative disorders in the endometrium and may be one of the main risk factors for the development of PGE. A 20% increase in the relative monocyte count can be interpreted as an increase in the activity of nonspecific immune system factors during the development of the pathological

process in a perimenopausal woman. Accordingly, we determined immune parameters in subsequent stages.

Based on recent routine tests available in all healthcare facilities, including gynecological departments of hospitals, we have established that the erythrocyte sedimentation rate (ESR) can be used to assess the activity of the pathological (inflammatory) process, and in questionable cases or for differential diagnosis, specific inflammatory diagnostic markers can be prescribed. Although the ESR in women with EHP is significantly elevated by 1.53 times relative to the reference value (R), it remains within the upper limits of normal, indicating the likelihood of an inflammatory reaction, albeit with signs of pre-pathological conditions in these women.

Thus, a comparative analysis of peripheral blood parameters in patients with EHP and a control group of perimenopausal women revealed that almost all the parameters studied differed significantly from the reference values. While the red blood cell count, hemoglobin, cirrhosis, hematocrit, and platelet counts in peripheral blood were decreased, the white blood cell count, subcutaneous and subcutaneous neutrophil count, monocyte count, and ESR were significantly elevated. Only the relative lymphocyte count showed divergent changes. The identified abnormalities indicate the presence of a pre-pathological condition and the development of a pathological process associated with hemodynamic impairment, as well as immune system stress. These changes indicated that the changes in the complete blood count in patients with proliferative endometrial disorders further confirmed that the frequency of unaccounted chronic inflammatory processes in the pelvic organs, accompanied by immune depression and the development of endothelial dysfunction, may be one of the causes of EHP progression.

There is evidence in the literature that many dyshormonal processes depend on the concentration of cholecalciferol, vitamin D, in the body, particularly in hyperplastic processes of the endometrium, especially in the perimenopausal period, since a deficiency of this vitamin increases the risk of developing proliferative diseases and the risk of transformation into endometrial cancer [8,52,86,110]. As

is already known, with the existing metabolic syndrome, when there is varying degrees of obesity, glucose tolerance or insulin resistance begins to develop in the body, especially in the perimenopausal age, when hormonal changes of varying degrees occur. In this regard, in our opinion, one of the preventive measures is the timely determination of vitamin D levels in the body (Table 2.3.2).

Table 2.3.2.

Comparative data of specific markers in patients with EHP and healthy perimenopausal women

Indicators	Reference vibrations	Control group , (n=36)	1st main group , (n = 40)	2nd main group, (n= 38)
25(OH)D ng/ml	30-100	26.8±1.22	20.5±0.88**	18.9±1.06** ^

Note: * – differences are significant compared to the data of the control group (* – p <0.05, ** – p <0.01), ^ – differences are significant compared to the data of the 1st group (^ – p <0.05).

The purpose of this subsection was to determine the comparative vitamin D status of both patients with EHP and women in the control group. The problem is that not always adding foods containing vitamin D to the diet can replenish its deficiency. Although we live in a sunny country , many residents of our country have a deficiency of this vitamin. Based on these considerations, we recommended that women with EHP have their vitamin D levels checked in the blood. We found that in the second group, the vitamin D level was 20.5 ± 0.88 ng/ml, and in the third group, 18.9 ± 1.06 ng/ml, while in healthy subjects it was 26.8 ± 1.22; it was 6.7 and 7.3 ng/ml, respectively, significantly lower, while the reference values for this vitamin normally range from 30 to 100 ng/ml. It's worth noting that women in the control group in our study also had lower levels than normal. Of the 36 women in

the control group, 7 had low vitamin D levels and were overweight, with serum vitamin D concentrations ranging from 15.8 to 21.9 ng/ml.

Based on the above data, we can conclude that all patients in the study groups had vitamin D deficiency, which was directly correlated with the severity of proliferative processes. Based on these data, we believe that vitamin D levels should be checked during routine clinical examinations of women at this age to prevent the development of potential proliferative conditions and to address the issue of preventive therapy, especially in patients with somatic pathologies.

Thus, EHP in perimenopausal women is a multifactorial disease. Diagnosis of the woman's true condition is based on comprehensive, reliable clinical and laboratory diagnostic tests: assessment of hormonal levels, blood count, determination of BMI and obesity, and assessment of serum vitamin D concentrations. The obtained indicators of imbalance between these indicators and their normal values can serve as markers and indicators for the preclinical diagnosis of EHP in women with clinical manifestations of AUB in perimenopausal women. Timely interpretation of these diagnostic markers will help reduce the expected complications of EHP and its pathological forms. Timely diagnosis and classified, adequate treatment can serve as a prerequisite for the timely prevention of hormonal imbalances and the development of pathological proliferative conditions and their progression to endometrial cancer.

§2.4. The role and significance of ultrasound examination in the prediction and early diagnosis of EHP in the perimenopausal period.

Currently, the most informative and non-invasive diagnostic method for screening endometrial hyperplastic pathologies is ultrasound, which allows for a current assessment of the endometrium and its dynamic monitoring. In the absence of clinical manifestations such as AUB, uterine ultrasound can detect various signs of pathological endometrial proliferation, including diffuse or focal changes.

According to the 2010 International Endometrial Tumor Analysis (IETA), the following parameters are recommended for assessing endometrial structure:

thickness, echogenicity, midline, intraluminal fluid, endometrial transition zone, and blood flow. We assessed endometrial echogenicity relative to myometrial echogenicity, as well as structural homogeneity. Heterogeneity was assessed by nonuniform structure, asymmetry, and the presence of cystic lesions. The endometrial-myometrial region was assessed for smoothness, irregularity, or discontinuity. Currently, the upper limit of normal M-echo in premenopause is considered to be 6-7 mm, and in postmenopause, 4 mm. If the upper limit is below this limit, the probability of endometrial cancer is very low, and a biopsy is not recommended. In perimenopausal women, pathological processes in the endometrium may occur without AMC, but the risk of developing ER may be higher than the general population data, and therefore it is necessary to conduct ultrasound screening, especially among patients with a high risk of progression of this pathological process and its recurrence.

In compliance with all the above requirements of this functional research method, we used ultrasound in all study groups (Table 2.4.1).

Table 2.4.1.

Comparative data on endometrial thickness in patients with EHP and healthy perimenopausal women

Indicators	Reference oscillations	Control group , (n=36)	1st main group , (n = 40)	2nd main group, (n= 38)
Endometrial thickness M-echo (mm)	up to 15 mm	9.6±0.2 6	20.3±0.80 ***	23.9±1.02 *** ^

Note: * – differences are significant compared to the data of the control group (*** – p <0.001), ^ – differences are significant compared to the data of the 1st group (^ – p <0.05).

As can be seen from the above table While in the control group this indicator averaged 9.6±0.26 mm, in the 3rd group the average endometrial thickness was 23.9±1.02 mm, but the contours in patients without polyps and fibroids were smooth,

with clearly distinguishable borders. In patients in the 2nd group, the results were similar, amounting to 20.3±0.80 mm, with smooth and clear borders. When comparing the results obtained in the 3rd and 2nd groups, the endometrial thickness exceeded the control group by 53% and 60%.

According to the homogeneity criterion, small anechoic inclusions were observed in one-half of the cases in the group with recurrent endometrial hyperplasia (REH), compared to one-third of the cases in patients with GE. Only one case of cancer identified during the study exhibited hyperechogenicity, irregular borders, and structural homogeneity.

Moreover, in patients with hyperplastic processes, the level of vascular visualization was better during Doppler ultrasonography than in the normal course and decreased in cancerous processes. Uterin A was visible in 93.1% of the first main group, in 95.0% of the second main group, a 1.9% increase, while in the control group it was recorded 2.1% less and amounted to 91.0%. Moreover, the specificity and sensitivity of Doppler ultrasonography in patients with EHP and recurrent EHP were 92% and 89%. Of all the above-mentioned results of uterine artery Doppler ultrasonography, the use of this method in determining EHP is highly informative, therefore it should be included in the mandatory diagnostic procedure. We conducted an ultrasound examination of the ovaries, which determined that the follicular apparatus is depleted, and there are disturbances in follicle maturation - persistence or, in rare cases, there were atretic changes. This position once again confirms that the patients in the study groups are in the perimenopausal period, a dyshormonal state, and all changes occurring in the follicular apparatus and endometrium are associated with this process. This decrease is considered to be entirely physiological, as evidenced by the results of ovarian ultrasound. In the two main groups, estradiol was also 129.4 ± 9.77 and 154.8 ± 16.0 pg / ml and was higher than the data of healthy women in the control group. The obtained results of ovarian ultrasound and hormonal levels in the study groups had a direct correlation with the M-echo parameters of the uterine endometrium, as described above, in the second main group in women with EHP it was 20.3 ± 0.80, while in the third with recurrent

EHP it was found at a level of 23.9 ± 1.02 mm. group - endometrial hyperplastic processes (n = 17). Benign endometrial pathology clinically manifested itself as menstrual irregularities such as menometrorrhagia and grades I-II anemia in 47.1% of patients. Examination revealed an increase in the M-echo thickness in benign endometrial pathology, averaging 13.8 mm (range 6-23 mm). Transvaginal ultrasound revealed glandular cystic hyperplasia as a highly echogenic, homogeneous, spongy structure with multiple, punctate, anechoic inclusions and acoustic amplification. Atypical hyperplasia revealed a heterogeneous, hyperechoic structure in the uterine cavity. Polyps were noted as oval or round, hyperechoic formations, distorting the uterine cavity, with a small amount of fluid. Benign endometrial neoplasms were characterized by a clear, smooth outer M-echo contour.

Thus, the significant clinical significance of endometrial hyperplasia (EH) lies in its role as a common etiology of AUB in women aged 45-55 years due to the decline of hormonal function in the hypothalamic-pituitary and ovarian systems. A comprehensive examination and ultrasound screening using Doppler ultrasound is a highly informative non-invasive diagnostic method. The obtained results demonstrate the high accuracy of this method in the differential diagnosis of pathological endometrial hyperplasia and in predicting the progression of the process and the transition to ER. This may necessitate a morphological examination of the obtained endometrial scraping.

§2.5. Morphological picture of the endometrium of women with EHP in the perimenopausal period

In perimenopausal women, endometrial hyperplasia can be caused by changes in hormone levels, such as estrogen and progesterone. The histological picture of endometrial hyperplasia in these patients may differ from that in other groups of patients. For example, perimenopausal women may exhibit a more pronounced thickening of the epithelial layer and an increase in the number of glandular structures. Abnormalities in epithelial structure and the presence of mitoses may also be detected. The primary diagnostic indicator for hyperplastic processes is

morphological examination, as the true picture is revealed by microscopic and macroscopic analysis of the endometrium. In our study, histological analysis of the endometrium was performed in all patients in the main study groups during the proliferative phase (days 7–10 of the menstrual cycle). In the two main groups, samples were collected after separate curettage, from which microscopic preparations were made using standard technology. Histological examination of endometrial samples from patients with hyperplasia revealed signs of thickening of the epithelial layer, which became denser and higher, indicating cell growth. An increase in the number of glandular structures in the endometrium increased, making them more prominent and dilated. The presence of abnormal epithelial structures was also detected. Furthermore, abnormalities in epithelial structure were frequently observed, such as uneven cell size, nuclear polyploidy, dysplasia, and mitosis with cell division, indicating active epithelial growth. Overall, the histological description of endometrial hyperplasia was characterized by thickening of the epithelial layer, an increase in the number of glandular structures, and the presence of abnormalities in epithelial structure and mitosis, indicating active epithelial growth.

Since the control group included patients of the same age but without a history of AUB, separate curettage and subsequent histological analysis were not performed. However, glandular hyperplasia of the endometrium was detected in 16 cases (44.4%) in the second study group and in 6 cases (17.6%) in the third study group. Glandular hyperplasia associated with chronic inflammation was detected in 12 cases (33.3%) and 4 cases (11.8%) in the two study groups. Glandular cystic hyperplasia was not detected in the second study group, whereas in the third study group, it was verified in 8 cases (23.5%). Glandular cystic uterine encephalopathy against the background of chronic inflammation was identified in the second main group in 2 patients, while in the third it was found 5 times more often or in 10 cases (29.4%). Hormonally altered uterine mucosa was observed in 8 (22.2%) and 5 (14.7%) cases in the above-mentioned groups. The study identified only one case (2.94%) of adenocarcinoma in the third group. All the above data are presented in Table 2.5.1.

Table 2.5.1.

Results of histological analysis in patients in the study groups

Histological picture of endometrial scraping	I - group , (control group), n = 36		II - group, main (women with GE), n = 40		Group III , main group (women with GE with transition to PGE), n = 38	
	abs.	%	abs.	%	abs.	%
Glandular HE	-	-	16	44.4	6	17.6
Glandular hepatitis associated with chronic inflammation	-	-	12	33.3	4	11.8
Glandular cystic hepatitis	-	-	-	-	8	23.5
Glandular cystic hepatitis associated with chronic inflammation	-	-	2	5.56	10	29.4
Hormonally altered mucous membrane of the uterus	-	-	8	22.2	5	14.7
Adenocarcinoma of the uterus	-	-	-	-	1	2.94

As can be seen from this table, it can be stated that a complicated histomorphological picture was detected in the third group of patients with recurrent GE.

Histological analysis revealed marked vascularization with thrombosis. The stroma had a fibrous structure, predominantly composed of small fibroblast-like cells. The endometrial glands varied in shape, with some glands being cystically distended and hyperplastic. The glandular epithelium contained hyperchromatic nuclei. A secretory mass was visible within the glandular lumen (Fig. 2.5.1).

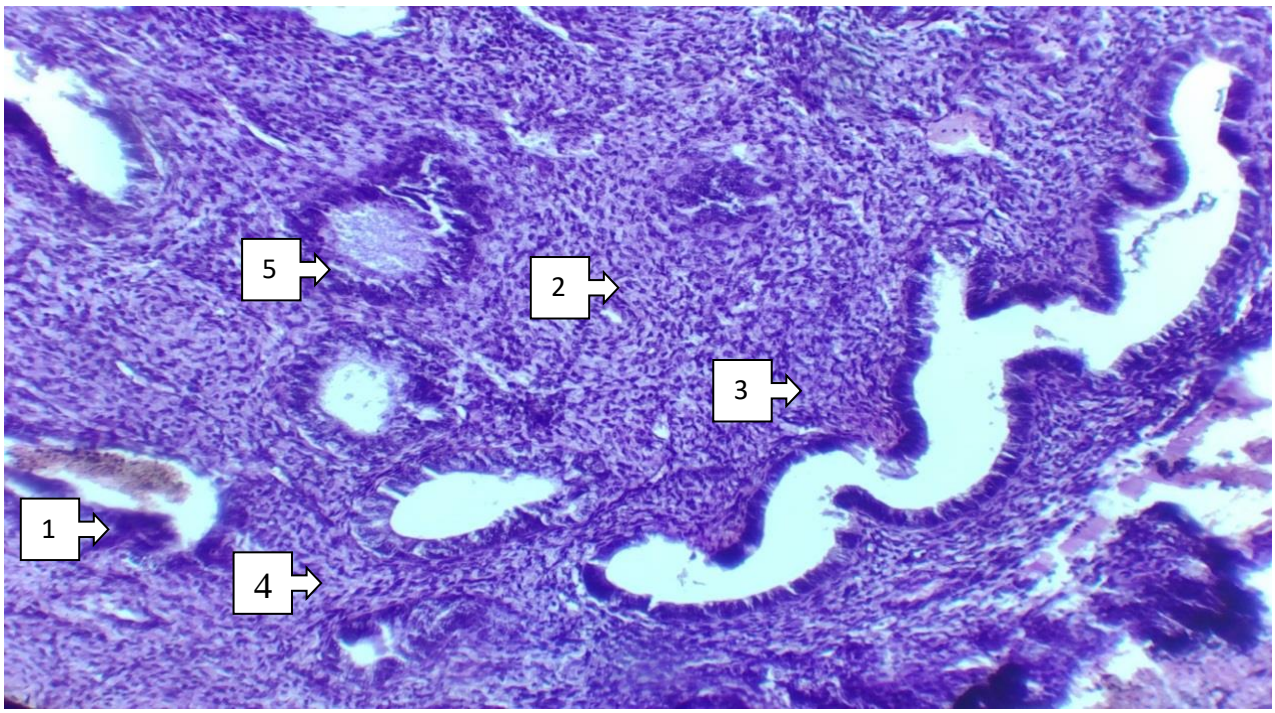


Figure 2.5.1. Glandular hyperplasia of the endometrium. Hemotoxylin and eosin staining (personal observations). Marked vascularization with thrombosis (1). The stroma has a fibrous structure, consisting of small fibroblast-like cells (2). The endometrial glands are of varying shapes, some glands are cystically stretched and hyperplastic (3). The epithelium of the glands has hyperchromic nuclei (4). A secretory mass is present in the lumens of the glands (5).

Glandular endometrial hyperplasia was verified in the second study group in 16 patients (44.4%) and 6 patients (17.6%). Endometrial hyperplasia in this study was observed in two forms:

1. Focal endometrial hyperplasia.
2. Diffuse endometrial hyperplasia.

Statistical analysis confirmed focal endometrial hyperplasia in 4 patients (11.1%) and diffuse endometrial hyperplasia in 12 patients (33.3%) in the second main group. This condition is associated with inflammatory processes in the endometrium, which are present in the perimenopausal women studied. In the remaining 2 patients (5.8%) Focal endometrial hyperplasia and 4 patients (11.7%) had diffuse endometrial hyperplasia. Diffuse endometrial hyperplasia is associated with hormonal imbalances typical of this period of life. These data suggest that the third group of women with recurrent GE predominantly had inflammatory processes

in the endometrium, which may be considered one of the main causes of AUB recurrence in perimenopausal women.

Furthermore, histological analysis of the endometrium reveals glands of various shapes, primarily oval and irregular, hyperplastic, and with a stroma composed of small, rounded cells bordered by lymphocytic infiltration. The nuclei of the endometrial gland epithelium stain hyperchromically, and a secretory mass can be detected within their lumens. This pattern is shown in Figure 3.

In biopsies of glandular endometrial hyperplasia against the background of chronic endometrial inflammation, pronounced stromal edema was observed in 12 patients (33.3%) of the second and in 4 patients (11.8%) of the third main group ($p>0.05$). Inflammatory infiltration can be detected in the stroma, containing a large number of lymphocytes including plasma cells, eosinophils, and macrophages located around the blood vessels and glands. In the second main group, 12 patients (33.3%) demonstrated sclerosis of the vascular walls, on which dense fibrous tissue can be identified; in the third main group, this was observed in 16 cases (47.0%) ($p>0.05$).

Microscopic analysis of the endometrium in patients with inflammatory processes (endometritis) reveals a significantly more complex histological picture of glandular hyperplasia. Congestive plethora and vascular thrombosis are observed in the cellular stroma. The stroma has a fibrous structure, consisting of small fibroblast-like cells with mild edema and lymphocytic infiltrate. The endometrial glands vary in shape and are hyperplastic, with multiple hyperchromic nuclei , as shown in Figure 2.5.2.

The underlying cause of the observed patterns was a hormonal imbalance affecting proliferative processes in the endometrium and directly causing the development of glandular-cystic changes. Glandular-cystic endometrial hyperplasia was detected in only 8 patients (23.5%) in the third group. The endometrial glands had various shapes, were cystically dilated , and hyperplastic. The stroma had a fibrous structure, consisting of small fibroblast-like cells. The glandular epithelium

was depicted by hyperchromatic nuclei. A secretory mass was detected in the lumen of the glands . These histological changes are shown in Figure 2.5.3.

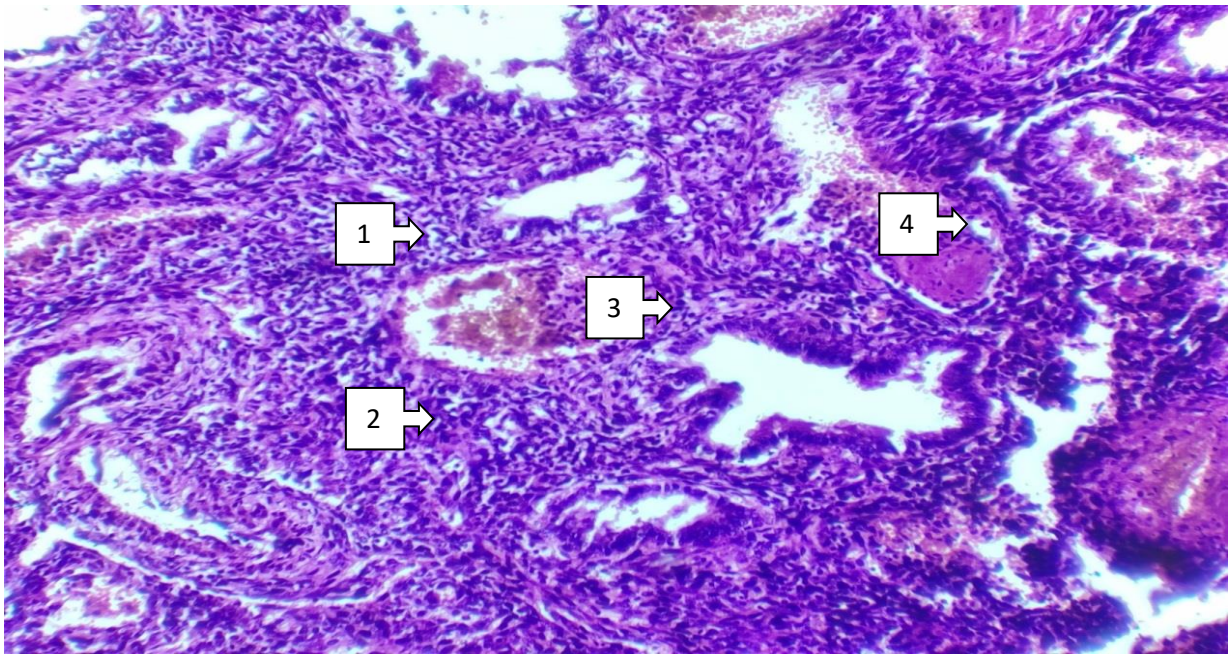


Figure 2.5.2. Glandular hyperplasia of the endometrium against the background of endometritis. Hemotoxylin and eosin staining (personal observations). The stroma shows congestive plethora and vascular thrombosis (1). The stroma has a fibrous structure, consisting of small fibroblast-like cells with mild edema and lymphocytic infiltrate (2). The endometrial glands are of varying shapes and hyperplastic (3). The epithelium of the glands has hyperchromic nuclei (4).

Endometrial glandular cystic hyperplasia is a pathological condition in which glandular structures surrounded by cysts form in the endometrial epithelium. A histological specimen reveals an increase in the size of the glandular structures and the presence of fluid-filled cysts. The cells in these glands may be hyperplastic, meaning they increase in size but maintain their shape and function. However, if hyperplasia continues, the cells may become atypical and begin dividing abnormally, potentially leading to the development of endometrial cancer.

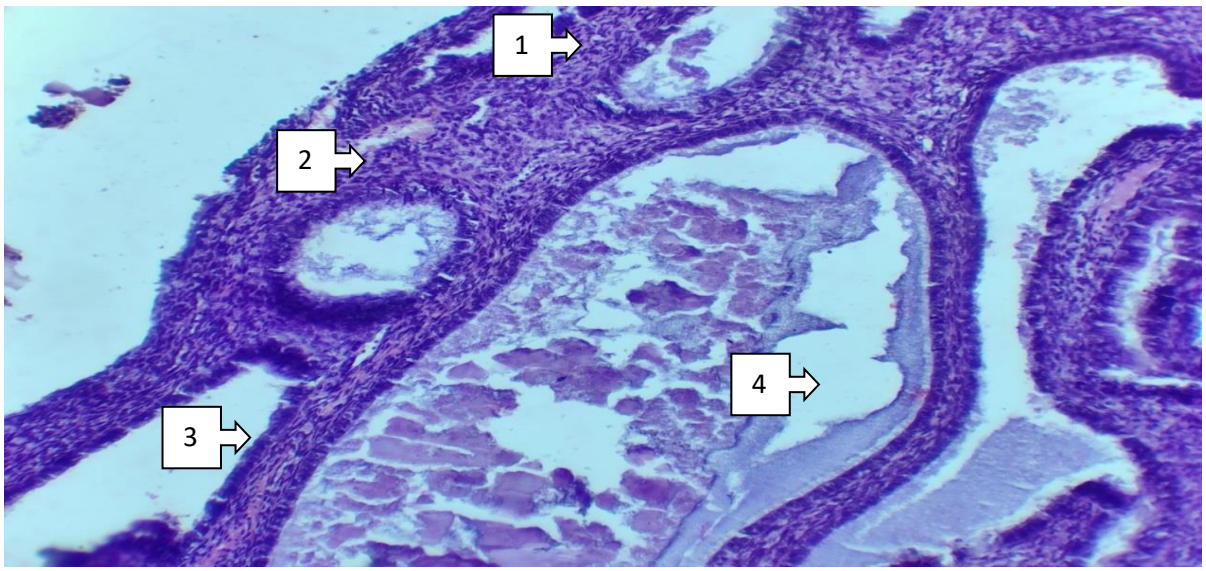


Figure 2.5.3. Glandular cystic hyperplasia of the endometrium. Hemotoxylin and eosin staining (personal observations). The endometrial glands are of varying shapes, cystically dilated, and hyperplastic (1). The stroma has a fibrous structure and consists of small fibroblast-like cells (2). The epithelium of the glands has hyperchromatic nuclei (3). A secretory mass is present in the lumens of the glands (4).

The histological specimen may also show signs of inflammation and bleeding. Sometimes, glandular cystic hyperplasia (GCH) was observed against a background of chronic inflammation in patients in the second group; it occurred in 2 (5.56%) and 10 (29.4%) of the third group. In this case, the histological picture was more complex, with inflammatory elements such as lymphocytes and macrophages added to the aforementioned elements of GCH. This picture is shown in Figure 2.5.4.

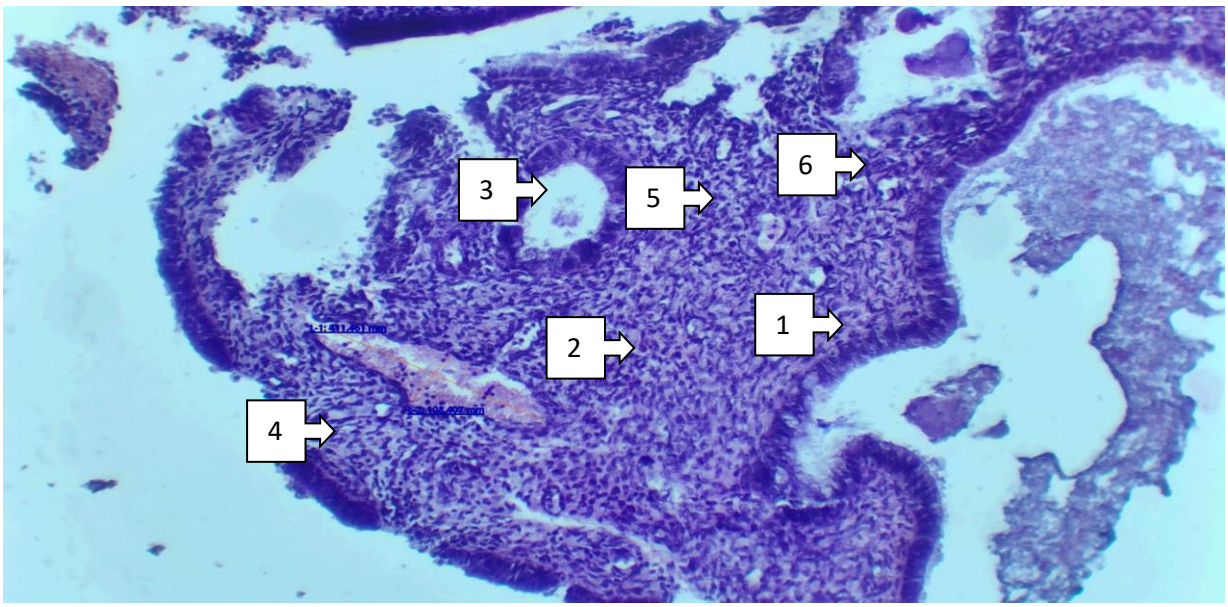


Figure 2.5.4. Glandular cystic hyperplasia of the endometrium against the background of chronic inflammation. Hemotoxylin and eosin staining (personal observations). The glandular epithelium of the endometrium is cylindrical, cystically dilated, and hyperplastic (1). The stroma has a fibrous structure and consists of small fibroblast-like cells (2). The epithelium of the glands has hyperchromatic nuclei (3). It is rich in vessels (in size) with congestive plethora and thrombosis (4). Numerous lymphocytes and macrophages (5, 6).

Hormonally altered uterine mucosa was detected in 8 patients (22.2%) in the second group and 5 (14.7%) in the third group. Adenomatous endometrial hyperplasia was also detected in both study groups. Adenomatous endometrial hyperplasia is a pathological condition characterized by an increase in the number of glandular structures in the endometrial epithelium. Histological findings revealed an increase in the size of the glandular structures and their dense arrangement. In one patient, histological examination revealed abnormal division of these glands, which became atypical. The cells in these glands were hyperplastic, atypical, and began to divide abnormally, indicating the development of endometrial cancer. The data are shown in Figure 2.5.5.

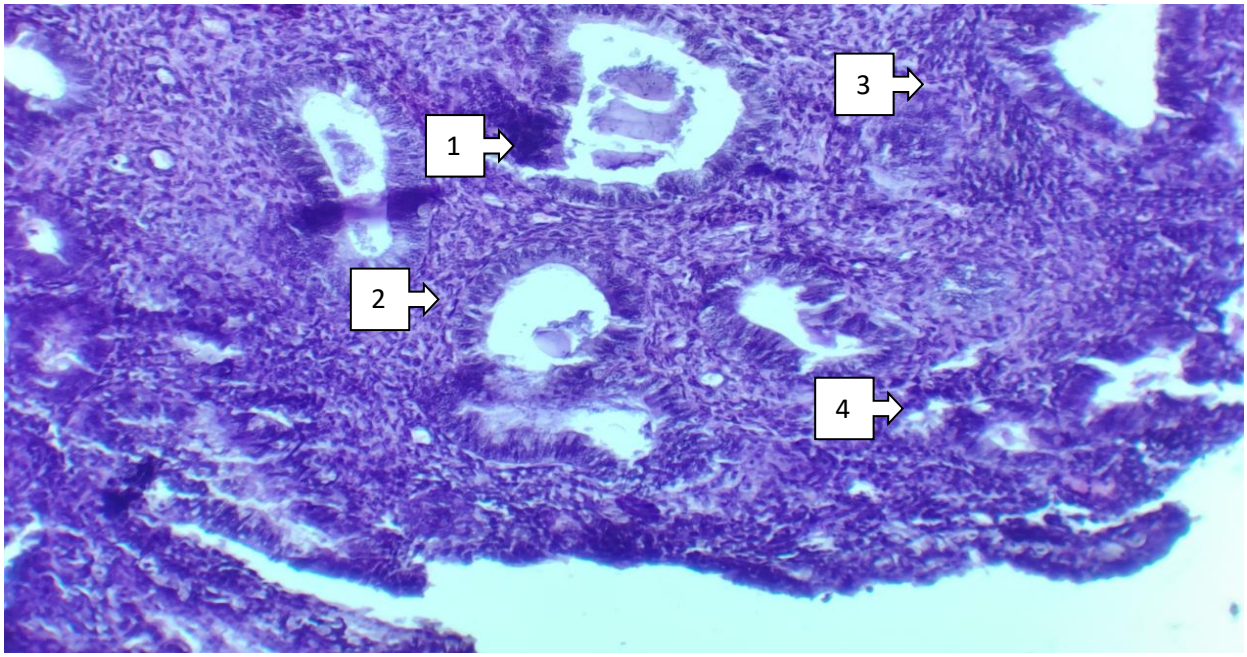


Figure 2.5.5. Adenomatous hyperplasia of the endometrium. Hemotoxylin and eosin staining (personal observations). The endometrial glands are scattered, the epithelium is proliferative, and some glands are cystically dilated (1). The stroma has a fibrous structure and consists of small fibroblast-like cells (2). The epithelium of the glands has

hyperchromatic nuclei (3). Weak vascularization, varying degrees of sclerosis with lymphomacrophage infiltration (4).

Adenocarcinoma was detected in only one case (2.94%) in the third group. The histological specimen may also show signs of inflammation and bleeding.

Thus, the obtained study results allow us to conclude that all morphological features should be combined with the functional features of ultrasound examination for greater diagnostic accuracy. Furthermore, clinical and anamnestic factors should be taken into account, followed by prediction of the degree of risk of endometrial cancer development based on data-based diagnostic markers: clinical laboratory, immunological, ultrasound, and morphological studies, to select a differentiated approach to treatment. Particularly in cases of recurrent hyperplasia during hormonal therapy, screening using the above-mentioned diagnostic methods is necessary to promptly decide on radical treatment options.

CHAPTER III. FEATURES OF THE IMMUNE SYSTEM IN ENDOMETRIAL HYPERPLASIA IN THE PERIMENOPAUSAL PERIOD

In the case of cervical intraepithelial processes, the dynamics of interactions between immune cells and cytokines often undergo changes, which can lead to disruption of the body's antihyperplastic defense mechanisms. In both acute and, especially, chronic infectious diseases, microorganisms often act as triggers, initiating self-sustaining pathological processes, particularly during the perimenopausal period. Given a specific genetic configuration, dependent on individual characteristics of the expression of cellular histocompatibility components, this can lead to persistent and long-term impairments in the functional activity of both cellular and humoral immunity.

To conduct immunological studies, we selected 78 patients diagnosed with endometrial hyperplasia in the perimenopausal period, who were divided into two groups:

- Group 1 – 40 patients diagnosed with endometrial hyperplasia (EH).

- Group 2 – 38 patients diagnosed with recurrent endometrial hyperplasia with transition to PGE.

- the third group (control) – 36 healthy patients of similar age.

§3.1. Characteristics of immunological markers in the first group of patients with endometrial hyperplasia in the perimenopausal period

The immunological response, regardless of whether the humoral or cellular response predominates, begins with the activation of the proliferation process. One of the criteria for this proliferation may be associated with an increase or decrease in the number of lymphocytes possessing the IL-2 receptor (CD25+).

To assess the activation of lymphocytes in women with endometrial hyperplasia (group 1), we used a marker of early activation - CD25 + interleukin-2 receptor, which stimulates rapid proliferation and subsequent differentiation of naive T cells into mature forms, and the expression level of CD95 +, which reflects their

readiness for apoptosis, activating the mechanism of programmed cell death through the Fas-dependent pathway.

Table 3.1.1.

Absolute and relative values of early and late activation markers in the first group of women with endometrial hyperplasia M ± m (μl, %)

Groups	CD25+ (Abs)	CD25+ (Rel)	CD95+ (Abs)	CD95+ (Rel)
Control group (n=36)	355.4 ± 7.20	20.6 ± 0.62	436.4 ± 6.19	25.3 ± 0.68
GE (n=40)	285.4 ± 7.44 *	18.8 ± 0.76	360.2 ± 4.14 *	23.7 ± 0.698

Note: * – differences are significant compared to the data of the control group (* – $p < 0.05$).

The study revealed changes in the expression level of CD25 + and CD95 + cell markers in patients with endometrial hyperplasia (EH) compared to the control group.

A study of the level of lymphocyte activation in the blood revealed that patients in the first group had a reduced number of low-affinity IL2-CD25+ receptors on lymphocytes, indicating a 1.24-fold decrease in their readiness for proliferation and differentiation processes, compared to the control group. For the control group, the value was 355.4 ± 7.20 μl, while for the group with GE, it was 285.8 ± 7.44 μl .

When comparing the absolute value of CD95+ lymphocytes in patients with endometrial hyperplasia (EH) and the control group, a tendency towards a decrease in the EH group by 1.21 times was also found (360.2 ± 4.14 μl versus 436.4 ± 6.19 μl in the control).

The relative number of CD25+ lymphocytes in the peripheral blood of patients in the first group was reduced by 1.095 times and amounted to 18.8 ± 0.76 compared to the control group, where this indicator was 20.6 ± 0.62 .

In addition, patients with GE showed a slight decrease in the relative number of CD95+ cells compared to the control group. The level of CD95+ cells was 23.7 ± 0.698 in patients with GE, while in the control group this indicator was slightly higher and amounted to 25.3 ± 0.68 (Table 4.1).

Thus, the decrease in expression of CD25 + and CD95 + lymphocytes in endometrial hyperplasia indicates an imbalance in the processes of proliferation and cellular apoptosis in the immune system , which are associated not only with the pathogenesis and development of this disease, but also with other concomitant pathologies.

Currently, considerable attention is being paid to the role of angiogenesis and inflammation in the development of endometrial hyperplasia. These processes are essential for the development of this disease, particularly in the context of the endometrial cavity. The attachment of endometrioid heterotopias to the walls of the pelvic organs and their ability to survive are associated with the formation of an extensive vascular network around them. Inflammatory factors significantly influence these processes, particularly in the context of hyperplastic processes within the uterus, leading to a local reaction, predominantly of a nonspecific inflammatory nature, with an increase in the number of tissue basophils around the site of inflammation. An increase in the number and activity of macrophages, which form the basis of endometrial fluid, is also observed [8,16,28,42,87,90,102,124].

Activated macrophages can produce various cytokines and growth factors that influence angiogenesis and inflammation at the tissue level. Cytokines produced by endometrial and endothelial cells play a significant role in the function and pathology of the female reproductive system. They regulate the formation of new vessels, programmed cell death, cell growth and division in the endometrium, and control the production of inflammatory cytokines [32,54,89,115].

The study of local immune mechanisms is of great interest for understanding the fundamental processes involved in the development of endometrial hyperplasia. However, the study of the systemic immune response in endometrial hyperplasia also provides important information on the mechanisms of the disease, since the state of circulating cytokines often reflects the nature of immune disturbances occurring locally in organs [45,56,94,109].

To clarify the role of cytokines in the pathogenesis of HE, we studied the concentrations of IL -1β, IL-2, IL6 and TNFα in the blood serum of the first group of patients (n = 40).

Table 3.1.2.

The level of proinflammatory cytokines in patients of the first main group, pg/ml

Groups	IL-1β	IL-2	IL-6	TNFα
Control	6.33±0.49	8.75± 0.49	5.67±0.40	25.7± 0.99
GE (n=40)	17.9±0.82 * **	7.39±0.43 *	18.4±0.90 * **	55.2±1.46 * **

Note: * – differences are significant compared to the data of the control group (* – p <0.05, ** – p <0.01, *** – p <0.001).

Role in endometrial pathology

- In endometrial tissues, IL-1β:

- regulates the processes of cell proliferation and apoptosis;

- participates in menstrual desquamation;

- contributes to angiogenesis and stromal remodeling;

- with hyperexpression, supports chronic endometritis;

- mediates the disruption of endometrial progesterone sensitivity;

- can contribute to the recurrence of endometrial hyperplasia through the activation of inflammatory-proliferative cascades.

Elevated levels of IL-1β are associated with persistent endometrial inflammation and impaired implantation window.

IL - 1β is a cytokine that activates inflammatory processes by stimulating T- and B-lymphocytes and increasing the synthesis of other cytokines. Increased IL - 1β levels lead to the activation of endothelial cells, which leads to increased expression of adhesion molecules on them, activation of neutrophils, and increased synthesis of acute-phase proteins. IL - 1β is believed to have properties associated with endometriosis [36,68,82,105].

In our study, the level of IL -1 β in patients of the first group, compared with the control group, revealed a significant increase in this indicator by 2.83 times, which amounted to an average of 17.9 ± 0.82 pg/ml ($p<0.05$).

Interleukin-2 (IL-2) is a key pro-inflammatory cytokine primarily synthesized by activated CD4+ T-lymphocytes (Th1-cells), as well as CD8+ T-cells and NK-cells. It plays a central role in regulating the cellular immune response, ensuring the proliferation, differentiation, and functional activity of immunocompetent cells.

immunobiological role of IL-2 in the endometrium

Normally, IL-2 participates in:

maintenance of endometrial local immune homeostasis;

activation of cytotoxic T-lymphocytes and NK-cells;

control of endometrial cell proliferation;

antitumor immune supervision.

Under physiological conditions, the expression of IL-2 in the endometrium changes cyclically and depends on the hormonal background.

Changes in IL-2 levels in endometrial hyperplasia

In endometrial hyperplasia, dysregulatory changes in IL-2 production are detected, manifesting as:

decrease in local expression of IL-2 in endometrial tissue;

disruption of the balance between Th1- and Th2-cytokines;

weakening of cellular immune control over the proliferation of endometrial cells.

Decreased IL-2 activity is associated with:

suppression of the cytotoxic activity of NK cells;

reduction of apoptosis of hyperplastic cells;

increased endometrial resistance to immune control.

The role of IL-2 in recurrent endometrial hyperplasia

Insufficient expression of IL-2 is considered one of the factors in recurrent endometrial hyperplasia, as:

elimination of atypically proliferating cells is impaired;

Local immunodeficiency develops;

endometrial sensitivity to estrogen stimulation increases.

Th1 cells are known to produce interleukin-2 (IL-2), which is a factor stimulating and differentiating T lymphocytes and NK cells, promoting the formation of differentiated T killers, and activating the functional activity of T helper cells. IL-2 also enhances the synthesis of immunoglobulins in previously activated B lymphocytes. Furthermore, IL-2 has a direct effect on monocytes that express the IL-2 receptor [24,35,57,73,107,116].

When comparing the IL-2 level in patients with endometrial hyperplasia (EH) and the control group, a tendency towards a decrease in the synthesis of this cytokine in the EH group by 1.19 times was revealed (7.39 ± 0.43 pg/ml versus 8.75 ± 0.49 pg/ml in the control). In all likelihood, the reduced IL -2 level is associated with a decrease in the content of activated T-lymphocytes and NK cells in patients with EH.

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine synthesized by macrophages, T-lymphocytes, fibroblasts, endothelial and epithelial cells, including

endometrial cells. IL-6 participates in the regulation of the inflammatory response, immune reactivity, cellular proliferation processes, angiogenesis, and apoptosis.

Sources and expression of IL-6 in the endometrium

In normal endometrium, IL-6 expression is phase-dependent and increases during the proliferative phase of the menstrual cycle. In endometrial hyperplasia, a persistent increase in local IL-6 production is observed due to:

activated macrophages of the stroma;

endometrial epithelial cells;

cells of the endothelium of microvessels;

infiltrating immunocompetent cells.

Increased IL-6 expression is most pronounced in combination with endometrial hyperplasia with chronic endometritis and metabolic disorders.

When analyzing the synthesis of IL-6, a significant increase in its content in the blood serum of women with endometrial hyperplasia (EH) was revealed compared to the control group, amounting to 18.4±0.90 pg/ml versus 5.67±0.40 pg/ml, respectively, which indicates the presence of a reliable increase of 3.25 times ($p<0.05$).

Increased IL-6 synthesis is also associated with tissue damage and the presence of long-term chronic stress. Both of these factors play a significant role in cases of nonspecific hepatic encephalopathy [3,14,22,31,45,75,90].

The increased level of this indicator during perimenopause in patients in the first group may be a consequence of chronic stress associated with prolonged pain syndrome, as well as one of its possible causes, creating a vicious cycle. The pathogenesis of the spread of GE suggests the presence of microtrauma during the invasion of pathological foci, which may also explain the increased levels of IL-6 as an indicator of inflammation [4,13,26,34,65].

Analysis of the TNFα level in patients of the first group revealed a reliable increase in this indicator by 2.14 times, averaging 55.2±1.46 pg/ml compared to the control group - 25.7±0.99 pg/ml ($p<0.05$).

It should be noted that changes in the synthesis of proinflammatory cytokines may be associated with various pathological conditions of the body.

§3.2. Characteristics of immunological markers with recurrent endometrial hyperplasia in the perimenopausal period with transition to PGE

The study of CD25+ and CD95+ lymphocytes in perimenopausal women with recurrent endometrial hyperplasia is highly relevant in the context of the search for biomarkers associated with the development of proliferative-hyperplastic processes (PHE). This transition represents a serious medical problem, as PHE can be a precancerous condition and ultimately lead to malignant oncological processes in the endometrium. Studying the levels of CD25+ and CD95+ lymphocytes can help to determine the immunological mechanisms underlying this transition, as well as to identify potential risk markers and new approaches to the prevention and treatment of PHE. Understanding the changes in the immune response during perimenopause and their relationship with the development of PHE can facilitate the development of personalized approaches to the treatment and monitoring of this disease, which will lead to an improved prognosis and quality of life for patients. Based on the above, we studied the levels of CD25+ and CD95+ lymphocytes in patients in Group 2.

Table 3.2.1.

Absolute and relative values of early and late activation markers M ± m (µl, %) .

Groups	CD25+ (Abs)	CD25+ (Rel)	CD95+ (Abs)	CD95+ (Rel)
Control (n=36)	355.4 ± 5.42	20.6 ± 0.88	436.4 ± 5.81	25.3 ± 0.63
Rec. GE with lane on PGE (n=38)	245.4 ± 4.41 *	15.9 ± 0.58 *	325.6 ± 3.65 *	21.1 ± 1.10 *

Note: * – differences are significant compared to the data of the control group (* – $p < 0.05$).

When analyzing the obtained results of absolute and relative indicators of CD25+ and CD95+ lymphocytes in women with recurrent endometrial hyperplasia transitioning to the proliferative-hyperplastic form in comparison with the control group, a decrease in the level of CD25+ lymphocytes in absolute values by 1.44 times (245.4±4.41 μl compared to 355.4± 5.42 μl) and relative values by 1.29 times (15.9± 0.58 and 20.6± 0.88 , respectively) ($p \leq 0.05$) was observed.

It is known that the level of CD95+ expression on lymphocytes reflects their readiness to activate apoptosis, that is, the inclusion of the mechanism of programmed cell death through the Fas-dependent pathway. According to our data for the apoptosis marker - CD 95+ lymphocytes, a decrease in the level of this indicator is also noted in the second group, compared to the control group. In particular, the level of CD 95+ lymphocytes was reduced in absolute values by 1.34 times (325.6 ± 3.65 μl compared to 436.4 ± 5.81 μl) and in relative values by 1.19 times (21.1 ± 1.10 compared to 25.3 ± 0.63) ($p \leq 0.05$) (Table 4.2).

Suppression of apoptosis can lead to the development of hyperplasia, proliferative disorders, and tumor formation. Hormonal regulators play a key role in regulating apoptosis at the body level. Hormonal action at the cellular and molecular levels is mediated by cytokines, interleukins, growth factors, genes, and specific oncoproteins.

During the initial phase of proliferation and early secretion, apoptosis remains at a low level, which is of significant physiological significance. During the late phase of proliferation, expression of the apoptosis inhibitor (bcl-2 inhibitor gene) is reduced to a minimum, promoting apoptosis in cells susceptible to infection, damage, or those with low biological potential, including those with high proliferative potential.

It is believed that some of the most important and frequently damaged cells in the immune system are T-helper cells, which produce cytokines. [4,9,12,30,58].

The next stage of our and their research was the study of the cytokine profile (IL-1β, IL-2, IL-6, TNFα) in the second group of patients (n = 38) with recurrent GE with transition to PGE.

Table 3.2.2.

The level of proinflammatory cytokines in patients with recurrent hepatitis C, pg/ml

Groups	IL-1β	IL-2	IL-6	TNFα
Control	6.33±0.40	8.75± 0.49	5.67±0.40	25.7± 0.99
Rec. GE with translation. on PGE (n=38)	21.3±1.01 * **	5.87±0.29 *	18.6±1.84 * **	67.6±1.95 * **

Note: * – differences are significant compared to the data of the control group (* – p <0.05, ** – p <0.01, *** – p <0.001).

Most interleukins stimulate prostaglandins, fibroblast proliferation, and IL - 1β synthesized by activated macrophages and endometrial implants stimulates VEGF and IL-6. Analysis of IL - 1β levels in patients in the second group (21.3±1.01 pg/ml) compared to the control group revealed significant changes. The difference was 3.37-fold, indicating a significant increase in the level of the proinflammatory cytokine in this patient sample (p<0.05).

It was found that in women with recurrent endometrial hyperplasia, transitioning to the proliferative-hyperplastic form (PHE), the level of interleukin-2 (IL-2) was reduced compared to the control group, amounting to 5.87 ± 0.29 pg/ml, which is 1.49 times lower than the value of the control group (8.75 ± 0.49 pg/ml) (Fig. 4.6).

It is possible that the decrease in IL-2 levels is associated with immunological reactions aimed at compensating for changes in the endometrium.

Interleukin-6 (IL -6) plays a key role in the immunological mechanism of proliferative-hyperplastic inflammation. This cytokine promotes immune cell

activation and is also involved in the regulation of apoptosis and proliferation, which can lead to changes in the endometrium and ultimately contribute to the development of malignant transformation.

In our study, the synthesis of interleukin-6 (IL-6) in women with recurrent endometrial hyperplasia, developing into the proliferative-hyperplastic form (PHE), was significantly increased and amounted to 18.6 ± 1.84 pg/ml compared to the control group, which is an average difference of 3.28 times ($p<0.05$).

TNFα is known to be a product of the activity of monocytes/macrophages, endothelial, mast, and myeloid cells, LAK cells, neuroglial cells, and, in certain cases, activated T lymphocytes. TNF release leads to increased capillary permeability, damage to the vascular endothelium, and the development of intravascular thrombosis [40,53,64,78].

Analyzing the obtained data on the study of tumor necrosis factor α (TNFα) in women of the second group, we found a significant increase in its concentration to 67.6 ± 1.95 pg/ml, which is 2.64 times higher than the values in the control group (25.7 ± 0.99 pg/ml) ($p<0.05$).

Analyzing the data we obtained on the cytokine profile and activation markers in peripheral blood, it can be noted that the detected changes in these parameters were unidirectional for both groups of patients with endometrial hyperplasia.

§3.3. Comparative characteristics of immune parameters of the studied groups in GE in the perimenopausal period

One of the risk factors for the development of endometrial hyperplasia is the inflammatory process caused by persistent viral invasion.

It is known that abnormalities in the reproductive system may be associated with the development of immunological tolerance to various viruses, which can contribute to hyperplastic processes in the endometrium. One of the mechanisms leading to the development of such tolerance involves cytokine-mediated suppression due to the predominance of Th2/Th3 cytokines. Conversely, the predominance of Th1 cytokines may be associated with the level of viral load.

To clarify the role of early and late activation markers and cytokine status in the development of endometrial hyperplastic processes, we conducted a comparative analysis of previously studied activation markers in the examined groups.

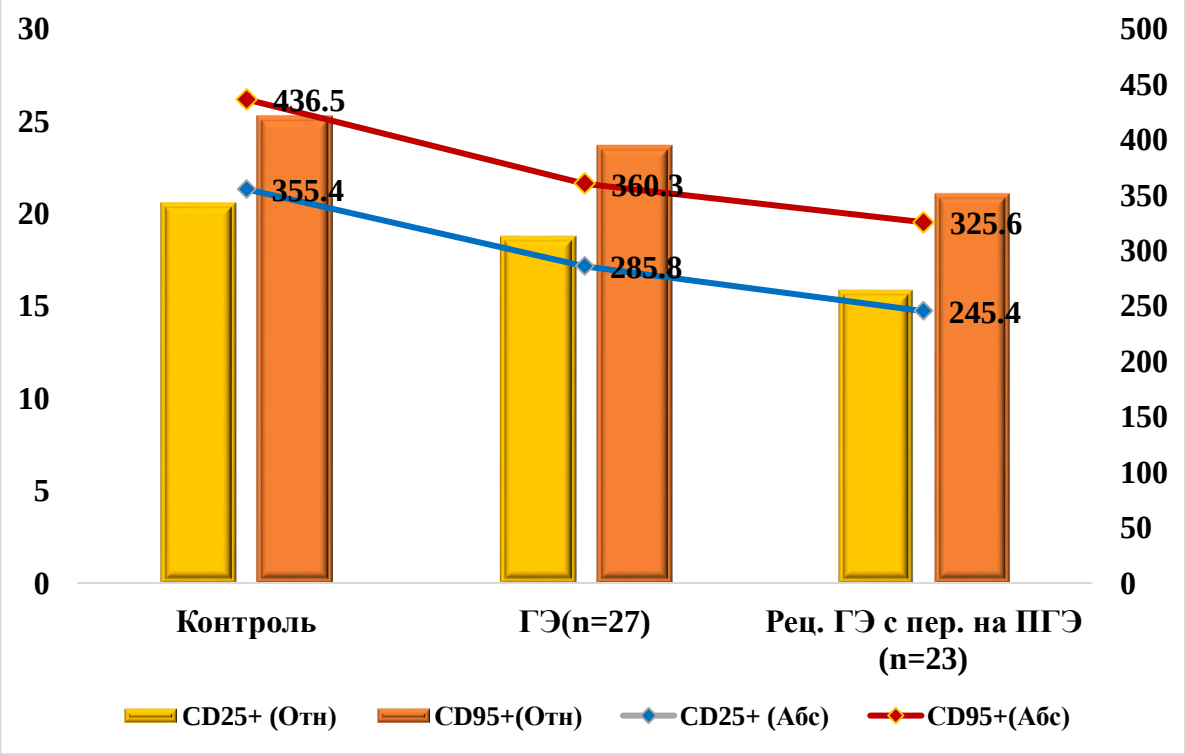


Figure 3.3.1. Comparative characteristics of activation markers in the examined subjects (µl, %), (P ≤0.05)

A comparative analysis of the obtained data on absolute values of CD25+ lymphocytes between the groups revealed a decrease as progression occurred from the control group (355.4 ± 7.20 µl) to the group with endometrial hyperplasia (285.4 ± 7.44 µl) and further to the group of women with recurrent endometrial hyperplasia transitioning to the proliferative-hyperplastic form (245.4 ± 4.41 µl). A significant decrease in the CD25+ level (abs) was noted by 1.24 times between the control group and the HE group, as well as by 1.16 times between the first group (HE) and the second (PGE).

The study showed that the number of CD95+ lymphocytes in the group of patients with recurrent endometrial hyperplasia developing into a proliferative-hyperplastic form decreased by 1.34 times (325.6 ± 3.65 µl compared to 436.4 ± 6.19 µl) compared to the control group.

Comparison of the relative values of CD25+ lymphocytes showed that the level of lymphocytes in patients with recurrent endometrial hyperplasia progressing to proliferative-hyperplastic endometritis is significantly lower than in the control group and the group with HE, by 1.29 and 1.18 times, respectively.

Apoptosis is a well-established genetic mechanism of cell death in the body. Disruption of this process is essential for the development of cancer at all stages. In the early stages, mutationally altered cells can be destroyed by apoptosis, and tumors do not form. Factors that inhibit apoptosis (in addition to the bcl-2 family of genes) include excessive secretion of gonadotropic hormones (FSH and LH), unbalanced secretion of these hormones, accumulation of mutation factors in cells, aging, metabolic disorders (oxidative stress), and others. [32,45,73,96]

A comparative analysis of the relative value of CD95+ cells between the three groups revealed the following: in patients with endometrial hyperplasia (EH), a decrease in the relative number of CD95+ cells was observed compared to the control group. In particular, the level of CD95+ cells was 23.7 ± 0.698 , which is lower than the control group (25.3 ± 0.68). A decrease in this indicator was also noted in patients with recurrent endometrial hyperplasia turning into a proliferative-hyperplastic form, where the level of CD95+ cells was 21.1 ± 1.10 . The difference in the level of CD95+ cells between the EH groups and the control group was 1.06 times, between the recurrent endometrial hyperplasia groups and the control group by 1.19 times.

Table 3.3.1.

The level of proinflammatory cytokines in the examined patients, pg/ml

Groups	IL-1β	IL-2	IL-6	TNFα
Control	6.33±0.49	8.75± 0.49	5.67±0.40	25.7± 0.99
GE (n=40)	17.9±0.82 ***	7.39±0.43 *	18.4±0.90 * **	55.2±1.46 * **
Rec. GE with translation.	21.3±1.01 * **^	5.87±0.29 **^	18.6±1.84 * **	67.6±1.95 * **^

on PGE (n=38)				

Note: * – differences are significant compared to the data of the control group (* – p <0.05, ** – p <0.01, *** – p <0.001), ^ – differences are significant compared to the data of the 1st group (^ – p <0.05).

A comparative analysis of cytokine levels in each examined group revealed the following: the level of interleukin-1β (IL-1β) in patients with endometrial hyperplasia (EH) was 17.9 ± 0.82 pg/ml, which significantly exceeds the level in the control group (6.33 ± 0.40 pg/ml). The ratio between these groups was 2.83 times, indicating a significant increase in the IL-1β level in the EH group. In the group of patients with recurrent EH transitioning to the proliferative-hyperplastic form, the IL-1β level was 21.3 ± 1.01 pg/ml, which is also significantly higher than in the control group. The difference between recurrent EH transitioning to PHE and the control group was 3.37 times.

The level of interleukin-2 (IL-2) in the HE group was 7.39 ± 0.43 pg/ml, which is 1.19 times lower than the level in the control group (8.75 ± 0.49 pg/ml). In the group with recurrent HE and transition to PGE, the level of IL-2 was also slightly lower than the control value, amounting to 5.87 ± 0.29 pg/ml. The difference between the recurrent HE and transition to PGE and the control group was 1.49 times. Both groups with endometrial hyperplasia demonstrated a decrease in IL-2 synthesis.

The concentration of IL-6 was significantly elevated in women with GE (18.4 ± 0.90 pg/ml) and in the second group with recurrent GE (18.6 ± 1.84 pg/ml) compared to the control group (5.67 ± 0.40). The difference between GE and the control group was 3.25 times, and between recurrent GE with the transition to PGE and the control group - 3.28 times. Both differences are statistically significant ($p \leq 0.001$).

A comparative analysis between the two groups revealed that in patients of the first (55.2 ± 1.46 pg/ml) and second group (67.6 ± 1.95 pg/ml), TNFα synthesis significantly increased compared to the control group (25.7 ± 0.99 pg/ml). The difference between the group of patients with HE and the control group was 2.14

times, and between recurrent HE with transition to PGE and the control group - 2.64 times ($p \leq 0.05$).

In summarizing our studies of cytokine levels and markers of cellular activation and apoptosis, it should be noted that the observed changes in these parameters were common to various forms of endometrial hyperplasia. Since disturbances in the general immune system in endometrial hyperplasia are most often associated with concomitant diseases rather than with the general mechanisms underlying the development of hyperplastic processes in the endometrium, it is necessary to study local immune responses. To better understand the underlying mechanisms underlying the development of hyperplastic processes in foci, studies of local immune processes are particularly important. However, analysis of the systemic immune response in endometrial hyperplasia also provides important data on factors contributing to the development of the disease, as the state of immunocompetent cells in the blood often reflects the direction of immune disturbances at the local level.

§3.4 . Assessment of local cytokine status in women with GE in the perimenopausal period

The transition of endometrial hyperplasia to a recurrent course represents a significant clinical challenge, as it is associated with increased inflammatory activity, hormonal imbalances, comorbidities, and an imbalance in the immune system, characterized by changes in the expression of various cytokines [4,15,35,48,94]. Studying these changes is important for the development of effective diagnostic and therapeutic methods. The relevance of this study is due to the high incidence of endometrial hyperplasia and its significant impact on the quality of life of perimenopausal patients.

All local cytokine data allow for a more accurate assessment of the local inflammatory response in the endometrium compared to serum analysis. This underscores the importance of local inflammation in the pathogenesis of endometrial hyperplasia in perimenopausal women.

When comparing the cytokine levels between the control group, the GE group, and the recurrent GE group with transition to PGE, significant differences were revealed.

IL -1β is a key inflammatory mediator that contributes to the development of chronic inflammation. In the literature, IL -1β is associated with increased expression of adhesion molecules and increased penetration of immune cells into the endometrium [4,12,26,36,67]. The IL -1β level increased by 1.55 times in the GE group ($P < 0.01$) and by 1.85 times in the recurrent GE with transition to PGE group ($P < 0.01$) compared to the control. When comparing groups with GE and rec.GE with the transition to PGE, no reliable difference was found .

IL -2 plays an important role in regulating the immune response, especially in T-cell activation. A decrease in IL -2 levels may indicate suppression of the cellular immune response, which may contribute to the persistence and progression of hyperplasia. A decrease in IL -2 levels may be associated with chronic inflammation and decreased immune surveillance. In our studies, IL -2 levels decreased by 1.52 times in the GE group ($P < 0.05$) and by 1.82 times in the recurrent GE with transition to PGE group ($P < 0.05$) compared with the control and without a significant difference in the mean intergroup values.

IL -6 is a multifunctional cytokine involved in the regulation of the immune response, inflammation and hematopoiesis. IL -6 is often considered as a marker of inflammation and tissue remodeling, it is capable of inhibiting the synthesis of proinflammatory cytokines (IL -1 β and TNFα), can have a hormone-like effect on the liver, maintaining glucose homeostasis, stimulates the secretion of somatotropic hormone and suppresses the secretion of thyroid-stimulating hormone, has pyrogenic properties, reduces the synthesis of albumin and prealbumin [1.7.38.99].

In our study, the concentration of IL -6 increased by 1.57 times in the GE group ($P < 0.01$) and by 1.71 times in the recurrent GE with transition to PGE group ($P < 0.01$) compared with the control.

TNFα is a potent proinflammatory cytokine that plays a central role in the development of inflammation and the immune response. Elevated TNFα levels in recurrent GE with transition to PGE indicate an increase in the inflammatory process, which contributes to the chronic course of the disease. Literature data confirm that TNFα is associated with tissue damage and an increase in the inflammatory response in the endometrium. TNFα levels increased 1.53 - fold in the GE group ($P < 0.01$) and 1.72 - fold in the recurrent GE with transition to PGE group ($P < 0.01$) compared with the control.

It should be noted that when comparing the studied groups (GE and rec. GE with transition to PGE), no reliable difference was found.

Table 3.4.1.

Local levels of proinflammatory cytokines in examined patients, pg/ml

	IL-1β	**IL-2**	**IL-6**	**TNFα**
Control	5.21±0.40	6.28±0.23	5.67±0.42	14.1±0.68
GE (n=40)	24.5±0.67 ***	4.15±0.24 **	21.6±0.48 ***	64.7±0.95 ***
Rec. GE with translation. on PGE (n=38)	29.2±0.13 *** ^	3.45±0.12 ** ^	26.8±0.10 *** ^	82.6±3.78 *** ^^

Note: * – differences are significant compared to the data of the control group (** – p <0.01, *** – p <0.001), ^ – differences are significant compared to the data of the 1st group (^ – p <0.05, ^^ – p <0.01).

The obtained data indicate the presence of pronounced dysfunctional changes in the Th-1 cellular immune response at the local level, which are characterized by an imbalance in the secretion of proinflammatory cytokines: a statistically

significant decrease in the concentration of IL -2 ($p<0.05$) and an increase in IL -1β, IL -6 and TNF-α ($p<0.05$);

Thus, the obtained data demonstrate that in perimenopausal women, the groups with endometrial hyperplasia and recurrent endometrial hyperplasia with transition to PGE are accompanied by significant changes in the levels of local key proinflammatory cytokines (IL -1β, IL -2, IL -6, TNF-α), reflecting the degree of inflammation and changes in the immune response. These changes emphasize the importance of early detection in conjunction with anamnestic data that take into account age, disease duration, premorbid background, gynecological history, and hormonal imbalance to select personalized and appropriate treatment for endometrial hyperplasia, with the goal of preventing its progression and transition to precancerous forms.

§3.5. Correlation analysis of biochemical, instrumental and immunological parameters.

Correlation of biochemical parameters is important because some parameters have a positive or negative relationship. A positive relationship indicates a relationship in which an increase in one parameter leads to an increase in another. A negative relationship indicates that an increase in one parameter leads to a decrease in another.

To determine whether the CA-125 tumor marker and vitamin D predict the development of recurrent endometrial hyperplasia, the linear correlation coefficient (Pearson's correlation coefficient) between endometrial thickness was studied, as an increase in endometrial thickness is a marker of endometrial hyperplasia. According to our studies, the correlation between endometrial thickness and CA-125 was r =

0.64 and r = 0.78 in groups II and III , respectively, indicating a moderate to strong direct correlation (Fig. 3.5.1).

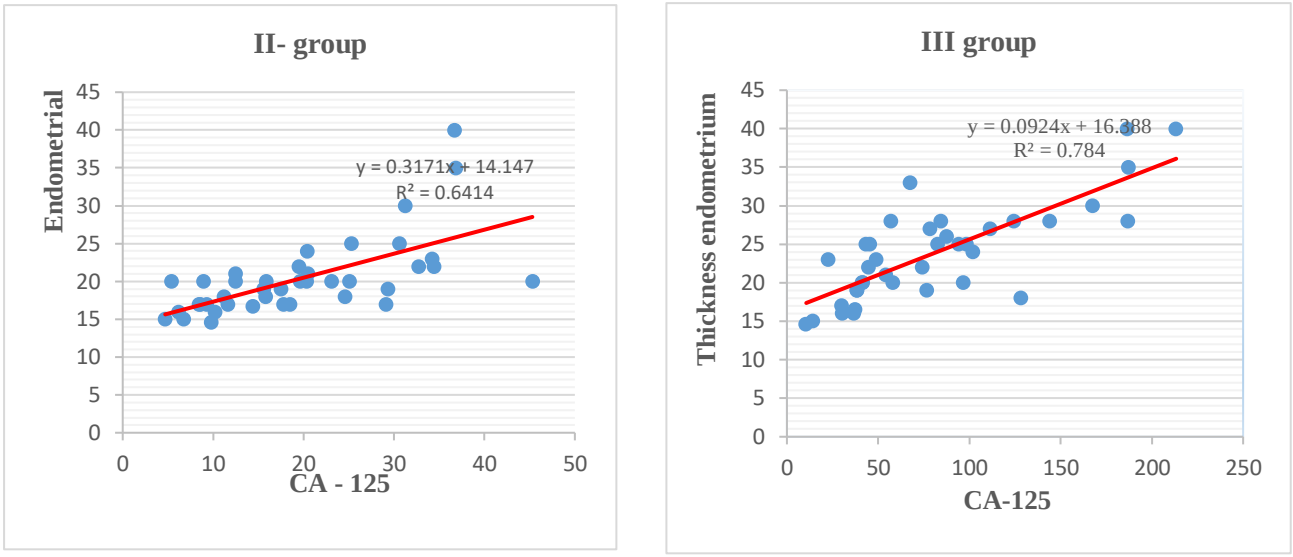


Figure 3.5.1. Linear correlation between endometrial thickness and the tumor marker CA-125.

Whereas the correlation between endometrial thickness and vitamin D showed a moderate and strong inverse correlation, amounting to r = -0.59 and r = -0.76 in the main groups (Fig. 3.5.2.).

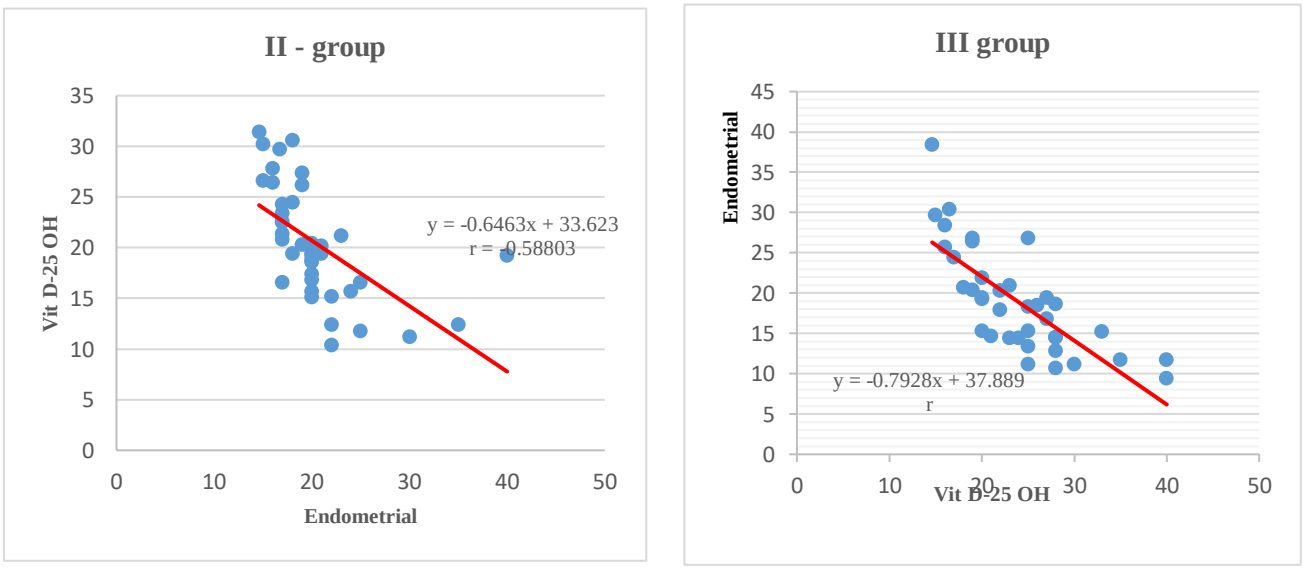


Figure 3.5.2. Linear correlation between endometrial thickness and vitamin D.

We also studied the correlation between TNF-α and CA-125 levels. In the first main group, r = 0.67 and in the second main group, r = 0.83, which corresponded to a moderate and strong direct correlation, respectively (Fig. 3.5.3.).

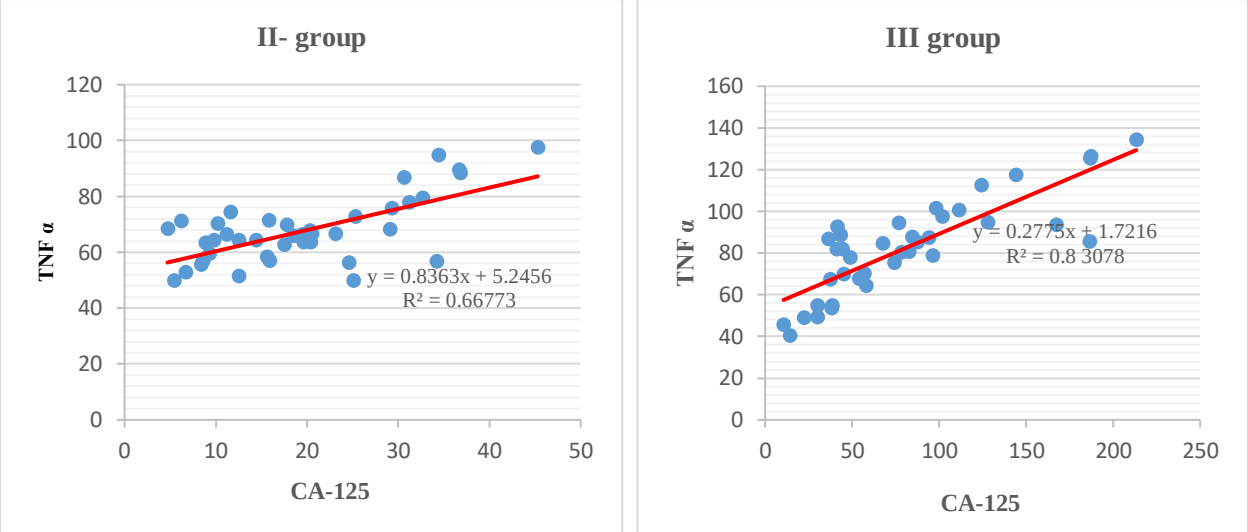


Figure 3.5.3. Linear correlation between interleukin TNFα and the tumor marker CA-125.

CHAPTER I V. MODERN ASPECTS OF THE TREATMENT OF HYPERPLASTIC PATHOLOGIES OF THE ENDOMETRIUM AND PREVENTION OF ITS PROGRESSION

Endometrial hyperplasia has been and remains a pressing issue in modern gynecology due to its high prevalence, particularly in patients entering the perimenopausal period. Of particular interest is its long course, the absence of specific pathognomonic symptoms, and the difficulty in differential diagnosis and, consequently, the selection of treatment methods. Consequently, there are currently no uniform guidelines dictating patient management approaches.

The treatment strategy for GPE should be determined by clinical and anamnestic data, the patient's age, reproductive potential, metabolic status, identified somatic pathology, clinical and biochemical test results, endometrial thickness parameters determined by ultrasound, and the morphological characteristics of endometrial scrapings. In GPE, treatment strategies should be determined after a comprehensive examination of women who first present to a gynecological clinic with complaints of AUB during perimenopause. Separate diagnostic curettage of the uterine cavity and cervical canal should be performed, followed by a review of the pathomorphological results.

According to many authors, a differential approach to the treatment of AMC in women during menopause is increasingly recognized as the most effective, since it allows one to take into account the variety of factors causing this disease in different patients and prescribe the most appropriate treatment in each specific case [4,6,9,18,26,65,107,118].

We chose a differentiated approach based on the aforementioned comprehensive research methods and the immune status of the patients in the study groups. Patients in the first main group with newly diagnosed hyperplasia were divided into two subgroups: main group A (22 patients) and comparative group B (18 patients). The main subgroup received our proposed treatment (indole 3-carbinol, endonasal β-interferon gel, vitamin D, and antianemic therapy with an iron-containing drug. Its dosage was calculated based on red blood cell parameters and

anemia severity. Overweight patients were prescribed the insulin sensitizer metformin), while subgroup B received standard treatment.

According to the latest data available in numerous literature sources, indole 3-carbinol has the ability to reduce hyperplastic processes, normalize hormonal imbalances, induce individual cell apoptosis, and reduce tumor growth factors, as well as certain interleukins and cytokines affecting the mammary gland and endometrium. It also has a positive effect on estrogen metabolism. Unlike hormonal medications, indole preparations have a wide range of applications and rare side effects. Since the drug is synthesized from natural components belonging to the cruciferous family, its negative effects on the body are minimal. This supplement is considered a phytonutrient that promotes epigenetic changes in DNA. Patients in this group were recommended to take indole for 6 months at a dose of 400 mg once daily . os , against the background of monitoring the studies we conducted, especially taking into account the thickness of the endometrium in dynamics.

According to many authors, hyperplasia is considered a pathological regenerative response of the endometrium, which mainly has an inflammatory genesis [1,5,7,14,22,56,78,103,116].

Since the hyperplasia process is associated with immunological changes in the body, and therefore some inflammatory elements, we decided to use medications that boost immunity and reduce pathological regeneration of the endometrium. In our study, we used an endonasal gel for patients in the first main group, and Σ-interferon suppositories (Viferon) up to twice daily rectally for 10 days for patients in the second main group, as this drug has an antiproliferative effect, normalizing estradiol levels in the blood and the hormone dependence of endometrial tissue. If laboratory testing confirmed vitamin D3 deficiency in patients (Lamira), 5,000 IU was prescribed once daily for 6 months to correct its level to reference values (40 ng/ml or more).

The results of the monitoring showed a fairly high effectiveness of indole in the treatment of GE in perimenopausal patients; in 20 (90.9%) women, this treatment method was effective; no relapse of endometrial proliferative processes was detected

during 6 months of observation and no recurrence of AMC, which indicated the role of this drug in suppressing aggressive estrogen fractions in the body of women.

Patients in the second main group were also divided into two subgroups: main group A (20 patients) and comparative group B (17 patients). The main subgroup received our proposed treatment (progestogen, Σ-interferon rectal suppositories, vitamin D3, antianemic therapy; overweight patients were prescribed the insulin sensitizer metformin), while subgroup B received standard treatment. In making this decision, we took into account that during this period of a woman's life, the production of steroid sex hormones is disrupted with an imbalance in their ratio—excess estrogen and progesterone deficiency. Taking these factors into account, we considered it appropriate to prescribe progestogens with antiestrogenic activity. For this purpose, the drug of choice was an injectable progestogen (Depo-Provera)—at a regimen of 300 mg/ml once a week for one month, then 150 mg/ml once a month for 5 months intramuscularly. The effectiveness of the therapy was monitored by analysis of hormones (estradiol, progesterone, FSH, LH), vitamin D3, tumor markers CA-125, CA-15-3, ultrasound assessment of M-ECHO, control pipelle biopsy with aspirate from the uterine cavity and assessment of some interleukins.

Hormonal levels before and after treatment in subgroups A and B: FSH, LH, and estradiol decreased, while progesterone levels increased inversely, and this was significantly observed in the main subgroup A of the first main group. As can be seen, FSH decreased 1.06 times in the comparative subgroup B after treatment, while this value significantly decreased 1.2 times in the main subgroup A. LH decreased 1.06 times in the comparative subgroup B after treatment, while this value decreased 1.12 times in the main subgroup A. Estradiol decreased 1.5 times and 1.04 times in subgroups A and B, while progesterone levels increased 1.9 times and 1.12 times in the corresponding subgroups (Table 4.1).

Table 4.1.

Comparative data on the hormonal status of women in the main groups before and after treatment, n = 77.

Hormonal indicators	First main group (n=40)				Second main group (n=37)			
	A subgroup (n=22)		Subgroup B (n=18)		A subgroup (n=20)		Subgroup B (n=17)	
	And the main subgroup before treatment	And the main subgroup after treatment	B comparative subgroup before treatment	B comparative subgroup after treatment	And the main subgroup before treatment	And the main subgroup after treatment	B comparative subgroup before treatment	B comparative subgroup after treatment
FSH, mlU/ml	24.95±0.56	20.62±0.15*	24.95±0.56	23.62±0.15	29.0±0.87	22.2±0.61 *	29.0±0.87	28.1±0.61
LH, mlU/ml	28.8±0.61	24.1±0.48 *	28.8±0.61	27.1±0.48	33.4±0.78	28.3±0.66 *	33.4±0.78	32.1±0.66
Estradiol, E pg/m	129.4±9.77	85.9±8.3 **	129.4±9.77	124.3±8.3	154.8±16.0	98.5±12.1 **	154.8±16.0	144.2±12.1
Progesterone, ng/ml	2.41±0.27	4.56±0.51 ***	2.41±0.27	2.74±0.51	1.98±0.22	3.89±0.43 ***	1.98±0.22	2.01±0.43

Note: * – differences are significant compared to data before treatment (* – p <0.05, ** – p <0.01, *** – p <0.001).

Similar changes were also observed in the second main group, where FSH levels decreased by 1.3 times in main subgroup A after treatment, compared to 1.03 times in comparative subgroup B. LH levels decreased by 1.18 times in main subgroup A after treatment, compared to 1.04 times in comparative subgroup B. Estradiol levels decreased by 1.6 and 1.07 times in subgroups A and B, respectively, while progesterone levels increased by 2 times and 1.02 times in the corresponding subgroups.

As a result of the analysis of tumor markers after 6 months of using combination therapy in the main groups, the fact was revealed that the level of the CA-15-3 tumor marker decreased by 1.29 and 1.65 times in subgroups A and B of the two main groups, while the concentration of this tumor marker decreased by 2.13 and 2.07 times in subgroups A and B of the main groups. A significant decrease was in the indicators of the CA-125 tumor marker, where its concentration decreased by 1.33 and 1.09 times in subgroups A and B, while after the therapy we proposed, its concentration decreased by 2.39 and 1.83 times in subgroups A and B of the two main groups (Fig. 4.1.).

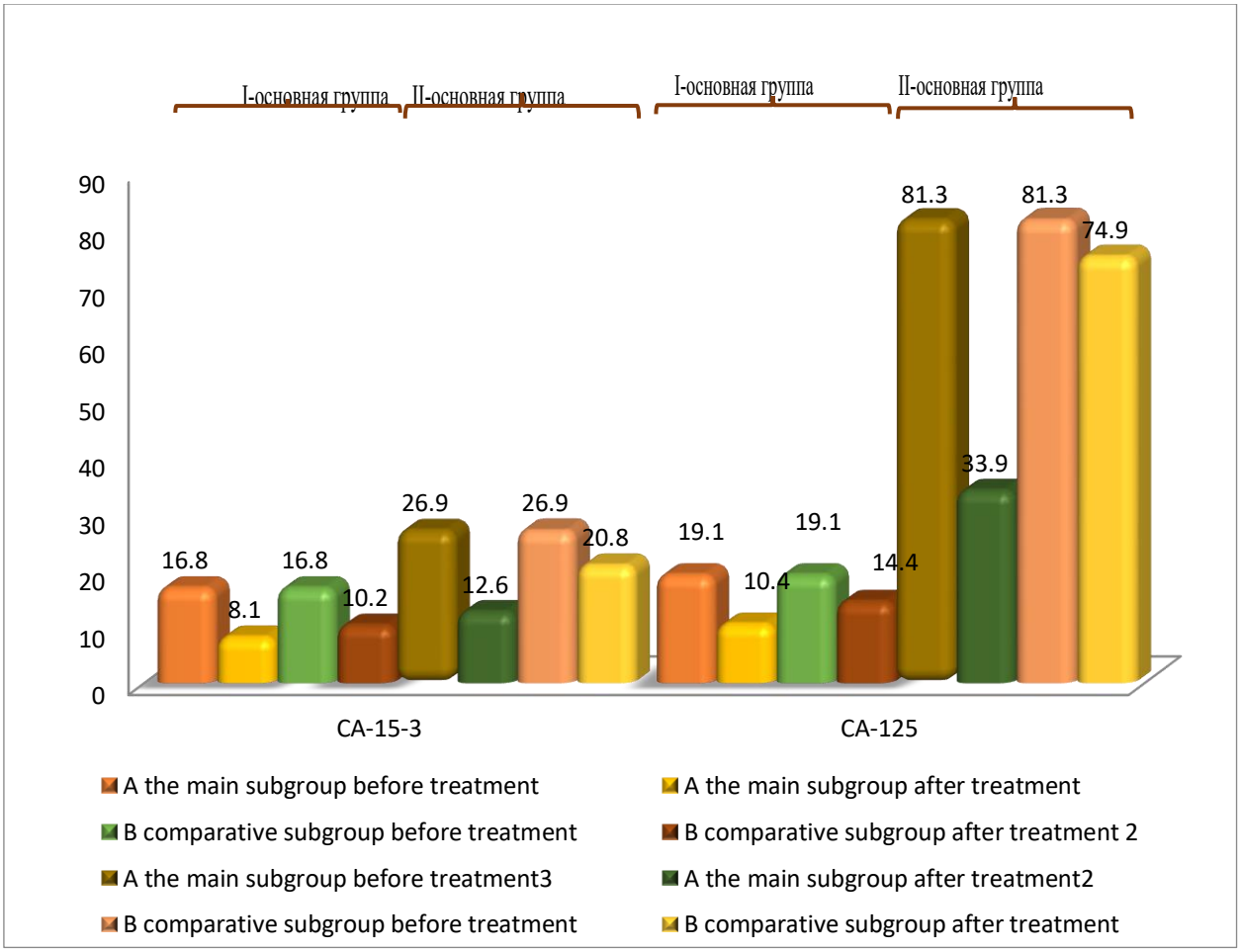


Figure 4.1. Parameters of tumor marker results in the study groups before and after treatment

After the recommended immunocorrective therapy, the IL-2 indicator increased, while IL-1β, IL-6, and TNF-α decreased at the systemic level. The IL-1β indicator increased by 0.18 pg/ml, IL-6 by 6.0 pg/ml, TNF-α by 16.9 pg/ml, IL-2 significantly decreased by 0.62 in subgroup A of the first main group, and in

subgroup A of the second main group, IL-1β increased by 0.14 pg/ml, IL-6 by 4.1 pg/ml, TNF-α by 24.3 pg/ml, IL-2 decreased by 0.31 pg/ml.

To determine the local level of the immune status of endometrial hyperplasia, a Pipelle biopsy was performed. The IL-1β indicator increased by 0.51 pg/ml, IL-6 by 0.79 pg/ml, TNF-α by 1.7 pg/ml, IL-2 decreased by 0.33 in subgroup A of the first main group, and in subgroup A of the second main group, IL-1β increased by 0.28 pg/ml, IL-6 by 2.43 pg/ml, TNF-α by 0.6 pg/ml, IL-2 decreased by 0.44 pg/ml. Significant changes in the concentration of interleukins in B comparative subgroups of main groups I and II were not revealed. Thus, the change in these cytokines in relation to the pre-treatment indicators allows us to conclude that the proposed treatment has a sufficient therapeutic effect.

During a repeat ultrasound examination after the traditional treatment method, the M-echo decreased by 2.85 and 4.3 mm in subgroups B of the two main groups, whereas after the therapy we proposed, a significant decrease in the thickness of the endometrium was observed, amounting to 11.45±0.37 mm and 12.89±1.27 mm in subgroups A of the two main groups , which is a reliable sign of the effectiveness of the therapy (Table 4.2.).

Table 4.2.

Changes in endometrial thickness before and after treatment in patients of two main groups, n = 78

Indicators	**1st main group, before treatment (n = 40)**	**1st main group, after treatment (n = 40)**	**2nd main group, before treatment (n=38)**	**2nd main group, after treatment (n=38)**
Endometrial thickness M-echo (mm)	20.3±0.80	11.45±0.37 **	23.9±1.02	12.89±1.27 **

Note: * – differences are significant compared to data before treatment (* – p <0.05, ** – p <0.01).

Following our proposed differentiated combination therapy in the two main groups, only 2 (9.9%) patients in the first main group and 3 (15%) patients in the second main group showed no significant changes in test results; these patients also had concomitant pelvic pathologies. These patients underwent surgical treatment.

Indications for surgical treatment include recurrent pathological endometrial hyperplasia, combined pelvic pathology, and simple and complex hyperplasia with atypia. Hysterectomy is considered the most radical treatment option.

According to the Royal College of Obstetricians and Gynaecologists, total hysterectomy is recommended for patients diagnosed with atypical hyperplasia due to the risk of malignancy. For premenopausal women, the decision to remove the uterine appendages should be individualized. When choosing a treatment strategy for patients with recurrent hyperplasia and identified atypia, we followed the above recommendation. Given the ineffectiveness of conservative therapy in women aged 45-47, hysterectomy with tubal dissection was performed, as this approach reduces the risk of ovarian malignancies. For women aged 48-49 years or older who had been menopausal for a year or more, total hysterectomy with adnexal dissection was performed, taking into account oncological suspicion. The postoperative period was uneventful, and macroscopic examinations confirmed the preoperative diagnoses.

Thus, endometrial hyperplasia is a pathology associated with abnormal proliferation of endometrial glands and stroma, directly correlated with extragenital diseases, especially metabolic disorders, and particularly obesity of varying severity. Its prevalence in the premenopausal period is high, ranging from 60% to 70%. This problem of endometrial hyperplasia remains relevant for the prevention of endometrial cancer, and the primary approach is to promptly assess the effectiveness of conservative therapy, taking into account ultrasound monitoring, clinical and laboratory markers, and histological analysis of endometrial scrapings. The effectiveness of therapy should be assessed based on clinical symptoms and a decrease in endometrial thickness, as determined by ultrasound after 3-6 months of hormonal therapy. It should be noted that the primary criterion for the effectiveness of conservative therapy is the relief of clinical symptoms and the absence of signs

of recurrent AUB. It is important to take into account that the conservative treatment options used in modern gynecology are not completely etiopathogenetic and cannot stop the progression of this pathology, and a situation arises in which surgical correction is required.

Predictive markers of PGE may include: decreased red blood parameters, increased BMI >29 kg/m2, significant changes in the levels of local key proinflammatory cytokines (IL-1β, IL-2, IL-6, TNFα), decreased expression of CD25+ and CD95+ lymphocytes, insufficient vitamin D levels, imbalance of the steroid sex hormones estrogens and progesterone, increased M-echo parameters, an increase in the number of glandular structures in the endometrial epithelium during a morphological examination of an endometrial scraping.

The lack of reliable predictors of GE recurrence and its progression to ER requires long-term hormonal therapy monitored by clinical, laboratory, and functional testing methods. Women of reproductive age should be advised to undergo treatment with an LNG-IUD to reduce the risk of recurrence and manifestation of AUB.

During hormonal therapy, it is necessary to conduct an ultrasound examination to determine the thickness of the endometrium and, if necessary, morphological monitoring of the condition of the endometrium at least every 6 months; deregistration can be decided upon after receiving two negative endometrial biopsy results.

Based on the results of the study, an algorithm for managing women with endometrial hyperplasia was developed.

CONCLUSION

Endometrial hyperplasia (EH) is a major medical, biological, and socioeconomic problem, accounting for a significant share of gynecological morbidity. EH is receiving close attention because, on the one hand, it is one of the most common causes of uterine bleeding in women. On the other hand, it carries the potential for malignant transformation. The relevance of EH is due to its high incidence (10-55%) in women, especially during menopause.

Endometrial hyperplasia (EH) is a pathological condition characterized by abnormal proliferation of the endometrial glands and stroma. The main characteristic feature of this disease is the growth of the endometrium, the inner layer of the uterus, leading to thickening and an increase in its volume.

The development of endometrial hyperplasia in the perimenopausal period is associated with a disruption in the estrogen-progesterone ratio, in which:

estrogen stimulation persists or is dominant,

progesterone inhibition of endometrial proliferation decreases.

Added to this:

chronic inflammation of the endometrium and low-grade endometritis,

metabolic disorders (obesity, insulin resistance),

changes in the vascular and immune microenvironment of the endometrium.

As a result, a disbalance of cell proliferation and apoptosis is formed, and the expression of pro-inflammatory cytokines (e.g., IL-6) and angiogenesis factors (VEGF) increases, contributing to the progression of hyperplastic changes.

Endometrial hyperplasia is a form of proliferative changes in the endometrium, with preferential proliferation of the glandular component over the stromal component. Currently, the 2014 World Health Organization (WHO) binary classification (remaining unchanged in the 2020 edition) is used in clinical practice. According to the WHO classification, only two forms are distinguished: endometrial hyperplasia without atypia and endometrial hyperplasia with atypia.

The increase in endometrial hyperplasia in perimenopause in recent years is associated with changes in women's reproductive and hormonal function.

Difficulty of differential diagnosis with normal proliferative endometrium of the perimenopausal period.

Insufficient study of molecular and immunological mechanisms, including the role of cytokines, microbiocenosis, and progesterone resistance.

Clinical significance for the prevention of endometrial cancer, the development of effective treatment algorithms, and dispensary observation.

The incidence and timing of malignant transformation of endometrial hyperplasia vary considerably. Some authors estimate the incidence of endometrial oncotransformation to range from 25% to 50%, while others estimate it to be as high as 80%. Factors influencing the likelihood of malignancy include the patient's age, morphological features, and the duration and recurrence of the disease.

Endometrial hyperplastic processes typically develop against a background of absolute or relative hyperestrogenism or absolute or relative progesterone deficiency. Estrogens, which normally cause proliferative changes in the endometrium, lead to the development of hyperplastic processes in the absence of sufficient progesterone.

Metabolic and endocrine disorders play a significant role in the pathogenesis of endometrial hyperplasia: changes in lipid metabolism, sex hormone metabolism due to hepatobiliary and gastrointestinal tract pathologies, immune dysfunction, and thyroid function. Therefore, patients with endometrial hyperplasia often experience obesity, hyperlipidemia, diabetes mellitus, hypertension, and metabolic syndrome.

However, endometrial hyperplasia can develop even without disruption of hormonal balance. Impaired tissue reception, infectious and inflammatory changes in the endometrium, and immune disorders play a significant role in the development of endometrial hyperplasia.

In recent years, it has been established that, in addition to estrogens, a number of biologically active compounds—such as growth factors, cytokines, arachidonic acid metabolites, and the cellular and humoral immune systems—are involved in the regulation of endometrial cell proliferative activity. It has been proven that an imbalance between cell proliferation and apoptosis plays a significant role in tissue

homeostasis and the pathogenesis of proliferative diseases. Endometrial cell resistance to apoptosis leads to the accumulation of altered and excessively proliferating cells, a characteristic feature of endometrial neoplastic changes.

Despite numerous scientific studies devoted to hyperplastic diseases of the endometrium, the study of risk factors for malignancy of the process and management tactics, the issues of prognosis, early diagnosis and treatment of subclinical forms of HE still remain not fully understood and scientifically substantiated.

The study participants' ages ranged from 45 to 55 years, with an average age of 49±2 years. An analysis of their place of employment revealed that most of the women were temporarily unemployed. Female manual laborers predominated in the study group.

Comparative BMI indicators for the study groups showed that in the two main groups of patients, the percentage of overweight and obese patients was significantly higher than in the control group, which was 27.22% in the first main group and 35.38% in the second main group, respectively.

When analyzing somatic pathology data in the study groups, we found that gastrointestinal and endocrine diseases, as well as varicose veins, were diagnosed more frequently than other premorbid conditions, but anemia of varying degrees was the most common. A comparative analysis shows that extragenital pathology was diagnosed five times more frequently in women in the study group than in women in the control group.

All identified gynecological pathologies and interventions were significantly more common in the second study group. Inflammatory diseases of the genital organs were particularly prevalent in this regard, accounting for 23% and 40% in study groups I and II , respectively.

Pain at the onset of menstruation also impacts quality of life during the perimenopausal period, and this was assessed based on the severity of pain. As the diagram shows, grade III dysmenorrhea was four times more common in the recurrent group.

Comparisons of contraceptive methods used in the study groups showed that 55% of women used IUDs. Hormonal contraceptives were the lowest percentage.

A study of women's reproductive function revealed that all pregnancy-related complications were almost twice as common in the first and second study groups compared to the control group. Surgical deliveries were twice as common among the total number of births in the study groups compared to the control group.

When studying the reproductive potential of the patients, we found that women in the groups experienced up to six pregnancies, three to four of which resulted in births. The remaining cases were non-viable pregnancies or abortions, which were common in the main group.

A comparative analysis of peripheral blood parameters in the study patients revealed that almost all parameters differed significantly from the reference values. While the red blood cell count, hemoglobin, cirrhosis, hematocrit, and platelet counts in peripheral blood were decreased, the white blood cell count, subcutaneous and subcutaneous neutrophil count, monocyte count, and ESR were significantly elevated. Only the relative lymphocyte count showed inconsistent changes. These abnormalities indicate the development of a pathological process associated with hemodynamic compromise and stress on the body's immune system.

Comparison of hormonal status data in the study groups revealed that FSH blood levels were 2-2.5 times higher than in the control group. In the two main groups, LH was also high compared to the control group, at 28.8 and 33.4 mlU/ml, respectively. The LH to FSH ratio was 1.2 in three groups. Estradiol levels were 1.5 times higher than in the control group, but there was a significant decrease in progesterone levels by 2-2.5 times or more . Despite the relative increase in FSH, estradiol concentrations were relatively elevated in the main group. This is explained by the fact that with age, along with follicular depletion, the number of gonadotropin receptors also decreases, a phenomenon reflected in our studies. In our opinion, the relatively high content of estradiol and constant progesterone deficiency led to the pathological transformation of proliferation into hyperplasia in the endometrium,

which echoes the data of the authors Kushner R. (2021) and Maksudova N.M. (2015).

CA-15-3 tumor marker titers in the study group were twice as high as those in the control group of women of the same age, although these values were within the reference range. CA-125 tumor marker fluctuations averaged 9.15 in the control group, 19.1, and 81.3 U/ml in study groups I and II , respectively. These values were within the normal range in patients in the control and study groups I , while 76.3% of patients in the relapse group achieved very high values.

Vitamin D levels in the study group were significantly lower (6.7 and 7.3 ng/ml) than those in the control group. Based on our data, we can conclude that all patients in the study groups had vitamin D deficiencies, which directly correlated with the degree of increase in proliferative processes, as confirmed by other authors. They believe that decreased serum 25(OH)D levels indicate insufficient antiproliferative defenses, which can trigger recurrent endometrial hyperplasia (Khamoshina, M.B., 2023). Based on these data, we believe that vitamin D levels should be checked during routine clinical examinations of women at this age to prevent the development of potential proliferative conditions and to address preventive therapy, especially in patients with somatic pathologies.

When comparing the results obtained in the study groups, endometrial thickness was 2 and 2.5 times greater than in the control group. Furthermore, Doppler ultrasound imaging in patients with hyperplastic processes demonstrated better vascular visualization than in those with normal processes.

Histological analysis of the first study group revealed a higher incidence of glandular hyperplasia and glandular hyperplasia associated with chronic inflammation compared to the second group. Glandular cystic hyperplasia was not detected in the first study group, whereas it was verified eight times more often in the second study group. Glandular cystic hyperplasia associated with chronic inflammation was detected in two patients in the first group, whereas it was detected five times more often in the second study group. Hormonally altered uterine mucosa

was detected in eight cases in the aforementioned groups, respectively. Only one case of adenocarcinoma was identified in the second group.

Histological analysis of glandular hyperplasia revealed pronounced vascularization with thrombosis. The endometrial glands varied in shape, with some glands being distended and hyperplastic . In the histological picture of glandular-cystic hyperplasia, the endometrial glands varied in shape, were cystically dilated, and hyperplastic. A secretory mass was detected within the glandular lumen. Histological findings in adenocarcinoma revealed enlarged glandular structures and their dense arrangement, as well as irregular divisions and their atypical development, which was observed in one case. Thus, our study results allow us to conclude that all morphological features should be combined with functional ultrasound examination features to enhance the accuracy of the diagnosis. Furthermore, clinical and anamnestic factors should be considered, followed by prediction of the risk of endometrial cancer based on data-based diagnostic markers: clinical laboratory, immunological, ultrasound, and morphological studies, to select a differentiated approach to treatment. Particularly in cases of recurrent hyperplasia during hormonal therapy, screening using the above-mentioned diagnostic methods is necessary to promptly decide on radical treatment options.

A comparative analysis of the obtained data revealed a 1.2-fold decrease in absolute CD25+ lymphocyte counts between the control and GE groups, and a 1.16-fold decrease between the first and second study groups. A decrease in absolute CD95+ lymphocyte counts was also observed between the control and relapsed groups.

A comparison of the relative values of CD25+ lymphocytes showed that the lymphocyte level in patients with recurrent endometrial hyperplasia was significantly lower than in the control group and the group with GE, by 1.3 and 1.2 times, respectively. A comparative analysis of the relative value of CD95+ cells between the three groups also revealed a decrease from the control to the recurrent group. Thus, a decrease in the expression of CD25 + and CD95 + lymphocytes in endometrial hyperplasia indicates an imbalance in the processes of proliferation and

cellular apoptosis in the immune system, which are associated not only with the pathogenesis and development of this disease, but also with other concomitant pathologies, which was confirmed in the studies of other authors (Tkachenko L.V. 2016).

A comparative analysis of cytokine levels in each study group revealed that IL-1β levels in patients with endometrial hyperplasia were 2.83 times higher than in the control group, while they were 3.37 times higher in the recurrent hyperplasia group. Both groups with endometrial hyperplasia demonstrated decreased IL-2 synthesis. IL-6 concentrations were significantly elevated in women with endometrial hyperplasia and recurrent hyperplasia compared to the control group. A comparative analysis between the two groups revealed that TNFα synthesis was significantly increased in patients in both groups compared to the control group.

In summarizing our studies of cytokine levels and markers of cellular activation and apoptosis, it should be noted that the observed changes in these parameters were common to various forms of endometrial hyperplasia. Since disturbances in the general immune system in endometrial hyperplasia are most often associated with concomitant diseases rather than with the general mechanisms underlying the development of endometrial hyperplasia, it is necessary to study local immune responses. Therefore, the next stage of our study was to examine local cytokine levels.

When studying the local level of cytokines, an increase in the level was determined IL -1β increased 5-fold in the GE group and 6-fold in the recurrent GE group compared to the control, while IL -2 concentration decreased 1.5 - fold in the GE group and 2-fold in the recurrent GE group compared to the control. IL -6 levels increased 4-fold in group 1 and 5-fold in main group 2 compared to the control, and TNF-α levels increased 5-fold in group 1 and 6-fold in main group 2 compared to the control. The obtained data demonstrate that in perimenopausal women in the GE and recurrent GE groups, the transition to PGE is accompanied by significant changes in the levels of local key proinflammatory cytokines (IL -1β, IL -2, IL -6, TNF-α), which reflects the degree of the inflammatory process and changes in the

immune response. These changes emphasize the importance of early detection in combination with anamnestic data taking into account age, duration of the disease, premorbid background, gynecological history, hormonal imbalance for the selection of personalized adequate treatment for endometrial hyperplastic processes, with the aim of preventing its progression and transition to precancerous forms.

The final stage of our study involved differentiated treatment after the above-mentioned comprehensive research methods and the status of the immune system of the patients in the study groups.

The effectiveness of the therapy was monitored by the analysis of hormones (estradiol, progesterone, FSH, LH), vitamin D3, tumor markers CA- 125, CA-15-3, ultrasound assessment of M-ECHO, control pipelle biopsy with aspirate from the uterine cavity, assessment of some interleukins, which showed an increase in the effectiveness of treatment, amounting to 90.1% in the 1st main group and 85% in the 2nd main group.

Following our proposed differentiated combination therapy in the two main groups, only 2 (9.9%) patients in the first main group and 3 (15%) patients in the second main group showed no significant changes in test results; these patients also had concomitant pelvic pathologies. These patients underwent surgical treatment.

Thus, endometrial hyperplasia is a pathology associated with abnormal proliferation of endometrial glands and stroma, directly correlated with extragenital diseases, especially metabolic disorders, and particularly obesity of varying severity. Its prevalence in the premenopausal period is high, ranging from 60% to 70%. This problem of endometrial hyperplasia remains relevant for the prevention of endometrial cancer, and the primary approach is to promptly assess the effectiveness of conservative therapy, taking into account ultrasound monitoring, clinical and laboratory markers, and histological analysis of endometrial scrapings. The effectiveness of therapy should be assessed based on clinical symptoms and a decrease in endometrial thickness, as determined by ultrasound after 3-6 months of hormonal therapy. It should be noted that the primary criterion for the effectiveness of conservative therapy is the relief of clinical symptoms and the absence of signs

of recurrent AUB. It is important to take into account that the conservative treatment options used in modern gynecology are not completely etiopathogenetic and cannot stop the progression of this pathology, and a situation arises in which surgical correction is required.

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