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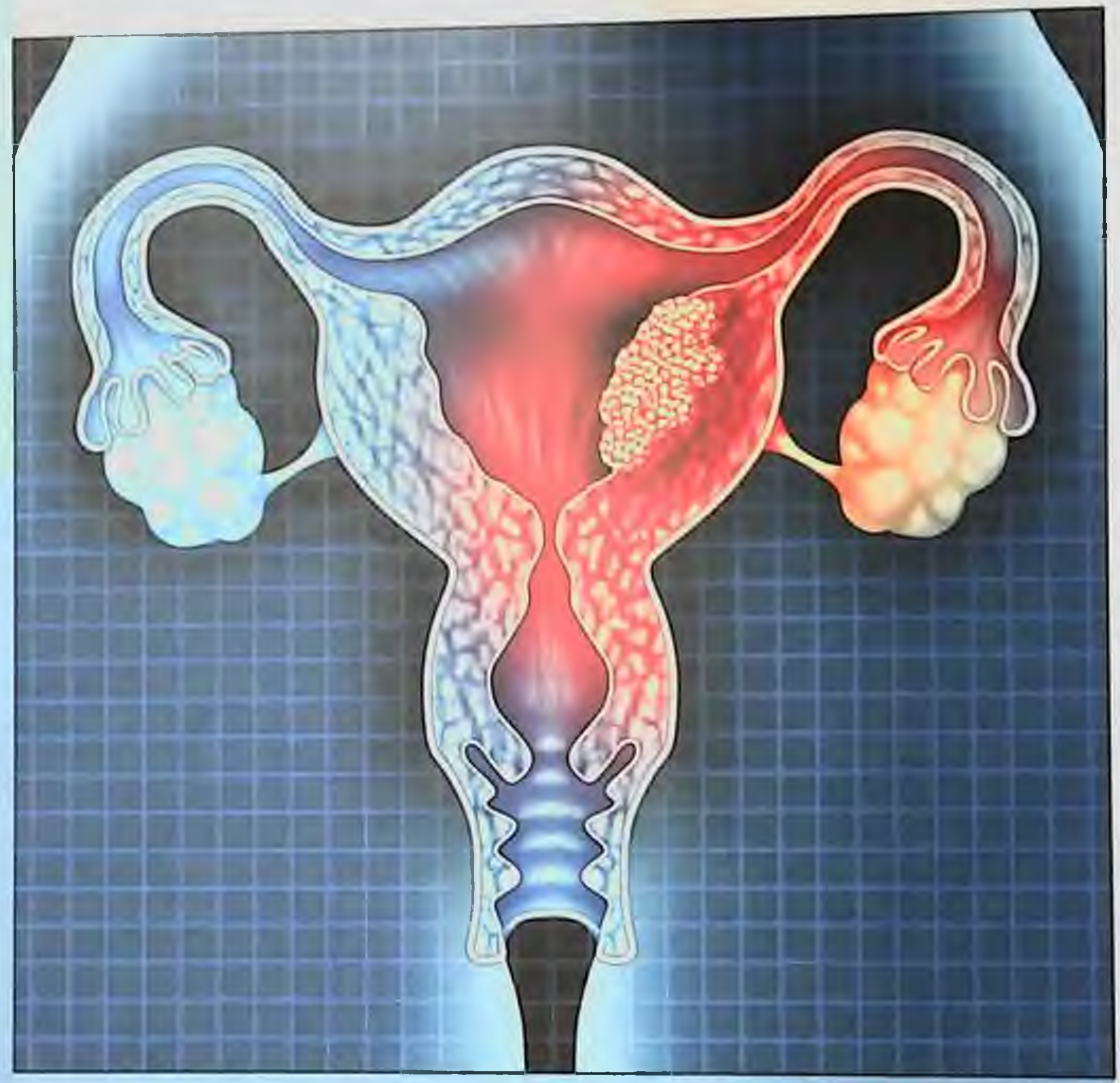

ABNORMAL UTERINE BLEEDING IN PERIMENOPAUSE WOMEN

MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

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The book presents modern data in the diagnosis and treatment of abnormal uterine bleeding during perimenopause.

Despite great achievements, relapses and malignancies are still observed. They lead to repeated manipulations, unsatisfactory results, disability and worsen the prognosis.

The monograph describes the causes of abnormal uterine bleeding, their classification, clinical manifestations, diagnosis, including molecular genetic methods, and the treatment algorithm for women with abnormal uterine bleeding during perimenopause. Based on the analysis of our own clinical observations and literature data on the management of women with abnormal uterine bleeding, an algorithm of measures for the management of women with abnormal uterine bleeding has been developed, depending on clinical, morphological and genetic studies.

The book is intended for obstetrician-gynecologists, general practitioners, researchers, masters and clinical residents of medical universities.

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CONTENT

LIST OF ABBREVIATIONS

AUB - abnormal uterine bleeding
AMK-A-adenomyosis
AMK-C-coagulopathy
AMK-E - dysfunction of the endometrium
AMK-M - malignancy
AMK-L- leiomyoma
BUN-N - unclassifiable abnormal uterine bleeding
AMK-I - iatrogenic AMK
AMK-R-polyp
APAF-1 - apoptotic protease activating factor
IUD-LNG-intrauterine devices - levonorgestrel containing.
WHO - World Health Organization
GnRH- gonadotropin releasing hormone
HPE - endometrial hyperplastic process
GE—endometrial hyperplasia
GLC - glandular cystic hyperplasia of the endometrium
Gastrointestinal tract
COC-combined oral contraceptives
KI-67 - nuclear protein, cell cycle regulator
LH - lutenizing hormone
MMP9-matrix metalloprotease 9
MRI magnetic resonance imaging
m RNA-messenger RNA
NSAIDs - non-steroidal anti-inflammatory drugs
PGE - simple endometrial hyperplasia
RDV-Separate Diagnostic Curettage
PTEN - tumor suppressor
GHS sonohysteroscopy
SGE - complex endometrial hyperplasia
SIF - sonohysteroscopy with infusion of isotonic sodium chloride
TP53 transcription factor 53
FSH - follicle stimulating hormone
HR - the number of heartbeats
UAE - uterine artery embolization
ECM extracellular matrix
FIGO - International Federation of Obstetricians and Gynecologists

INTRODUCTION

Abnormal uterine bleeding (AMB) is one of the most common gynecological pathologies worldwide. In women of perimenopausal age, AUB is much more likely to occur in the form of recurrent bleeding, leading to anemia of the body and the need for surgical treatment. [84.85]. According to the International Federation of Obstetricians and Gynecologists (FIGO), "...70% of women with abnormal uterine bleeding occur in the perimenopausal period..."[1]. To date, the study of gene polymorphism in women with abnormal uterine bleeding in the perimenopausal period, the development of an algorithm for managing women with this pathology is of great importance.

There are scientific studies in the world on the prevention of development, early diagnosis, optimization of the treatment of women with abnormal uterine bleeding during the perimenopause. Such scientific studies as the determination of clinical risk factors for the development of abnormal uterine bleeding, the determination of the occurrence of allelic and genotypic variants of gene polymorphism in women with abnormal uterine bleeding during the perimenopause, as well as the study of the significance of these genes in predicting the disease, depending on clinical morphogenetic studies drawing up an algorithm for managing women with this pathology is one of the urgent problems posed to specialists.

In the healthcare of the Republic of Uzbekistan, large-scale targeted measures have been taken to radically improve the quality and significantly expand the range of medical care provided to women perimenopausal age, especially inimproving the methods of diagnosis and treatment of women with abnormal uterine bleeding. In this regard, "... improving the health of the family, protecting the health of mother and child, expanding the provision of quality medical care to mother and child, providing them with qualified and high-tech medical care and thereby reducing child morbidity and mortality»[2]is a strategic directionon the further development of the Republic of Uzbekistan. In accordance with this, the optimization of the management of women with abnormal uterine

[1]S.O. Dubrovina, L.V. Kirevnina, M.N. ForestAbnormal uterine bleeding: causes, diagnosis and treatment Obstetrics and Gynecology No. 1 / 2021.doi:https://dx.doi.org/10.18565/aig.2021.1.170-177

[2]Uzbekiston Republica Presidential 2017 Yil February 7 PF-4947-son "2017-2021 yillarda Uzbekiston Republicsini yanada rivojlantirish bўyicha harakatlar strategyai tKrrisida"gi Farmoni /: www.lex.uz.

bleeding during the perimenopausal period by determining the genetic determinants is one of the current directions for research.

This dissertation research to a certain extent serves to fulfill the tasks provided for in the Decrees of the President of the Republic of UzbekistanNo. UP-6110 "On measures to introduce fundamentally new mechanisms in the activities of primary health care institutions and further increase the effectiveness of reforms in the healthcare system" dated November 12, 2020. in Decrees of the President of the Republic of Uzbekistan No. PP-4887 "On additional measures to ensure healthy nutrition of the population" dated November 10, 2020, No. PP-4891 "On additional measures to ensure public health by further improving the efficiency of medical prevention work" dated November 12, 2020 year, as well as in other legal documents adopted in this area.

CHAPTER I

MAIN PROBLEMS OF DIAGNOSTICS AND TREATMENT OF ABNORMAL UTERINE BLEEDING IN WOMEN DURING PERIMENOPAUSE

The frequency of AUB varies widely and depends on the age of the woman. In hospitalized women with AUB, 35 to 70% of cases occur in the perimenopausal period [65].

According to modern concepts, abnormal uterine bleeding is caused by disorders in the hypothalamus-pituitary-ovarian system, which are based on disorders in the secretion of ovarian hormones [12,102,151]. Endocrinological features of perimenopause are associated with ovarian exhaustion, impaired cyclic release of gonadotropins, anovulation, luteal phase insufficiency, relative hyperestrogenism, lack of progesterone effect on the endometrium, resulting in disturbances in the processes of proliferation and secretory transformation of the endometrium [20, 71, 76].

According to L.G. Tumilovich (2010), abnormal uterine bleeding always occurs from altered endometrium, more often from hyperplastic one, excludes the concept of AUB as a pathology not associated with organic changes in the reproductive organs [80].

It should be noted that there is bleeding from the uterine cavity that has no connection with the endocrine system [102]. Studies based on laboratory studies have shown that the cause of uterine bleeding in some cases is increased fibrinolytic activity and increased production of prostaglandins [48, 102].

One of the main causes of uterine bleeding in perimenopause is endometrial hyperplastic processes [10, 24, 38, 47, 49]. Abnormal uterine bleeding is an early and sometimes the only symptom of endometrial hyperplastic processes [70,117]. The incidence of endometrial hyperplastic processes in women of perimenopausal age is 50-60%, which is associated not only with age-related changes in ovarian function, but also with a greater incidence of somatic diseases and age-related immunosuppression [86].

According to the results of many studies, during the period of perimenopause, glandular cystic hyperplasia of the endometrium is the predominant cause of uterine bleeding (53% - 89%), leading to relapses

and repeated curettage of the uterine mucosa, which are a risk factor for the development of thromboembolic complications [2, 28, 38, 49 , 54].

It is known that the frequency of abnormal bleeding in combined hyperplastic processes of the uterus is 65%. Endometrial hyperplasia is often combined with myoma and adenomyosis: combination with myoma was noted in 30.8% of cases, with adenomyosis in 12.5-34.8% of cases [10, 84, 150].

Early detection of endometrial hyperplasia is of great importance in the prevention of endometrial cancer, which may precede or serve as a background for its development [13,52]. The occurrence of uterine body cancer in patients with recurrent endometrial hyperplasia was noted in 20-30% of cases [11]. With endometrial hyperplasia without atypia, the transition to carcinoma is noted only in 1-2%, with atypical hyperplasia, neoplasia occurs in 20-80% of patients [8, 152].

Among the causes of various menstrual disorders, endometrial polyps are of no small importance. According to different authors, the clinical manifestations of endometrial polyps in perimenopausal women are menstrual disorders in the form of uterine bleeding [29, 87, 90].

According to E.N. Popov, among patients aged 50-54 years, a glandular-fibrous polyp of the endometrium was found in 31% of clinical cases, in women over 55 years old - in 35% of cases [54]. There is evidence of the predominance of glandular-fibrous endometrial polyps in the perimenopausal period [87].

Endometrial polyps in 25-50% of cases are detected as a single disease, in other cases they are combined with other benign hyperplastic processes of the reproductive system, including endo- and myometrium, and the mammary gland [14].

Adenomyosis of the uterusis a common cause of uterine bleeding in perimenopause [17, 31, 135,]. With deep invasion of the endometrium into the myometrium, pain syndrome joins the uterine bleeding [122, 141].

Despite the fact that the endometrium is a hormone-dependent tissue, its ectopic fragments acquire different properties: they do not have progesterone receptors, they remain viable and spread for a very long time, and are resistant to hormone therapy [67].

An increase in estradiol receptors in the ectopic endometrium leads to a local increase in the effect of estradiol, which is a predictor of cell proliferation [140]. This may be the reason for the high frequency of

combination of adenomyosis with other hormone-dependent intrauterine pathology, such as endometrial hyperplasia and uterine leiomyoma [28, 120].

In connection with uterine bleeding, which is the main and frequent manifestation of adenomyosis, patients undergo multiple medical and diagnostic curettage of the uterus, surgical interventions, and often useless therapeutic interventions [17, 31,67,115].

The study of the distribution of morphological variants of adenomyosis by groups showed that in the metrorrhagic form of the disease, the diffuse variant of the pathology prevails in 70% compared to the focal one. [91]. The severity of clinical manifestations does not always correspond to the prevalence of the process itself in the myometrium. However, some authors point to a direct dependence of the severity of clinical manifestations of the disease on the depth of damage to the walls of the uterus in adenomyosis [91].

Submucosal localization of myomatous nodes occurs in 20-32% of patients with myoma, and in most cases is an indication for surgical treatment due to severe clinical symptoms such as: heavy menstruation anemic the patient, rapid tumor growth and a high risk of malignancy and pain [139].

Foreign bodies in the uterus, trauma, infection, and iatrogenic causes can also cause uterine bleeding [107, 126].

Classification and diagnostic methods for uterine bleeding in perimenopause

The problem of timely and effective diagnosis of the causes of abnormal uterine bleeding in perimenopausal women continues to be relevant today and in the future. It is in these patients that endometrial cancer is subsequently diagnosed, and the cause of neglect is associated with ineffective primary diagnosis (G.M. Savelyeva et al., 1990; E.M. Vikhlyaeva et al., 1999; Ya.V. Bokhman, 2004; Gambrell , 2006; Mencaglia et al., 2010). Along with this, the point of view that has been dominating for many years about the prevalence of endometrial hyperplastic processes and endometrial cancer in uterine bleeding syndrome is not shared by a number of researchers, which implies completely different tactical decisions at the stage of primary nosological diagnosis (Yu.Yu. Tabakman et al., 2006; West, Lumsdem, 2009; Vollenhoven et al., 2010;).

Until recently, the absence of a unified classification system for uterine bleeding has significantly hampered scientific research and the development of standards for managing patients with this pathology. [1,11,17,33,45,].

In 2011, an international expert group under the auspices of the International Federation of Obstetricians and Gynecologists (FIGO) created a new system of nomenclature and classification of the causes of AUB. It is approved by the Executive Committee of the International Federation of Obstetricians and Gynecologists and the American College of Obstetricians and Gynecologists (ACOG), and is used in many European countries and the United States.

PALM COIN

P-polyp
A-adenomyosis
L-leiomyoma
M-malignancy

C- coagulopathy
O-ovulation disorder
E-endometriosis
I- iatrogenic
N-unknown causes

In the AUB nomenclature, it is proposed to distinguish between chronic and acute uterine bleeding [7,20].

Chronic bleeding is abnormal in volume, regularity, uterine bleeding observed for 6 months or more, which does not require immediate medical attention.

Acute bleeding is an episode of heavy uterine bleeding that requires urgent intervention to prevent blood loss [7,20].

Clinical classification of endometrial polyps.

1. Polyps covered with a functional layer of the endometrium
2. Glandular polyps
3. Fibrous polyps
4. Glandular fibrous polyps
5. Adenomatous polyps

Adenomyosis (AMK-A)

The relationship between adenomyosis and the genesis of AUB requires further study. Due to the limited use of MRI, adenomyosis is diagnosed primarily by sonographic criteria. there are diffuse and nodular forms [2,3,7,8,11,13].

Classification of internal endometriosis (adenomyosis):

Stage I - the pathological process is limited to the endometrium;
Stage II - the pathological process passes to the muscle layer;

Stage III - the spread of the pathological process throughout the entire thickness of the muscular membrane of the uterus to its serous cover;

Stage IV - involvement in the pathological process, in addition to the uterus, the parietal peritoneum of the small pelvis and neighboring organs.

Leiomyoma (AMK-L)

The classification system includes only the presence or absence of leiomyoma, regardless of the location, number and size of nodes. An additional classification makes it possible to differentiate leiomyoma, which deforms the uterine cavity, i.e., a submucosal myomatous node, which causes AUB [11,15,23,28].

Суб-мукозная	0	Узел на ножке полностью в полости матки
	1	<50% узла расположено интрамурально
	2	≥50% узла расположено интрамурально
Другие	3	100% интрамурально, но контактирует с эндометрием
	4	Интрамуральный узел
	5	Субсерозный ≥50% интрамуральный
	6	Субсерозный <50% интрамуральный
	7	Субсерозный на ножке
	8	Другие (например, шеечный узел, паразитарные образования и др.).

Гибридная лейомиома (включает эндометрий и серозную оболочку)	В этом случае две цифры указываются через дефис. При этом первая цифра соответствует отношению узла к эндометрию, вторая — отношению узла к серозной оболочке.	
	2–5	Узел расположен субмукозно и субсерозно. Субмукозно выступает менее половины диаметра узла и субсерозно выступает менее половины диаметра узла.

Malignancy and hyperplasia (AMK-M)

Endometrial hyperplasia is the most common form of pathology of the uterine mucosa, accompanied by a structural reorganization of the glandular and stromal tissue components. Despite a large number of studies, the mechanisms of development of endometrial hyperplastic processes are still not well understood, which makes it difficult to develop

a pathogenetically substantiated treatment for patients with this pathology [94, 92]. The lack of a unified classification of endometrial hyperplastic changes leads to disagreements between clinicians and morphologists [51].

According to the histological classification of tumors of the female genital tract, developed by a group of WHO experts [116] and published in 1975, three types of endometrial hyperplastic processes were distinguished: polyp, endometrial hyperplasia and atypical endometrial hyperplasia. Currently, the classification proposed in 1994 by the International Society of Gynecological Pathologists and WHO is considered to be the most accurately reflecting the structural and cytological changes in the endometrium [115]. According to her, endometrial hyperplasia is divided into typical and atypical, in which, along with structural changes in the glands, cellular and nuclear atypia is observed. Depending on the severity of structural tissue disorders, in each of these groups, simple and complex hyperplasia are distinguished.

Until now, in the domestic literature, one can find many terms characterizing atypical endometrial hyperplasia, such as "adenomatous hyperplasia", "cystic-adenomatous hyperplasia", "complex adenomatous hyperplasia", etc. [50, 91, 90, 92]. HoweverN. A. Shcherbinaet al. (2015) [89] believe that such terms have no analogues. So, the term "adenomatous" should be interpreted as "glandular". Therefore, according to the authors, the term glandular hyperplasia without atypia is synonymous with complex typical hyperplasia, and glandular hyperplasia with atypia is synonymous with complex atypical hyperplasia.

Thus, the issues of terminological evaluation of morphological criteria for endometrial hyperplasia still remain debatable. While a unified knowledge of the morphological features and terminology of hyperplastic processes is important not only for mutual understanding between the pathologist and clinician, but also for the choice of adequate treatment and evaluation of its effectiveness [89].

Clinical and morphological classification of endometrial hyperplasia:

1) adenomatous polyps
2) glandular hyperplasia
3) recurrent glandular hyperplasia of the endometrium [7,20].

The risk of HPE malignancy increases with metabolic disorders caused by somatic diseases such as obesity, disorders of carbohydrate and

lipid metabolism, disorders of the functions of the hepatobiliary system and the gastrointestinal tract. Atypical endometrial hyperplasia turns into endometrial cancer in 10% of patients (according to different authors, from 2 to 50%) [8,9,13,30,40].

Of particular oncological alertness is adenomatosis with intensive proliferation and atypia of the glandular epithelium, as well as atypical hyperplasia in the basal layer of the endometrium [5,22]

Glandular and glandular cystic hyperplasia is a qualitatively ambiguous process. The expansion of the lumen of the glands is also observed with glandular hyperplasia of the endometrium. A rare variant of glandular cystic hyperplasia is stromal hyperplasia, which is characterized by large, sometimes polymorphic nuclei of stromal cells [14,22,28].

Atypical hyperplasia (adenomatosis) is characterized by structural restructuring and more intense proliferation of glands compared to other types of hyperplasia.

Coagulopathy (AMC-C)

Approximately 10% of perimenopausal women with heavy menses have coagulopathy: von Willebrand disease, thrombocytopenia; less often acute leukemia, liver disease. Doctors often do not consider violations of the hemostasis system as possible causes of AUB [2,7,20,28,30].

Ovulatory dysfunction (AMK-O)

AUB associated with ovulation disorders are divided into ovulatory and anovulatory [8,9,17,33].

Anovulatory are the type of persistence of the follicle and atresia of many follicles. The pathogenesis of persistence is the asynchronous production of GnRH, LH, FSH. Ovulation does not occur, the follicle functions, the corpus luteum does not form and ends with abnormal uterine bleeding against the background of proliferating endometrium [5,8,11,54]

Atresia many follicles. It occurs more often in adolescence. This is due to the absence of the circoral rhythm of GnRH and the acyclic release of gonadotropic hormone. Prolonged action of estrogen leads to endometrial hyperplasia [25,36,51].

Ovulatory are divided into:

- hypofunction of the corpus luteum
- hyperfunction of the corpus luteum
-hypofunction of the maturing follicle

-hyperfunction of the maturing follicle.

Endometrial dysfunction (AMK-E)

The development of AUB can be caused by disturbances in reception, angiogenesis, an increase in local synthesis of prostaglandin E2, prostacyclin (I2) endothelin-1, or accelerated lysis of blood clots formed during menstruation due to excessive production of plasminogen activator. Category AMK-E is diagnosed after the exclusion of other objectively existing disorders [40,41].

Iatrogenic category (AUB - I)

AUA can be caused by drugs or the use of intrauterine devices that have a direct effect on the endometrium and coagulation processes, as well as a systemic effect on the mechanisms of ovulation. Continuous use of COCs or progestogens can also lead to AUB. Treatment with antibiotics, anticoagulants, antidepressants can also lead to bleeding [20,27,40].

Unclassified AMK(AMK-N)

There are disorders leading to AUB that are detected only by specific biochemical or molecular genetic methods, which are classified as "unclassified". As new data are obtained, they can be separated into a separate category or included in existing ones [7,11].

For the correct choice of the method of treatment of patients with uterine bleeding, the clinician must differentiate abnormal uterine bleeding from uterine bleeding due to organic pathology of the endometrium and myometrium, using instrumental methods of examination and ancillary analyzes to identify structural and endocrinological abnormalities that may explain the cause of bleeding.

Diagnosis of uterine bleeding is carried out using non-invasive and invasive research methods.

Ultrasound Scanis one of the leading methods in diagnosing the causes of pathological uterine bleeding [5, 18, 124, 201]. Ultrasound determines the size of the uterus, the thickness of the endometrium, reveals echo signs of uterine fibroids and internal endometriosis, as well as pathological formations in the ovaries [30, 118, 105].

To identify the pathology of the endometrium, the study of the thickness and structure of the median uterine M-echo is more often used [23, 25, 72, 128]. Studies prove the high sensitivity of the method in detecting endometrial pathology with an unchanged uterus, which ranges from 70% to 100% [23, 124], as well as high information content in a

comprehensive study of the state of the pelvic organs in patients with abnormal uterine bleeding in perimenopause, as in the initial stage of differential diagnosis of the cause of uterine bleeding, and in assessing the effectiveness of treatment [22, 49, 52].

The combination of transvaginal sonography with Doppler sonography increases the reliability of the diagnosis of endometrial proliferative processes. Color Doppler mapping and doplerometry allow not only to record blood flow in the arteries of the uterus and endometrium, but also to quantify its parameters [47, 73, 85, 100]. This method is effective and valuable in the diagnosis of neoplasms and pathology of the endometrium in women with uterine bleeding, but does not replace the histological examination of the uterine mucosa [103].

New opportunities in assessing the state of the endometrium and myometrium are associated with the emergence of three-dimensional echography, which, according to many authors, is a highly informative method for diagnosing intrauterine pathology, which is achieved by obtaining frontal sections and a more visual demonstration of the shape of the uterine cavity. The method has significant advantages in determining the localization of formations in the uterine cavity (myomatous nodes, endometrial polyps) [18, 19, 140]. However, the possibilities of three-dimensional echography have not been studied enough.

Ultrasound can detect not only tumors, but also retention formations and polycystic ovaries, which seems important in the management of patients with AUB in perimenopause [144].

Thus, transvaginal ultrasonography is the method of choice for primary diagnosis in perimenopausal women with uterine bleeding [148].

In the perimenopausal period, it is important for the clinician to exclude cancer and endometrial hyperplasia [136,151]. It is known that the final method for diagnosing endometrial pathology is its histological conclusion after diagnostic curettage. There are a significant number of works indicating the low efficiency of blind intrauterine curettage (curettage), especially in situations with early forms of endometrial cancer [3, 4, 48, 57, 109]. With separate diagnostic curettage of the uterine mucosa without hysteroscopy, in 96% of cases, the pathological substrate in the uterus is not completely removed or the pathological substrate in the uterus is not diagnosed [59].

A comparative evaluation of intrauterine curettage and curettage under hysteroscopy control, as a method for obtaining material with subsequent histological examination, in perimenopausal women showed that hysteroscopy with direct biopsy has superiority over curettage in detecting all types of intrauterine pathology, due to direct visualization of the uterine cavity.

Hysteroscopy is the leading diagnostic method for uterine bleeding, an invaluable addition to curettage of the uterine cavity, due to visual quality control of diagnostic curettage [59,105,109,128]. Hysteroscopy allows you to control the quality of removal of the pathological focus, has a positive predictive value of 93.2% in the diagnosis of intrauterine pathology [60, 90, 120]. There is evidence of the high efficiency of survey hysteroscopy with targeted biopsy of the endometrium in the differentiation of pathological processes and conditions in perimenopause - efficiency 91.2%, sensitivity 93.8%, specificity 91.3% [48].

Thus, hysteroscopy with separate diagnostic curettage of the endometrium and subsequent histological examination of the scraping and transvaginal ultrasound of the pelvic organs are the first priority in the perimenopausal period [133,146]. Despite the information content of hysteroscopy, the main and final method for diagnosing the nature of changes in the endometrium is the histological examination of scrapings taken under hysteroscopic control [36,59]. The combined use of various clinical and instrumental methods in the diagnosis of intrauterine pathology improves the quality and timeliness in identifying the cause of uterine bleeding [130].

Significance of matrix metalloproteinases in the development of abnormal uterine bleeding

Hyperestrogenism may have an effect on gene expression. Expression is regulated by different genes, which is indicated by the chromosomal localization of the latter [11, 29]. At present, a relationship has been found between the activity of estrogen metabolites and the development of tumors in estrogen-dependent tissues [7, 29]. Other factors are likely to play a role in the development of AUB: an increase in the activity of growth factors with a mitogenic effect, cytokines, prostaglandins, as well as an imbalance in the processes of proliferation and apoptosis. [65.89]

Known risk factors for perimenopausal AUB and endometrial cancer are overweight and obesity. Their influence seems to be mediated by increased estrogen synthesis in adipose tissue or by an increase in their biological activity [84].

Research results«case control»showed: with a body mass index (BMI) of 30–39 kg/m, the risk of AUB increases by 3.7 times, AHE - by 4.6 times, with a BMI > 40 kg/m - by 13 and 23 times, respectively [104]. There are data on the risk of developing EC already at a BMI of 25–30 kg/m and, quite naturally, in older people more often than in young people [75].

An association between diabetes mellitus and cancer is known [126]. According to recent meta-analyses, type 2 diabetes mellitus can approximately double the risk of developing AUB [96, 142].

This is thought to be related to insulin resistance and hyperinsulinemia. This impact can be both direct and indirect. The mechanism is implemented by increasing the insulin-like growth factor and its stimulating effect on cell proliferation [126]. Insulin resistance, hyperinsulinemia, and chronic anovulation are considered as pathophysiological mechanisms of endometrial hyperplasia in PCOS. This has been proven by a number of well-known studies indicating a 3–5-fold increase in the risk of AUB [104, 105, 134]. AUB risk factors include a history of infertility [62].

The importance of gene expression in the pathogenesis of both HE and EC has already become apparent. As the severity of the pathological process in the endometrium increases, the frequency of mutations in the anti-oncogenic protein TP53 increases [56, 142, 144,148]. Defects in the genes of the DNA repair system have been found [124, 136, 142].

The endometrium is one of the tissues of the body that cycles through the process of proliferation and apoptosis, depending on the levels of estradiol (E2) and progesterone [7, 93, 111].

According to the literature, the process of apoptosis occurs in the secretory phase and during menstruation, and practically does not occur in the proliferation phase and at the beginning of the secretory phase [98, 143, 149]. The process of apoptosis is controlled by stimulators and inhibitors [99]. A family of apoptosis inhibitory proteins affect apoptosis by reducing caspase activity [61].

Along with the determination of the receptor status of the endometrium in hyperplastic processes, the role of molecular genetic

factors in the pathogenesis of hyperplasia of the uterine mucosa is being actively studied at the present stage. Studies have shown that genetic disorders, such as mutations in the BRAF, PTEN, TP53, etc. genes that alter cell metabolism, contribute to the onset and progression of endometrial hyperplastic processes [117, 105, 108].

In the literature of recent years, much attention has been paid to studies of the regulation of the ability of cells to reproduce, survive, and differentiate. Of particular interest to researchers are matrix metalloproteinases that affect cells due to their ability to change the intercellular environment [144].

Matrix metalloproteinases (MMPs) are a group of structurally related zinc-dependent endopeptidases that play a key role in tissue remodeling processes [136]. It is known that these proteins are expressed in all tissues at all stages of ontogeny, and their expression is activated under conditions of intense tissue restructuring. Among the MMP family of at least 26 species, there are collagenases, gelatinases, stromelysins and membrane-type MMPs (MT-MMPs). Under physiological conditions, these proteins degrade basement membranes and components of the extracellular matrix, which play a dynamic role in metabolic processes affecting cell proliferation, differentiation, migration, apoptosis, and angiogenesis [90, 105, 114, 143].

As a result of numerous studies, data on the substrate specificity of MMP6 have been obtained. For example, MMP1, MMP8, and MMP13 collagenases degrade fibrillar and non-fibrillar collagens, in contrast to MMP2 and MMP9 gelatinases, which lyse only denatured collagens [149]. MMP3, MMP7, and MMP10, belonging to the stromelysin subclass, lyse both collagens and proteoglycans, fibronectin, and gelatin. It is also known that MMP9 interacts with collagen IV and elastin, which are components of basement membranes, while MMP2, in turn, interacts with collagen I. Metalloelastase MMP-12 actively destroys elastin and, to a lesser extent, fibronectin [101, 126, 135] .

MMP3 natural antagonists that regulate and modulate their activity are metalloproteinase inhibitors, which, like MMP3, are expressed in all organs and tissues [88, 135]. Among MMP3 inhibitors, plasma and tissue inhibitors (TIMP3) are distinguished, which are predominantly secreted proteins [49, 107]. Along with the regulation of metalloproteinase activity, an experimental study of the biological role of TIMP3 revealed

both an activating and an inhibitory effect on the process of programmed cell death [120, 102, 107, 115].

Data on the expression of MMP9 in the organs of the female reproductive system, which naturally undergo significant tissue restructuring, support the view that metalloproteinases are the key effectors of tissue remodeling. The cyclical growth, differentiation, and death of endometrial cells represent the most dynamic example of steroid-controlled tissue remodeling. According to studies, MMP9 and their specific inhibitors, regulated by ovarian steroids and locally by cytokines, are active participants in this process [71, 72, 129, 143].

The specific profile of MMP9 expression in different phases of the menstrual cycle indicates their active participation in the processes of angiogenesis, growth, and degradation of endometrial tissue. The highest level of expression of MMP7 and 11 was found in the proliferative phase, while MMP1, 3, 8, 9, 10 and 12 are expressed in the endometrium mainly in the perimenstrual period. MMP26 activity is maximal in the periovulatory period, which may indicate its specific role in the process of implantation [15, 16, 111, 112].

It is known that tissue-specific growth factors take an active part in the process of tissue reconstruction. In particular, vascular endothelial growth factor plays an important role in angiogenesis and endometrial regeneration.

Thus, the dynamic interaction of the MMP9 and TIMP9 systems during the menstrual cycle ensures an adequate flow of cyclic processes of growth and degradation of the endometrium by reconstructing the intercellular matrix in accordance with the hormonal status of the body. This specific biological function of metalloproteinases suggests their participation in the development of pathological processes in the endometrium.

The results obtained indicate the need for further study of the role of MMP family proteins in the development of pathological processes in the endometrium, as well as their prognostic value.

Clinical presentation and treatment of AUB in the perimenopausal period AUB may begin with regular, heavy, and prolonged (more than 7 days) menses. Prior to the introduction of the new classification system, it was designated as menorrhagia, currently as heavy menstrual bleeding (heavy menstrual bleeding). Common causes

of these bleedings are adenomyosis, submucosal uterine fibroids, coagulopathy, endometrial hyperplasia.

AUB clinically occurs after menstrual delay and is manifested by irregular, prolonged and profuse bleeding. This type of menstrual irregularity is more characteristic of endometrial hyperplasia and cancer [55, 77,114, 117].

Abnormal uterine bleeding is one of the main causes of iron deficiency anemia. An increase in blood loss can be diagnosed with a combination of three signs: a decrease in the level of ferritin in the blood serum, the appearance of blood clots, and frequent changes in sanitary protective equipment during the day. It is known that ferritin plays an important role in the mechanisms of intracellular iron homeostasis and the creation of its depot; therefore, its decrease is regarded as an indicator of iron deficiency in the body. The normal range for ferritin levels in women is 18-160 ng/mL. Given the difficulties in assessing monthly blood loss, the choice of management tactics determines not the result of measuring blood loss, but the patient's self-perception.

Differential diagnosis is carried out with the following pathological conditions: blood diseases, diseases of the cervix, inflammatory diseases, ovarian tumors.

At the present stage, medical and surgical methods are used to treat uterine bleeding.

ATnon-hormonal (hemostatics, prostaglandin inhibitors, uterotonics, non-specific anti-inflammatory drugs) and hormonal drugs (progestogens, antigonadotropins, antiprogestins, gonadotropin-releasing hormone analogues) are used as drug therapy. Surgical treatment includes minimally invasive hysteroscopic surgery and hysterectomy [50, 75,114, 117].

As you know, the endometrium has an active fibrinolytic system, with bleeding there is an increased level of fibrinogen activators, in connection with this, in order to treat dysfunctional uterine bleeding, fibrinogen activator inhibitors are used, which inhibit the conversion of fibrinogen to plasmin, reduce the permeability of the walls of blood vessels. According to the literature, the most effective in the treatment of AUB is the administration of tranexamic acid, which reduces blood loss by 50% [50,114].

The most common treatment for most conditions that cause uterine bleeding is hormone therapy. Hormones are known to be often prescribed

for AUB, endometrial hyperplastic processes, adenomyosis, uterine myoma, either as monotherapy or in combination with hysteroscopic operations. Schemes of hormone therapy and its types are well covered in the literature [13,20,64].

Hormone therapy in perimenopause should contain suppressive production of estrogen and have an antiproliferative effect on the mitotic activity of endometrial cells. It is difficult to choose the type of hormonal drug in the perimenopausal period, and hormonal treatment is often an absolute or relative contraindication due to the high incidence of extragenital diseases of the neuroexchange-endocrine nature [10, 21, 54].

The most commonly used progestins at this age are contraindicated in patients with a history of thromboembolic diseases, severe varicose veins, hepatitis and cholecystitis [34, 38, 58, 69, 144]. There is evidence that the systemic use of progestogens may cause side effects of steroids: headache, depression, weight gain, withdrawal bleeding. These side effects often lead patients to refuse the prescribed therapy [137].

Antiestrogens and antigonadotropins induce a hypoestrogenic and hyperandrogenic state, which in turn lead to numerous systemic and metabolic disorders, as well as side effects of hypoestrogenism and hyperandrogenism [6, 66, 79, 82].

The use of GnRH agonists leads to hypoestrogenism, the onset of pseudomenopause, accompanied by a number of side symptoms characteristic of menopausal syndrome, but there are no anabolic disorders and an androgenic effect, which are most difficult for patients to tolerate [66, 79, 148]. Due to possible severe side effects of GnRH-a, especially on the skeletal system, their intake is limited to 6 months.

When comparing the side effects of various hormonal drugs, it was found that the quality of life of patients taking buserelin or diferelin (a GnRH), determined by the severity of adverse reactions, suffered slightly and was higher than when using other drugs [10, 39, 66, 77, 79].

A large number of side effects justifies the high rate of refusals of treatment, the frequency of which after 6 months was 53% of women [134], in the first year of follow-up, according to other authors, 43% [105]. However, 60% of women state that they would prefer drug treatment if the success of this treatment were 80% [115].

Along with a large number of side effects, relapses are quite common [2, 79]. So, according to the results of studies, the frequency of ineffectiveness of hormonal treatment in benign hyperplastic processes of

the endometrium is 57% - 82.4%, in the case of glandular hyperplasia - from 2.5 to 37%, in the case of endometrial polyps ranges from 25.9 to 78% [54, 60, 86].

In adenomyosis, hormonal therapy leads to a decrease in pain, dysmenorrhea, dysparenia, and promotes temporary atrophy of heterotopias [104,116]. After discontinuation of drugs, there is a gradual return of symptoms [101,102].

Thus, hormonal therapy for uterine bleeding in perimenopause is often ineffective. Possible causes of recurrent bleeding in the perimenopausal period after hormone therapy are: undiagnosed organic pathology of the endo- and myometrium, as well as their combination [21, 38, 58, 69,], local damage to the endometrial receptor appuratus due to frequent curettage of the uterus in history [82], violation the mechanism of hormone inactivation as a result of a reduced function of the hepatobiliary system in chronic cholecystitis [21], ovarian pathology - thecagranulosa cell tumors, focal stromal hyperplasia and ovarian thecamatosis [20,21], incorrect choice of the dose of the drug or individual response to it, discontinuation of the course of treatment before completion [69].

A variant of hormone therapy, and according to some researchers, a good alternative to surgical treatment for uterine bleeding, is the use of a levonorgestrel-containing IUD [99, 114, 147]. According to the literature, there are promising preliminary results of this type of treatment, especially in patients with combined pathology of the endo- and myometrium (adenomyosis, endometrial hyperplasia), as well as the treatment of menorrhagia in patients of the perimenopausal period [50, 55,110,137,149], which in 80% of cases can be avoided hysterectomy [143].

According to Vep-Nagoiz A., in patients who used LNG IUD, in the treatment of menorrhagia, a positive effect was noted in 50% [110]. The contraceptive and therapeutic effects of the LNG IUD are based on a local effect on target tissues: the endometrium and mucus of the cervical canal, which is expressed in a pronounced antiproliferative effect on the endometrium [127]. Also, the use of LNG IUDs is accompanied by a decrease in the production of prostaglandins, estrogen and estrogen-progesterone inducible growth factors and an increase in the activity of cyclooxygenase-2 and insulin-dependent growth factor [149]. The use of the LNG IUD reduces menstrual blood loss by 80-95%. Approximately

20% of women experience amenorrhea after a year, which is reversible [46]. However, there is evidence that after 12 months, 57% of patients interrupted treatment due to ongoing bleeding,

Randomized trials of the efficacy of levonorgestrel containing an IUD in women with menorrhagia have shown that hysterectomy can be avoided in 80% of cases [143].

P.Crosignani et al. [139] conducted a comparative study of the results of treatment of AUB in 70 women aged 38–53 years using an LNG-IUD and endometrial resection. The results of using the LNG-IUS were less satisfactory, but good enough to consider this conservative method of treatment as an alternative to surgery.

However, based on the literature data, there are few randomized trials comparing LNG-IUS and 2nd generation endometrial ablation techniques.

The deterioration of the population's health index, the high cost of hormonal drugs, the high percentage of ineffectiveness of hormonal therapy, the high frequency of radical operations associated with uterine bleeding forced researchers to look for new possible methods for their treatment and prevention for many years.

In recent decades, due to the rapid development of endoscopic surgery, an alternative to hormonal treatment and hysterectomy in patients with uterine bleeding has emerged [1, 2, 30, 86, 114]. The fundamental advantage of hysteroscopy is the preservation of healthy uterine tissues with a radical effect on pathologically altered tissues of the endometrium and myometrium.

The most common hysteroscopic surgery is resection and ablation of the endometrium, which are performed using a laser or electric current. A large number of publications are devoted to this problem in the specialized literature [1,2, 42, 92, 136].

Endometrial ablation is the operation of choice for women who are somatically burdened with such diseases as diabetes mellitus, hypertension, obesity, diseases of the respiratory and cardiovascular systems, etc., which are a limitation for hormone therapy [107].

Data on the effectiveness of endometrial ablation available in the literature are very diverse. The leading criteria for the effectiveness of endosurgical treatment are the elimination of acyclic uterine bleeding, the formation of amenorrhea, the absence of changes in the uterine echo during dynamic transvaginal ultrasound scanning, and unchanged mucosa

(according to hysteroscopy) [74]. Patient satisfaction with the results of treatment is also important. Thus, according to different authors, women who underwent resection (ablation) of the endometrium expressed satisfaction with the results of treatment in 79%-80% of cases [95,107]. The reasons for dissatisfaction are mainly related to the woman's expectation of amenorrhea, although normalization of menstrual function has been noted [95].

According to different authors, the efficiency of endometrial ablation is 60-98% [1, 32, 47, 83]. Looking at the long-term results of endometrial ablation, the success rate at 5 years of follow-up is 80% and this percentage remains fairly stable over the next 4 years [123]. In another study over a follow-up period of 6 months. up to 5 years, the effectiveness was 90%, while amenorrhea occurred in 69.4% [33].

In general, the effectiveness of laser and resectoscopic endometrial ablation is almost the same [107].

There is evidence that endometrial ablation cannot completely prevent the development of malignant neoplasms in the remaining areas of endometrial tissue [33, 34, 51], which were detected in 67% of cases. With repeated hysteroscopy after resection of the endometrium, these data were confirmed histologically. Growth of the endometrium after ablation, according to some authors, is most often observed with glandular-cystic and glandular hyperplasia of the mucous membrane of the uterine body, which is possibly associated with insufficient destruction of the endometrium in the area of the mouths of the fallopian tubes [83]. Other authors found growth zones of the endometrium after ablation in 27.9% of patients, of which hyperplastic transformation was observed in 11.6% of cases, moreover, against the background of amenorrhea and mainly in the reproductive period [7].

There are studies on the treatment of superficial forms of adenomyosis using operative hysteroscopy - resection (ablation) of the endometrium with an efficiency of 37-67% [33].

Hysteroscopic techniques in the treatment of benign endometrial diseases in Europe have reduced the frequency of radical surgical interventions for HPE by 30-75% [79, 113]. The effectiveness of treatment by the method of electrical destruction of the endometrium is to a certain extent associated with visual control over the complete removal of the hyperplastic endometrium.

Hysteroscopic resection (ablation) of the endometrium is currently one of the first generation endometrial destruction techniques that require hysteroscopic control, highly skilled surgeons, and general anesthesia [114, 131]. In this regard, methods of the 2nd generation were developed: thermal, microwave, radiofrequency, laser, cryogenic ablation. Among these methods, intrauterine balloon thermal endometrial ablation is considered the most effective, which is based on a combination of high temperature and pressure within the uterine cavity [98, 113, 149]. Balloon ablation can reduce blood loss in 85-90% of cases. The frequency of amenorrhea varies from 20-70%, depending on the applied surgical techniques. Against this background, there is a high satisfaction of patients with treatment, so in 70-90% it allowed to avoid hysterectomy [98, 111, 113].

When comparing the effectiveness of two second-generation methods: ablation with adjustable bipolar radiofrequency impedance and balloon ablation in the treatment of menorrhagia, without intrauterine pathology, high patient satisfaction was revealed (90% and 79%, respectively), but ablation with adjustable bipolar impedance was more effective in the treatment of menorrhagia [113].

In general, a comparison of first and second generation endometrial ablation methods showed high efficiency of these methods in the treatment of uterine bleeding, the differences between the results were insignificant [118, 133, 120, 126]. However, 1st generation techniques have the advantage of direct imaging. The disadvantages of the balloon technique include the disposability of the applicator, which increases the cost of the operation for the patient, in addition to the often arising technical difficulties [120].

Thus, the analysis of modern methods of endometrial destruction indicates that they all have certain advantages and disadvantages. In this regard, individualization in the choice of the method of therapy is necessary.

It has been proven that diagnostic curettage of the uterine mucosa does not allow complete removal of the endometrial polyp, especially for polyps with a fibrous and muscular component, which are completely removed during curettage only in 12% [29, 34, 90, 141].

When comparing the efficiency of removal of the endometrial polyp by curettage under the control of hysteroscopy and hysteroresectoscopic polypectomy using loop and ball electrodes, polyp recurrence after

curettage was observed in 25% and in no case after resectoscopic polypectomy [29].

Difficulties occur with the removal of an endometrial polyp in the area of the mouths of the fallopian tubes, which is associated with a high surgical risk of uterine perforation, because. the wall thickness in this area does not exceed 3-4 mm. Of the existing methods of targeted polypectomy, the safest and most effective in this case is the mechanical method, the orifices of the fallopian tubes can only be treated with a ball electrode [34, 90].

Currently, hysteroscopic access is considered optimal for the treatment of submucosal myoma nodes [32, 37, 60, 121].

The therapeutic effect of endosurgical treatment for submucosal uterine myoma is to correct menstrual dysfunction, reduce the size of the uterus, the absence of signs of uterine fibroids and deformation of the median uterine echo.

According to Kazaryan L.S. (2012), there is a direct dependence of the degree of effectiveness of the operation on the size of the surgical intervention: with submucosal uterine myoma type 0-1, the efficiency reaches 100%, with submucosal uterine myoma type 2 - 90.6% [32].

Analyzing the results of hysteroscopic myomectomy, which was performed on 120 patients of perimenopausal age, Muñoz JL (2013) obtained a clinical effect in 88.5% of patients. Moreover, there was a combination of this operation with polypectomy, resection of the endometrium, which did not affect the results of treatment [129].

With hysteroscopic resection of submucosal fibroids using a bipolar intrauterine system, Clark TJ et al noted good results - no bleeding in 78% of cases, patient satisfaction in 92% of cases. Moreover, the cost was 40% less than with hysterectomy [121].

Thus, at present, operative hysteroscopy is widely used in the treatment of patients with uterine bleeding.

Hysterectomy is the only treatment for uterine bleeding that provides 100% amenorrhea. It is during the period of perimenopause that the number of hysterectomies increases due to persistent menstrual disorders and associated pathology of the endo- and myometrium [137]. A quarter of American women undergo perimenopausal hysterectomy for uterine bleeding [125]. Every year in the United States, 700,000 hysterectomies are performed due to menorrhagia, and in a large number,

pathology is not detected after histological examination of the removed tissues [126].

However, the high complication rate of hysterectomy is the reason for many refusals of radical surgical methods of treatment.

Also, hysterectomy can lead to psychological and physical changes in a woman, inhibition of sexual function [41, 145]. According to Western European statistics, 50% of women aged 44 and 30% of women aged 45–54 are sexually active [50].

In 80.0% of cases, women with surgical menopause had a combination of several somatic diseases [45]. In 44.1% of cases, already in the first 3-7 days after surgery, existing vegetative-vascular and psycho-emotional disorders appear or worsen; surgical menopause syndrome develops within a year after surgery in 94.7% of perimenopausal women [28].

When some researchers compared the effect of hysterectomy and long-term medical treatment on the quality of life of perimenopausal women with uterine bleeding, it was noted that 53% of patients with hormonal treatment failure insisted on hysterectomy and noted an improvement in quality of life outcomes within 2 years [99, 125]. However, hysterectomy was accompanied by a long stay in the hospital, an increase in the number of days of limited activity [99].

According to some authors [132, 141], hysterectomy has a distinct advantage over hysteroscopic surgery in the treatment of menorrhagia, but is more invasive than the hysteroscopic approach.

Thus, from the analysis of the presented data, it can be seen that the problem of rational diagnosis and treatment of women with AUB in the perimenopausal period has not been finally resolved and is a very difficult task requiring further study. Difficulties encountered in choosing the optimal method of treatment in each case are due to the complex and heterogeneous patho- and morphogenesis of the disease, the ambiguity of the causes of relapses, and the individual sensitivity of the organism to various therapeutic factors.

In recent years, there has been some progress in the study of risk factors, the mechanisms of formation of AUB and its relapses. Convincing evidence has been obtained for the effectiveness of various methods of drug therapy, the effect of which, unfortunately, is often temporary. Prospects for the development of the problem are seen in the further study of the molecular genetic basis of the origin of AUB, the

study of which will improve the system of diagnostic and therapeutic measures aimed at preventing uterine bleeding and maintaining women's health.

Untimely diagnosis of intrauterine pathology does not always lead to the correct choice of treatment method, long-term drug therapy, an unjustified number of invasive interventions and a large number of radical traumatic operations. This implies the need to improve the examination and tactics of managing women with AUB in premenopausal age, taking into account clinical, morphogenetic and genetic examinations.

CHAPTER 2

CLINICAL CHARACTERISTICS OF THE MATERIAL AND APPLIED METHODS OF INVESTIGATION

Clinical characteristics of patients

In this work, we examined 125 patients of the perimenopausal period with indications of abnormal uterine bleeding, who were treated in the gynecological department of the 1st clinic of the State Medical Institute for the period from 2018 to 2020.

The examined women were divided into two groups: the main - patients with indications of abnormal uterine bleeding, which in turn was divided into two: Group I - 90 women with the first abnormal uterine bleeding (AMB); group II included 35 women with indication of recurrent abnormal uterine bleeding.

The control group included 40 women of the same age without indications of any menstrual irregularities.

The age of the examined patients ranged from 43 to 51 years.averaged 46.9±1.6 years.

By the time of the examination, the duration of clinical manifestations of uterine bleeding in patients of the main group ranged from 1 month to 2 years.

Examination of patients upon admission to the hospital was carried out according to a single scheme, including an assessment of the data of the general and obstetric-gynecological anamnesis, taking into account age, body mass index, the nature of complaints, the presence and nature of the course of somatic diseases, the characteristics of menstrual, sexual and reproductive functions, past gynecological diseases and their treatment, ultrasound data (ultrasound) of the pelvic organs.

A comprehensive clinical and laboratory examination included examination of the external genitalia, vagina, cervix in the mirrors; bimanual examination, ultrasound examination of the pelvic organs, endoscopic examination of the uterine cavity, histological examination of endometrial biopsy specimens, molecular biological studies.

Inclusion criteriaThe study included the following data: perimenopausal age, a morphologically confirmed diagnosis of endometrial hyperplasia, the absence of antibiotic therapy over the past 3 months for an objective assessment of the infectious status, the absence

of hormonal therapy over the past 3-6 months. Informed consent was a prerequisite for participation in the study.

Exclusion Criteria:the studies did not include patients with coagulopathy and iatrogenic bleeding, as well as with malignant diseases of any localization.

A survey of patients in both groups showed that a history of malignant tumors of various localization in grandmothers, mothers and sisters was observed in every tenth examined - 11 (8.8%) (Table 2.1). In the control group, only 1(2.5±2.5%) indicated bowel cancer among relatives. As for cervical cancer and bowel cancer, only 3 (2.4±1.4%) patients in the main group indicated their presence among their relatives, there was no this pathology in the control. When considering groups I and II separately, both cervical cancer and intestinal cancer were noted 5 times more often in their relatives, patients with recurrent uterine bleeding, p <0.05.

At the same time, among the relatives of patients with recurrent bleeding (group II), the anamnesis was 4.5 times more likely to be aggravated in terms of oncology: 7 (20%) versus 4 (4.4%).

Table 2.1

Structure of cancer history in patients with abnormal uterine bleeding, M±m

The structure of the family oncological anamnesis of the examined women	I group n=90	II group, n=35	main group, n=125	Control, n=40
Cancer of the body of the uterus	-	1(2.9±2.8%)	1(0.8±0.8%)	-
ovarian cancer	-	-	-	-
Cervical cancer	1(1.1±1.1%)	2(5.7±3.9%)*	3(2.4±1.4%)	-
bowel cancer	1(1.1±1.1%)	2(5.7±3.9%)*	3(2.4±1.4%)	1(2.5±2.5%)
Mammary cancer	2(2.2±1.6%)	2(5.7±3.9%)	4(3.2±1.6%)	-

Note:

**-R <0.05 significance of differences between groups I and II*

In the study of somatic pathology (Table 2.2) in patients, it was found that half of the patients of the main group - 49 (39.2 ± 4.4%) had chronic inflammatory diseases of the upper and lower respiratory tract, which is significantly more common than in the control group - 7(17.5±6%), p<0.001. Every fifth patient in the main group - 29 (23.2±3.8%) and every 8 in the control suffered from chronic bronchitis

5 (12.5±5.2%), p<0.05. The presence of chronic tonsillitis was indicated three times more often by patients with AUB compared with controls, p <0.001.

Diseases of the cardiovascular system, mainly varicose veins and hypertension, affected a significant proportion of patients with AUB - 97 (77.6±3.7%)women of the main group and only every fifth - 9 (22.5±6.6%) from the control group, p<0.001. Varicose veins were diagnosed in 87(69.6±4.1%) versus 7(17.5±6%) in the control group, p<0.001. Hypertension occurred twice as often in patients with AUB - 12(9.6±2.6%) versus 2(5±3.4%), p <0.05.

Patients of the main group significantly more often suffered from various diseases of the urinary system 112(89.6±2.7%) versus 14(40±8.3%), p<0.001. Most often, patients with AUB had chronic pyelonephritis - 56 (44.8±4.4%) versus 7 (17.5±6%) in the control, p<0.05. Every 18 patients of both groups noted chronic cystitis 7(5.6±2.1%) and 2(5±3.4%), respectively.

Analysis of diseases of the endocrine system indicates that the patients of the main group 106 (84.8±3.2%) suffered 4.8 times more often compared to the control 7 (17.5±6%), p<0.05. Pathology of the thyroid gland, mainly diffuse goiter I st. and II stage, occurred 4 times more often in the main group than in women without menstrual dysfunction -

65(52±4.5%) versus 5(12.5±5.2%), respectively, p<0.05. At the same time, the frequency of diffuse goiter in patients with recurrent bleeding - 22 (62.9±8.2%) was significantly more frequent than in women with AUB - 43 (47.8±5.3%), p<0.05. Nodular goiter was found in one patient of the 1st group.

Every third patient of groups I and II - 26 (28.9±4.8%) 11 (31.4±7.8%), respectively, was obese. At the same time, patients of the main group 37 (29.6±4.1%) were 2.4 times more likely to be overweight - 5 (12.5±5.2%), p<0.05.

Type 2 diabetes mellitus was detected in 5(5.6±2.4%) and 4(11.4±5.4%) patients in groups I and II, respectively. Diabetes mellitus in patients of the main group - 9 (7.2±2.0%) occurred 2.9 times also significantly more often than in the control group - 1 (2.5±2.5%), p<0.05.

Iron deficiency anemia was diagnosed in 94 (75.2±3.9%) patients of the main group and only in 3 (7.5±4.2%) patients in the control group, p<0.001. In addition, the frequency of anemia in patients with recurrent

bleeding was significantly more frequent than in patients with AUB - 34(97.1±2.8%) and 60(66.7±5.0%), p<0.05.

Patients of the main group had a combination of two or more pathologies 1.5 times more often.

Table 2.2

Structure of somatic pathology in examined women, M±m

The structure of somatic pathology	I group n=90	II group, n=35	main group, n=125	Control, n=40
Respiratory diseases	**34(37.8±5.1%)**	**15(42.9±8.4%)**	**49(39.2±4.4%)**	**7(17.5±6%) ^^**
-Chronical bronchitis	19(21.1±4.3%)	10(28.6±7.6%)	29(23.2±3.8%)	5(12.5±5.2%) ^
-chronic tonsillitis	15(16.7±3.9%)	5(14.3±5.9%)	20(16±3.3%)	2(5.0±3.4%) ^^
Diseases of the cardiovascular system	**69(76.7±4.5%)**	**28(80±6.8%)**	**97(77.6±3.7%)**	**9(22.5±6.6%) ^^**
- varicose disease	61(67.8±4.9%)	26(74.3±7.4%)*	87(69.6±4.1%)	7(17.5±6%)^^
hypertonic disease	8(8.9±3%)	4(11.4±5.4%)	12(9.6±2.6%)	2(5±3.4%) ^
Diseases of the urinary system	**78(86.6±2.8%**	**34(97.1±2.8%) ***	**112(89.6±2.7%)**	**14(40±8.3%) ^^**
-chronic pyelonephritis	38(42.2±5.2%)	18(51.4±8.4%)	56(44.8±4.4%)	7(17.5±6%) ^
-MKD	35(38.9±5.1%)	15(42.9±8.4%)	50(40±4.4%)	5(12.5±5.2%) ^
- chronic cystitis	5(5.6±2.4%)	2(5.7±3.9%)	7(5.6±2.1%)	2(5±3.4%)
Diseases of the endocrine system	**72(80±4.2%)**	**34(97.1±2.8%) ***	**106(84.8±3.2%)**	**7(17.5±6%) ^^**
- thyroid disease	43(47.8±5.3%)	22(62.9±8.2%)*	65(52±4.5%)	5(12.5±5.2%) ^^
-obesity	26(28.9±4.8%)	11(31.4±7.8%)	37(29.6±4.1%)	5(12.5±5.2%) ^
-diabetes	5(5.6±2.4%)	4(11.4±5.4%)	9(7.2±2.0%)	1(2.5±2.5%)
Iron-deficiency anemia	**60(66.7±5.0%)**	**34(97.1±2.8%) ***	**94(75.2±3.9%)**	**3(7.5±4.2%) ^^**
Combination of two or more pathologies	**27(30±4.8%)**	**16(45.7±8.4%)**	**43(34.4±4.2%)**	**9(22.5±6.6%)**

Note:

*-R	<0.05	*significance of differences between groups I and II*
**-R	<0.001	*significance of differences between groups I and II*
^-R	<0.05	*significance of differences between the main group and control*
^^-R	<0.001	*significance of differences between the main group and control*

We have carefully analyzed the formation of the menstrual function of the examined women. Table 2.3 shows that in most patients of I - 60 (66.7 ± 5%) and II groups - 20 (57.1 ± 8.4%), as well as from the control - 33 (82.5 ± 6%) menarche occurred on time at the age of 12-14 years. Early age of menarche (10-11 years) was noted significantly more often in those examined with abnormal uterine bleeding - 39 (31.2±4.1%) compared with the control group 2 (5.0±3.4%) cases, p< 0.001; late menarche (at the age of 15—17 years) was detected in 6(4.8±1.9%) and 5(12.5±5.2%) patients of the main group and in the control, respectively, p<0.05.

Fig.2.1 *Information about the menarche of the surveyed groups*

The number of pregnancies in the examined women is presented in Table 2.3.

In the main group 7(5.6±2.1%) patients indicated primary infertility. At the same time, in group II, patients significantly more often suffered from primary infertility than in group I, p <0.05. There were no indications of this pathology in the control group.

Pregnancies in history were in 529 (100%) patients with AUB and in 114 (100%) women in the control group. It was found that in total, patients of group I had 369 pregnancies, patients of group II - 160. On average, each woman in group I had 3.6 pregnancies, in group II - 3.56, which does not have significant differences (p <0, 05).

In the control, women had significantly more often one 5 (12.5±5.2%), five - 34 (27.2±4%) and six 22 (17.6±3.4%) pregnancies in history, compared with data of the main group 6(4.8±1.9%), 4(10±4.7%) and 2(5±3.4%), respectively (p<0.05).

Table 2.3

The number of pregnancies in the examined, M±m

Number of pregnancies	I group n=90	II group, n=35	main group, n=125	Control, n=40
0	3(3.3±1.9%)	4(11.4±5.4%)*	7(5.6±2.1%)	-
one	6(6.7±2.6%)	-	6(4.8±1.9%)	5(12.5±5.2%)^
2	10(11.1±3.3%)	1(2.9±2.8%)	11(8.8±2.5%)	14(40±8.3%)^^
3	15(16.7±3.9%)	3(8.6±4.7%)*	18(14.4±3.1%)	11(27.5±7.1%)^
four	12(13.3±3.6%)	5(14.3±5.9%)	17(13.6±3.1%)	4(10±4.7%)
5	24(26.7±4.7%)	10(28.6±7.6%)	34(27.2±4%)	4(10±4.7%)^
6	15(16.7±3.9%)	7(20±6.8%)	22(17.6±3.4%)	2(5±3.4%)^
7	-	3(8.6±4.7%)	3(2.4±1.4%)	-
eight	5(5.6±2.4%)	2(5.7±3.9%)	7(5.6±2.1%)	-
Total	369(100%)	160(100%)	529(100%)	114(100%)

Note:

**-R* *<0.05* *significance of differences between groups I and II*

***-R* *<0.001* *significance of differences between groups I and II*

^-R *<0.05* *significance of differences between the main group and control*

^^-R *<0.001* *significance of differences between the main group and control*

At the same time, none of the examined from the control group had indications of 6 or more pregnancies (p <0.05).

An obstetric history with AUB did not show significant differences (p>0.05) in the frequency of timely delivery and artificial abortions compared with patients in the control group (Table 2.4). In the main groups, 204 (55.3±2.6%) and 53 (33.1±3.7%) pregnancies ended in delivery, in the control group - 84 (50.6±3.9%) pregnancies. At the same time, none of the women in the control group reported cases of preterm birth, antenatal fetal death, and spontaneous miscarriage.

The frequency of medical abortions in groups I and II was 133 (36 ± 2.5%) and 88 (55 ± 3.9%) cases, respectively, among patients of the main and control groups, about half of the examined - 221 (41.8 ± 2.1 %) 74 (46.8±3.8%) indicated artificial termination of pregnancy.

Table 2.4

Pregnancy outcomes in patients of the study groups, M±m

Pregnancy outcomes	I group n=90	II group, n=35	main group, n=125	Control, n=40
Term delivery	204(55.3±2.6%)	53(33.1±3.7%)*	257(48.6±2.2%)	84(50.6±3.9%)
preterm birth	13(3.5±1.0%)	6(3.8±1.5%)	19(3.6±0.8%)	-
Antenatal fetal death	6(1.6±0.7%)	3(1.9±1.1%)	9(1.7±0.6%)	-
Spontaneous miscarriage	13(3.5±1.0%)	10(6.3±1.9%)	23(4.3±0.9%)	-
medical abortion	133(36±2.5%)	88(55±3.9%) *	221(41.8±2.1%)	74(46.8=3.8%)
Number of pregnancies	369(100%)	160(100%)	529(100%)	50(100%)

Note:

*-*R* <0.05 *significance of differences between groups I and II*

The structure and frequency of gynecological morbidity in the past in women with AUB deserves special attention. All women of groups I and II and 18.7% of the control group were previously observed and treated for various gynecological diseases. Table 2.5 shows that, despite some differences, uterine fibroids, chronic inflammatory diseases of the internal genital organs were most common in all groups, and to a lesser extent infertility and ovarian tumors.

Table 2.5

Information about past gynecological diseases in the examined, M±m

Gynecological pathology in history	I group n=90	II group n=35	main group, n=125	Control, n=40
uterine fibroids	13(14.4±3.7%)	7(20.0±5.8%)	20(16.0±3.7%)	-
Menstrual irregularity	-	31(88.5±2.8%)	31(24.8±3.9%)	-
Chronic inflammatory diseases of the genital organs	24(26.7±4.7%)	12(34.3±8.0%)*	36(28.8±4.1%)	4(10±4.7%)^
Infertility	3(3.3±1.9%)	4(11.4±5.4%)*	7(5.6±2.1%)	-
ovarian cysts	13(14.4±3.7%)	6(17.1±6.4%)	19(15.2±3.2%)	1(2.5±2.5%)^

Note:

*-R <0.05 *significance of differences between groups I and II*
^-R <0.05 *significance of differences between the main group and control*

Every 7th patient - 13 (14.4±3.7%) in group I and every 5th patient - 7 (20.0±5.8%) in group II indicated uterine myoma in the past. There were no indications of uterine myoma in the control group. Every 4th patient - 31 (24.8±3.9%) from the main group noted the presence of menstrual disorders in the form of delays, heavy and prolonged, painful menstruation.

It should be noted that chronic inflammatory diseases of the genital organs in history were observed significantly more often in group II - 36 (28.8 ± 4.1%) than in group I - 24 (26.7 ± 4.7%), ($p < 0.05$). Almost three times less often women from the control group noted inflammation of the genitals in the past than patients with AUB - 36 (28.8 ± 4.1%) versus 4 (10 ± 4.7%), ($p < 0.05$).

A history of infertility was noted only in 7 patients with AUB: in 3 (3.3±1.9%) patients of group I, in 4 (11.4±5.4%) patients of group II.

Ovarian cysts in the past were noted in 13 (14.4±3.7%) patients of group I and in 6 (17.1±6.4%) patients of group II, while in the control group - only in 1 (2.5± 2.5%) women, ($p<0.05$).

Table 2.6

Postponed gynecological operations in patients, M±m

Operation types	I group n=90	II group, n=35	main group, n=125	Control, n=40
Diagnostic curettage of the uterus	-	31(88.5±0.8%)	31(24.8±3.9%)	-
Cystectomy	3(3.3±1.9%)	5(14.3±5.9%)*	8(6.4±2.2%)	1(2.5±2.5%)
Conservative myomectomy	2(2.2±1.6%)	6(3.8±1.5%)	8(6.4±2.2%)	-
Tubectomy for ectopic pregnancy	4(4.4±2.2%)	2(5.7±3.9%)	6(4.8±1.9%)	-
Voluntary surgical sterilization	15(16.7±3.9%)	7(20.0±6.8%)	22(17.6±3.4%)	7(17.5±6%)
Total operations	31(100%)	50(100%)	81(100%)	8(100%)

Note:

*-R <0.05 significance of differences between groups I and II

Among the examined patients, 31 patients from group I and 50 operations from group II had previously undergone various surgical interventions on the pelvic organs. It should be noted that the vast majority of patients with recurrent AUB (group II) indicated curettage of the uterine cavity due to AUB - 31 (88.5%). Women in the control group underwent only 8 operations, the vast majority - 87.5% of which were voluntary surgical sterilization (VCS).

22 (17.6±1.1%) patients of the main group had a history of indications for laparotomy and only one patient - 1 (2.5±2.5%) from the control group, p<0.001. In group I, 3 (3.3±1.9%) underwent cystectomy for ovarian cysts, in group II their number was significantly higher -5 (14.3±5.9%), p<0.05. 2.5 times less often cystectomy was carried out by those examined from the control group. Laparotomy with tubectomy was transferred in 6 (4.8±1.9%) patients of the main group. Thus, patients of the main group had 8 times more gynecological operations in their history than women in the control group.

Paraclinical and instrumental examination methods

All patients underwent clinical and laboratory examination, including: examination - body type, features of the distribution of subcutaneous adipose tissue, the nature of hair growth. For accurate diagnosis of the nature of the violation of fat metabolism, the calculation of BMI was carried out according to the formula (index G. Brey)

BMI = weight (kg) / height (m2)

The BMI value from 20 to 24.9 kg/m2 was regarded as an indicator of normal body weight, from 25 to 29.9 kg/m2 - as overweight, 30-39.9 kg/m2 - as obesity over 40 kg/m2 as sharp pronounced (morbid)

The mass-height coefficient (Bray index) corresponded to the norm in 16 (17.8±4%) examined women of group I, in 46 (51.1±5.3%) women overweight was stated, in 25 (27.8±4, 7%) revealed obesity, 3 (3.3±1.9%) pronounced obesity. In group II of the women examined, the mass-height coefficient corresponded to the norm of 5 (14.3 ± 5.9%), overweight in 19 (54.3 ± 8.4%), obesity in 9 (25.7 ± 7.4%) and pronounced obesity was observed in 2 (5.7±3.9%) women of this group. In the control group, excess body weight was noted in 11 (27.5±7.1%) women, obesity - in 1 (2.5±2.5%), the weight of the remaining patients in 70% corresponded to the normative indicators.

The average BMI in patients of group I was 28.2 ± 0.6 kg/m2, in group II - 29.4 ± 0.8 kg/m2. In the control group, this indicator was significantly lower - 23.08 ± 0.6 kg/m ($p < 0.05$).

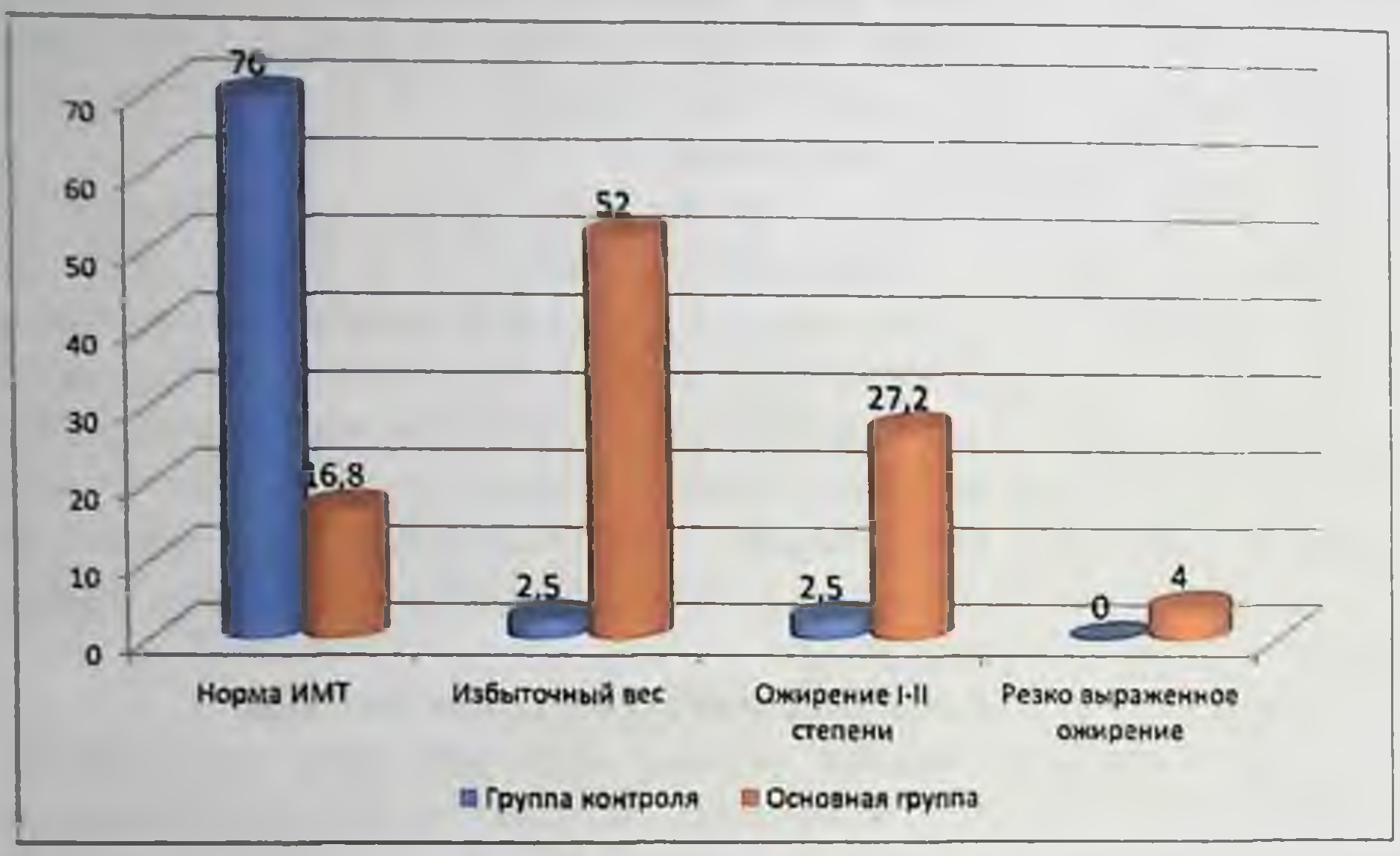

Fig.2.7 *Distribution of patients by BMI*

Normal BMI was registered 4 times more often in the control 28 (70.0±7.9%) patients compared to 21 (16.8±3.3%) patients of the main group ($p < 0.05$). 1.9 times more overweight patients were among patients with AUB - 65 (52.0 ± 4.5%) compared with the control group - 11 (27.5 ± 7.1%) ($p < 0.05$). BMI in the range of 30-39.9 kg/m² was 10.9 times more common in patients of the main group - 34 (27.2±4%) compared with the control group - 1 (2.5±2.5%), ($p<0.001$). Another 5 (4.0±1.8%) patients from the main group had pronounced obesity, BMI >40 kg/m².

*Ultrasonic research methods*pelvic organs were performed upon admission of patients and during treatment. Ultrasound examination was performed on devices "Voluson730-Expert" (Japan), related to contact scanning systems and working in real time, with transabdominal sensor RA 134-8-D and transvaginal sensor RIC 6-12-D and "Aloka SSD 500" (Japan) with a transvaginal convex probe with a frequency of 5 MHz. An echographic examination assessed the size and location of the uterus, the structural features of the myometrium, endometrium, ovaries, and pathological formations. Particular attention was paid to the value of the median uterine echo (M-echo).

Hysteroscopy and separate diagnostic curettage of the cervical canal and uterine cavity.

Hysteroscopy was performed under intravenous anesthesia using a rigid 7 mm hysteroscope manufactured by Karl Storz (Germany) after preliminary dilatation of the cervical canal to 7.5 mm. A 0.9% sodium chloride solution was used as a distance medium. The constancy of pressure in the uterine cavity was created and maintained at the level of 100 mm Hg. using Hysteroma t from Karl Storz (Germany). During hysteroscopy, the size, shape of the uterine cavity, the presence of its deformation, color, thickness, folding of the endometrium, the presence of polyps and other variants of intrauterine pathology were assessed.

Mandatory hysteroscopic control ensured the thoroughness of the performed curettage of the walls of the uterine cavity.

The morphological section of the research included a histological examination of the surgical material, performed by the head of the Department of Pathological Anatomy of the State Medical Institute Ph.D. Associate Professor Eshkobilov T.Zh.

Histological examination. The removed tissue fragments were fixed in 10% neutral buffered (phosphate) formalin and processed in an STP-120 carousel histological apparatus (Microm, Germany). The filling of the fabric was carried out using a modular station EC-350-1 (Microm, Germany). Then, at least 10 stepped sections 4 μm thick were made from each block, followed by staining with hematoxylin-eosin.

The morphological type of HE was determined using the WHO classification (2002):

I. Endometrial hyperplasia without atypia:

Glandular hyperplasia of the endometrium

Glandular cystic hyperplasia of the endometrium

II. Atypical endometrial hyperplasia.

Molecular biological researchconducted on the basis of the laboratory of the scientific center "Oncohematology" by Professor MD. Babaev K.T. With this method of examination, the allele polymorphism in the MMP9 gene and the TP53 mutation were determined in 90 women from the main group and 95 from the control group (conditionally healthy donors).

Matrix metalloproteinases(MMP) is a family of extracellular zinc-dependentendopeptidase,capable of destroying all types of proteinsextracellular matrix. MMPs were first described in1962, later

found in invertebrates and plants. The main difference between MMP and other endopeptidases is their dependence onions metals, the ability to destroy the structure of the extracellular matrix [10,12].

In women with various pathological conditions, such as AUB and endometrial cancer, MMP-9 levels are elevated. It has been shown that in patients with AUB, the concentration of MMP-9 in the blood serum is significantly higher than in practically healthy individuals.

Among the tumor suppressor genes is the anti-oncogenic protein TP53. Its product is a phosphoproteinp53. In a normal cell, p53 is inactive, but during emergency events it is activated and plays the role of a "guardian of the genome", performing various anti-cancer functions. If the DNA is damaged, p53 delays the mitosis of dividing cells by blocking the transition from G1 phase to S phase and allowing the repair system time to repair the damage; if DNA damage cannot be eliminated, p53 switches on the cell death program—apoptosis. At the same time, the TP53 gene is very often mutated in cancerous tumors of many types [23, 40, 102].

PCR diagnostics of the venous blood serum of the examined women was placed in a test tube and stored at -20°C. The study of all obtained samples was performed simultaneously. DNA was isolated from tissue samples using the RNeasy MiniKit (QIAGEN), then complementary DNA (cDNA) was constructed using reverse transcription using oligo (dT) nucleotides and M-MLV reverse transcriptase as part of the First Strandc DNA Synthesis reverse transcription kit Kit (Fermentas, Russia). To study the expression of selected genes, real-time polymerase chain reaction (Real-timePCR, RT-PCR) was used, performed on a RotorGene6000 cycler (Corbett Research) using an intercalating dye SYBR-greenI (ZAO Sintol, Russia).). Quantification was carried out using the method of relative quantitative analysis (AACt). To do this, for each studied gene (A), the difference in cycles (ACt) between the studied gene (A) and the house-keeping gene B2 microglobulin (HS-gene) was calculated when the amplification curve entered the exponential growth stage. The threshold level (Threshold) was set manually, according to the recommendations for the device and literature data. Next, the level of expression of each gene (MMP9 and mutated TP53), expressed in the number of copies, was calculated. For this, the reaction efficiency was taken equal to 2. Then, in accordance with the AS values, the number of copies equal to 2" ACt was calculated. Then, the difference in the values

of the expression level between the test and control groups (2" AACt) was statistically calculated.

Statistical data processing

The research results data were statistically processed on a Pentium-IV computer using the Microsoft Office Excel-2013 software package. Methods of parametric and non-parametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard error of the mean (m), relative values (P).

The statistical significance of the results obtained when comparing the mean values was determined by Student's test (t) with the calculation of the error probability (P) when checking the normality of the distribution (by the kurtosis criterion) and the equality of general variances (F - Fisher's criterion). Statistical significance for qualitative variables was calculated using the $\chi 2$ test (chi-square) and p-test [55]. Significance level $P<0.05$ was taken as statistically significant changes.

Prediction of AUB in women of the perimenopausal period was carried out using the following calculation methods and statistical methods. The degree of influence of factors on the development of AUB was studied by the method of single-factor analysis of variance. The value of the Fisher criterion and its significance were determined. In our studies, to establish the degree of association between risk factors and the development of AUB, we determined the odds ratio (OR) and the relative risk of development (RR). For example, determining the chance of OR and the risk of RR of developing AUB in women with early menarche. The risk of developing AUB in women with early menarche is 4 times greater than in the control group.

To determine the prognostic significance of tests, sensitivity, specificity, predictive value of a prognostic result, predictive value of a negative result were determined.

Sensitivity is the likelihood of a positive test result in individuals with a disease. The higher the sensitivity of the method, the more often pathological changes are detected with its help. Therefore, it is more efficient.

$$Se = \frac{a}{a+c} = \frac{ИП}{ИП + ЛО}$$

IP (a) - true - positive cases;
LP (b) - false-positive cases;
LO (c) - false-negative cases;
IR (d) - true-negative cases.

Specificity is the probability of a negative result in individuals without the disease. The higher the specificity of the method, the more reliably the disease is confirmed with its help.

$$Sp = \frac{d}{d+b} = \frac{\text{ИО}}{\text{ИО} + \text{ЛП}}$$

The predictive positive result is the probability of disease in a positive test result.

$$Pv+ = \frac{d}{a+b} = \frac{\text{ИП}}{\text{ИП} + \text{ЛП}}$$

The predictive negative result is the probability of not having the disease in a negative test result.

$$Pv- = \frac{d}{d+c} = \frac{\text{ИО}}{\text{ИО} + \text{ЛО}}$$

The predictive coefficient was calculated by the following formula

PC \u003d 100 × P (x / A1) ÷ P (x / A2)

PC - prognostic coefficient of the main group and sign x;

X sign or symptom

P (x/A1) conditional probability of the information group of sign x in the totality of patients with individual complications or symptoms (A1);

P (x/A2) is the conditional probability of the information group of the feature x in the control group A2 [55].

CHAPTER 3 CLINICAL AND MORPHOLOGICAL CHARACTERISTICS OF THE ENDOMETRIUM OF PATIENTS WITH ABNORMAL UTERINE BLEEDING DURING THE PERIMENOPAUSE

Survey data of patients of the studied groups

Patients with abnormal uterine bleeding applied to the gynecological department of the 1st clinic of the Samarkand Medical Institute with complaints of bleeding from the genital tract.

When analyzing the complaints of patients of both main groups, it was found that upon admission to the clinic, bleeding of varying intensity was noted by the majority of the examined - 59 (65.6 ± 5.0%) patients of group I and 25 (71.4 ± 7.6%) of group II . The average duration of spotting before admission to the hospital was 22.6 ± 3.6 days in group I, and 35.1 ± 3.6 days in group II.

The surveyed presented various complaints about menstrual irregularities, pain in the lower abdomen, vasomotor and emotional-vegetative symptoms (Fig. 3.1).

Most patients of group I with abnormal uterine bleeding complained of heavy menstruation 49 (54.4±4.8%) and almost every second of group II - 13 (37.0±8.0%).

Almost half of the patients of each of the groups - I and II, noted profuse, prolonged, and painful uterine bleeding, 41 (45.6 ± 5.2%) and 17 (48.6 ± 8.4%) noted.

Also, patients with recurrent AUB - 12 (34.3 ± 8.0%) complained of pain in the lower abdomen and lumbosacral region twice as often compared to 13 (14.4 ± 3.7%) patients from group I, however the difference was not significant. Patients with AUB reported pain in the lower abdomen eight times more often than those in the control group ($p<0.001$).

A small number of patients with AUB complained of vasomotor and emotional-vegetative symptoms of menopausal syndrome. Thus, only 8 (8.9±3%) and 2 (5.7±3.9%) patients of groups I and II, respectively, indicated sweating, headaches and palpitations. When comparing the complaints of patients of the main group and the control group on sweating, poor sleep, irritability, no significant differences were observed between the main group and the control - 10 (8.0 ± 2.4%) 2 (5.0 ± 3.4%) - respectively .

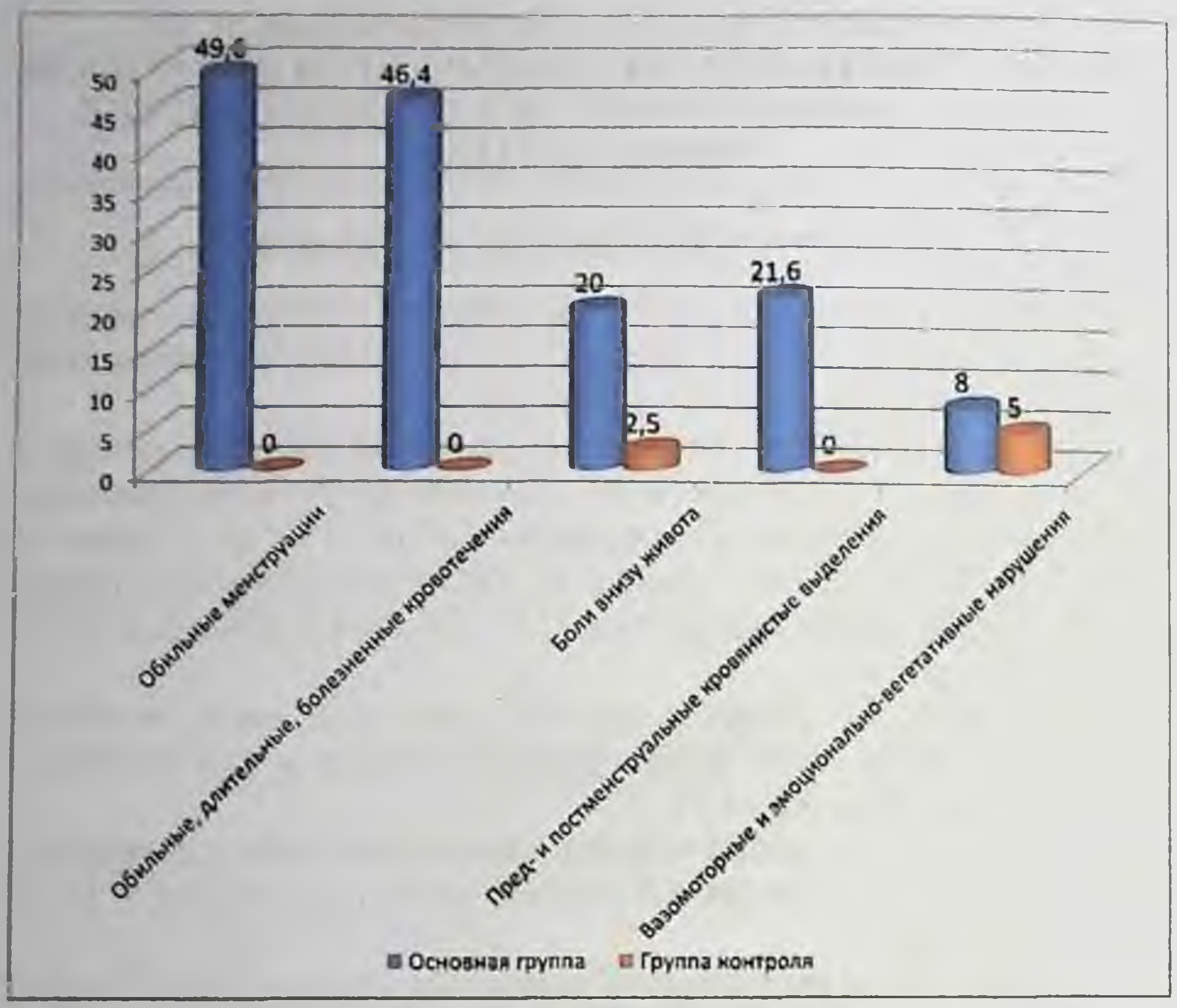

Fig. 3.1 *Complaints made by the examined women*

The duration of menstrual irregularities varied from 2 to 6 years and averaged 4.2 ± 2.2 years in group I and 3.6 ± 2.3 years in group II ($p>0.05$).

As a result of an objective examination, it was revealed that in all the examined patients, the physique is of the female type, secondary sexual characteristics are developed correctly. When examining the gynecological status, the external genital organs are developed correctly in all women. The urethra, paraurethral passages, ducts of the large glands of the vestibule of the vagina without pathological changes at the time of examination in all examined patients. In 20 (22.2±4.4%) patients of group I and in 8 (22.9±7.1%) patients of group II, vaginal wall prolapse was diagnosed.

Among the pathological changes in the cervix (Table 3.1), the majority of patients in both groups had chronic cervicitis.

Table 3.1

Identified pathological changes in the cervix among the examined, M±m

Pathological changes	I group n=90	II group, n=35	main group, n=125	Control, n=40
Chronic cervicitis	53(58.9±5.2%)	30(85.7±5.9%)*	83(66.4±4.2%)	6(15.0±2.1%)^^
Old ruptures of the cervix I and II degrees	17(18.9±4.1%)	10(28.6±7.6%)*	27(21.6±3.7%)	2(5.0±3.4%)^
Scar deformity	6(6.7±2.6%)	4(11.4±5.4%)	10(8.0±2.4%)	2(5.0±3.4%)
Endometriosis of the cervix	8(8.9±3%)	4(11.4±5.4%)	12(9.6±2.6%)	-
coagulated cervix syndrome	9(10.0±3.2%)	2(5.7±3.9%)	11(8.8±2.5%)	-

Note:

**-R* *<0.05* *significance of differences between groups I and II*

^-R *<0.05* *significance of differences between the main group and control*

^^-R *<0.001* *significance of differences between the main group and control*

At the same time, in patients of group II - 30 (85.7 ± 5.9%), the inflammatory process of the cervix was noted significantly more often than in group I - 53 (58.9 ± 5.2%), (p <0.05). Also in the main group, chronic cervicitis was registered 4.4 times more often than in the control group - 83(66.4±4.2%) versus 6(15.0±2.1%), (p<0.001).

Old ruptures of the cervix were found 1.5 times more often in patients with recurrent AUB - 10 (28.6 ± 7.6%) compared with group I 17 (18.9 ± 4.1%), (p <0, 05). At the same time, in the main group, their frequency - 27 (21.6 ± 3.7%) exceeded the same indicator in the control - 2 (5.0 ± 3.4%) by 4.3 times (p <0.05).

Cicatricial deformity of the cervix occurred in6(6.7±2.6%)female patientsinI group and in 4 (11.4±5.4%) in group II, respectively. There were also no differences in its frequency in the main and control groups - 10(8.0±2.4%) and 2(5.0±3.4%), respectively.

Endometriosis of the cervix was diagnosed in 8 (8.9±3%) and 4 (11.4±5.4%) patients, coagulated cervix syndrome in9(10±3.2%)and 2 (5.7±3.9%) patients of groups I and II, respectively. In the group of

women without indications of menstrual irregularities, no such conditions were found.

In a bimanual study, none of the patients with AUB showed normal sizes of the uterus (Fig. 3.2). 6±8.4%) Group II.

In every third patient - 29 (32.2±4.9%) of group I and almost half of group II - 15 (42.9±8.4%), the size of the uterus corresponded to 7-8 weeks of pregnancy.

In the remaining 11 patients, the size of the uterus corresponded to 9-10 weeks of pregnancy.

Only in 2 (5±3.4%) control patients, the size of the uterus corresponded to 5-6 weeks of pregnancy. Sizes corresponding to 7-8 and 9-10 weeks of pregnancy were not observed in the control.

Pathological changes in the area of the uterine appendages (heaviness, sensitivity on palpation), which may indicate an inflammatory process, were noted in the vast majority of patients with abnormal uterine bleeding, both in I -75 (83.3 ± 3.9%) and in II groups - 30 (85.7±5.9%).

Fig. 3.2 *Dimensions of the uterus according to bimanual examination*

The results of ultrasound examination of the pelvic organs

An important stage of the examination was a transvaginal scan of the pelvic organs both before diagnostic hysteroscopy (HSC) and curettage of the uterine cavity, and after surgery during treatment and dynamic observation.

When performing echography, the size of the uterus, the structural features of the myometrium, endometrium, and ovaries were evaluated, special attention was paid to the structure, echogenicity and size of the median uterine echo (P50 P25 P75).

Taking into account the impossibility of performing an ultrasound examination (ultrasound) in all patients according to the standards in the 1st phase of the cycle, ultrasound was performed against the background of a delay in menstruation, against the background of bleeding and immediately after bleeding.

In the analysis of the violation of the cycle, it was revealed that upon admission to the clinic in patients of the main group, bleeding lasting from 26 to 45 days was observed in 77 (61.6 ± 4.4%) (Table 3.2).

Table 3.2

The number of patients with ultrasound signs of endometrial pathology,M±m

Number of patients	The number of patients with bleeding n=77	Number of patients with delayed menstruation, n=48	main group, n=125
Number of patients with endometrial thickness from 7 to 20 mm	47 (61±5.5%)	38(79.2±5.9%)	85(68.0±4.2%)
Number of patients with endometrial polyp	9(11.7±3.7%)	17(35.4±6.9%)	26(20.8±3.6%)
Number of patients with endometrial thickness from 1 to 4 mm	-	14(29.0±5.71%)	14(11.2±2.8%)

Menstruation delay from 30 to 65 days was noted in 48 (38.4±4.4%).

All patients underwent ultrasound to assess the state of the endo- and myometrium.

M-echo in patients on the background of bleeding varied from 1 to 15 mm, on average it was 10.96 ± 5.6 mm in group I, and 11.7 ± 4.5 mm in group II.

At47 (61±5.5%)of 77 with bleeding M-echo varied from 7 to 15 mm, in9 (11.7±3.7%)endometrial polyp was diagnosed.

M-echo in 38 (79.2±5.9%) patients with delayed menstruation ranged from 10 to 20 mm, averaging 16.0±3.7 mm, in 17 (35.4±6.9%) - ultrasound revealed an endometrial polyp, the remaining 14 (29.0±5.71%) - endometrial atrophy - from 1 to 4 mm.

Table 3.4

Ultrasound signs of endometrial pathology,M±m

Ultrasound signs of endometrial pathology	**I group n=90**	**II group, n=35**	**main group, n=125**
Thickness of the endometrium from 1 to 4 mm	5(5.5±2.4%)	9(25.7±7.4%) *	14(11.2±2.8%)
Thickness of the endometrium from 7 to 20 mm	70(77.8±4.4%)	15(42.9±8.3%) *	85(68.0±4.2%)
The size of the endometrial polyp is from 10 mm to 20 mm	6(6.7±2.6%)	5(14.3±5.9%)	11(8.8±2.4%)
Polyp size up to 10mm	9(10±3.2%)	6(17.1±6.4%)	15(12.0±2.9%)

Note:

*-*R* *<0.05* *significance of differences between groups I and II*

When considering the ultrasound signs of endometrial pathology (Table 3.3) by groups, the following was revealed: endometrial thickness from 1 to 4 mm occurred 5 times more often in the group with recurrent bleeding compared to its frequency in group I,($p<0.05$). Total 14(11.2±2.8%) of patients in the main group had a thin endometrium. There were no significant differences among the groups in the number of patients with endometrial thickness from 7 to 20 mm.

Endometrial polyps in groups I and II were observed in6(6.7±2.6%)and5(14.3±5.9%)patients, which is significantly more frequent in group II than in group I.

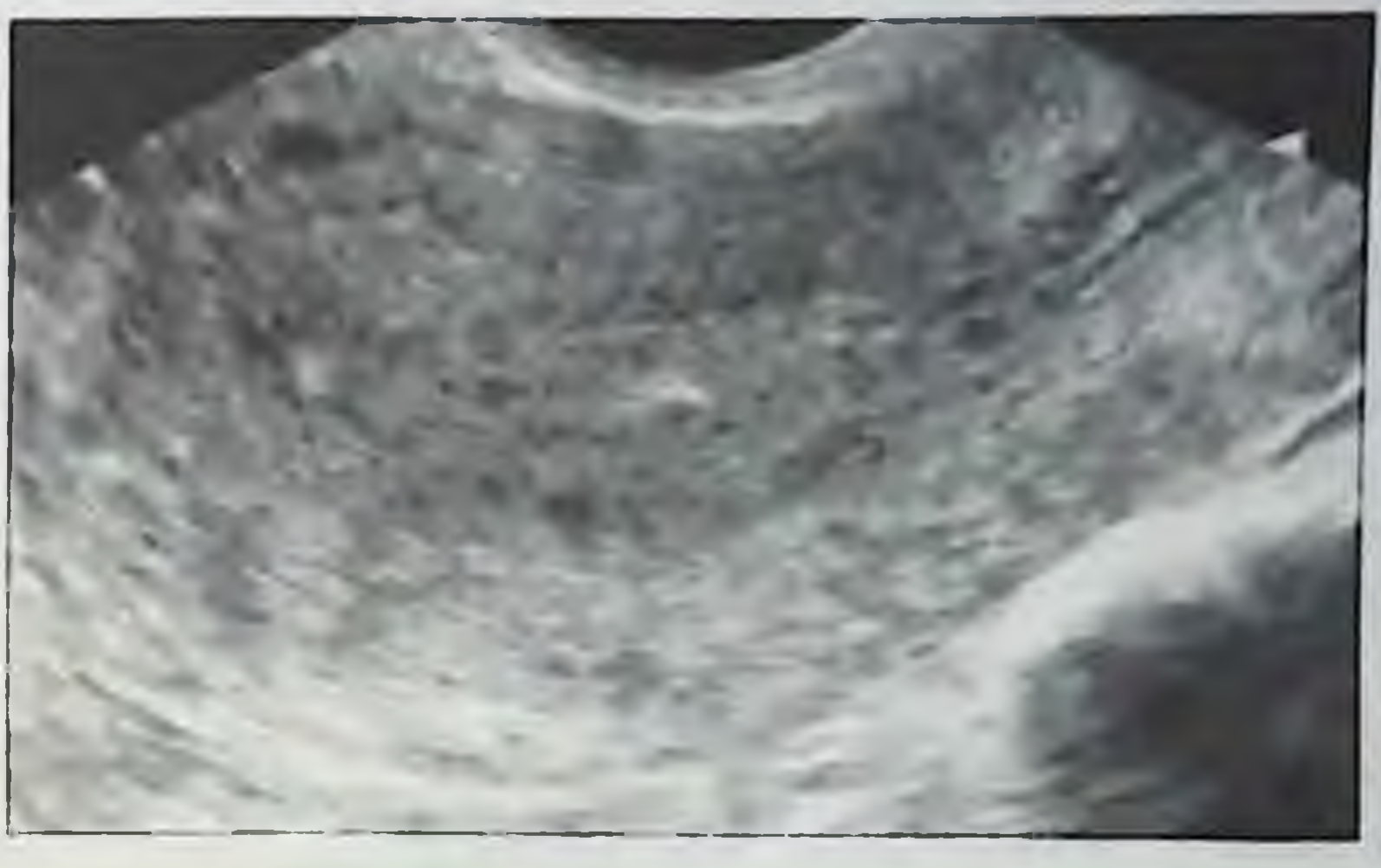

Fig. 3.3 *Ultrasound picture of glandular cystic endometrial hyperplasia*

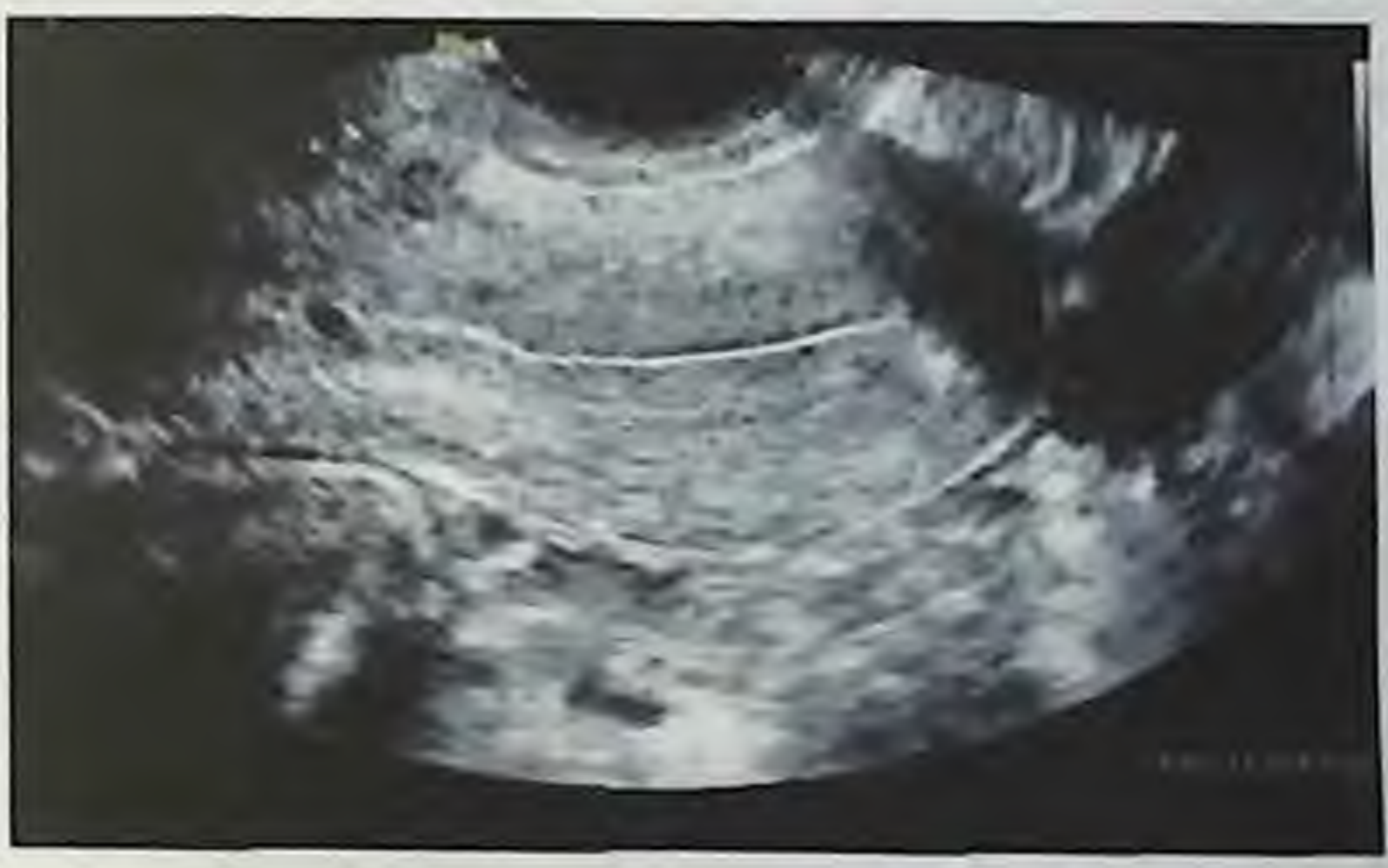

Fig.3.4 *Ultrasound picture of endometrial hyperplasia*

Among patients with AUB, every third -45 (36±4.4%) ultrasound revealed various types of uterine fibroids.Identified variants of uterinc myomas were distributed according toFIGO classification (Table 3.4).The frequency of fibroids did not differ by groups, except that the intramural variant of fibroids was significantly more often diagnosed by ultrasound in patients of group II - 11 (12.2 ± 5.1%) versus 8 (22.9 ± 7.1%) in group I , R<0.05.

At the same time, the size of the largest node is 31 mm in diameter, the average size of the myoma node in both groups was 17.0 (12.0-20.0) mm.

The features of the ultrasound picture of the myometrium were also studied (Fig. 3.5).

The structure of myometrial pathology according to ultrasound data is presented in Table 3.7. As can be seen from the table, the most common pathology of the myometrium was represented by uterine fibroids.45(36±4.4%) among patients with AUB against2(5.0±3.4%) in control, p<0.001. The second identified pathology in terms of frequency was adenomyosis - 34(27.2±4%) versus 4(10.0±4.7%) in the control, p<0.001. 9 patients had a combination of uterine fibroids and adenomyosis. In addition, it should be noted that only every third patient with AUB in perimenopause was not diagnosed with myometrial pathology - 37 (29.6±4.1%), while in the control group there was an overwhelming majority of them -34(85±5.6%),p<0.001.

Table 3.5

Distribution of patients with fibroids according to the FIGO classification,M±m

Types of fibroids	I group n=90	II group, n=35	main group, n=125
0 type- submucosal myomatous node on the leg	1(1.1±1.1%)	-	1(0.8±0.8%)
1type- submucosal-intramural uterine fibroids (<50%)	2(2.2±1.6%)	1(2.9±2.8%)	3(2.4±1.4%)
2type- submucosal-intramural uterine fibroids (≥50%)	-	1(2.9±2.8%)	1(0.8±0.8%)
3type-submucosal-intramural uterine myoma (100%)	-	-	
4type- intramural uterine fibroids	11(12.2±5.1%)	8(22.9±7.1%)*	19(3.6±0.8%)
5type-subserous intramural uterine fibroids (>50%)	9(10±3.2%)	2(5.7±3.9%)	11(8.8±2.5%)
6type- subserous-intramural uterine fibroids (<50%)	6(6.7±2.6%)		6(4.8±1.9%)
7type- subserous uterine fibroids on the leg	4(4.4±2.2%)	-	4(3.2±1.6%)
Total	33(36.7±5.1%)	12(34.3±8.0%)	45(36±4.4%)

Note * - p <0.05 significance of differences between groups I and II

Table 3.6

Frequency of echographic signs of myometrium pathology, M±m

The frequency and nature of the pathology of the myometrium	I group n=90	II group, n=35	main group, n=125	Control, n=40
Myoma	33(36.7±5.1%)	12(34.3±8.0%)	45(36±4.4%)	2(5.0±3.4%)^^
Internal endometriosis	25(27.8±4.7%)	9(25.7±7.4%)	34(27.2±4%)	4(10.0±4.7%)^^
Combination of uterine fibroids and internal endometriosis	6(6.7±2.6%)	3(8.6±4.7%)	9(1.7±0.6%)	-
Number of patients without visual pathology of the myometrium	26(28.9±4.8%)	11(31.4±7.8%)*	37(29.6±4.1%)	34(85±5.6%)^^

Note:

*-R <0.05 significance of differences between groups I and II

^^-R <0.001 significance of differences between the main group and control

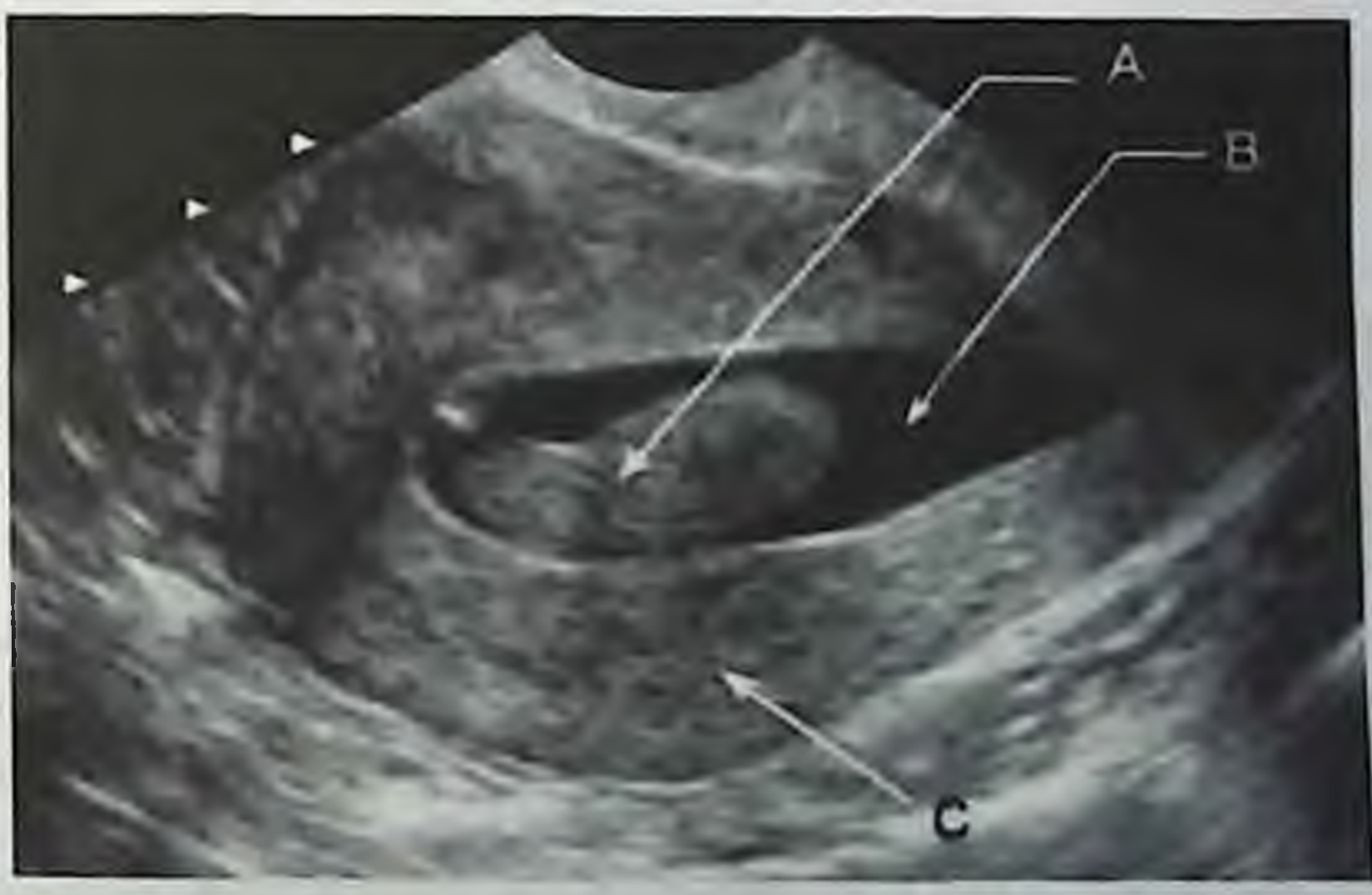

Fig. 3.5 *Ultrasound picture of the endometrial polyp*

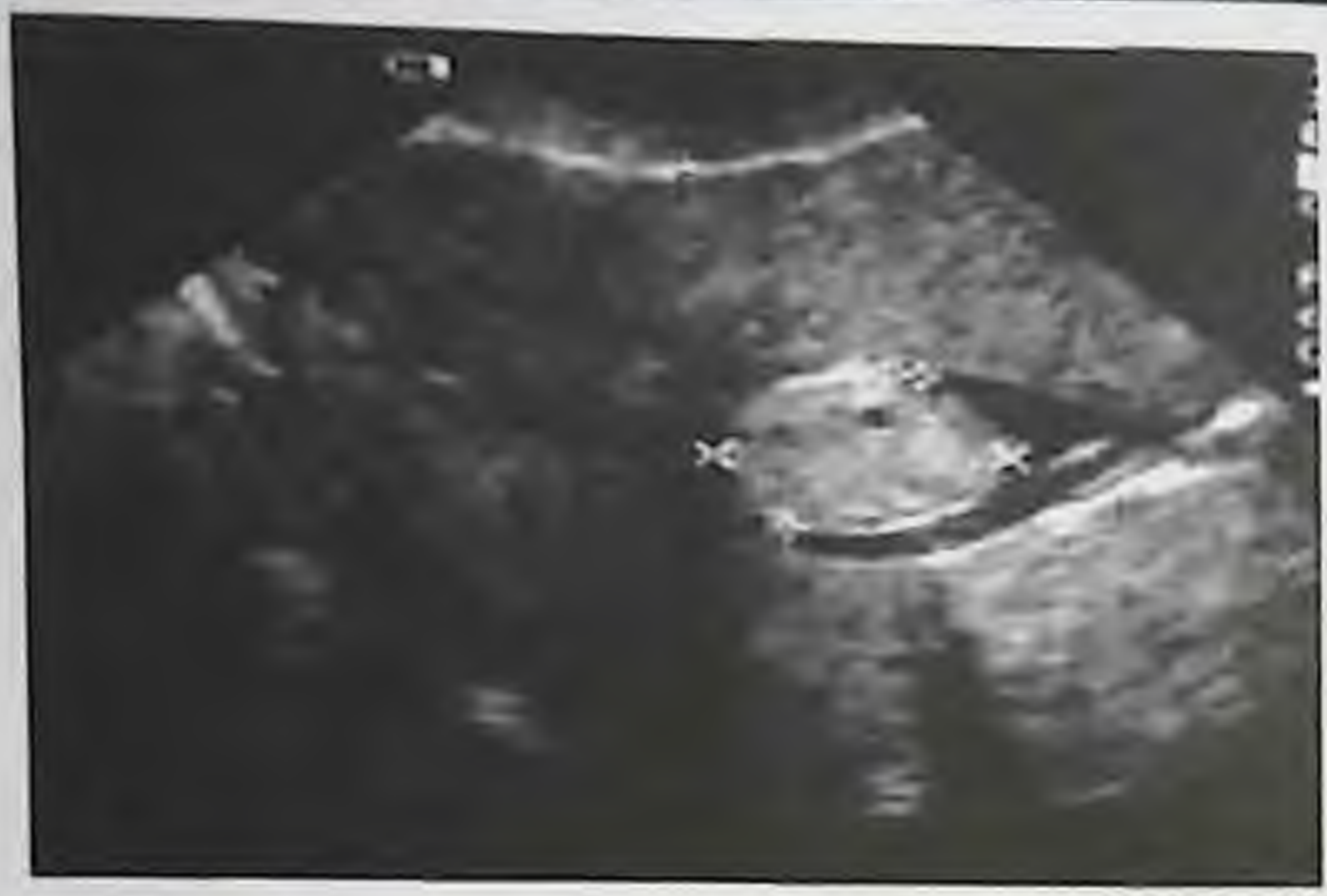

Fig. 3.5 *Ultrasound picture of submucosal myomatous node*

So, when comparing the results of ultrasound in the two groups, there is a statistically significant difference in both the structure of the myometrium and the endometrium.

Hysteroscopic characterization of the endometrium in patients with abnormal uterine bleeding

One of the main methods for studying patients with AUB was hysteroscopy (HSC) and diagnostic curettage of the uterine cavity, in the absence of bleeding, separate curettage of the uterine cavity.

Patients who were admitted to the hospital for urgent indications with AUB, for the purpose of hemostasis, were carried out therapeutic and diagnostic curettage of the uterine cavity on an urgent basis, taking into account contraindications to diagnostic HSC. Hysteroscopy with separate curettage of the uterine cavity was performed in 111 (88.8±2.8%) patients of the main group, 85 (94.4±2.4%) patients of group I and in 26 (74.2±7.4%) patients Group II.

Thickening and swelling of the mucous membrane of a pale pink color in the form of numerous folds of various heights, in the form of polypoid growths, the presence of a large number of gland ducts, undulating movement of the endometrium with a change in the rate of fluid flow into the uterine cavity (the "underwater plants" phenomenon) were detected only in 32 (28.8±4.3%) patients of the main groups. The low frequency of detection of hysteroscopic signs of endometrial

hyperplasia is due to the fact that 61 (71.8 ± 4.9%) and 18 (69 ± 9.0%) patients of groups I and II, respectively, underwent hysteroscopy in the presence of blood discharge of various duration and intensity. In this regard, in most cases, 79 (71.1 ± 4.3%) hysteroscopic picture was characterized by the presence of a thin pale endometrium with small hemorrhages in separate areas,

Table 3.7

Hysteroscopic signs of uterine cavity pathology, M±m

Hysteroscopic signs	I group n=85	II group, n=26	Number of patients undergoing hysteroscopy and curettage n=111
Criteria for endometrial hyperplasia	18(21.1±4.4%)	6(23.0±8.2%)	24(21.6±3.9%)
"underwater plants	10(11.7±3.5%)	4(15.4±7.0%)	14(12.6±3.1%)
polypoid growths	8(9.4±2.3%)	2(7.6±5.2%)	10(9.0±2.7%)
Combination of endometrial hyperplasia with endometrial polyp	4(4.7±2.3%)	2(7.6±5.2%)	6(5.4±2.1%)
Endometrial polyp + fragments of unrejected endometrium	2(2.35±1.6%)		2(1.8±1.3%)
No hysteroscopic signs were found	61(71.8±4.9%)	18(69±9.0%)	79(71.1±4.3%)

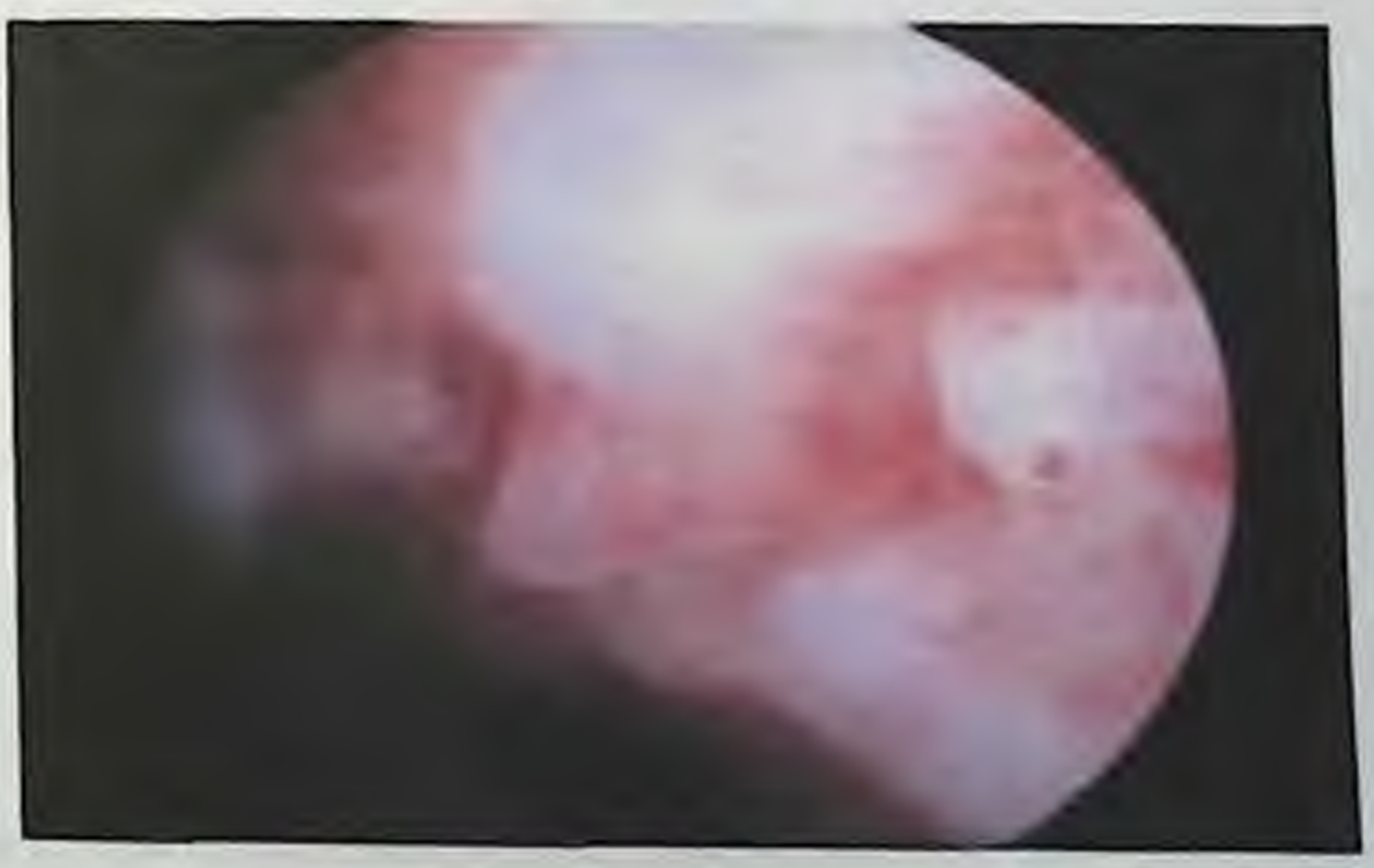

Fig.3.7 *Hysteroscopic picture of endometrial hypertrophy*

Fig.3.8 *Hysteroscopic picture of the endometrial polyp*

3.4. Histological structure of the endometrium in women with abnormal uterine bleeding during perimenopause

As you know, uterine bleeding is a syndromic diagnosis, the cause of which can be a large number of different diseases. In the period of perimenopause, which is a critical period in terms of the occurrence of various neoplasms, with abnormal uterine bleeding, along with ultrasound, a morphological study of the uterine mucosa is mandatory.

All patients with endometrial hypertrophy 111 (88.8 ± 2.8%) underwent a morphological study of scrapings (Table 3.6). The exception was 14(11.2±2.8%)in which the ultrasound diagnosed endometrial thickness from 1 to 4 mm.

Table 3.8

Histological structure of the endometrium in women with abnormal uterine bleeding during perimenopause

Structure of the endometrium	I group n=85	II group, n=26	main group, n=111
Glandular hyperplasia of the endometrium	32(37.6±5.2%)	5(19.2±7.7%) *	37(33.3±4.5%)
Glandular hyperplasia of the endometrium and submucosal myomatous node	3(3.5±2.0%)	2(7.6±5.2%)	5(4.5±1.9%)
Glandular cystic hyperplasia	9(10.6±3.3%)	2(7.6±5.2%)	11(9.9±2.8%)
Endometrial polyps	41(48.2±5.4%)	10(38.4±9.5%)	51(45.9±4.7%)
Atypical endometrial hyperplasia	-	6(23.0±8.2%)	6(5.4±2.1%)
endometrial cancer	-	1(3.8±3.7%)	1(0.9±0.9%)

Note:

*-R <0.05 significance of differences between groups I and II

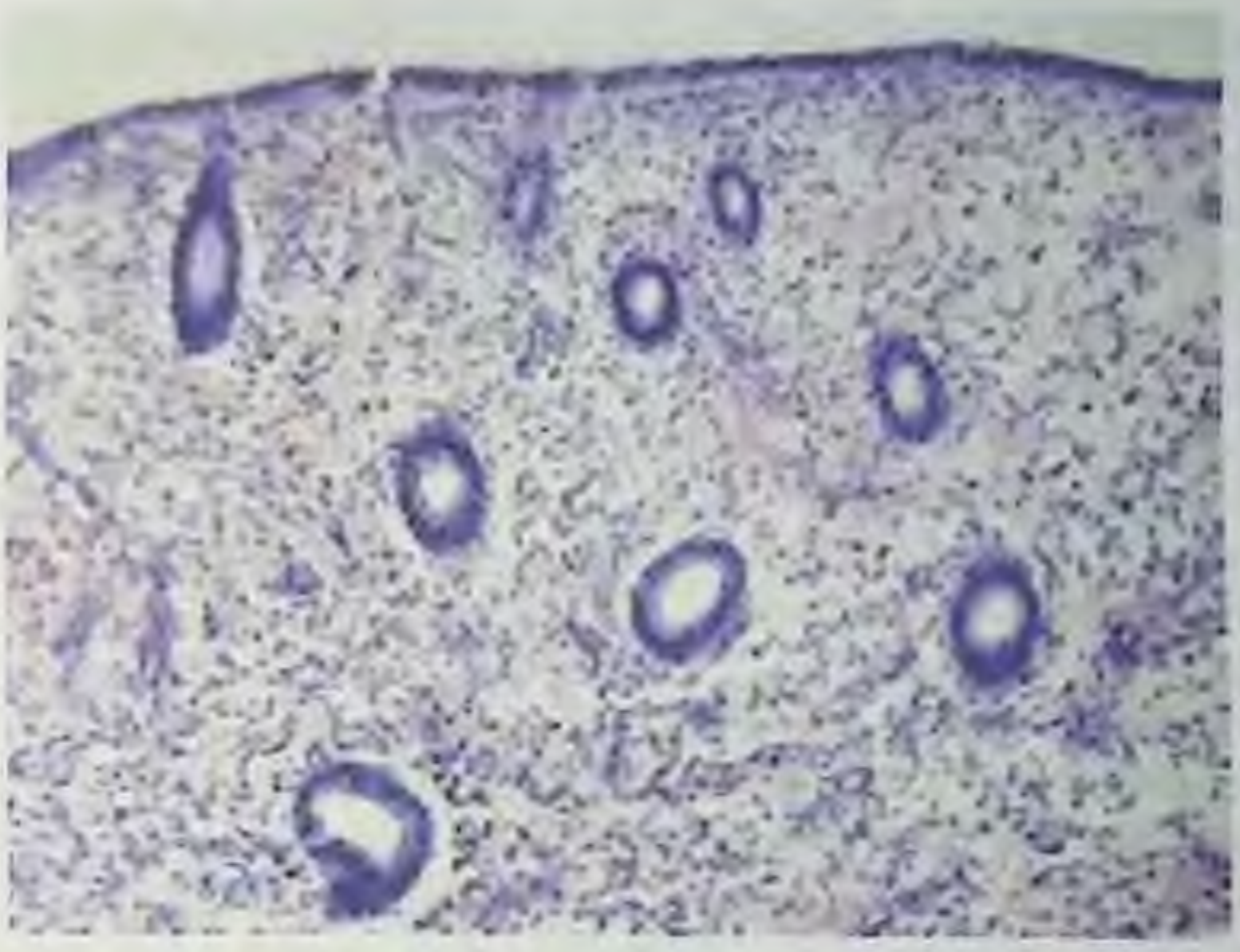

Fig. 3.9 *Glandular cystic endometrial hyperplasia*

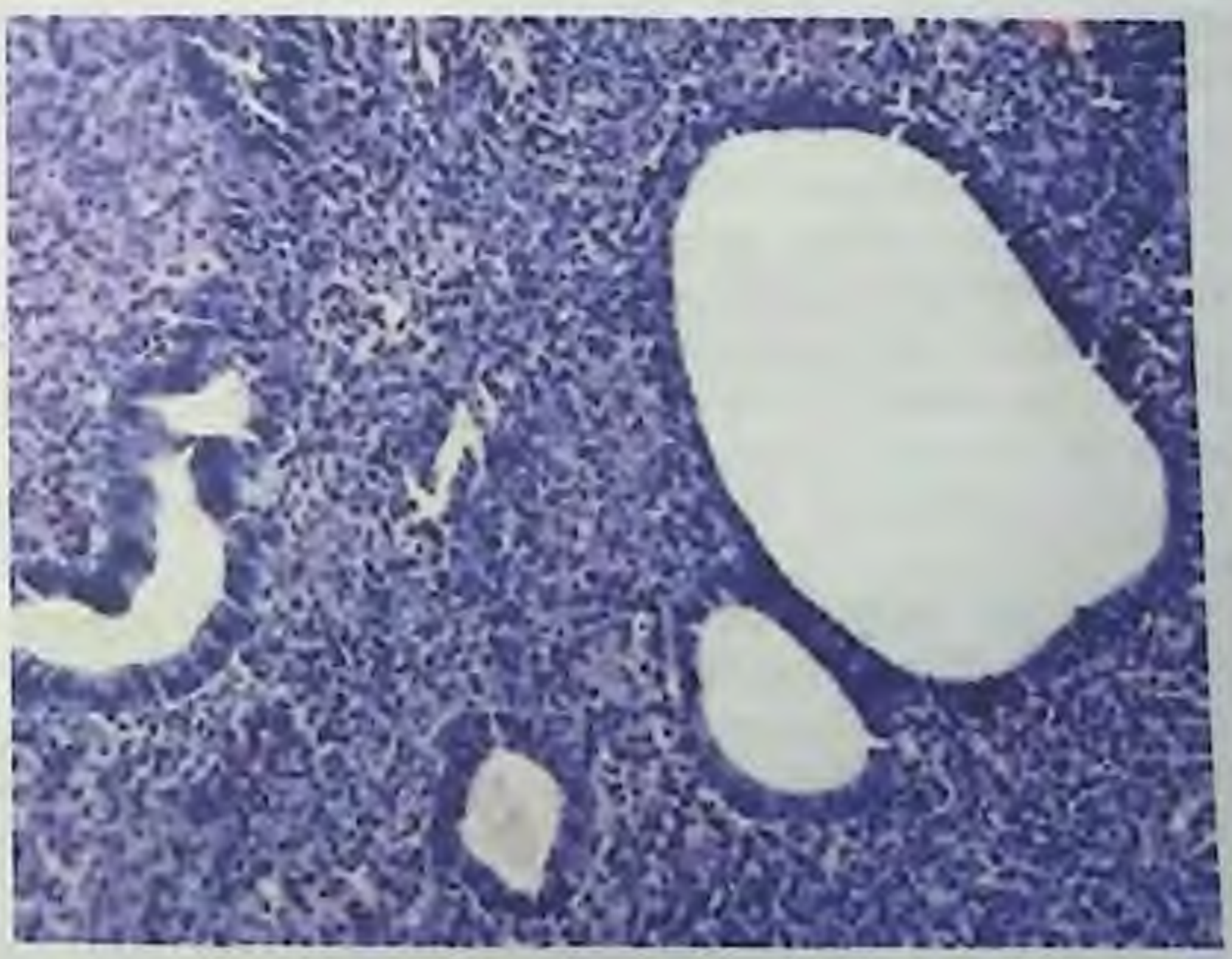

Fig. 3.10 *Glandular hyperplasia of the endometrium*

According to the histological examination of group I, 32 (37.6±5.2%) diagnosed with glandular hyperplasia of the endometrium, in 3 (3.5±2.0%) patients, glandular hyperplasia of the endometrium was combined with a submucosal myomatous node, in9(10.6±3.3%)-glandular-cystic hyperplasia of the endometrium, endometrial polyps - in 41 (48.2±5.4%) patients.

According to the histological examination of group II scrapings in5(19.2±7.7%) diagnosed with endometrial glandular hyperplasia, 2 (7.6±5.2%)glandular cystic hyperplasia, polyps in 10(38.4±9.5%), y 2(7.6±5.2%)patients against the background of glandular hyperplasia of the endometrium, a submucosal myomatous node was found, atypical hyperplasia of the endometrium in6(23.0±8.2%)and endometrial cancer in1(3.8±3.7%) sick.

Thus, histological examination of endometrial scrapings in patients with abnormal uterine bleeding in the group with recurrent AUB verified atypical endometrial hyperplasia 6(23.0±8.2%) and in one patient, endometrial cancer was detected, while in patients of group I, atypical endometrial hyperplasia and endometrial cancer were not detected.

Analysis of the results of histology of the endometrium, depending on the data of the ultrasound structure of the myometrium of patients with AUB, showed a combination of endometrial glandular hyperplasia (GEH) with endometrial myoma in9(7.2±0.6%), also with adenomyosis 9(7.2±0.6%), combination with adenomyosis and myoma4(3.2±1.6%), FHPE without myometrial pathology 15(12.0±2.9%) and5 (4.0±1.8%) patients with FHP were combined with a submucosal myomatous nodule.

Glandular cystic hyperplasia of the endometrium (ECHPE) was combined with pathologies of the myometrium in11(8.8±2.5%)cases, of which with uterine myoma in6(4.8±1.9%), with adenomyosis in 2(1.6±1.9%), combination with myoma and adenomyosisat3(2.4±1.4%) patients.

Endometrial polyps (PE) were associated with myometrial pathology in34(27.2±3.9) patients, of which 19(15.2±3.2%) had PE combined with uterine myoma, 13(10.4±2.7%) had adenomyosis, 2(1.6±1.9%) was associated with uterine myoma and adenomyosis. Endometrial polyps without myometrial pathology occurred in 17 (13.6±0.8%) cases.

Table 3.9

Analysis of the results of endometrial histology depending on the data of the ultrasonic structure of the myometrium of patients with AUB,

Structure endometrium n=125 / The structure of the myometrium n=125	Myoma	Adenomyosis	Myoma in combination with adenomyosis	No myometrial pathology	Total
Glandular hyperplasia of the endometrium	9(7.2±0.6%)	9(7.2±0.6%)	4(3.2±1.6%)	15(12.0±2.9%)	37(25.6±8.4%)
Glandular hyperplasia of the endometrium and submucosal myomatous node	5(4.0±1.8%)	-	-	-	5(4±1.8%)
Glandular cystic hyperplasia	6(4.8±1.9%)	2(1.6±1.9%)	3(2.4±1.4%)	-	11(8.8±2.5%)
Endometrial polyps	19(15.2±3.2%)	13(10.4±2.7%)	2(1.6±1.9%)	17(13.6±0.8%)	51(40.8±4.4)
Atypical endometrial hyperplasia	2(1.6±1.9%)	-	-	4(3.2±1.6%)	6(4.8±1.9%)
endometrial cancer	-	-	-	1(0.8±0.8%)	1(0.8±0.8%)
Patients who have not undergone curettage	4(3.2±1.6%)	10(8.0±2.4%)			fourteen(11.2± 2.8%)
Total	45	34	9	37	125

Atypical endometrial hyperplasia (AGE) was associated with uterine myoma in2(1.6±1.9%) cases, in 4 (3.2±1.6%) patients AHE was not combined with myometrial pathology.

In patients who have not undergone curettage (fourteen(11.2±2.8%)) uterine myoma was found in 4 (3.2±1.6%) and adenomyosis in10(8.0±2.4%.

Thus, the analysis of complaints of patients with AUB, gynecological status, ultrasound data, hysteroscopy data and histological examination of scrapings showed that the selected groups are comparable in terms of the following indicators, almost half of the patients with AUB complained of heavy and prolonged uterine bleeding and eight times more often indicated pain in the lower abdomen compared with the control group;

- pathological changes in the cervix were significantly more common in patients with AUB compared with the control group, and chronic cervicitis was significantly more common in patients with recurrent AUB in30 (85.7%) than in group I 53 (58.9%) patients
- Bimanual examination showed that none of the patients with AUB had normal uterine dimensions. Whereas, in the control group, the size of the uterus corresponded to 5-6 weeks of pregnancy in only two women. Sizes corresponding to 7-8 and 9-10 weeks of pregnancy were not observed in the control;
- at ultrasound examination of the thickness of the endometrium in patients with AUB, thin endometrium was significantly more often observed in the group with recurrent AUB in 9 (25.7%) of patients than in group I in 5(5.5%) of patients;
- hysteromyoma was found in every third patient with AUB during ultrasound examination. The intramural type of fibroids was significantly more common in patients with AUB relapses in8 (22.9%);
- hysteroscopy with curettage of the uterine cavity was performed in 111 (88.8%) patients with AUB, and hysteroscopy was not performed in 14 (11.2%) patients with thin endometrium;
- histological examination of endometrial scrapings in patients with relapses of AUB verified such patterns as atypical endometrial hyperplasia and endometrial cancer was detected in one patient, while atypical endometrial hyperplasia and endometrial cancer were not detected in group I patients.

CHAPTER 4

MOLECULAR GENETIC FEATURES IN PATIENTS WITH ABNORMAL UTERINE BLEEDING DURING THE PERIMENOPAUSE

Abnormal uterine bleeding is known to be a widespread and rather debilitating condition for women. The causal factors in the development of AUB are multiple and varied, but the mechanisms of their development, in particular, the relationship with molecular genetic factors, remains not fully understood. An integrated approach to the study of this problem will provide an opportunity to discover and understand new aspects of the mechanisms of development of AUB, which will contribute to an individualized approach to managing patients, increasing the effectiveness of treatment and improving their quality of life without the use of potentially complex surgical interventions [61,115,122].

As is known, at present, an important direction of modern research in the field of preventive medicine is the determination of the risk of developing pathology based on the search for significant molecular genetic predictors.

In this regard, in this chapter of the dissertation the results are given:

1) studying the frequency distribution of alleles and genotypespolymorphism rs1042522 of the TP53-72 (Arg72Pro) gene.

2) study of rs17576 gene MMP9 (Gln279Arg)in patients with AUB and conditionally healthy female donors.

To analyze the distribution of frequencies of alleles and genotypes of polymorphisms in the study group, their distribution by the studied polymorphic loci was checked for compliance with RHB using Fisher's exact test. The sample group included 95 apparently healthy female donors, which constituted the control group. As well as 90 patients with AUB, which are divided into two groups: group I - patients with AUB, n=55 and group II - patients with relapses of AUB, n=35.

Features of the distribution of allelic and genotypic frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in women withabnormal uterine bleedingduring perimenopause

For variational estimation of the frequency of genotypes of the studied polymorphismrs1042522 gene TP53-72 (Arg72Pro)we conducted an analysis for compliance with the expected (Hexp) and observable

(Hobs) the frequencies of their distribution in the groups of patients with AUB and control, in accordance with the Hardy-Weinberg equilibrium (RHV,p>0.05).

In the main group of patients with AUBexpected(Hexp) and observables (Hobs)genotype frequenciesArg/Arg,Arg/Pro and Pro/Propolymorphismrs1042522 gene TP53-72 (Arg72Pro)were 0.14 and 0.14 ($\chi2$=0.02); 0.47 and 0.46 ($\chi2$=0.03); 0.39 and 0.4 ($\chi2$=0.01), respectively, with an unreliable difference in the results (p=0.81).

In the control groupexpected(Hexp) and observables (Hobs)frequencies of Arg/Arg, Arg/Pro and Pro/Pro polymorphism genotypesrs1042522 gene TP53-72 (Arg72Pro)corresponded to the values of 0.13 and 0.14 ($\chi2$=0.02); 0.46 and 0.45 ($\chi2$=0.02); 0.41 and 0.41 ($\chi2$=0.01), respectively, also with an unreliable difference in the results obtained (p=0.83).

Andindex of heterozygosity for the observed (Hobs) and expected (Hexp) indicators in the main group of patients with AUB according to the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro)practically did not differ from those in the control group(0.46 and 0.47 vs. 0.45 and 0.46, respectively;D was 0.02 and 0.02).

A similar pattern was observed forexpected (Hexp) and observables (Hobs)frequencies of the Arg/Arg, Arg/Pro and Pro/Pro genotypes of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) in groups I and II of patients.

In particular, in group I in patients they had values of 0.18 and 0.20 ($\chi2$=0.09); 0.49 and 0.45 ($\chi2$=0.14); 0.33 and 0.35 ($\chi2$=0.05) with a non-significant difference (p=0.6), while in group II of patients with AUB relapses they had values of 0.08 and 0.06 ($\chi2$=0.26); 0.41 and 0.46 ($\chi2$=0.21); 0.51 and 0.49 ($\chi2$=0.04) with a difference equal to p=0.48.

Values andindex of heterozygosity for the observed (Hobs) and expected (Hexp) indicators in group I of patients with AUB according to polymorphismrs1042522 of the TP53-72 gene (Arg72Pro) in relation to the control was0.45 and 0.49 vs. 0.45 and 0.46, respectively (D was 0.09 and 0.02). In group II of patients with AUB relapses, these indicatorsin relation to control amounted to0.46 and 0.41 (D=-0.11) versus 0.45 and 0.46 (D=0.02), respectively.

Between groups I and II, these indicators were 0.45 and 0.49 versus 0.46 and 0.41 with a heterozygosity deviation (D) of 0.09 and -0.11, respectively.

Our analysis of the distribution of frequencies of alleles and genotypespolymorphic variant rs1042522 of the TP53-72 gene (Arg72Pro) in the group of conditionally healthy donors (control)made it possible to establish the following facts: the frequency of the Arg allele was 36.3%, and the Pro allele was 63.7% of the case. At the same time, the carriage of the homozygous Arg/Arg genotype was determined in 13.7% (n=13), the heterozygous Arg/Pro genotype in 45.3% (n=43), and the homozygous Pro/Pro in 41% (n=39) cases (Table 15.).

The study of the frequency distribution of alleles and genotypes of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) showed that in the main group the frequency of the Arg allele was 37.2% (n=67), and the Pro allele was 62.8% (n=113) . Along with this, in the study group of patients, the frequency of carriage of the homozygous genotype Arg/Arg was equal to 14.4% (n=13), the heterozygous genotype Arg/Pro– 45.6% (n=41), and the homozygous mutant genotype Pro/Pro – 40% (n=36).

Table 4.1

Frequency distribution of alleles and genotypes of polymorphism rs1042522 gene TP53-72 (Arg72Pro) in patients with AUB

Group	n	Allele frequency				Frequency distribution of genotypes					
		Arg		Pro		Arg/Arg		Arg/Pro		Pro/Pro	
		n	%	n	%	n	%	n	%	n	%
Main group	90	67	37.2	113	62.8	13	14.4	41	45.6	36	40.0
I - group	55	47	42.7	63	57.3	eleven	20.0	25	45.5	19	34.5
II - group	35	twenty	28.6	fifty	71.4	2	5.7	16	45.7	17	48.6
Control	95	69	36.3	121	63.7	13	13.7	43	45.3	39	41.0

In addition, we conducted a comparative analysis of the frequencies of alleles and genotypes in both groups of patients with AUB.

The results of the assessment of the distribution of frequencies of alleles and genotypes of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) show that in the main group the proportion of allelesArgand Pro practically corresponded to those in the control group ($\chi2$=0.03; p=0.9; OR=1.0;95%CI:0.6-1.5).

With regard to the distribution of genotypes, a similar pattern was also observed: Arg/Arg ($\chi2$=0.02; p=0.9; OR=1.1; 95% CI: 0.46-2.4), Arg/Pro ($\chi2$= 0.002; p=0.97; OR=1.0; 95%CI:0.6-1.8) and Pro/Pro($\chi2$=0.02; p=0.9; OR=1.0; 95% ARGLNI: 0.5-1.7).These data indicate no differences in the distribution of allele and genotype frequencies of the rs1042522 polymorphism of the TP53-72 (Arg72Pro) gene between the main group and conditionally healthy donors (Table 16.).

Table 4.2

Analysis of the difference in the distribution of frequencies of alleles and genotypes of the rs17576 polymorphism of the TP53 gene (Gln279Arg) between the main group of patients with AUB and the control group

Alleles and genotypes	Main group, n=90		Control, n=95		$\chi2$	R	OR	95%CI
	n	%	n	%				
Arg	67	37.2	69	36.3	0.03	0.9	1.0	0.6-1.5
Pro	113	62.8	121	63.7				
Arg/Arg	13	14.4	13	13.7	0.02	0.9	1.1	0.5-2.4
Arg/Pro	41	45.6	43	45.3	0.002	0.97	1.0	0.6-1.8
Pro/Pro	36	40	39	41	0.02	0.9	1.0	0.5-1.7

An assessment of the distribution of allele and genotype frequencies of the studied genetic polymorphism in groups I and II also made it possible to establish the absence of differences in relation to the indicators in the control: in group I, the allele frequencyArg and Pro($\chi2$=0.21; p=0.3; OR=0.8;95% CI: 0.5-1.2), Arg/Arg genotype frequency($\chi2$=1.03; p=0.3; OR=1.6;95% CI: 0.6-3.8), Arg/Pro($\chi2$=0.001; p=0.98; OR=1.0;95% CI: 0.5-1.9) and Pro/Pro($\chi2$=0.6; p=0.4; OR=0.8;95% CI: 0.4-1.5) (Table 17.).

Table 4.3

Analysis of the difference in the distribution of allele and genotype frequencies of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) between the I group and the control group

Alleles and genotypes	Group I n=55		Control, n=95		χ2	R	OR	95%CI
	n	%	n	%				
Arg	47	42.7	69	36.3	1.21	0.3	0.8	0.5-1.2
Pro	63	57.3	121	63.7				
Arg/Arg	eleven	20.0	13	13.7	1.03	0.3	1.6	0.6- 3.8
Arg/Pro	25	45.5	43	45.3	0.001	0.98	1.0	0.5-1.9
Pro/Pro	19	34.5	39	41.0	0.62	0.4	0.8	0.4-1.5

When evaluating the results in the distribution of allele and genotype frequencies between groups I and II of patients with AUB, we did not establish significant differences in the distribution of both Arg and Pro alleles (χ2=3.67; p=0.1; OR=0.5;95% CI: 0.28-1.02), and Pro/Pro genotypes (χ2=3.53; p=0.1; OR=4.1;95% CI: 0.86-19.9), Arg/Pro (χ2=0.001; p=0.98; OR=1.0;95% CI: 0.4-2,3) and Pro/Pro(χ2=1.8; p=0.2; OR=0.6;95% CI: 0.2-1.3) (Table 18).

Table 4.4

Analysis of differences in the distribution of allele and genotype frequencies of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) in patients with AUB

Alleles and genotypes	II group n=35		Control, n=95		χ2	R	OR	95%CI
	n	%	n	%				
Arg	twenty	28.6	69	36.3	1.36	0.2	1.4	0.8- 2.6
Pro	fifty	71.4	121	63.7				
Arg/Arg	2	5.7	13	13.7	1.59	0.2	0.4	0.1-1.8
Arg/Pro	16	45.7	43	45.3	0.002	0.96	1.0	0.5-2.2
Pro/Pro	17	48.6	39	41.0	0.59	0.4	1.4	0.6-2.9

Thus, the obtained results confirm the absence of a significantly significant association between the carriage of the Arg and Pro alleles, as well as the Arg/Arg, Arg/Pro and Pro/Pro genotypes of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) with the development of AUB.

The results obtained can be explainedthe fact that the rs1042522 polymorphism of the TP53-72 (Arg72Pro) gene, apparently, is not a

driver mutation in the development of AUB. In addition, the relationship of this polymorphism between patients of both groups was not revealed.

In this regard, a change in one gene encoding a particular factor may not affect the entire system as a whole, however, a change in two or more genes can radically change the systemic process and cause pathology. Therefore, when studying the association of genetic polymorphisms with the development of pathology, it is advisable to evaluate the influence of not one, but several genes.

Features of the distribution of allelic and genotypic frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in patients withabnormal uterine bleedingduring perimenopause

We also studied the comparative results of the study of the distribution of the proportion of alleles and genotypes of the polymorphism of the rs17576 gene of the MMP9 gene (Gln279Arg) in groups of conditionally healthy donors and patients with AUB.

Analysis for compliance with the expected (Hexp) and observable (Hobs) distribution frequencies of genotypic variants of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) showed compliance with the Hardy-Weinberg equilibrium (HWB,$p>0.05$). In particular,patients with AUBexpected (Hexp) and observables (Hobs)genotype frequenciesGln/Gln,Gln/Arg and Arg/Arg of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) were 0.296 and 0.2 ($\chi2=0.004$); 0.497 and 0.46 ($\chi2=0.01$); 0.208 and 0.211 ($\chi2=0.01$), respectively, with an unreliable difference in the results ($p=0.89$).

In the control groupexpected (Hexp) and observables (Hobs)frequencies of Gln/Gln, Gln/Arg genotypes andArg/Argpolymorphism rs17576 of the MMP9 gene (Gln279Arg) corresponded to the valucs of 0.47 and 0.46 ($\chi2=0.01$); 0.43 and 0.44 ($\chi2=0.02$); 0.1 and 0.09 ($\chi2=0.02$), respectively, also with an unreliable difference in the results obtained ($p=0.82$).

Andindex of heterozygosity for the observed (Hobs) and expected (Hexp) indicators in the main group of patients with AUB according to polymorphismrs17576 of the MMP9 gene (Gln279Arg) corresponded to the values0.49 and 0.50 (D was 0.02) versus 0.44 and 0.43 in the control (D was -0.02).

In groups I and II of patients with AUB, the analysisexpected (Hexp) and observables (Hobs)Gln genotype frequencies/Gln, Gln/Arg and

Arg/Arg of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) showed the following:

- in group I, they had values of 0.37 and 0.42 ($\chi2$=0.33); 0.48 and 0.38 ($\chi2$=1.03); 0.15 and 0.20 ($\chi2$=0.80) with insignificant difference (p=0.14);

- in group IIHexpandHobsthe frequencies of the studied genotypes corresponded to the values of 0.20 and 0.11 ($\chi2$=1.2); 0.49 and 0.66 ($\chi2$=1.9); 0.31 and 0.23 ($\chi2$=0.76) with a difference of p=0.05.

Andindex of heterozygosity for the observed (Hobs) and expected (Hexp) indicators in group I by polymorphismrs17576 of the MMP9 gene (Gln279Arg) matched0.38 and 0.48 versus 0.44 and 0.43 in the control group, while the deviation of heterozygosityD was 0.26 and -0.02, respectively, for the studied groups. At the same time, in group II, these indicatorsamounted to0.66 and 0.49 (D=-0.26) versus 0.44 and 0.43 (D=-0.02) in the control.

Between groups I and II, these indicators were 0.38 and 0.48 versus 0.66 and 0.49 with a heterozygosity deviation (D) of 0.26 and -0.26, respectively.

Taking into account the absence of deviations from the Hardy-Weinberg equilibrium in the analysis of the expected (Hexp) and observed (Hobs) frequencies of the distribution of genotypic variants of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in the studied groups, we studied the distribution of allele and genotype frequenciespolymorphic variant rs17576 of the MMP9 gene (Gln279Arg).

In the control group, the proportion of occurrence of the Gln allele was 68.4% (n=130), and the Arg allele was 31.6% (n=60). At the same time, the share of homozygous genotype Gln/Gln was 46.3% (n=44), heterozygous genotype (Gln/Arg) - 44.2% (n=42). At the same time, it should be noted that, as in relation to the studied polymorphism rs1042522 of the TP53-72 (Arg72Pro) gene, in this case, the presence of a mutant homozygous genotype (Arg/Arg) was also determined, which was registered in 9.5% (n=9) of individuals (Table 19).

Analysis of the distribution of the proportion of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in the main group showed that the Gln allele was registered in 54.4% (n=98), and the Arg allele in 45.6% (n=82) cases. Meanwhile, the carriage of the homozygous genotype Gln/Gln was registered in 30% (n=27),

heterozygous Gln/Arg genotype in 48.8% (n=44), and homozygous Arg/Arg mutant genotype in 21.1% (n=19) cases.

Table 4.5

Frequency distribution of alleles and genotypes of polymorphism rs17576 of the MMP9 gene (Gln279Arg)

Groups	n	Allele frequency				Frequency distribution of genotypes					
		Gln		Arg		Gln/Gln		Gln/Arg		Arg/Arg	
		n	%	n	%	n	%	n	%	n	%
Main group	90	98	54.4	82	45.6	27	30.0	44	48.9	19	21.1
I - group	55	67	60.9	43	39.1	23	41.8	21	38.2	eleven	20.0
II - group	35	31	44.3	39	55.7	four	11.4	23	65.7	eight	22.9
Control	95	130	68.4	60	31.6	44	46.3	42	44.2	9	9.5

Along with this, it seemed interesting to us to conduct a comparative analysis of the distribution of allele and genotype frequencies in groups I and II of patients with AUB. In patients with AUB in group I, the share of the Gln allele was 60.9% (n=67), the Arg allele was 39.1% (n=43). Homozygous Gln genotype/Gln was determined in 41.8% (n=23) cases, while heterozygous Gln/Arg and homozygous Arg/Arg genotypes were detected in 38.2% (n=21) and 20% (n=11) cases.

Some differences in the distribution of frequencies of alleles and genotypes were determined in group II of patients with recurrent AUB, the Gln allele was recorded in 44.3% (n=31), and the Arg allele in 55.7% (n=39) cases. Proportion of carriage of homozygous Gln/Gln genotype was 11.4% (n=4), heterozygous Gln/Arg genotype 65.7% (n=23), and homozygous Arg/Arg genotype 22.9% (n=8) cases.

A comparative assessment of the share of carriage of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) made it possible to establish that in the main group the proportion of alleles Gln andArgalmost two times significantly higher than the share of such indicators in the control group ($\chi2$=7.63; p=0.01; OR=1.8;95%CI: 1.19-2.77).

A somewhat different picture was observed in relation to the distribution of the homozygous genotypeGln/Gln($\chi2$=5.202p=0.9; OR=0.5; 95% CI: 0.27-0.91) and heterozygous genotypeGln/Arg ($\chi2$=0.41; p=0.52; OR=1.2; 95% CI: 0.68-2.15). However, the occurrence of the mutant homozygous genotype Arg/Arg significantly prevailed in

patients with AUB compared to its proportion in the control.($\chi2$=4.87; p=0.03; OR=2.6; 95% CI: 1.09-6.0).

Thus, the data obtained indicate the presence of statistically significant differences in the distribution of allele frequenciesArgand mutant genotypeArg/Argrs17576 polymorphism of the MMP9 gene (Gln279Arg) between the main group of patients and without indication of menstrual dysfunction, which in turn allows us to identify this allele and genotype as genetic factors predisposing to an increased risk of developing AUB in perimenopausal women (Table 20).

Comparative assessment of the frequency distribution of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) carried out in group I of patients with AUB compared to those in the control group made it possible to establish the following facts: in group I, allele frequencies

gln andArgstatistically insignificantly differed from their shares in the control ($\chi2$=1.7; p=0.2; OR=1.4;95% CI: 0.85-2.27), genotype frequenciesGln/Gln ($\chi2$=0.3; p=0.6; OR=0.86;95% CI: 0.4-1.6),Gln/Arg ($\chi2$=0.5; p=0.5; OR=0.8;95% CI: 0.4-1.54) also did not differ statistically significantly from those in the control. However, it should be noted that the Arg genotype/arg,although not statistically significant, but still more than twice the values of the same genotype in the control group ($\chi2$=3.3; p=0.1; OR=2.4;95% CI: 0.9-6.2)(Table 21.).

Table 4.6

Analysis of the difference in the distribution of frequencies of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) between groups of patients with AUB and the control group

Alleles and genotypes	Main group, n=90		Control, n=95		χ2	R	OR	95%CI
	n	%	n	%				
Gln	98	54.4	130	68.4	7.63	0.01	1.8	1.2-2.8
Arg	82	45.6	60	31.6				
Gln/Gln	27	30.0	44	46.3	5.20	0.02	0.5	0.3-0.91
Gln/Arg	44	48.9	42	44.2	0.41	0.52	1.2	0.7-2.1
Arg/Arg	19	21.1	9	9.5	4.87	0.03	2.6	1.09- 6.0

Table 4.7

Analysis of the difference in the distribution of frequencies of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) between the I group and the control group

Alleles and genotypes	Group I n=55		Control, n=95		χ2	R	OR	95%CI
	n	%	n	%				
Gln	67	60.9	130	68.4	1.7	0.2	1.4	0.8-2.3
Arg	43	39.1	60	31.6				
Gln.Gln	23	41.8	44	46.3	0.3	0.6	0.8	0.4-1.6
Gln/Arg	21	38.2	42	44.2	0.5	0.5	0.8	0.4-1.5
Arg/Arg	elev en	20.0	9	9.5	3.3	0.1	2.4	0.9-6.2

A comparative analysis of the distribution of allele and genotype frequencies in the group of patients with AUB relapses revealed the opposite picture in relation to the above data in group I patients compared with the control. Namely, in group II, the allele frequencyArg statistically significantly exceeded its values in the control by 2.7 times($\chi2$=12.64; p=0.0004; OR=2.7;95% CI: 1.5-4.8).

Along with this, in comparison with the control, a significant difference in the frequency of occurrence of the heterozygous genotypeGln/Arg was 2.4 ($\chi2$=4.73; p=0.03; OR=2.4;95% CI: 1.1-5.4), and the homozygous genotype Arg/Arg- 2.8 times ($\chi2$=4.03; p=0.04; OR=2.8;95% CI: 1.0-8.1) (Table 21).

Table 4.8

Analysis of differences in the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg)

Alleles and genotypes	II group, n=35		Control, n=95		χ2	R	OR	95%CI
	n	%	n	%				
Gln	31	44.3	130	68.4	12.64	0.0004	2.7	1.5-4.8
Arg	39	55.7	60	31.6				
Gln/Gln	four	11.4	44	46.3	13.37	0.0003	0.1	0.05-0.5
Gln/Arg	23	65.7	42	44.2	4.73	0.03	2.4	1.1-5.4
Arg/Arg	eight	22.9	9	9.5	4.03	0.04	2.8	1.0-8.1

A comparative analysis carried out between groups I and II of patients with AUB made it possible to establish the absence of statistically significant differences in the distribution of allele and genotype frequencies: the frequency of the Arg allele ($\chi2$=4.77; p=0.03; OR=0.5;95% CI: 0.3-0.9), frequencies Gln/Arg($\chi2$=6.49; p=0.01; OR=0.3;95% CI: 0.1-0.8) and Arg/Arg($\chi2$=0.1; p=0.7; OR=0.8;95% CI: 0.3-2.4).

At the same time, significant differences between groups I and II were registered in relation to the proportion of carriers of the Gln genotype./Gln,which was 5.6 times more common in patients with AUB in group I ($\chi2$=9.41; p=0.002; OR=5.6;95% CI: 1.7-18.0)(Table 23).

Thus, in contrast to the data obtained in the study of the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) in relation to the results of the distribution of allele frequencies and genotypesrs17576 polymorphism of the MMP9 gene (Gln279Arg)statistically significant differences were established in comparison with the values in conditionully healthy donors.

Table 4.9

Analysis of differences in the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) between groups II and II

Alleles and genotypes	Group I n=55		II group, n=35		$\chi2$	R	OR	95%CI
	n	%	n	%				
Gln	67	60.9	31	44.3	4.77	0.03	0.5	0.3-0.9
Arg	43	39.1	39	55.7				
Gln/Gln	23	41.8	four	11.4	9.41	0.002	5.6	1.7-18.0
Gln/Arg	21	38.2	23	65.7	6.49	0.01	0.3	0.1-0.8
Arg/Arg	elev en	20.0	eigh t	22.9	0.10	0.7	0.8	0.3-2.4

In particular, in the main group of patients with AUB, an increase in the frequency of the alleleArgalmost twice and homozygous Arg/Arg genotype 2.6 times due to their levels in group II patients with recurrent AUB. These facts prove the role of the Arg allele and the homozygous Arg/Arg genotype of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in the risk of developing AUB in perimenopausal women.

Analysis of prognostic value and intergenic interactions of polymorphisms rs1042522 of the TP53-72 gene (Arg72Pro) and rs17576 of the MMP9 gene (Gln279Arg) in the risk of developing AUB in perimenopausal women

The study analyzed the predictive value of the studied polymorphic variants of genes in the risk of developing AUB in perimenopausal women of the Uzbek ethnic group.

To determine the predictive value of a genetic marker, sensitivity (SE), specificity (SP), and the likelihood of a patient being different from a healthy AUC polymorphism (Area Under ARGL Nurve) were calculated. The predictive value was determined as follows: the marker was considered a random classifier with AUC≤0.5, poor - 0.5<AUC<0.6, average - 0.6<AUC<0.7, good - 0.7<AUC< 0.8 and excellent - AUC>0.8.

The AUC estimate for the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) as an independent genetic marker of the risk of developing AUB was 0.4, and in groups I and II its values were 0.4 and 0.5. The obtained AUC values do not allow us to determine the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) as an independent prognostic marker for the development of AUB in perimenopausal women, because in patients, this polymorphism acts as a poor prognostic marker.

Determination (Area Under Curve) for the rs17576 polymorphism of the MMP9 gene (Gln279Arg), also heterozygous (Gln/Arg) and homozygous (Arg/Arg) genotypes at the risk of developing AUB in perimenopausal women, showed that in the main group AUC=60.3 in group I AUC=60.0 and in group II AUC=62.0. Thus, the MMP9 gene acts as a marker for the average AUC classifier. At the same time, this gene should be considered as an independent marker in the risk of developing AUB recurrence (Table 23).

Table 4.10

Indicators of diagnostic and prognostic efficiency of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in the risk of developing AUB in women

Study Groups	Genotypes	Prognostic Indicators					
		Se(sensitivity) % (95%AUC)	Sp(specificity) % (95%AUC)	AUC	OR (95%AUC)	χ2	P
main group, (n=90)	Gln/Arg	48.89 (38.2–59.7)	55.79 (45.2 - 66.0)	52.3	1.2 (0.68–2.15)	0.41	0.52
	Arg|Arg	63.89 (58.2–66.7)	55.79 (45.2 - 66.0)	60.3	2.4 (1.08–5.42)	2.8	0.05
Group I, (n=55)	Gln/Arg	38.18 (25.4–52.3)	55.79 (45.2 - 66.0)	47.0	0.8 (0.4–1.54)	0.5	0.5
	Arg\Arg	52.8 (29.6-55.7)	55.79 (45.2 - 66.0)	60.0	2.2 (1.08–5.42)	2.2	0.05
II group, (n=35)	Gln/Arg	65.71 (47.8–80.9)	55.79 (45.2 - 66.0)	60.8	2.4 (1.08–5.42)	4.73	0.03
	Arg\Arg	68.7(48.9-85.6)	55.79 (45.2 - 66.0)	62.0	2.6(1.2-6.02)	5.02	0.02

Thus, the determination of the AUC of polymorphisms rs1042522 of the TP53-72 gene (Arg72Pro) and rs17576 of the MMP9 gene (Gln279Arg) in the risk of developing AUB in perimenopausal women in the main group of patients with respect to the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) was less than 0.5, which indicates the absence of their predictive value in the risk of developing AUB in perimenopausal women, while the AUC for the rs17576 polymorphism of the MMP9 gene (Gln279Arg) was more than 60.0, which proves its significant role in the risk of developing AUB in perimenopausal women.

In this way,analysis of the results of the study of polymorphismrs17576 of the MMP9 gene (Gln279Arg)allowed to establish the presence of statistically significant differences in the main group of patients with AUB in comparison with the values in conditionally healthy donors, for allele frequenciesArg($\chi2$=7.63; p=0.01; OR=1.8; 95%CI: 1.19-2.77) and homozygous Arg/Arg genotype ($\chi2$=4.87; p=0.03; OR=2.6; 95%CI:1.09-6.0), which allows us to consider the Arg allele and the homozygous Arg/Arg genotype of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) as genetic factors predisposing to an increased risk of developing recurrent AUB in premenopausal women.

CHAPTER 5

THE CHOICE OF MANAGEMENT OF WOMEN WITH ABNORMAL UTERINE BLEEDING DURING THE PERIMENOPAUSE

Calculation of the prognostic coefficient depending on the risk factors for the development of abnormal uterine bleeding

We have calculated the prognostic coefficient (Table 24), respectively, of various indicators; somatic and genital pathology, data on oncological diseases in close relatives, menstrual function and detection of an unfavorable genotype in the MMP9 gene.

As can be seen from Table 5.1, the calculation of the prognostic coefficient was carried out according to statistical indicators such as the odds ratio (OR) and the risk of development (RR). PC in somatic diseases, early onset of menarche, in gynecological diseases and a history of operations, with an unfavorable genotype in the MMP9 gene, was significantly high. When two or more factors were combined, PC was equal to 4.12. This indicator is also significantly significant in the risk of developing abnormal uterine bleeding. In the scale of risk factors for the development of abnormal uterine bleeding, the presence of factors was assessed as "+",

The prediction results were evaluated by sequential analysis of Waald-Genkin (Table 5.3).

In those cases when the PC is +8, +11 points, there is a 75% probability of the forecast, and when the PC is below +8, an uncertain forecast is made. The proposed AUB prediction table makes it possible to predict the occurrence of AUB in 78% of cases.

Table 5.1

Predictive risk factors for the development of AUB

Prognostic Factors	Women with AMK (n=125)	Women without AUB (n=40)	F	OR	RR	PC
one	2	3	four	5	6	7
I. Somatic pathology						
Diseases of the cardiovascular system	77.6	22.5	6.4	11.9	3.4	5.4
Diseases of the urinary function	89.6	40	6.1	12.9	2.2	3.5
Overweight	52	27.5	2.8	2.9	1.9	2.8
Obesity	29.6	2.5	4.6	16.4	11.8	10.7
Thyroid diseases	52	12.5	4.9	7.6	4.2	6.2
Diabetes	3.2	2.5	0.2	1.3	1.3	1.1
II. Oncological diseases of the genitals in close relatives						
	8.8	5	0.8	1.8	1.8	2.5
III. Gynecological pathology						
fibroids	29.6	5	3.9	8.0	5.9	7.7
Diseases of the cervix	48	17.5	3.7	4.4	2.7	4.4
Inflammatory diseases of the genitals	66.4	2.5	8.7	77.1	26.6	14.2
ovarian cysts	15.2	2.5	2.7	7.0	6.1	7.8
III. Menstrual function						
early menarche	31.2	5	4.0	8.6	6.2	8.0
IV.Molecular genetic parameters						
Unfavorable Arg\Arg genome in the MMP9 gene	21.1	9.5	1.8	2.5	2.2	5.5
unfavorable genome Gln\ Arg gene MMP9	20.6	5.0	1.7	2.1	2.0	3.5
Combination of two or more factors	**40.5**	**2.5**	**21.6**	**14.1**	**13.6**	**4.12**

Table 5.2

Scale for assessing risk factors for the development of AUB with the calculation of the prognostic coefficient (PC "+" or "-")

Risk factor for AUB	PC "+"	Signs indicating the absence of AUB	PC "-"
Oncological diseases of the genitals in close relatives	+5	Absence of genital cancer in close relatives	-2
Diseases of the cardiovascular system	+4	Absence of diseases of the cardiovascular system	-3
Overweight	+3	Normal BMI	-2
Obesity	+4	BMI norm	-2
Thyroid diseases	+4	No thyroid disease	-2
Diseases of the urinary system	+4	Absence of diseases of the urinary system	-2
early menarche	+3	Timely menarche	-one
History of menstrual dysfunction	+4	There are no menstrual disorders	-2
Number of pregnancies 5 or more	+4	Number of pregnancies 1 to 5	-one
History of antenatal fetal death	+2	No history of antenatal fetal death	0
Spontaneous miscarriage	+2	No history of spontaneous miscarriage	0
infertility	+5	Lack of infertility	-2
Myoma in history	+6	No history of fibroids	-3
Inflammatory diseases of the genitals	+5	No inflammatory diseases of the genitals	-2
ovarian cysts	+3	no ovarian cysts	-2
Unfavorable Arg\Arg genome in MMP9	+6	Absence of unfavorable Arg\Arg genome in MMP9	-four
Unfavorable Gln\Arg genome in the MMP9 gene	+2	Absence of Arg\Arg in the MMP9 gene	-2

Table 5.3

Scheme for evaluating forecasting results (sequential analysis of Waald-Genkin)

Sum of predictive coefficients						
-fifteen	**-eleven**	**-eight**	**0**	**+8**	**+11**	**+15**
95% chance of forecast failure	75% chance of forecast failure	Lack of AMK development trend	Uncertain forecast	Development trend of AMK	75% chance of developing AUB	95% chance of developing AUB

The choice of management tactics for patients with abnormal uterine bleeding during perimenopause

Treatment of patients with AUB was carried out taking into account the results of a comprehensive examination (Table 27). When choosing treatment tactics, the morphology of the endometrium, the state of the myometrium, the presence of somatic diseases, as well as the features of gene polymorphism were taken into account. Each patient was informed about the treatment option and informed consent was obtained.

Table 5.4

Selection of the type of treatment depending on the morphology of the endomyometrium and genotype polymorphism in the MMP9 gene

Types of treatment		**Endomyometry pathologies and MMP9 polymorphism, abs(%)**
Dydrogesterone cyclically	I main - group, n=90	Glandular hyperplasia of the endometrium. 5(5.5%)
	II main group, n=35	-
Dydrogesterone continuously	I main - group, n=90	Glandular hyperplasia of the endometrium + unfavorable Arg\Arg genotype in the MMP9 gene, 21(23.3%)

Table 5.4 continued

	II main group, n=35	Glandular endometrial hyperplasia-3(8.6%) Endometrial polyps-7(20.0%) 10(28.6%)
Navy-LNG	I main - group, n=90	Glandular hyperplasia of the endometrium + uterine fibroids-6 (6.7%) Endometrial polyps + uterine fibroids-20(22.2%) 26(28.9%)
	II main group, n=35	Glandular hyperplasia of the endometrium + uterine fibroids-2 (5.7%) Endometrial polyps + uterine fibroids 4(11.4%)
dienogest	I main - group, n=90	Endometrial polyps + adenomyosis, 19(21.1%)
	II main group, n=35	Endometrial polyps + adenomyosis, 5(14.3%)
aGnRH	I main - group, n=90	Glandular cystic hyperplasia of the endometrium + uterine myoma-5 (5.5%)
ablation	I main - group, n=90	Endometrial polyps + Arg \ Arg genotype in the MMP9- gene 2(2.2%)
	II main group, n=35	Endometrial polyps + Arg \ Arg genotype in the MMP9- gene 2(5.7%)
hysterectomy	I main - group, n=90	1. Glandular cystic hyperplasia of the endometrium + uterine fibroids + unfavorable genotype Arg\Arg in the MMP9-4 gene (4.4%) 2. Glandular-hyperplasia of the endometrium + submucosal myomatous node unfavorable genotype Arg\Arg in the MMP9-3 gene (3.3%) 3.combination of uterine fibroids and adenomyosis-5(5.5%)
	II main group, n=35	1. Glandular cystic hyperplasia of the endometrium + uterine fibroids + unfavorable genotype Arg\Arg in the MMP9 gene 2. Glandular-hyperplasia of the endometrium + submucosal myomatous node unfavorable genotype Arg\Arg in the MMP9-2 gene (5.7%) 3.combination of uterine fibroids and adenomyosis-3(8.6%) 4. atypical endometrial hyperplasia-6(17.1%)
Oncologist's consultation	II main group, n=35	endometrial cancer, one

According to the national protocol, patients admitted to the clinic with complaints of bleeding were prescribed tranexamic acid 5%-5ml intramuscularly twice a day, and anti-inflammatory and empiric antibiotic therapy was prescribed [28,67]

Patients received dydrogesterone, dienogest, IUD-LNG, and a gonadotropin-releasing hormone (GnRH) agonist as hormonal therapy [44,45]

Treatment with dydrogesterone 20 mg/day from 5 to 25 days of the cycle was carried out 18 (20 ± 0.6%) patients of group I with FGE without atypia with a normal blood level of MMP 9.

A continuous course of dydrogesterone 10 mg per day for 6 months was carried out in 8 (8.9 ± 3%) patients of group I:

- five patients with FGE with an unfavorable Arg\Arg genotype in the MMP 9 gene polymorphism;
- two patients with an endometrial polyp and an unfavorable Arg\Arg genotype in the MMP 9 gene polymorphism;
- one patient with FGE and submucosal node on the leg.

Of group II, a continuous course of dydrogesterone was prescribed to 6 (17.1±6.4%) patients.

- three patients with an endometrial polyp,
- one patient with adenomyosis and AUB without curettage,
- two patients with myoma and FGE.

In patients with FGE in combination with uterine myoma, an LNG containing an IUD was inserted.

- 26 patients from group I, 25 of them with GE in combination with uterine myoma;
- 1 patient from group I with HE and adenomyosis and 2 with HE against the background of uterine fibroids and adenomyosis;
-7 patients from group II with GE against the background of uterine fibroids.

Gonadotropin releasing hormone (GnRH) agonists were prescribed to 5 patients with endometrial glandular cystic hyperplasia (GCHE).

Taking into account the fact that dienogest effectively inhibits the formation of prostaglandin E2, the most important mediator involved in the mechanism of proliferation, apoptosis in hyperplastic processes. dienogest 2 mg per day continuously for 6 months was prescribed and treated in 20 (22.2±4.4%) patients of group I and 7 (20±6.8%) patients of group II with signs where adenomysis.

Endometrial ablation - surgical treatment in the amount of removalendometriumis an alternative to hormonal therapy for patients with contraindications to major surgery.

We performed hysteroscopic loop ablation of the endometrium in 4 patients, taking into account contraindications:

- categorical refusal of the patient from hormone therapy,
- recurrent endometrial hyperplasia without signs of atypia.

Endometrial ablation performed:

- two patients with FGE from group I,
- two patients with FGE with recurrent course of AUB, in whom an unfavorable Arg \ Arg genotype in the MMP9 gene polymorphism was registered in the blood serum.

Hysterectomy was performed in 11 (12.2±3.5%) patients of group I, they were:

-5 patients with FGE and intramurally located myomatous nodes, in whose blood an unfavorable Arg \ Arg genotype in the MMP9 gene polymorphism was detected;

-2 patients with FGE in combination with submucosal myomatous nodes;

-2 patients with FGE and adenomyosis in the blood with an unfavorable Arg\Arg genotype in the MMP9 gene polymorphism;

-1 patient with an endometrial polyp against the background of uterine fibroids and adenomyosis;

-1 patient with ZhKGE and uterine myoma.

12 (34.3%) patients with recurrent AUB underwent hysterectomy:

- 6 patients with AGE,

-2 patients with an endometrial polyp and adenomyosis and an unfavorable Arg\Arg genotype in the MMP9 gene,

-2 patients with an endometrial polyp against the background of submucosal myomatous nodes,

-2 patients with endometrial polyp on the background of uterine fibroids in combination with adenomyosis.

One patient of group II, whose histological examination, endometrial scraping revealed endometrial cancer, was assigned to consult an oncologist.

Thus, hormonal treatment of patients with AUB was 97 (77.6%), endometrial ablation 4 (3.2%) and hysterectomy 23 (18.4%), including one patient - 1 (0.8%) referred for a consultation with an

oncogynecologist. It follows from the study that the study of the polymorphism of the MMP 9 gene made it possible to significantly narrow the indications for radical surgical interventions.

The results of studying the effectiveness of treatment of patients with abnormal uterine bleeding

We monitored the outcomes of treatment effectiveness in all patients who received conservative treatment: 77 (100%) patients of group I and 21 (100%) patients of group II.

To assess the effectiveness of the results of treatment of patients, the first ultrasound control of the M-echo of the endometrium was carried out 3 months after the start of hormone therapy, the second - after 6 months. At the same time, in no case did ultrasonic criteria for endometrial thickening have been identified. The average thickness of the endometrium was 3.1±0.4

The second control of the results of treatment was carried out after 6 months. At the same time, in no case, ultrasound criteria for thickening of the endometrium were identified. The average thickness of the endometrium was 3.3±0.3

Table 5.5

The results of the treatment of patients depending on the treatment option after 6 months

Conducted treatment	Group I, n=77		II group, n=21	
	recovery	relapses	recovery	relapses
Dydrogesterone cyclically	19 (24.7%)	-	-	-
dydrogesterone continuously	9 (11.7%)	-	5 (23.8%)	1 (4.8%)
aGnRH	6 (7.8%)	-	-	-
Navy-LNG	24 (31.2%)	-	8 (38.1%)	-
dienogest	19 (24.7%)	-	7 (33.3%)	-
Total	77 (100%)	-	20 (95.2%)	1 (4.8%)

Thus, the analysis of the results of treatment of patients in two groups 6 months after the therapy indicates the effectiveness of the treatment, 100% and 95.2%, respectively.

Taking into account a comprehensive examination, including the determination of an unfavorable genotype in the MMP9 gene, we have developed an algorithm for managing women with abnormal uterine bleeding during the perimenopause. In conclusion, we believe that a comprehensive examination of patients with AUB, determining the influence of genetic determinants on the course of the disease, made an addition to diagnostic issues and substantiated the need for a differentiated approach to organ-preserving treatment.

AFTERWORD

Perimenopause is a critical period in a woman's life, which is accompanied by numerous changes in all body systems [49, 70]. The same period accounts for the largest number of visits to gynecologists for uterine bleeding, often requiring radical gynecological operations [4,10,76]. And if we take into account that the duration of the period of perimenopause, according to various authors, ranges from 5 to 15 years, we can assume what a huge number of these patients are.

To date, extensive experience has been gained in the use of various methods for the treatment of uterine bleeding [30,46,86,87]. At the same time, the choice of one or another method of treatment is most often based on the subjective preferences of the attending physicians.

The aim of our work was to optimize the management of women with abnormal uterine bleeding during the perimenopause, taking into account the determination of certain genetic markers in the blood serum.

We examined 125 patients with uterine bleeding in the period of perimenopause who were treated in the gynecological department of the 1st clinic of SamMI for the period from 2019 to 2020.The control group consisted of 40 women of the same age without indications of any menstrual irregularities.

The age of the examined patients ranged from 43 to 51 years.averaged 46.9±1.6 years.

Group I consisted of 90 patients with AUB, group II included 35 patients with indication of recurrent uterine bleeding.

Adequate and rational management of any disease depends on its timely and correct diagnosis. Uterine bleeding is a syndromic diagnosis, the cause of which can be a large number of different diseases. It is during the period of perimenopause that ineffective primary diagnosis is the cause of a large number of radical surgeries, as well as long, sometimes unreasonable courses of hormonal therapy, and most importantly, late diagnosis of endometrial cancer [13, 23, 69].

A survey of patients in both groups showed that a history of malignant tumors of various localization in grandmothers, mothers and sisters was observed in every tenth examined - 11 (8.8%). In the control group, only 1 (2.5%) indicated bowel cancer among relatives. As for cervical cancer and bowel cancer, only 3 (2.4%) patients in the main

group indicated their presence among relatives, there was no this pathology in the control.

A factor that damages any link in the system of regulation of the menstrual cycle may be etiological for the occurrence of this pathology. These include overwork, psychological stress, hypovitaminosis, intoxication, genital and non-genital infections, somatic diseases, abortions, pathological childbirth, tumor processes of various localization [7, 28, 34].

Analysis of anamnestic data revealed an increased level of somatic pathology in patients with abnormal uterine bleeding with a predominance of cardiovascular diseases and pathology of the endocrine system. Thus, diseases of the cardiovascular system in 97 (77.6%)women of the main group and only every fifth - 9 (22.5%) from the control group. Varicose disease was diagnosed in 87 (69.6%) versus 7 (17.5%) in the control group. Hypertension occurred twice as often in patients with AUB - 12 (9.6%) versus 2 (5%).

Analysis of diseases of the endocrine system indicates that the patients of the main group suffered 4.8 times more often compared to the control, $p < 0.05$.

At the same time, the frequency of diffuse goiter in patients with recurrent bleeding was significantly more frequent than in women with AUB. Patients of the main group were significantly overweight 2.4 times more often, $p<0.05$.

In addition, every third patient was obese. Undoubtedly, a violation of carbohydrate and lipid metabolism leads to hyperestrogenism, in turn, hyperestrogenism leads to the development of AUB [6,111].

Diabetes mellitus in patients of the main group occurred 2.9 times significantly more often than in controls, $p < 0.05$. which is consistent with the results of studies by other authors [146].

The structure and frequency of gynecological morbidity in the past in women with AUB deserves special attention. All women of groups I and II and only every fifth of the control group were previously observed and treated for various gynecological diseases. Despite some differences, uterine fibroids, chronic inflammatory diseases of the internal genital organs were most common in all groups, and to a lesser extent infertility and ovarian tumors. Every 7 patients in group I and every 5 in group II indicated uterine myoma in the past. Every 4th patient from the main

group noted the presence of menstrual disorders in the form of delays, heavy and prolonged, painful menstruation.

Almost three times less often women from the control group noted inflammation of the genitals in the past than patients with AUB.

According to the authors, one of the common symptoms of ovarian cysts is menstrual dysfunction and uterine bleeding.[43, 60]. Ovarian cysts in the past were noted in 13 (14.4±3.7%) patients of group I and in 6 (17.1%) of group II, while in the control group - only in 1 (2, 5%) of women, which is consistent with the data of other authors [55, 60].

2.5 times more often, patients with AUB underwent laparotomy - cystectomy. Laparotomy with tubectomy was transferred in 6 (4.8%) patients of the main group. Among the examined patients, 31 patients from group I and 50 operations from group II had previously undergone various surgical interventions on the pelvic organs. It should be noted that the vast majority of patients with recurrent AUB indicated curettage of the uterine cavity in the past, which gave us reason to separate patients with recurrent AUB into a separate group. Women in the control group underwent only 8 operations, the vast majority - 87.5% of which were voluntary surgical sterilization (VCS). The presence of a burdened gynecological history of patients with surgical interventions is consistent with the data of other researchers [43, 60].

When analyzing the menstrual function of the examined, it was found that the average age of menarche in patients with AUB significantly differed from the average age of menarche in women in the control group ($p < 0.05$). According to various authors, the early age of menarche is a risk factor for the development of endometrial hyperplasia and cancer, and is also an independent predictor of an increase in body mass index [135]. Early age of menarche (10-11 years) was noted significantly more often in those examined with abnormal uterine bleeding - 39 (31.2%) compared with the control group 2 (5.0%) cases, $p<0.001$; late menarche (at the age of 15—17 years) was detected in 6 (4.8%) and 5 (12.5%) patients of the main group and in the control, respectively, $p<0.05$. According toAylamazyan E.K(2017) [4], more than 40% of patients with endometrial hyperplasia have various menstrual irregularities, starting from the period of puberty and during childbearing age.

When analyzing the complaints of patients of both main groups, it was found that upon admission to the clinic, spotting of varying intensity was noted by the majority of the examined - 84 (67.2%) - 59 (65.6%)

patients of group I and 25 (71.4%) of group II . The average duration of spotting before admission to the hospital was 22.6 ± 3.6 days in group I, and 35.1 ± 3.6 days in group II.

The examined patients complained of various menstrual irregularities, lower abdominal pain, vasomotor and emotional-vegetative symptoms.

Bimanual examination of the uterus of the main group did not show normal size of the uterus in any of the patients. The size of the uterus corresponding to 5-6 weeks of pregnancy was diagnosed in 53 (58.9%) patients of group I and 17 (48.6%) of group II. In every third patient - 29 (32.2%) of group I and almost half of group II - 15 (42.9%) the size of the uterus corresponded to 7-8 weeks of pregnancy.

The data of gynecological examination were confirmed by the results of ultrasound examination of the pelvic organs of the patients of the studied groups.The reliability of the method in transvaginal examination is 86–90% [4, 14, 38].Sonographic signs of uterine fibroids were45(36±4.4%) among patients with AUB against2(5.0%) in control, p<0.001. The second identified pathology in terms of frequency was adenomyosis - 34 (27.2%) versus 4 (10.0%) in the control, p <0.001. 9 patients had a combination of uterine fibroids and adenomyosis. According to G.E. Chernukh [84,85], the combination of endometrial hyperplastic processes with myometrial pathology is 63.5%.

Ovarian cysts were detected significantly more often in patients of group II in 14 (40%) versus 16 (17.8%) in group I, P <0.05.

Our data on the high frequency of the combination of endometrial hyperplastic processes with other proliferative diseases of the uterus in perimenopausal women, which are consistent with the results of other studies [32,37].

The most important parameter assessed by ultrasound is the size of the median uterine echo [41.94]. According to our data, M-echo in patients with bleeding varied from 1 to 15 mm, on average, in group I, 10.96 ± 5.6 mm, in group II - 11.7 ± 4.5 mm.

In 46 (59.7%) of 77 patients with bleeding, M-echo varied from 7 to 15 mm, in 14 (18.2%) from 1 to 4 mm, in 17 (22.1%) endometrial polyps were diagnosed.

M-echo in 38 (79.2%) patients with delayed menstruation ranged from 10 to 20 mm, averaging 16.0 ± 3.7 mm; the remaining 14 (29.0±5.71%) - endometrial atrophy - from 1 to 4 mm.

Hysteroscopy for AUB is a method of direct visualization of cavitary pathology and facilitates direct biopsy.Hysteroscopy can be performed on an outpatient basis with or without anesthesia or in the operating room under local or general anesthesia. Direct biopsy under control vision is the main advantage before "blind" dilatation and curettage of the uterine cavity [6,105].

Hysteroscopy with separate curettage of the uterine cavity was performed in the majority of 88.8% of patients in the main group. Only 14 patients with endometrial thickness from 1 to 4 mm did not undergo curettage.

Thickening and swelling of the mucous membrane of a pale pink color in the form of numerous folds of various heights, in the form of polypoid growths, the presence of a large number of gland ducts, undulating movement of the endometrium with a change in the rate of fluid flow into the uterine cavity (the phenomenon of "underwater plants") [6,105] - only detected in 32 (28.8±4.3%) patients of the main groups.

The low frequency of detection of hysteroscopic signs of endometrial hyperplasia is due to the fact that 61 (71.8±4.9%)and 18(69±9.0%)in patients of groups I and II, respectively, hysteroscopy was performed in the presence of blood discharge of various duration and intensity.

All patients after curettage of the uterine cavity underwent a morphological study of scrapings.

The exception was 14(11.2%),in which the ultrasound diagnosed endometrial thickness from 1 to 4 mm.

According to N.A. Sheshukov, endometrial glandular hyperplasia is often the cause of AUB in perimenopause (77.1%), polyps (33.8%), were detected almost equally rarely [87].

In our studies, endometrial polyps were a common cause of AUB, their frequency was 31.3%, endometrial hyperplasia (EH), mostly non-atypical, was diagnosed 2 times less often. Atypical EH and endometrial cancer as the cause of AUB were detected only in 1.3%. Chronic endometritis was found in 12.7% of cases. In 8% of patients, AUB was associated with the submucosal location of the myomatous node. In 30.7%, no intrauterine pathology was detected, the endometrium corresponded to the stage of proliferation or, in rare cases, secretion.

The key point in ensuring the normal functioning of the endometrium is the balance between the processes of proliferation and

cell death [40,52,61]. According to studies of the molecular mechanisms of apoptosis, the final stage in the implementation of the apoptotic signal is the cascade activation of caspases, enzymes that catalyze limited cleavage of cellular proteins [90, 102]. The extracellular matrix plays an important role in metabolic processes affecting cell proliferation, apoptosis, and neoangiogenesis. The degradation of its components is carried out by proteins with proteolytic activity - matrix metalloproteinases [23,40,61,72,85].

We have studied the significance of polymorphisms rs1042522 of the TP53-72 gene (Arg72Pro) and rs17576 of the MMP9 gene (Gln279Arg) in the mechanisms of AUB formation in perimenopausal women.

The results of modern studies conducted to date prove the significant role of genetic polymorphisms in the mechanisms of disease development, including AUB in women [8,108,128]. Meanwhile, the evidence that polymorphic variants of various genes are involved in triggering a particular pathological process is very contradictory [128]. In this regard, in this chapter of the work, we present the results of the study of the frequencies of alleles and genotypes of the rs1042522 polymorphisms of the TP53-72 gene (Arg72Pro) and rs17576 of the MMP9 gene (Gln279Arg) in groups of patients with AUB, followed by an assessment of both the role and significance in the risk of developing AUB in women during perimenopause.

Analysis of the results of the study of polymorphismrs17576 of the MMP9 gene (Gln279Arg)allowed to establish the presence of statistically significant differences in the main group of patients with AUB in comparison with the values in conditionally healthy donors, for allele frequenciesArg($\chi2$=7.63; p=0.01; OR=1.8; 95%CI: 1.19-2.77) and homozygous Arg/Arg genotype ($\chi2$=4.87; p=0.03; OR=2.6; 95%CI:1.09-6.0), which allows us to consider the Arg allele and the homozygous Arg/Arg genotype of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) as genetic factors predisposing to an increased risk of developing recurrent AUB in premenopausal women.

Evaluation of the prognostic significance of the AUS genotypes of polymorphisms rs1042522 of the TP53-72 gene (Arg72Pro) and rs17576 of the MMP9 gene (Gln279Arg) in the risk of developing AUB in perimenopausal women in the main group of patients with AUB made it possible to establish the following: in relation to the genotypes of the

rs1042522 polymorphism of the TP53-72 gene (Arg7Pro) - the lack of their predictive value in the risk of developing AUB in women in the perimenopausal period

With regard to the genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg), their predictive value in relation to the heterozygous genotype (AUS=0.61) in the II group of patients, which proves the significant role of the genotypeGln/Argin the risk of developing AUB relapses in perimenopausal women as an independent genetic marker.

At present, computational methods for diagnosing and predicting a number of diseases have been developed. The proposed technique helps the doctor to easily identify individuals with varying degrees of risk of AUB. Based on this, specific preventive measures will be implemented, and patients will be offered advice on eliminating or reducing the influence of these factors [111].

We have calculated the prognostic coefficient, respectively, of various indicators; somatic and genital pathology, data on oncological diseases in close relatives, menstrual function and detection of an unfavorable genotype in the MMP9 gene.

Treatment of patients with AUB was carried out taking into account the results of a comprehensive examination. When choosing the treatment of patients, the morphology of the endometrium and the state of the myometrium, the presence of somatic diseases, as well as the features of gene polymorphism were taken into account [30,46,71,77]. After receiving the results of the histological conclusion and additional research methods, the patients were offered and carried out various methods of treatment.

For hormonal therapy in patients with AUB during the perimenopausal period, we used dydrogesterone, dienogest [44,45,145].

Gonadotropin-releasing hormone agonists have been used as long-term monotherapy for endometrial hyperplasia (EH) over the past decade.(GnRH)[1, 4], which, on the basis of a reversible blockade of the secretion of pituitary gonadotropins ("selective drug-induced hypophysectomy"), lead to a complete blockage of ovarian function. We prescribed five patients with FHPE and uterine myoma(GnRH).

Dydrogesterone has an antiproliferative effect, the drug increases the activity of some growth factors, reducesexpression of metalloproteinases and, as a result, inhibits the proliferation of glandular

and stromal cells of the endometrium, reduces the expression of estrogen receptors, reduces the time of presence of estradiol in the cell nucleus.[2, 27,48],

The most recognized type of hormone therapy is the appointment of progestogens, however, the types, duration and regimens of treatment are not universal.

A continuous course for 6 months with dydrogesterone 10 mg per day was treated in 8 (8.9%) patients of the 1st group, 5 of them with pure HE, who had an unfavorable Arg \ Arg genotype in the MMP9 gene polymorphism in the blood, 1 patient with HE and submucous node and 2 patients who had GE and uterine myoma with adenomyosis.

A continuous course of dydrogesterone was prescribed to 6(17.1±6.4%) patients II with GE.

In the literature, LNG containing an IUD is described as an alternative to hysterectomy in women with uterine fibroids [44,88]. Women who did not want to take duphaston tablets continuously and patients in whom FGE was associated with uterine fibroids or adenomyosis had an LNG containing an IUD inserted. In addition, the LNG IUD can be used in women with various somatic diseases (diabetes mellitus, cardiovascular, hepato-biliary pathology) due to the local effect of levonorgestrel [44,45]

LNG containing an IUD was inserted in 31 (34.4%) patients of group I, including 25 patients with HE in combination with uterine myoma, 4 women with EH and adenomyosis, and 2 patients with EH myoma and adenomyosis. Of the II group of patients with IUDs, LNG was inserted in 7 (20.0%) patients with HE and uterine myoma.

Dienogest effectively inhibits the formation of prostaglandin E2, the most important mediator involved in the mechanism of proliferation, apoptosis in adenomyosis [2,39]

Dienogest 2 mg per day continuously for 6 months was administered and treated to 20 (22.2%) patients of group I and 7 (20%) patients of group II where there was a combination of GE with adenomyosis.

Endometrial ablation Surgical treatment in volumeendometriumis an alternative to hormone therapy [6]. We performed hysteroscopic loop endometrial ablation in 4 patients.Hysterectomy was performed in 23 (18.4%) patients.

Analysis of the results of treatment of patients in two groups 6 months after the therapy indicates the effectiveness of the optimized treatment, 97.2% and 89.4%, respectively.

According to the literature, every third woman in the perimenopausal period with abnormal uterine bleeding undergoes a hysterectomy [6,39,44].

In conclusion, we believe that a comprehensive examination of patients with AUB, determining the influence of genetic determinants on the course of the disease, contributes to the introduction of additions on diagnostic issues, and also contributes to the rationale for the need to predict the recurrence of abnormal uterine bleeding, as well as the possibility of organ-preserving treatment.

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ABNORMAL UTERINE BLEEDING IN PERIMENOPAUSE WOMEN

(MONOGRAPH)

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