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# ABSTRACT

The dissertation presented for the degree of **Doctor of Sciences**

# MODERN ASPECTS OF THE PATHOGENESIS, PROGNOSIS, AND TREATMENT OF ADENOMYOSIS

Specialty: 3215.01 – Obstetrics and gynecology

Field of Science: Medicine

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## RELEVANCE OF THE PROBLEM AND DEGREE OF STUDY

Adenomyosis is considered one of the most pressing issues in modern gynecology, ranking third after inflammatory diseases of the uterus and uterine fibroids. The prevalence of adenomyosis varies widely, ranging from 7.4% to 53%. In recent years, there has been a significant increase in the incidence of this disease, with diagnoses often made at advanced stages (Stage III-IV), which poses serious risks to the health of patients, especially during their reproductive years. This is primarily due to the lack of clear non-invasive criteria for the early stages of adenomyosis[1,2]. In addition to its widespread nature, the relevance of the adenomyosis problem is also determined by the severity of the disease and the diversity of its clinical manifestations. Patients suffer from persistent disturbances in menstrual (menometrorrhagia or dysmenorrhea) and reproductive functions (infertility, pregnancy loss), and constitute the main group of women experiencing pelvic pain. These patients often undergo repeated diagnostic procedures, surgeries, prolonged medical and physiotherapeutic treatments - which are not always effective[3]. Other risk factors associated with adenomyosis include endometriosis, smoking, and surgical trauma (such as cesarean sections or uterine curettage procedures)[4,5]. According to epidemiological data, multiple childbirths, spontaneous

[1] Arestrup, J. Birth weight, childhood body mass index and height and risks of endometriosis and adenomyosis /J.Aarestrup, B.W.Jensen, L.C.Ulrich [et al.] // Ann Hum Biol. 2020, No 2, p.1–8

[2] Arena, A. Ureteral endometriosis, the hidden enemy: Multivariable fractional polynomial approach for evaluation of preoperative risk factors in the absence of ureteral dilation / A.Arena, S.Del Forno, B.Orsini [et al] // Fertil. Steril. 2021;116(2), p.470–477

[3] Habiba, M. Exploring the challenges for a new classification of adenomyosis / M.Habiba, S. Gordts, M.Bazot [et al.] // Reprod. Biomed. Online. 2020;40, - p.569–581

[4] Habiba, M. Exploring the challenges for a new classification of adenomyosis / M.Habiba, S. Gordts, M.Bazot [et al.] // Reprod. Biomed. Online. 2020;40, - p.569–581

[5] Johnatty, S.E. Co-existence of leiomyomas, adenomyosis and endometriosis in women with endometrial cancer / S.E.Johnatty, C.J.Stewart, D.Smith D [et al.] // Sci Rep. 2020;10(1). – p.3621

and induced abortions, and endometrial hyperplasia are linked to a higher risk of developing adenomyosis.

For many years, adenomyosis remained a histopathological diagnosis - typically made after hysterectomy in women in the perimenopausal period due to heavy menstrual bleeding or pelvic pain. Until recently, detecting adenomyosis was quite challenging. In its diagnosis, transvaginal ultrasonography (TVUS) is considered a preferred method due to its accessibility, non-invasiveness, and low cost. However, the detection rate of adenomyosis using ultrasound varies between 20% and 86% depending on the author, which is related to the low sensitivity of the method for detecting grade I adenomyosis.

Traditionally, the diagnosis of adenomyosis has been based on surgical resection and pathological examination. However, with the advancement of modern imaging techniques, adenomyosis is now often detected in patients with infertility[6,7]. The development of visualization methods—such as MRI and transvaginal ultrasound-has enabled clinicians to diagnose adenomyosis non-invasively in women undergoing conservative treatment or those exhibiting various forms of the disease. Magnetic resonance imaging (MRI) is considered one of the most expensive methods used to confirm adenomyosis and perform differential diagnosis[8,9]. Another significant challenge lies in determining the severity of the disease and identifying clinical signs that contribute to more severe forms of adenomyosis.

The long-term progression and severe symptoms of adenomyosis are accompanied by emotional distress, neurotic disorders,

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[6] Andres, M.P. Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis / M.P.Andres, G.M.Borrelli, J.Ribeiro [et al.] // J Minim Invasive Gynecol. 2018;25(2), - p.257–264

[7] Peng, Y. Impaired decidualization of human endometrial stromal cells from women with adenomyosis / Y.Peng, Z.Jin, C.Xu [et al.] // Biol. Reprod. 2021;104, - p.1034-1044

[8] Raimondo, D. Impact of adenomyosis on the prognosis of patients with endometrial cancer / D.Raimondo, A.Raffone, A.Travaglino [et al.] // Int. J. Gynecol. Obstet. 2021, - p.1–6

[9] Беженарь, В.Ф. Аденомиоз и фертильность: современный взгляд на проблему (обзор литературы) / В.Ф. Беженарь, В.А.Линде, А.С. Калугина // - Москва: Журнал акушерства и женских болезней. 2022, Т. 71. № 1, с.109–118

reduced work capacity, and diminished quality of life. The assessment of functional reserves, which is essential for evaluating autonomic homeostasis and detecting early adaptive impairments in patients with adenomyosis, remains underutilized and does not fully reflect the scope of the issue[10,11].

Among the clinical and instrumental diagnostic methods for adenomyosis, hysteroscopy is widely used; however, it is invasive, largely subjective, and, according to various authors, its sensitivity ranges from 32.9% to 91.4% due to low informativeness in the early stages of the disease[12]. There are also no specific laboratory markers for this disease. Nevertheless, there remains a great need for unified and standardized diagnostic criteria in both imaging and histological assessments, as well as for a common profile in registration and reporting systems to effectively identify all clinical and visual forms of adenomyosis[13,14]. Over the years, the development of surgical and hormonal treatments, along with efforts to prevent recurrences of adenomyosis, has continued. However, the psychoemotional responses of patients have not received adequate attention.

In the last decade, significant progress has been made in the study and treatment of adenomyosis. Increasingly, new findings are shedding light on the pathogenic mechanisms involved in the disease

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[10]Dior, U.P. The Association of Sonographic Evidence of Adenomyosis with Severe Endometriosis and Gene Expression in Eutopic Endometrium / U.P.Dior, D.Nisbet, J.N.Fung // J Minim Invasive Gynecol. 2019; 26(5), - p.941–948

[11]Donnez, J. What if deep endometriotic nodules and uterine adenomyosis were actually two forms of the same disease? / J.Donnez, M.M.Dolmans, L. Fellah // Fertil Steril. 2019;111(3), - p.454–456

[12] Moura, P.C. Accuracy of transvaginal sonography versus magnetic resonance imaging in the diagnosis of rectosigmoid endometriosis: Systematic review and meta-analysis / P.C. Moura, H.S.Ribeiro, W.M. Bernardo [et al.]// PLoS One. – 2019. – Vol. 14, № 4 [et al.]- p.214-222

[13] Li, Y.W. Clinical Manifestations of Adenomyosis Patients with or without Coexisting Endometriosis / Y.W. Li, Y.T. Liu, S.Wang [et al.] // Chinese Medical Journal (Engl). – 2018. – Vol. 131, № 20, - p. 2495–2498

[14] Nyundo Rukhliada, N.N. Adenomyosis and adenomyomectomy experience // Global reproduction 2019; 2, - p. 5-12

and on potential treatment options[15,16,17]. In modern gynecology, the treatment of adenomyosis is regarded as one of the most pressing challenges.

Adenomyosis is a pathological condition characterized by disruption of menstrual and reproductive functions. The lack of a definitive understanding of its etiology and pathogenesis, along with its frequent co-occurrence with hyperplastic processes in both the endometrium and myometrium, complicates the selection of appropriate treatment.

Despite the numerous studies dedicated to various aspects of adenomyosis, many issues regarding its etiology and pathogenesis still remain unclear[18]. There is a lack of precise diagnostic criteria and comparative data on the informativeness of different diagnostic methods (ultrasound, MRI, endoscopic examination).

Additionally, the issue of how treatment outcomes depend on the specific therapeutic approaches used remains unresolved. All of these factors underline the relevance of the present research study.

**Object and Subject of the Study**

Between 2021 and 2024, a comprehensive clinical, laboratory, and instrumental prospective examination was conducted on 224 patients aged between 30 and 50 years (mean age–42.0±1.8 years) diagnosed with adenomyosis. These patients formed the main study group. Based on the form of adenomyosis, the main group was divided into two subgroups: the first group included 106 women with the diffuse form, and the second group included 118 women with the nodular form. The control group consisted of 84 practically healthy women of reproductive age who had regular ovulatory menstrual cycles and no history of gynecological diseases.

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[15]Pengyang, K.., Li Inoue, S. Uterine adenomyosis is an oligoclonal disorder associated with KRAS mutations / S.Inoue, Y.Hirota, T.Ueno // Nat Commun 2019; 10(01), - p.5785

[16] Yoldemir, T. Adenomyosis and fertility outcomes // Gynecol. Endocrinol. 2020. Vol. 36. No. 6, - p. 473−474

[17] Tan, J. A critical review of recent advances in the diagnosis, classification, and management of uterine adenomyosis / J.Tan, P.Yong, M.A.Bedaiwy [et al.] // Curr Opin Obstet Gynecol 2019; 31 (4), - p. 212–221

[18] Szubert, M. Adenomyosis and Infertility-Review of Medical and Surgical Approaches / M.Szubert, E.Koziróg, O.Olszak [et al.] // Int. J. Environ. Res. Public Health. 2021;18, - p.1235

**Purpose of the Study**

To develop a comprehensive system for the diagnosis, treatment, and prognosis of adenomyosis, as well as to investigate the clinical, genetic, immunological and hemodynamic markers of the disease.

**Objectives of the study:**

1. To conduct prospective clinical and laboratory examinations of patients diagnosed with adenomyosis;
2. To identify risk factors for the development of adenomyosis and develop and implement a prognostic program for adenomyosis based on clinical-anamnestic data analysis;
3. To develop and substantiate an examination algorithm for gynecological patients to detect adenomyosis in women of reproductive age;
4. To identify the genetic, immunological, and hemodynamic aspects of adenomyosis pathogenesis to determine appropriate follow-up strategies for these patients;
5. To study the subpopulation composition of peripheral blood lymphocytes in patients with adenomyosis presenting different clinical variants;
6. To investigate the characteristics of blood flow in the uterine arteries, myometrial vessels, and ovarian branches of the uterine artery in women with adenomyosis;
7. To determine the optimal combination of priority diagnostic methods for adenomyosis to reduce the time required for diagnosis;
8. To develop pathogenetically based, stepwise conservative treatment protocols aimed at reducing the rate of surgical intervention in patients with adenomyosis;
9. To create a comprehensive program for improving diagnostic, therapeutic-rehabilitative, and preventive care that enhances somatic, psycho-emotional, and reproductive health, and improves the quality of life of patients with adenomyosis.

**Methods of the study**

The research employed clinical-laboratory, instrumental, bacteriological, immunological, morphological, sociological, statistical, and other methods.

**Main theses submitted for defense:**

1. In comparison to the nodular form, the diffuse form of adenomyosis is significantly more associated with heavy menstrual bleeding, which leads to anemia, prolonged menstruation, and an extended menstrual cycle. In contrast, the nodular form is significantly more associated with pain syndrome and both primary and secondary infertility.

2. 3D ultrasound is considered a reliable method for diagnosing adenomyosis, with high accuracy (89%) and sensitivity (95%), particularly effective in detecting the early stages of the disease, determining its type, differentiating it from uterine fibroids and developmental anomalies, and identifying changes in the junctional zone. The identification and quantitative assessment of echographic criteria specific to adenomyosis render 3D transvaginal echography (TVE) more reliable than the 2D method in early diagnosis.

3. Risk factors for the development of adenomyosis in women of reproductive age include complicated obstetric-gynecological history, hereditary predisposition to neoplasms, a high rate of extragenital pathology, and exposure to psycho-traumatic situations.

4. Assessment of the somatic, psycho-emotional, and reproductive health of women with adenomyosis revealed neurotic, endocrine, and hemorheological changes, which lead to increased anxiety and decreased adaptive capacity of the body.

5. Organ-preserving laparoscopic surgery for adenomyosis, followed by hormonal therapy, helps reduce clinical symptoms and facilitates the realization of reproductive function.

6. An optimized program for diagnostic, therapeutic, and rehabilitative measures in women of reproductive age with adenomyosis has been developed and implemented, contributing to improved treatment quality, better quality of life, and reduced discomfort.

**Scientific Novelty of the Study**

1. The diagnostic value of three-dimensional ultrasound in identifying different types and degrees of adenomyosis was confirmed through a comparative analysis of 2D and 3D TVE (transvaginal echography) results. The early stages of adenomyosis can be diagnosed with high informativeness. When two or more individual ultrasound characteristics were present, diagnostic accuracy of 2D and 3D

TVE was 83.3±4.5% and 90.7±3.5%, respectively. Compared to 2D parameters, 3D criteria demonstrated significantly higher sensitivity in diagnosing adenomyosis.

2. Assessment of hemodynamic parameters in uterine vessels and their branches during varying degrees of diffuse adenomyosis showed that, regardless of the disease's extent, uterine arterial blood flow resistance was significantly higher compared to healthy women (0.89±0.03). This indicates a reduced intensity of arterial circulation in the uterus during adenomyosis (from 0.84±0.02 to 0.46±0.02 in Group I, and from 0.43±0.01 to 0.37±0.01 in Group II).

3. The prevalence and key risk factors for adenomyosis progression were identified. Among patients with the diffuse form, extragenital diseases represented the highest relative risk: endocrine disorders (confidence interval – 2.58 (0.35–8.46)) and cardiovascular diseases (confidence interval – 2.38 (0.52–9.31)). For the nodular form, similar high-risk factors were found: endocrine disorders (CI – 2.63 (0.48–8.65)) and cardiovascular diseases (CI – 2.38 (0.52–9.31)). Obesity (BMI ≥30) was observed in 125 women (55.80±3.3%), and overweight status (BMI 25–29.99) in 33 women (14.73±1.3%).

4. For the first time, a connection between specific genotypes and the development of different clinical forms of adenomyosis was established, highlighting the importance of functional gene polymorphism in disease prognosis. The 1G/1G genotype of the MMP1 gene was more frequent in regressive and stable forms of adenomyosis (34.4% and 60.0% of women, respectively). A decrease in other genotypes was observed: 1G/2G – 38.5%, and 2G/2G – 7.7%. In the proliferative form, 1G/1G decreased to 11.1%, while 1G/2G and 2G/2G increased to 55.6% and 33.3%, respectively.

5. Psychological characteristics of patients with adenomyosis were analyzed, revealing that disease severity was proportional to increased emotional tension, indicating a reduced level of psychoemotional adaptation. In patients with adenomyosis and pain syndrome, the most common symptom was sleep disturbances-scoring 19.18±0.27 in Group I and 17.29±0.12 in Group II. Other findings included affective tension (16.18±0.21 and 13.16±0.11) and depressive symptoms (9.26±0.16 and 8.21±0.28, respectively).

6. Identification of the genetic, immunological, and hemodynamic aspects of adenomyosis pathogenesis enabled the development of pathogenetically justified conservative treatment protocols, potentially reducing the need for surgical intervention in this patient group.

7. A scientifically grounded optimization program for the diagnosis, treatment, and rehabilitation of adenomyosis was developed and implemented. This program contributed to the improvement of somatic, psycho-emotional, and reproductive health and enhanced patients' quality of life. A modern, differentiated strategy for comprehensive treatment of adenomyosis (surgical, hormonal, and rehabilitative) was also developed.

**Practical Significance of the Study**

In the study, priority markers (clinical, ultrasound, hysteroscopy data) used for determining the stages of adenomyosis were identified, which helps reduce the cost of diagnostic procedures. Future studies on the components of angiogenesis are expected to clarify the pathogenesis of adenomyosis, as well as identify correlations between the form and extent of adenomyosis and endothelial growth factors, which will provide additional value to the diagnostic process. Based on the conducted research, the understanding of the pathogenesis of adenomyosis has been deepened and expanded. Morphological, morphometric, and immunohistochemical parameters reflecting the excessive proliferative potential of utopic endometrium and the "transition zone" endometrial portion in the uterine "transition zone" have been thoroughly studied. Pathological angiogenesis, accompanied by a decrease in the volume of extracellular fibrillary components in the inner myometrium, and the growth and invasion of ectopic endometrial areas, were observed. The necessity of comprehensive examination of patients with adenomyosis, including studying hemostasis indicators, vegetative, and psycho-emotional states, was substantiated for the purpose of treatment and rehabilitation.

A diagnostic, treatment, and rehabilitation program for patients with adenomyosis has been developed, optimizing treatment, aiding in the selection of rational methods for surgical and hormonal treatment, and ensuring the strengthening of these women's somatic, psycho-emotional, and reproductive health, as well as improving their quality of life. Based

on the results of the study, a reproductive data bank reflecting the general functional and psycho-emotional state of the organism has been created, which is recommended for practical use for young women with adenomyosis. It was confirmed that three-dimensional transvaginal echography (3D TVE), based on the measurement of the transition zone (TZ), is effective in detecting the early stages of adenomyosis. An optimized algorithm for the early diagnosis of various forms of adenomyosis has been developed. The effectiveness of combined surgical and hormonal treatment using hormonal medications was proven, showing its efficiency in eliminating clinical symptoms and restoring reproductive function. Based on the clinical signs, morphological features, and reproductive function, modern differentiated tactics for the complex (surgical, hormonal) treatment of adenomyosis using minimal invasive technologies were developed.

**Approval and Application of the Dissertation**

The materials of the dissertation have been discussed:

1. "Достижения современной медицины в изучении эпидемиологии инфекционных болезней". Материалы международной научно-практической конференции (Узбекистан, г.Фергана, 10 июня , 2021);
2. «Global science and innovations 2022: Central Asia». Материалы международной научно-практической конференции (Казахстан, г.Нур–Султан, 2022);
3. "Актуальные проблемы эпидемиологии инфекционных и неинфекционных болезней". Материалы международной научно-практической конференции с участием международных партнерских вузов (Узбекистан, г. Фергана, 12 апреля, 2022);
4. "Beynəlxalq Tibbi Forum". Elmi-praktik konfransın materialları (Naxçıvan, 18-21 iyun, 2022)
5. "Elm və Təhsilin Əsasları" XII Beynəlxalq Elmi Konfransın materialları (Bakı, Azərbaycan Elm Mərkəzi, 07 fevral, 2025);
6. "Elmi Qaynaqlar" XX Respublika Elmi Konfransın materialları (Bakı, Azərbaycan Elm Mərkəzi, 08 fevra,l 2025);
7. ATU-nun profil kafedralarının birgə keçirdiyi kafedralararası iclasda (Bakı, ATU. 28 fevral 2025-ci il tarixli 06 saylı iclas);

8. ATU-nun nəzdində olan elmi seminarda (Bakı, ATU, 2025 protocol №6).

The materials of the dissertation are used in the educational process of the Department of Obstetrics and Gynecology II at Azerbaijan Medical University. The proposed practical recommendations are implemented in practice at the Educational Surgery Clinic of Azerbaijan Medical University.

**Organization Where the Dissertation Was Carried Out:** The dissertation work was conducted at the Department of Obstetrics and Gynecology II , Educational Surgery Clinic at Azerbaijan Medical University.

**Publications.** Based on the research conducted for the dissertation topic, 12 journal articles and 11 thesis papers have been published, including 7 abroad (3 journals indexed in the Web of Science and 4 journals in the Scopus database, included in the list of AAK).

**Volume and Structure of the Dissertation.**The dissertation, printed on a computer, consists of 271 pages (403,063 characters). It includes the following sections: "Contents," "Introduction" (10 pages, 17,001 characters), "Results" (3 pages, 5,334 characters), "Practical Recommendations" (1 page, 1,822 characters), and "References" (33 pages).

The main content of the dissertation is divided into 7 chapters: Chapter I**:** "Literature Review" (54 pages, 106,359 characters), Chapter II**:** "Materials and Methods of Research" (17 pages, 29,242 characters), Chapter III**:** "Research Results" (27 pages, 49,407 characters), Chapter IV**: (**26 pages, 47,807 characters**),** Chapter V: (28 pages, 39,996 characters)**,**Chapter VI: (33 pages, 61,904 characters) **,**Discussion of Results: (24 pages, 44,191 characters)

A total of 304 sources were used in writing the dissertation, including 15 from Azerbaijani authors, 69 from Russian authors, and 220 from foreign scholars. The dissertation includes 55 tables, 21 photos, and 16 graphics for illustration.

**Research Materials, Volume, and Methods**

The research was conducted between 2021-2024 as part of the scientific program of the Department of Obstetrics and Gynecology II at the Azerbaijan Medical University (AMU). The examinations were performed using a prospective method at the Department of Obstetrics

and Gynecology II and the Teaching Surgical Clinic of AMU. A total of 224 patients aged 30 to 50 years (mean age: 42.0 ± 1.8 years) with adenomyosis were comprehensively examined using clinical-laboratory and instrumental methods. These patients formed the main study group. Based on the form of adenomyosis, the main group was divided into two subgroups**:** Group 1: Diffuse form - 106 women, Group 2**:** Nodular form - 118 women. The control group consisted of 84 women who were relatively healthy, of reproductive age, with regular ovulatory menstrual cycles, and no history of gynecological diseases. Cohort studies were conducted prospectively.

Inclusion Criteria**:**

Patients diagnosed with adenomyosis

Patients aged between 30 and 50 years

Informed consent for participation in the study

Exclusion Criteria**:**

Detection of malignant pathological processes in the reproductive system organs or other localizations

Presence of hormone-secreting tumors in the ovaries

Pregnancy or lactation

Individuals under 30 years or over 50 years of age

Refusal to participate in the study

The clinical features of the examined women were based on complaints, obstetric-gynecological, and somatic histories. All patients had their general and gynecological medical histories, as well as menstrual function characteristics, studied. Special attention was paid to past inflammatory diseases of the genital organs, history of spontaneous abortions, ectopic pregnancies, fetal antenatal deaths, pregnancy course, and outcomes.

Anamnestic data collection included general, somatic, gynecological, reproductive histories, and Anthropometric data. Quality of life (QOL) was assessed using the MOS SF-36 Medical Outcomes 36-Item Short Form Health Survey questionnaire. Along with clinical and anamnestic examination methods, the complex examination included the following:

1. Ultrasonography**,** Dopplerometry, Color Doppler Mapping (CDM), and small pelvic organ compression elastography

2. Puncture biopsy with concurrent diagnostic scraping of the uterus via hysteroscopy

3. Laparoscopy

4. Morphological examination and morphometry of obtained specimens

5. Lymphocyte immunophenotyping

6. Statistical methods.

Initially, all patients underwent 2D (two-dimensional) transvaginal ultrasound. If necessary, small pelvic organs were further examined using 3D transvaginal ultrasound (3D TVE) based on indications. The ultrasound examination of the small pelvic organs was carried out using a Medison Co. Ltd (Korea) expert-class Accuvix XQ-EXP digital stationary ultrasound diagnostic device with transabdominal and transvaginal probes. Ultrasound measurements included three mutually perpendicular dimensions, the volume of the uterus, the thickness and structure of the myometrium and endometrium, and the size of the ovaries.

For patients with the diffuse form of adenomyosis, the following ultrasonographic features were considered:

- Increased length of the uterus, as well as anterior, posterior, and transverse dimensions
- Asymmetry in the thickness of the uterine walls

The following exographic signs are considered in women with the diffuse form of adenomyosis:

- Uneven thickness of the basal layer of the endometrium
- "Irregularity" of the basal layer of the endometrium
- Increase in the thickness of the functional zone ≥12 mm
- Small, round, and oval-shaped hypo- and anexogenic structures with a diameter of 1-2 mm in the basal layer of the endometrium
- Increase in the exogenic zone in the myometrium at varying thicknesses
- Detection of raised exogenic areas or small, dispersed fluid-filled spaces in hypo- and anexogenic formations with diameters between 2 and 6 mm

**Degrees of Adenomyosis:**

Grade 1 Adenomyosis (Early Stage):

1. Formation of small (approximately 1 mm in diameter) anexogenic tubes from the endometrium toward the myometrium
2. Small, rounded, and oval-shaped hypo- and anexogenic structures with diameters of 1-2 mm in the basal layer of the endometrium
3. Uneven thickness of the basal layer of the endometrium
4. Deformation and irregularity of the basal layer of the endometrium
5. Increase in exogeneity up to 3-4 mm in some areas of the myometrium directly adjacent to the uterine cavity

Grade II Adenomyosis (Moderate Stage):

1. Thickening of the uterus beyond the upper limit of normal
2. Thickening of one wall of the uterus by 0.4 cm or more compared to the other
3. Increase in exogeneity in varying thicknesses in separate areas of the myometrium directly adjacent to the uterine cavity
4. Small round nodules with a diameter of 2-5 mm in areas of increased exogeneity, as well as fluid-filled spaces of various shapes and sizes, containing small dispersed (blood) and sometimes low exogeneity thick adhesions (blood clots)

Grade III Adenomyosis (Severe Stage):

1. Enlargement of the uterus, mainly in the anterior-posterior dimension
2. Thickening of one of the uterine walls
3. A heterogeneous exogenic zone increasing in the myometrium, covering more than half of the thickness of the uterine wall
4. Detection of anexogenic formations or fluid-filled spaces of various shapes and sizes, containing small dispersed components (blood) within the exogenic zone with diameters of 2-6 mm
5. Formation of numerous medium and low exogenic strips close to each other at the site of pathological formation perpendicular to the examination plane
6. A high exogenic area is detected in the anterior part of the examination zone, and an anexogenic area in the distal part

A comparison of various exographic signs was conducted to clarify the diagnosis. The possibilities for visualizing the characteristic signs of adenomyosis were compared using these methods, and the diagnosis was later confirmed through histological examinations and surgical treatment.Transvaginal Exographic Examination: Conducted using Accuvix XQ-EXP digital stationary ultrasound diagnostic devices, classified as expert-level, manufactured by "Medison Co. Ltd" (Korea).

Performed using a 10 mm laparoscope from "Karl Storz" (Germany). Pneumoperitoneum was applied, and three trocars were inserted into the abdominal cavity for the laparoscope and surgical instruments.Electrophoresis and PCR: For electromorphological analysis, PCR products stained with ethidium bromide in agarose gel were evaluated. Visualization was carried out using a UV transilluminator. For morphological studies, 60 macro-preparatory samples obtained during hysterectomy in patients with severe pain syndrome and grade II-III diffuse adenomyosis were used.

The mathematical processing was carried out using the capabilities of the STATGRAPH 6 program (Microsoft, USA) and the general matrix of data from EXCEL 7.0 (Microsoft, USA). All quantitative data were recorded in the electronic spreadsheet format of MS Excel XP.Descriptive (summary) statistics methods applied include:Mean (M): A measure of central tendency.

Standard error of the mean (m): A measure of the variability of the sample mean.Frequency of occurrence for discrete characteristics: This refers to the frequency distribution of the characteristics with discrete values.To assess differences between groups for continuous variables, Student's t-test was used, and for comparing frequency values, Pearson's $\chi^2$ test and Fisher's exact method were applied.This approach enabled a comprehensive and accurate statistical analysis of the research data.

## RESULTS OF PERSONAL OBSERVATIONS AND THEIR DISCUSSION

The results of the treatment were derived from two prospective groups, which served as clinical material for the study: 106 patients with the diffuse form of adenomyosis and 118 patients

with the nodular form of adenomyosis. In total, 224 women with a diagnosis of adenomyosis, aged 30-50 years, were included in the study.

The main group was divided into two subgroups based on the form of adenomyosis: 1st group – diffuse form – 106 women, 2nd group – nodular form – 118 women. The control group consisted of 84 women in reproductive age with regular ovulatory menstrual cycles and no history of gynecological diseases.

The clinical characteristics of the examined women were based on their complaints, obstetric-gynecological, and somatic anamnesis. The age of the patients ranged from 30 to 50 years (mean age 42.5±1.5 years), with the age characteristics presented in Table 1.

**Table 1.**

**Age Characteristics of the Examined Patients**

| Age / Group | 30-35 age | | 36-40 age | | 41-50 age | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| I group (n=106) | 28 | 26,4±4,3 | 45 | 42,5±4,8 | 33 | 31,1±4,5 |
| II group (n=118) | 32 | 27,1±4,1 | 47 | 39,8±4,5 | 39 | 33,1±4,3 |
| Total (n=224) | 60 | 26,8±2,9 | 92 | 41,1±3,3 | 72 | 32,1±3,1 |
| control group (n=84) | 21 | 25,0±4,7 | 37 | 44,0 ±5,4 | 26 | 31,0±5,0 |

As it is known, the largest group of patients is in the 36-40 age group – in the main group, there are 92 women, which accounts for 41.1±3.3%, and in the control group, there are 37 women, accounting for 44.0±5.4%. Overall, in the main group, 152 patients (67.9±3.1%) were of reproductive age, while 72 patients (32.1±3.1%) were of premenopausal age. In the majority of patients with adenomyosis, the duration of the disease ranged from 5 to 10 years (Table 2).

**Table 2.**

**Duration of the disease in patients with adenomyosis**

| Duration of the disease | 1 group (n=106) | | II group (n=118) | |
|---|---|---|---|---|
| | No | % | No | % |
| First detected | 9 | 8,49±2,7 | 4 | 3,38±1,8 |
| Less than 5 years | 37 | 34,91±4,6 | 61 | 51,69±4,6 |
| 5- 10 years | 60 | 56,60±4,8 | 53 | 44,93±4,6 |

The menstrual cycle characteristics of patients with adenomyosis were as follows: heavy menstruation was observed in 55.37±3.3% of patients with adenomyosis (124 women). The distribution across the groups was as follows: in group 1 (diffuse form) 63 women (59.84±4.8%) had heavy menstruation, and in group 2 (nodular form) 61 women (51.69±4.6%) had heavy menstruation. Light menstruation was observed in 5.35±1.5% of patients (12 women). The distribution across the groups was as follows: in group 1 (diffuse form) 4 women (3.37%), and in group 2 (nodular form) 8 women (6.78±2.3%) had light menstruation. Moderate menstrual flow was observed in 39.28±3.3% of patients with adenomyosis (88 women). The distribution across the groups was as follows: in group 1 (diffuse form) 39 women (36.79±4.6%) had moderate menstruation, and in group 2 (nodular form) 49 women (41.53±4.5%) had moderate menstruation. In both groups, all patients with adenomyosis had regular and painful menstruation.

In women with the diffuse form of adenomyosis, primary infertility was observed in 9.43±2.9% of patients (10 women), and secondary infertility was observed in 13.20±3.3% of patients (14 women). In women with the nodular form of adenomyosis, primary infertility was observed in 5.93±2.9% of patients (7 women), and secondary infertility was observed in 10.17±2.9% of patients (12 women). Overall, primary infertility was found in 7.59±3.2% of women with adenomyosis (17 women), and secondary infertility was found in 11.60±2.2% of patients (26 women). In the 124 women with different forms of adenomyosis, most pregnancies ended in artificial abortion (55.36±3.3%). In women with the diffuse form of adenomyosis, 90.57±2.8% of women (96 women) gave birth, 54.72±4.8% (58 women) underwent artificial abortion, 11.32±3.2% (12 women) had spontaneous (miscarriage) abortion, and 2.83±1.6% (3 women) had ectopic pregnancy. In women with the nodular form of adenomyosis, 94.07±2.2% of women (111 women) gave birth, 55.23±4.6% (66 women) had artificial abortion, 9.32±2.6% (11 women) had spontaneous abortion, and 4.23±2.0% (5 women) had ectopic pregnancy. Overall, 92.41±1.7% of women with adenomyosis (207 women) gave birth, 55.36±3.3% (124 women) had artificial abortion, 10.27±2.1% (23 women) had spontaneous abortion, and 3.57±1.3% (8 women) had ectopic pregnancy.

Most patients with adenomyosis did not use contraception. Nearly one-third of the patients protected against pregnancy using an intrauterine device (IUD). Fewer used hormonal contraception or barrier methods. On average, in the diffuse form of adenomyosis, 44.33±4.8% of 47 women did not use contraception, only 8.49±2.7% used barrier contraception, 16.24±3.6% (18 women) used hormonal methods, and 31.94±4.5% (32 women) used IUDs. The study showed that in the nodular form of adenomyosis, 48.31±4.6% of 57 women did not use contraception, 5.09±2.1% used barrier methods, 17.79±3.5% (21 women) used hormonal methods, and 28.81±4.2% (34 women) used IUDs. Overall, among women with adenomyosis, 46.43±3.3% (104 women) did not use contraception, 6.69±1.7% (15 women) used barrier methods, 17.41±2.6% (39 women) used hormonal methods, and 29.47±6.0% (66 women) used IUDs. Based on the conducted examinations, it was determined that in the nodular form of adenomyosis, 55.23±4.6% of 66 women did not undergo diagnostic curettage of the cervical canal and uterine cavity mucosa, 40.54±4.5% of 47 women underwent diagnostic curettage once, and only 4.23±2.0% of 5 patients underwent two or more diagnostic curettages.

In total, on average, 56.25±4.8% of 126 women with different forms of adenomyosis did not undergo diagnostic curettage of the cervical canal and uterine cavity mucosa, 37.50±3.2% of 84 women underwent diagnostic curettage once, and 6.25±1.7% of 14 women underwent diagnostic curettage two or more times. According to the histological examination results of the endometrial specimens, hyperplasia (glandular-cystic) was detected in approximately 37.0% of cases, and proliferative endometrium was found in 27.55% of cases (Table 3).

The data regarding histological examinations after diagnostic curettage of the cervical canal and uterine cavity in patients with adenomyosis showed the following results:In patients with diffuse adenomyosis, proliferative endometrium was detected in 28.26±6.7% (13 women) of cases during diagnostic curettage. Secretory endometrium was found in 23.91±6.3% (11 women) of patients. Endometrial glandular hyperplasia was observed in 15.22±5.3% (7 women), and endometrial glandular cystic hyperplasia was detected in 19.57±5.9% (9 women).

**Table 3.**

**Histological examination results of cervical canal and uterine cavity mucosa after diagnostic curettage in patients with adenomyosis**

| Results | I group (n=46) | | II group (n=52) | | Total (n=98) | |
|---|---|---|---|---|---|---|
| | No. | % | No | % | No | % |
| Proliferative Endometrium | 13 | 28,26±6,7 | 14 | 26,92±6,2 | 27 | 27,55±4,5 |
| Secretory endometrium | 11 | 23,91±6,3 | 9 | 17,30±5,2 | 20 | 20,41±4,1 |
| Endometrial glandular hyperplasia | 7 | 15,22±5,3 | 9 | 17,30±5,2 | 16 | 16,27±3,7 |
| Endometrial glandu-lar cystic hyperplasia | 9 | 19,57±5,9 | 12 | 23,10±5,8 | 21 | 21,49±4,2 |
| Endometrial Polyps | 6 | 13,04±4,9 | 8 | 15,38±4,9 | 14 | 14,28±3,5 |

Endometrial polyps were identified in 13.04±4.9% (6 women) of cases. In patients with the nodular form of adenomyosis, proliferative endometrium was detected in 26.92±6.2% (14 women) during diagnostic curettage.

Uterine cervical pathologies were observed in 50.89±3.3% (114 women) of patients, uterine fibroids in 50.45±3.4% (113 women), and chronic cervicitisin 50.45±3.4% (113 women).Uterine cervical pathologies were most common, observed in nearly half of the patients.In women with the diffuse form of adenomyosis, cervical pathologies were found in 54.71±4.8% (58 women).

Uterine fibroids were found in 56.60±4.8% (60 women), and pelvic inflammatory diseases in 44.33±4.8% (47 women). In women with the nodular form of adenomyosis, polycystic ovarian syndrome (PCOS) was observed in 32.58±3.1% (73 women). The breakdown is as follows:Group 1 (diffuse form): 36.79±4.6% (39 women) Group 2 (nodular form): 28.81±4.2% (34 women)

External Genital Endometriosis was less common, observed in 31.25±3.1% (70 women), with the following distribution: Group 1: 34.9±4.6% (37 women) Group 2: 27.9±4.1% (33 women) Bacterial vaginosis (28.57±3.0%, 64 women) and vaginitis (25.27±2.8%, 56 women) were also observed in the patients.

Ovarian cyst-like tumors (13.39±2.3%, 30 women) and urinary tract infections (20.08±2.6%, 45 women) were less frequent. In patients with diffuse adenomyosis, hysterectomy was performed in 13.20±3.3% (14 women), and tubectomy in 8.49±2.7% (9 women).In patients with the nodular form of adenomyosis, hysterectomy was performed in 10.16±2.8% (12 women), and tubectomy in 6.7±2.3% (8 women).

The most common chronic extragenital pathologies were found in the gastrointestinal tract (gastritis, cholecystitis) in 40.62±3.3% (91 women), followed by nervous system diseases in 35.71±3.2% (88 women), and chronic rhinosinusitis in 35.29±3.2% (79 women). Endocrine disorders (24.55±2.8%, 55 women) and cardiovascular diseases (22.32±2.8%, 50 women) were less common. Skin diseases (20.98±2.7%, 47 women) and urinary system diseases (14.73±2.4%, 33 women) were also observed.

Mastopathy was detected in 11.16±2.2% (25 women) of those with different forms of adenomyosis, while it was not found in the control group.The relative risk of "extragenital diseases" was highest in women with diffuse adenomyosis for endocrine diseases (relative risk 2.58, confidence interval 0.35-8.46) and cardiovascular diseases (relative risk 2.38, confidence interval 0.52-9.31).

In patients with the nodular form of adenomyosis, the highest relative risk was found for endocrine diseases (relative risk 2.63, confidence interval 0.48–8.65) and cardiovascular diseases (relative risk 2.38, confidence interval 0.52–9.31).

After statistical analysis of the data, a significant association was found between the presence of endocrine diseases (relative risk NR=0.538; $p<0.001$) and cardiovascular diseases (NR=0.426; $p<0.001$) with the development of endometrial pathology in these patients.

Upon analyzing the data, it was observed that in patients with the diffuse form of adenomyosis, grade 2 obesity (BMI 35–39.99) was the most commonly observed condition, occurring in 35.84±4.6% (38 women) of the cases. Grade 1 obesity (BMI 30–34.99) was identified in 16.98±3.6% (18 women) of patients. Overweight (BMI 25–29.99) was recorded in 13.20±3.3% (14 women).

In total, obesity (BMI 30 or more) was observed in 54.71±4.8% (58 women) of the cases.In patients with the nodular form of adenomyosis,

grade 2 obesity (BMI 35–39.99) was also the most commonly observed condition, occurring in 33.38±4.4% (40 women). Grade 1 obesity (BMI 30–34.99) was recorded in 20.34±3.7% (24 women), while overweight (BMI 25–29.99) was found in 16.10±3.4% (19 women). Overall, obesity (BMI 30 or more) was observed in 56.78±4.6% (67 women).

In total, 125 women (55.80±3.3%) with different forms of adenomyosis were found to have obesity with a BMI of 30 or more. Overweight (BMI 25–29.99) was recorded in 14.73±1.3% (33 women) of the cases.

It was found that in patients with diffuse adenomyosis, the most common comorbidities were hypertension (13.20±3.3%, 14 women), varicose veins of the lower extremities (9.43±2.8%, 10 women), and non-toxic diffuse goiter (7.55±2.7%, 8 women).

In patients with the nodular form of adenomyosis, the most common comorbidities were hypertension (10.16±2.8%, 12 women) and varicose veins (6.78±2.3%, 8 women). Therefore, the somatic status of all patients was complicated by the presence of severe comorbidities.

To study the molecular biological aspects of the pathogenesis of diffuse adenomyosis, an assessment was made of the frequency distribution of alleles and genotypes of matrix metalloproteinase 1 (MMP1) (1G/2G), stromelysin-1 (MMP3) (5A/6A), and plasminogen activator inhibitor-1 (PAI-1) (4G/5G) genes.

The study aimed to identify possible correlations between these genetic variants and the clinical variants of the disease. This study included 32 patients with diffuse adenomyosis.

The inclusion criteria for the study were women of reproductive and perimenopausal age diagnosed with diffuse adenomyosis based on comprehensive clinical, anamnestical, and instrumental diagnostic data, including echography, Doppler studies, and hysteroscopic examination with myometrial puncture biopsy.

The patients' age ranged from 30 to 50 years (mean age 42.5±1.5 years). The duration of the clinical manifestations of the disease ranged from a few months to 10 years.The control group consisted of 11 women of reproductive age who had a regular ovulatory cycle and no history of gynecological diseases.

The analysis of the distribution of polymorphic variants of the studied genes showed the comparative frequency of the alternative alleles of MMP1, MMP3, and PAI-1 genes in patients with the diffuse form of adenomyosis (ADF) (Table 4).

**Table 4.**

**Distribution of Allele Frequencies of MMP1, MMP3, and PAI-1 Genes in the Examined Patient**

| Genes Investigated | The frequency of identified alleles | | | |
|---|---|---|---|---|
| | No | % | No | **%** |
| *MMP1* | *1G* | | *2G* | |
| ADF patients (n=32) | 19 | 59,4 | 13 | 40,6 |
| Control group (n=11) | 5 | 45,4 | 6 | 47,7 |
| *MMP3* | *5A* | | *6A* | |
| ADF patients (n=32) | 15 | 46,9 | 17 | 53,1 |
| Control group (n=11) | 4 | 36,4 | 7 | 63,6 |
| *PAI-1* | *4G* | | *5G* | |
| ADF patients (n=32) | 18 | 56,3 | 14 | 43,7 |
| Control group (n=11) | 6 | 54,5 | 5 | 45,4 |

The allele frequencies of the genes in this group did not differ significantly from those in the control group. Similarly, there were no significant differences in the distribution of genotype frequencies compared to the control group (Table 5)

**Table 5.**

**Distribution of Allele Frequencies for MMP1, MMP3, and PAI-1 Genes in the Examined Patient Groups**

| Genes Investigated | The frequency of identified alleles | | | | | |
|---|---|---|---|---|---|---|
| | No | % | No | **%** | No | % |
| *MMP1 1G/2G* | *1G/1G* | | *1G/2G* | | *2G/2G* | |
| ADF patients (n=32) | 10 | 31,3 | 15 | 46,9 | 7 | 21,8 |
| Control group (n=11) | 3 | 27,3 | 5 | 45,4 | 3 | 27,3 |
| *MMP3 5A/6A* | *5A/5A* | | *5A/6A* | | *6A/6A* | |
| ADF patients (n=32) | 6 | 18,8 | 19 | 59,4 | 7 | 21,8 |
| Control group (n=11) | 2 | 18,2 | 5 | 45,4 | 4 | 36,4 |
| *PAI-1 4G/5G* | *4G/4G* | | *4G/5G* | | *5G/5G* | |
| ADF patients (n=32) | 7 | 21,8 | 20 | 62,5 | 5 | 15,7 |
| Control group (n=11) | 3 | 27,3 | 6 | 54,5 | 2 | 18,2 |

Considering that diffuse adenomyosis is a hormone-dependent disease and that it has different clinical courses in various age groups, we conducted a study on the polymorphism of the MMP1 gene in relation to the age of patients during their reproductive or premenopausal periods (Table 6).

**Table 6.**

**Distribution of genotype frequencies of the MMP1 gene in patients with diffuse adenomyosis in different age periods**

| Groups | The frequency of genotypes | | | | | |
|---|---|---|---|---|---|---|
| | *1G/1G* | | *1G/2G* | | *2G/2G* | |
| | No | % | No | % | No | % |
| Reproductive period (n= 18) | 4 | 22,2 | 9 | 50,0 | 5 | 28,7 |
| Premenopausal period (n=14) | 10 | 71,4* | 1 | 7,1 | 3 | 21,5 |

*Note: * – The differences are significant compared to patients in the reproductive period.(p=0,02)*

As shown in Table 6, when comparing the prevalence of MMP1 genotypes 1G/2G and 2G/2G in patients with diffuse adenomyosis in the reproductive and perimenopausal periods, no significant differences were found ($p>0.05$). However, the MMP1 gene's 1G/1G homozygous genotype was significantly more common in perimenopausal patients ($p=0.02$). The data suggest that in women with a non-active course of the disease in the perimenopausal period (characterized by small, stable uterine size and rare episodes of menorrhagia), the 1G/1G genotype is present at a higher frequency. The main symptoms in this group included small amounts of dark brown discharge before or after menstruation. In these patients, the uterine size was consistent with a 5-6-week pregnancy. The 1G/1G homozygous genotype of the MMP1 gene is considered a prognostically favorable variant in the clinical course of adenomyosis.

Considering the difficulty and relevance of correcting immune disorders in adenomyosis (AM), as well as the limited research on the role of immune cells, the aim of our study was to investigate the role of immune system cells as key biomarkers in the diagnosis of adenomyosis in women of reproductive age. The analysis of cytokines in the

peripheral blood of patients with AM revealed the following findings. In patients with AM, compared to reference values, the levels of cytokines such as IL-1β, IL-2, IL-4, IL-6, Fas-L, and TNF-α were significantly ($p < 0.01$) elevated at moderate levels.

Before treatment, patients with AM exhibited a significant ($p<0.05$) increase in IFN-γ levels in their blood serum (134.2±8.20 pg/ml). After treatment, the concentration values remained high (40.3±0.48 pg/ml). The levels of IL-1β remained consistently high throughout the course of the disease, exceeding the reference values. Throughout the entire observation period, TNF-α indicators remained within reference values.

At all stages of AM, the levels of IL-2, IL-4, and IL-6 exceeded reference values, and they did not significantly change in the disease dynamics. After treatment, a decrease in the levels of these cytokines was observed, but their concentrations remained high during this period. It is also important to note that in AM, at all stages of the disease, the amount of anti-inflammatory IL-4 in blood serum increased. After treatment, the level of this cytokine decreased ($p<0.05$). The scientific literature on changes in T-lymphocyte subpopulations in AM patients is contradictory. A correlation was found between the level of TNF-α synthesis and the number of CD45+ cells ($r=0.64$, $p=0.023$), suggesting the formation of a Th1 response with an increase in IFN-γ and a reduction in immune response. No significant changes were observed in the main subpopulations of blood lymphocytes in the patients.

In AM, compared to reference values, a significant increase was found in all T-helper/inducer markers (CD3+CD4+CD45+) and in the immunoregulatory index of CD3+CD4+/CD3+CD8+ (T-helper/STL). Conversely, the number of NK cells expressing the CD8 antigen (CD3-CD8+CD45+), blood cells with high proliferative activity expressing the CD8+ receptor, and CD45+ lymphocytes decreased. This is a normal defense response of the organism, which leads to inflammation of the immune system and, consequently, a weakening of immune control.

Thus, the analysis of the immune status of patients with AM showed more distinct changes in the cellular component of immunity: a decrease in the number of NK cells expressing the CD8 antigen alpha

chain (CD3-CD8+CD45+) and values in lymphocytes and the immunoregulatory index of CD3+CD4+/CD3+CD8+ (T-helper/LST), with an increase in T-NK (CD3+CD56+CD45+) and T-lymphocytes (CD3+CD19-). The change in cytokine status in AM was accompanied by changes in the functional activity of lymphocytes, characterized by an increase in the synthesis of all the studied cytokines. Differences in the spectrum and levels of cytokines involved in the initiation and development of the inflammatory process in AM can provide a basis for various approaches to complex immunotropic and etiological therapy for AM, which can be used in the practical activities of physicians.

For morphological research, we used 47 uterine wall macropreparations obtained during hysterectomy in patients with II-III degree diffuse adenomyosis, accompanied by acute pain lasting more than 6 months. The women were operated on during the proliferative phase of their menstrual cycle. To study cell kinetics, monoclone antibodies (MAbs) for Ki-67 (DO-7 clone) and p53 (clone MM1; DAKO, Denmark) were used to assess their proliferation and apoptosis. In patients with adenomyosis, the eutopic endometrium was found to correspond to the proliferative phase of the menstrual cycle. The covering epithelium showed signs of immaturity, characterized by numerous proliferating cells (14.3±3.1%; 95% CI: 6.4-20.8%) with a high nuclear-cytoplasmic ratio and the absence of a formed apical portion. The glands constituted 28.5±2.8% (95% CI: 24.2-32.8%) of the volume of the endometrium, and, mainly, at the deeper parts of the endometrium, localized expansions with transitional movements were formed in some sections.

In the structure of the uterine glands, the maximum number of mitoses was observed in the cervical and fundal regions, where Ki-67-positive cells accounted for 16.7±3.2% and 24.7±3.3%, respectively. In the body region of the uterus, the proportion of proliferating cells did not exceed 8%.

At the same time, the high rate of epithelial proliferation in the endometrium led to the formation of a pseudostratified epithelium (characterized by the absence of a clearly defined apical pole of the uterine gland cells and tightly packed nuclei). In the stroma of the

eutopic endometrium, cell proliferation was also observed, but the number of proliferating cells was lower than in the epithelial structures of the endometrium, accounting for 9.9±3.8% (95% CI: 6.2-10.4%), although the stroma was characterized by a high cell density. This was associated with lymphocytic infiltration. At the same time, the number of cells expressing the p53 apoptosis marker was extremely low and did not exceed 3% in all patients with adenomyosis. Additionally, it should be noted that the renewing functional layer of the endometrium was rich in blood vessels, some of which were filled with erythrocytes. In some areas of the uterine wall, invasion of the uterine glands into the depth of the endometrium was observed. The glands varied in shape and size. In some cases, the invasion of single, non-branching tubular glands into the myometrium was observed.

Thus, in chronic pelvic pain associated with adenomyosis, disruption of epithelial-mesenchymal interactions reflecting defective morphogenesis of the uterine glands was also recorded. This was accompanied by an increase in epithelial cells in the context of high estrogen sensitivity in both epithelial and stromal cells.

In accordance with the study objectives, we conducted research to determine the diagnostic value of CA-125 as a marker, since it is the most commonly used first-line biomarker for screening ovarian malignancies. We would like to provide information about a rare case of adenomyosis in a 44-year-old perimenopausal patient. This patient, due to severe adenomyosis and high CA-125 levels, presented with an enlarged uterus in the pelvic-abdominal cavity. The patient suffered from diabetes mellitus and was taking oral hypoglycemic medications. For the past 3 months, she had been taking tranexamic acid (1-1.5g, 3 times a day) and cyclic progesterone (10 mg medroxyprogesterone acetate daily for 10 days each month) during bleeding episodes.

The patient had a painful mass located two fingers above the navel in the pelvic and abdominal regions (equivalent to a 28-week pregnancy). Initially, a diagnosis of complicated uterine fibroids was made, and the patient was referred for laboratory and radiological examinations. Curettage was performed due to heavy bleeding, with hemoglobin levels dropping from 11 g/dL to 8.8 g/dL.

Magnetic resonance imaging (MRI) of the abdominal cavity was performed to confirm the diagnosis. MRI confirmed the diagnosis of adenomyosis: diffuse asymmetric adenomyosis of the uterus, primarily involving the anterior wall of the myometrium, with an unclear endomyometrial junction. Both ovaries were normal. Except for elevated CA-125 tumor antigen levels (1032 and 1725 IU/ml, measured two days apart), all other standard tests, including the Papanicolaou smear, were within normative values.

The CA-125 test can be used in the initial screening of women with adenomyosis to differentiate it from fibroids, although the diagnostic accuracy of using only the CA-125 test is considered limited. The threshold values for CA-125 in the differential diagnosis of adenomyosis and fibroids, especially the 19 U/mL cutoff, improve the diagnostic indicators.

The main diagnostic criteria for adenomyosis include a round uterus, cystic spaces in the myometrial wall, and linear stripes in the endometrial zone. Color Doppler ultrasound is used for differential diagnosis with uterine leiomyomas.

When assessing blood flow velocity in the uterine vessels, the pulsatility index in arteries within or around the myometrium is greater than 1.17 in 82% of adenomyosis cases, while it is less than 1.17 in 84% of cases with uterine fibroids.

Thus, adenomyosis primarily occurs in women of reproductive age. Most women do not have specific complaints. The characteristic symptoms of adenomyosis include chronic pelvic pain and abnormal uterine bleeding. The diagnosis of adenomyosis using ultrasound can be compared with the diagnostic capabilities of MRI. Ultrasound is an effective, safe, and inexpensive method for diagnosis.

During the ultrasound examination, attention was given to the presence of adenomyotic foci and fibromatous nodules in the vaginal canal, as well as determining their number, size, type, and topography. In 119 patients, the forms of adenomyosis (AM), the extent of its spread, differential diagnosis, and early manifestations of the pathological process were studied using 3D transvaginal echography (TVE). The information value of various visualization techniques was evaluated considering the sensitivity and specificity of quality

ultrasound characteristics. The results of this evaluation are presented in Table 7.

The 100% sensitivity indicator had only one exographic feature – "perpendicular lines to the ultrasound section." In 2D exography mode, the same indicator was 32.3±6.4%. The 85% sensitivity indicator for "heterogeneous structure of the myometrium" was observed in 94.4±2.7% of 3D examinations and 78.5±5.5% in 2D exography. Indistinct M-exo contours or irregular contours at the boundary of the basal layer of the endometrium were detected in 90.7±3.5% and 35.4±6.5% of cases, respectively. For the diagnosis of adenomyosis, specificity greater than 85% was calculated for "cystic structures in the myometrium," with 3D TVE at 53.7±6.2% and 2D TVE at 27.6±6.1%. The clear visualization of changes in the junction zone (JZ) was only possible with three-dimensional exographic images, reaching 83.3±4.5%. The combined high sensitivity and specificity were only observed in "perpendicular lines to the ultrasound section."

**Table 7.**

**Frequency of Detection of Qualitative Exographic Signs of Adenomyosis in Patients with Adenomyosis**

| Exographic Signs | 2D (n=54) | | 3D (n=65) | |
|---|---|---|---|---|
| | No | % | No | % |
| Presence of changes in the basal zone (poor visualization) | 21 | 32,3±6,4 | 45 | 83,3±4,5 |
| Indistinct contour of the myometrium at the endometrium border | 23 | 35,4±6,5 | 49 | 90,7±3,5 |
| Myometrial cysts | 18 | 27,6±6,1 | 29 | 53,7±6,2 |
| Asymmetry of the myometrium of the uterine wall | 22 | 33,8±6,4 | 25 | 46,3±6,1 |
| Lines perpendicular to the ultrasound section ("linear stripes") | 21 | 32,3±6,4 | 54 | 100 |
| Heterogeneity of the myometrium | 51 | 78,5±5,5 | 51 | 94,4±2,7 |
| Adenomyotic nodules | 11 | 16,9±5,1 | 12 | 22,2±5,2 |
| Raoud-like form of uterus | 42 | 64,6±6,5 | 43 | 79,6±4,9 |

It was not possible to evaluate the characteristics of the JZ by measuring it. In this context, it was important to note the frequency of

detecting changes in the JZ structure: its poor visualization and irregular contour at the boundary with the endometrium. With 2D exography, only 35.4±6.5% of cases showed the characteristic qualitative features of changes in the JZ. We considered that identifying infiltration and disorganization in the contact zone of the endometrial tissue with the JZ, though subjective, could be an important criterion for diagnosing adenomyosis. In all 54 (100%) patients, an increase in the volume of the uterine body was detected through 2D TVE, with an average value of 255±76 (236-425) $cm^3$, which was above the norm (128 $cm^3$). When two or more distinct ultrasound characteristics were present, the diagnostic accuracy of 2D and 3D TVE was 83.3±4.5% and 90.7±3.5%, respectively. Compared to 2D parameters, 3D criteria had significantly higher sensitivity in diagnosing adenomyosis. To eliminate subjectivity in evaluating "heterogeneous JZ," we used 3D transvaginal imaging, analogous to MRI.

In patients with different forms of adenomyosis, Doppler blood flow indicators in uterine vessels were analyzed. Depending on the phase of the menstrual cycle, in the second phase, the final diastolic blood flow velocity was found to be approximately twice as high compared to the first phase. Lower blood flow resistance was observed in the second phase, which manifested as a significant reduction in SDA, MI, and PI.

Of the 224 patients included in the study, 165 (73.7±2.9%) complained of pain. In total, 113 (68.5±3.6%) patients had dysmenorrhea, of which 65 (57.5±4.6%) had progressive worsening. Regarding the degree of pain during dysmenorrhea, 33 (29.2±4.3%) had mild pain, 17 (15.2±3.4%) had moderate pain, and 63 (55.6±4.7%) had severe pain. In total, 59 (35.8±3.7%) patients had chronic pelvic pain, 87 patients (52.7±3.9%) had dyspareunia, and 19 patients (11.5±2.5%) experienced anorectal pain.

Dysmenorrhea was most common in the second group, i.e., the group with nodular adenomyosis. No significant differences were found between the first and second groups of adenomyosis patients in terms of dysmenorrhea scores according to VAŠ. However, in the first group, the minimum score for dysmenorrhea was 5, while in the second group, the maximum score was 7, respectively.

In the diffuse form of adenomyosis, compared to the nodular form, heavy menstruation, prolonged menstruation, and a longer menstrual cycle, which led to anemia, were significantly more common. In the nodular form, compared to the diffuse form, the presence of pain syndrome and primary and secondary infertility were more frequently observed.

Hormonal investigations were carried out: luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, anti-Müllerian hormone (AMH), prolactin, testosterone, and 17-hydroxyprogesterone levels were determined on the 2nd-3rd day of the menstrual cycle; progesterone levels were determined on the 22nd-23rd day of the menstrual cycle. After 3 and 6 months, LH, FSH, estradiol, and AMH levels were re-evaluated. Ultrasound examinations of the pelvic organs were conducted, and the size of the uterus and the width of the uterine transition zone were determined.

The analysis revealed that in patients with the diffuse form of adenomyosis, compared to the control group, FSH and LH levels were higher, although the differences were not statistically significant ($p>0.05$). In patients with the nodular form of adenomyosis, the level of estradiol was significantly higher compared to the control group. Despite all indicators being within normative values, there was a statistically significant increase in prolactin levels in the first group compared to the control group.

In patients of the second group with adenomyosis, low progesterone levels indirectly indicated a deficiency in the second phase of the menstrual cycle, while no disturbances in ovulation were detected (according to functional diagnostics and folliculogenesis monitoring tests). Testosterone and 17-hydroxyprogesterone levels were comparable between the groups.

One of the objectives of the treatment was to increase the frequency of pregnancy in women with infertility and adenomyosis, so we determined the frequency of pregnancy and the time to conception in patients from different groups depending on the treatment methods. It was found that in the 1A subgroup, pregnancy occurred on average 6.2±1.4 (2-7) months after, while in the 2A subgroup, it occurred on average 5.8±1.4 (5-8) months after. In

patients from the 1B and 2B subgroups, the pregnancy rate was assessed from the moment dienogest was discontinued. In the 1B subgroup, this period was on average 4.0±1.2 (3-6) months ($p \leq 0.05$ compared to 1A subgroup and group 2), and in the 2B subgroup, it was 5.3±1.6 (4-8) months. In the control group, pregnancy occurred after 4.5±1.2 (3-9) months.

The results of the ultrasound data analysis showed that uterine fibroids were present in 53 (44.93±4.6%) patients with nodular adenomyosis, while uterine fibroids were most commonly observed in 60 patients (56.60±4.8%, $p<0.01$) with diffuse adenomyosis. The study of the localization of myomatous nodules in conjunction with different forms of adenomyosis revealed that mainly diffuse adenomyosis coexisted with intramural myomatous nodules (FIGO type 4) in 64 (60.4%) patients, followed by diffuse adenomyosis with intramural-subserosal (FIGO type 5) myomatous nodules in 18 (16.9%) patients.

In the nodular form of adenomyosis, the coexistence with intramural (FIGO type 4) myomatous nodules was most commonly found, observed in 8 (7.5%) and 5 (4.7%) patients, respectively. Rarely, type 0 (submucosal fibroids on a stalk) was found in just 1 (0.9%) patient, and type 2 (intramural fibroids extending less than 50% into the uterine cavity) was observed in 2 patients (1.9%). We also studied the number of nodules (multiple/single nodules) in conjunction with different forms of adenomyosis. The coexistence of multiple myomatous fibroids with adenomyosis was found in 58 patients (54.7%), and the coexistence of single fibroids with adenomyosis was found in 48 (45.3%) patients. When studying ultrasound results according to the forms of adenomyosis, we observed the coexistence of diffuse adenomyosis with multinodular fibroids in nearly half of the women, 49 (53.9%) patients. By frequency, the coexistence of diffuse adenomyosis with a single myomatous nodule was observed in 42 (46.1%) cases. In cases of coexisting myomatous nodules and adenomyosis, the majority of the nodules were proliferating (65 nodules, 61.3±4.6%), while the coexistence with simple adenomyotic nodules (41 nodules, 38.7±4.6%) was also noted.

Ultrasound examination results in patients with symptomatic uterine fibroids showed that the total uterine volume ranged from 9-

10 weeks to 12 weeks, with the maximum number of nodules being 8 in two patients. However, in some patients, it was not possible to calculate the total number of nodules during the ultrasound due to larger nodules covering the smaller ones. The nodule sizes ranged from diameters of 4.5-5 mm to larger sizes of up to 60-65 mm.

However, the presence of a single large nodule proved to be less informative in determining the type of myomatous nodule for assessing uterine volume. To determine the proliferative activity of fibroids, we used color Doppler ultrasound to assess blood flow quality around and within the myomatous and adenomyotic nodules in diffuse adenomyosis.

The study of nodule location in patients with uterine fibroids revealed that the nodules were located in the middle third of the uterine body in 52.6% of cases, at the uterine fundus or upper third in 37.4% of cases, and rarely (10.0%) in the lower third of the uterine body. This topography was similar in cases of coexisting adenomyosis. The ultrasound examination showed that the myomatous nodules were most commonly located in the middle third of the uterine body in 51.3±4.7% of cases, at the fundus or upper third in 34.5±4.5%, and in the lower third of the uterine body in 10.6±2.9%. The nodules were located on the anterior wall in 43.4±4.7% of cases, on the posterior wall in 39.8±4.6%, and less frequently on the lateral walls in 13.3±3.2%.

Ultrasound showed that the uterine volume ranged from 7-8 weeks to 13-14 weeks, with the maximum number of nodules reaching 12. The nodule sizes ranged from the smallest (4.2-4.8 mm) to the largest (106-135 mm). At the same time, the diffuse form was most commonly diagnosed as grade 1 in 33 (55.0±6.4%) patients, followed by grade 2 in 8 (13.3±4.5%) patients, and grade 3 in 19 (31.7±6.0%) patients. The nodular form of adenomyosis was identified in 53 (44.9±4.6%) patients, of which 14 (26.4±6.0%) had grade 1 nodular adenomyosis, 27 (51.0±6.7%) had grade 2, and 12 (22.6±5.8%) had grade 3.

Based on the results of the study, it is emphasized that not only does ultrasound examination with expert-class devices help in making an accurate diagnosis, but it also allows for determining the type of myomatous nodules (whether simple or actively proliferating), as well as the degree of spread of adenomyosis in the uterus. The first degree

of the diffuse form of adenomyosis is often not detected or depicted on ultrasound, which leads to incorrect treatment and low efficacy.

For the morphological study, the uteri of 43 women who had undergone hysterectomy were taken as objects. The age of the patients who underwent radical surgery ranged from 39 to 45 years. The combined presence of endometrial hyperplasia and adenomyosis is considered a significant factor in the development of uterine body cancer. Pathological processes, often combined, were mainly observed in the age group of 40–45 years (60.5%). The macroscopic examination of the uterus removed along with myoma revealed that myomatous nodules varied in number and size. Generally, they had a dense consistency and lacked capsules. The nodules were located in various areas, but intramural nodules were more common, and submucosal nodules, which grow into the uterine cavity, were less frequent.

In the search for various probable factors influencing the development of adenomyosis, great attention was paid to damage to the subendometrial basal membrane and to the "junctional zone" (JZ) described using magnetic resonance imaging (MRI) for the first time. Thus, the results of the pathomorphological studies have enabled accurate diagnosis and confirmation of combined or isolated forms of myoma and adenomyosis, determination of the proliferative activity of myomatous nodules, and identification of the risk of malignant degeneration of the endometrium when adenomyosis is associated with endometrial hyperplasia.

The findings of the pathomorphological studies confirmed the need for high-quality examinations using high-resolution devices. This method allows for accurate diagnosis, selection of conservative treatment methods, and reduction of the frequency of radical surgeries, which leads to economic benefits such as a shorter hospital stay and fewer days of work lost after surgery when compared to radical surgery for myomectomy.

Based on the conducted studies and obtained results, we proposed an algorithm for the examination and treatment of combined uterine fibroids and adenomyosis (Figure 1).

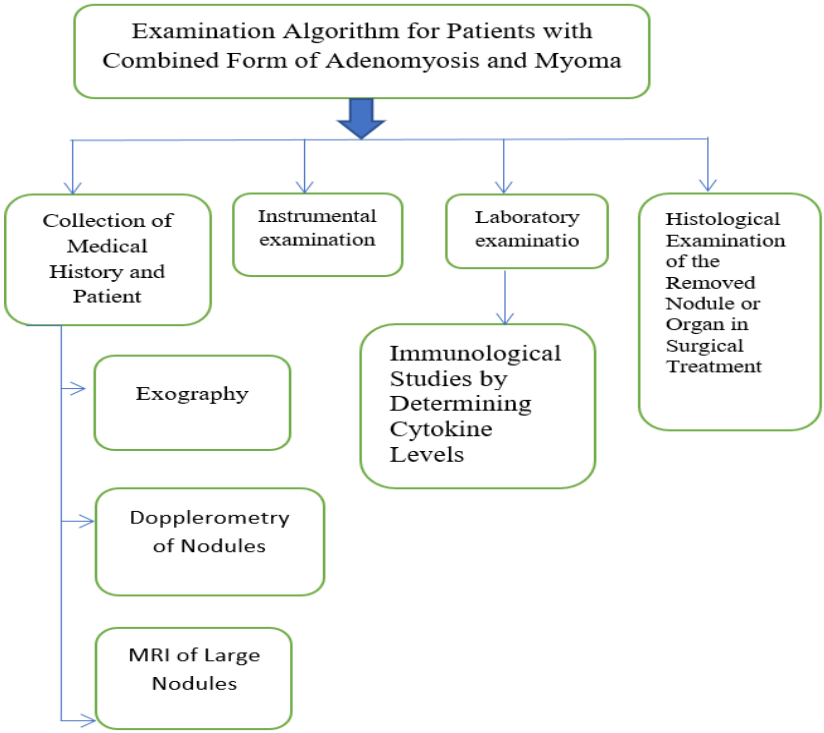


**Figure 1. Examination algorithm for patients with the combined form of myoma and adenomyosis**

The diagnostic algorithm we suggest for patients with the combined form of myoma and adenomyosis includes the following:

- Collection of complaints: Clarify which symptoms are causing the most discomfort in order to assign the correct therapy. This helps in properly selecting medications and their application methods.
- Careful collection of anamnesis (disease progression, disease duration, family history, reproductive history);
- Bimanual examination;
- Ultrasound examination with a transvaginal probe of high informativeness;
- Dopplerometry of blood flow around and within the myomatous node or nodular adenomyosis, in order to determine the

clinical and morphological variant of uterine fibroids (simple or proliferating fibroids);

- Pelvic organ MRI (if necessary);
- Immunological blood test to determine the levels of anti-inflammatory cytokines: IL-1, IL-6, TNF-α, and anti-inflammatory cytokines: IL-10, VEGF;
- Histological examination of the excised node or organ in surgical treatment.

Additionally, we have also proposed an algorithm for the treatment of patients with the combined form of myoma and adenomyosis (see Fig. 2).The priority choice of medications depends on the activity of the myomatous nodes. In proliferating fibroids, the Ulipristal acetate (UPA) preparation is initially prescribed starting from the 2nd day of the menstrual cycle for 84 days continuously at a dose of 5 mg daily, followed by Dienogest 2 mg, continuously for 6 menstrual cycles at a dose of 1 tablet daily. For simple fibroids, on the contrary, Dienogest is prescribed first for 6 menstrual cycles continuously, followed by daily UPA for 84 days.

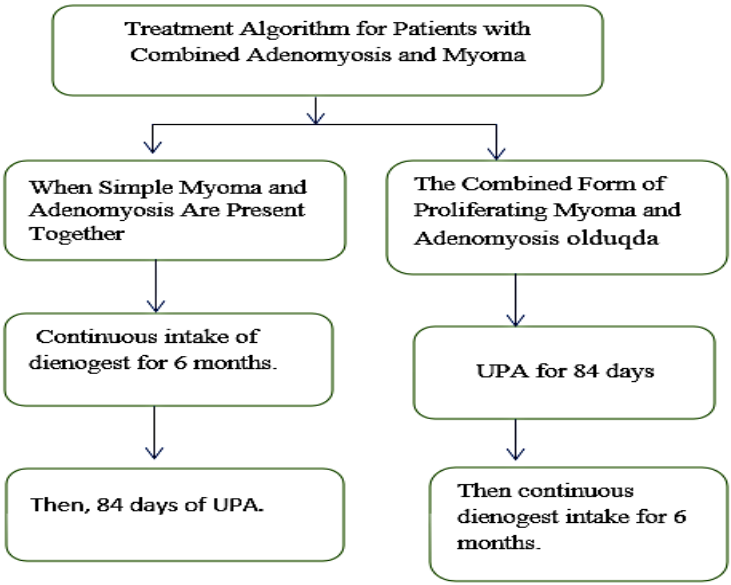


**Fig. 2: Treatment Algorithm for Patients with Combined Myoma and Adenomyosis**

Adenomyosis is often associated with endometriosis and is considered an analogous disease. Both of these conditions can carry significant psychosomatic and social burdens, and may require additional research to understand the interdependence of various factors involved in the development of chronic processes.

In addition to somatic symptoms, patients with adenomyosis often face increased discomfort, higher levels of stress, and various types of pain, all of which impact their social lives.

The quality of life of reproductive-aged women with adenomyosis has been studied using the SF-36 (or MOS (Medical Outcome Study) Short Form-36) general questionnaire. The SF-36 includes a multi-point scale that evaluates 8 health concepts:1) Physical activity (PA);2)Role of physical problems in limiting life activities (FP);3)Body pain (BP);4)General health (GH);
5)Vitality (V);6)Social activity (SA);7)Role of emotional problems in limiting life activities (EP);8)Mental health (MH).

It was found that in patients with adenomyosis and pain syndrome, the most common symptom in the first group of patients (19.18±0.27 points) was sleep disorders, while in the second group, the most common symptoms were affective tension (17.29±0.12 points) and depressive disorders (16.18±0.21 points). Symptoms such as obsessive-compulsive disorders (10.56±0.23 and 7.32±0.03 points) and anankastic disorders (12.25±0.29 and 9.18±0.32 points) were observed less frequently.

In reproductive-aged women with adenomyosis and pain syndrome, the values of reactive and personal stress characteristics were significantly higher compared to women with adenomyosis without pain syndrome (1.5 times and 1.18 times higher, respectively, $p<0.001$). The analysis of quality of life criteria across various age groups showed statistically significant differences in indicators reflecting both physical and psychosocial functioning. Comparisons were made between patient groups.

Suggestions for studying the quality of life in women with adenomyosis are expected to characterize new approaches to the treatment of this condition and contribute to the development of informed and operational measures. This study should be considered

as the first step in understanding the treatment perspective for women with adenomyosis.

When analyzing gynecological diseases and extra-genital pathology in the examined patients, it was found that all women had a history of gynecological diseases associated with various forms of adenomyosis. The obtained data showed that adenomyosis negatively affects various aspects of the quality of life in reproductive-aged patients. The majority of patients with pain syndrome exhibited symptoms such as anxiety-phobic and depressive disorders, affective tension, obsessive and anankastic disorders.

The application of these results in practice can guide the reduction of the negative effects of adenomyosis, with future research aimed at providing more effective treatments and services for women with this condition.

Given the lack of consensus on the most appropriate treatment for adenomyosis, when preserving the uterus is desired, the following treatments are recommended: COCs (Combined Oral Contraceptives), danazol, GnRH (Gonadotropin-Releasing Hormone analogs), gestrinone, LNG-IUD (Levonorgestrel Intrauterine Device), NSAİDs or organ-preserving surgery in cases of nodular adenomyosis, often combined with multiple treatment methods. All women in both groups underwent surgical treatment. Surgical indications included menorrhagia causing anemia, severe pain syndrome, lack of effect from previous conservative therapy, and the absence of pregnancy in reproductive-aged women.

The extent of the surgery depended on clinical manifestations of the disease, the patients' age, their reproductive plans, and the presence of accompanying pathology. Out of 224 patients, 137 (61.2±3.3%) underwent hysterectomy (with or without increments): 75 patients (70.8±4.4%) in the first group, and 62 patients (52.5±4.6%) in the second group. The average age of patients who underwent hysterectomy was 42.8±4.6 years.

Among the 137 patients who underwent hysterectomy, 80 (58.4±4.2%) were under the age of 40, experiencing severe pain syndrome and/or menorrhagia, with either diffuse or nodular adenomyosis, and had hormonal treatment. However, the

effectiveness and feasibility of organ-preserving surgeries for adenomyosis are of special interest. Specifically, 87 (38.8±3.3%) reproductive-aged women who were insistent on preserving their uterus underwent organ-preserving treatments, with 31 patients (29.2±4.4%) in the first group, and 56 patients (47.5±4.6%) in the second group. The average age of these patients was 34.2±5.2 years.

It is worth noting that larger adenomyotic nodules (over 7 cm) were less common, with the majority of nodules being between 3-6 cm (82.1% of cases). In cases of larger adenomyotic nodules, 8 patients underwent hysterectomy. Depending on the disease stage, endometrioid infiltration spread to either a small or significant portion of the myometrium. However, due to the lack of a clear demarcation line, separating healthy tissue from altered tissue was challenging in some cases.

Myometrium Limits and Organ-Preserving Surgical Treatment in Adenomyosis

The boundaries of the myometrium resection depend on the identified extent of the lesion during examination, which is assessed through ultrasound, MRI, and 3D ultrasound imaging.

Based on the analysis of the indications for organ-preserving surgery in patients from the first and second groups, it was found that the average operation time for removing diffuse adenomyosis was 135.0 ± 42.2 minutes, whereas for nodular adenomyosis it was 118.2 ± 45.0 minutes. This suggests that organ-preserving surgery is more challenging in cases of diffuse adenomyosis.

The blood loss during surgery was 147.5 ± 65.2 ml in the first group and 161.5 ± 87.2 ml in the second group. The nodules were predominantly located along the posterior wall of the uterus (59.4 ± 4.8%), followed by the anterior wall (31.1 ± 4.5%), and the uterine fundus (9.5 ± 2.9%).

The choice of suture technique for the bed of the nodules was dependent on their size and location within the uterine cavity. In 55.6 ± 3.3% of cases, the bed was closed with a separate eight-shape Vicryl suture, while in 44.4 ± 3.3% of cases, two-row sutures were used. In 7.5% of cases, a hystero-resectoscopic removal of the submucosal nodules was performed.

According to our data, "pure" adenomyosis was observed in 46.0 ± 3.3% of all cases. Furthermore, significant statistical differences were noted when adenomyosis coexisted with external genital endometriosis. Adenomyosis in its diffuse form was observed more frequently in patients with external genital endometriosis (65.1 ± 4.6%) compared to those with nodular adenomyosis (44.1 ± 4.6%) ($p = 0.001$). Endometriotic ovarian cysts were found in 16.24 ± 3.6% of cases in the first group and 10.16 ± 2.8% in the second group.

In terms of combined gynecological conditions, when adenomyosis was associated with other pathological processes, the extent of surgical intervention was expanded. In the first group, 19.1 ± 3.8% of patients underwent excision of external genital endometriosis foci, and 15.1 ± 3.5% underwent coagulation of these foci. In the second group, 20.3 ± 3.7% of patients had excision of external genital endometriosis, and 7.6% had coagulation. Ovarian resection for endometriotic cysts was performed in 16.24 ± 3.6% of cases in the first group and 10.16 ± 2.8% in the second group.

The excision of retrocervical endometriosis was performed in 13.20 ± 3.3% of the diffuse adenomyosis group and 5.93 ± 2.1% of the nodular adenomyosis group. In all surgical interventions, adhesiolysis was necessary in 26.4 ± 4.3% of cases in the first group and 23.7 ± 3.9% in the second group. The average hospital stay post-surgery was 5.8 ± 1.2 days, depending on the volume and severity of the surgical treatment. Postoperative treatment in the hospital included antibacterial, symptomatic, and, when necessary, anti-anemic therapy. Physiotherapy was also conducted as part of the rehabilitation process. Various types of physiotherapy, often in combination, were prescribed to patients who had organ-preserving surgery. The treatments involved the use of low-frequency impulse currents, low-frequency magnetic fields, and electromagnetic fields. These physical agents help restore the permeability of cell membranes in inflamed tissues, reduce edema, alleviate pain, and provide local anti-inflammatory, desensitizing, analgesic, vasoactive, and metabolism-stimulating effects.

A magnetic field with a frequency of 50 Hz and an inductivity of 35 mTl was used. Procedures were performed 1-3 times a day, starting from the first day post-surgery, with up to 20 sessions.

Following organ-preserving surgery, hormonal therapy was provided based on the patient's age, the extent of the surgery, and reproductive plans. If the patient was interested in preserving reproductive function, GnRH agonists (such as Goserelin 3.6 mg) were prescribed, typically for 3-4 months, depending on the presence and extent of external genital endometriosis and associated infertility factors. If the patient was not interested in reproductive function but sought to preserve the uterus, an intrauterine therapeutic system (LNG-IUD) containing levonorgestrel (52 mg) was placed for 6 months or more.

In summary, the treatment strategy for patients with adenomyosis depends on the clinical presentation of the disease, the patient's age, reproductive plans, and the presence of any concomitant pathologies. For patients with diffuse adenomyosis accompanied by heavy menstruation and pain syndrome, the primary treatment approach was laparoscopic hysterectomy. For reproductive-aged women, organ-preserving treatments were prioritized to preserve fertility. The coexistence of adenomyosis with external genital endometriosis was observed in 54.0 ± 3.3% of cases. Post-surgical hormonal therapy was prescribed based on the extent of the surgery, the patient's age, and reproductive plans. The most significant improvement in symptoms, including heavy and painful menstruation, was noted when LNG-IUD was used after surgery, compared to surgery alone.

The goal of choosing organ-preserving surgical technologies for adenomyosis is to prevent severe intraoperative and postoperative complications associated with hysterectomy, especially in patients of reproductive and premenopausal age or those with somatic complications. The main goal during interventions is to remove clinically significant nodules—both fibromatous and adenomiotic—to prevent their growth during subsequent pregnancies. The analysis of the intraoperative stage included assessing the risks of blood loss, the duration of the surgery and hospitalization, as well as any complications.

The combination of intervention characteristics appears to be significant for the formation of a quality scar in the uterus.

In 113 patients with combined adenomyosis and uterine fibroids, the following surgical interventions were performed: laparoscopic myomectomy in 45 women (39.8±4.6%), laparotomic myomectomy in 13 women (11.5±3.0%), uterine artery embolization in 25 women (22.1±3.9%), and laparoscopic uterine artery occlusion combined with laparoscopic myomectomy in 30 women (26.6±4.2%) (Figure 3).

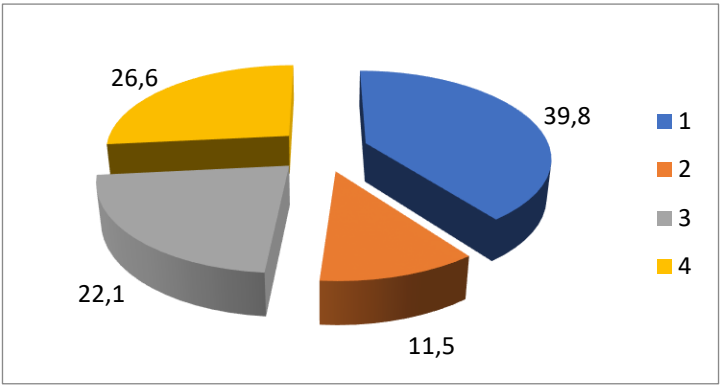


**Fig. 3. Surgical Interventions in Patients with Adenomyosis and Uterine Fibroids**
**(1 - Laparoscopic Myomectomy; 2 - Laparotomic Myomectomy; 3 - Uterine Artery Embolization; 4 - Laparoscopic Uterine Artery Occlusion with Laparoscopic Myomectomy)**

After LTM (Laparoscopic Myomectomy), the longest duration of surgery, the volume of blood loss, and the complex course of the early postoperative period ($p<0.05$) were found to result in a longer hospital stay ($p<0.05$). Laparotomic myomectomy was performed in 11.5±3.0% of patients. The diameters of the myomatous nodules ranged from 55 to 125 mm (mean size - 90±12 mm), and the number of nodules ranged from 5 to 11. The duration of surgery ranged from 55 to 190 minutes (mean time - 115±28.2 minutes). Total blood loss ranged from 180 to 500 ml, with an average of 250±3.6 ml. In 30.7% (4 women) of cases, small myomatous nodules not detected on preoperative ultrasound were found during intraoperative palpation of the uterine walls.

In the postoperative period, pain intensity was rated between 9-10 on the Visual Analog Scale (VAS) in 11 (84.6±9.9%) patients,

requiring narcotic analgesics for the first two days. Despite the implementation of anti-adhesion measures (intraoperative anti-adhesion barriers, anti-inflammatory therapy course in the hospital postoperatively), in three patients (23.1%), the late postoperative period was complicated by adhesions and pain syndrome in the abdomen. The average number of bed days in the hospital was 7.5±3.4 days.

After laparoscopic intervention, the rapid rehabilitation and activation of the women facilitated earlier discharge compared to the laparoscopic myomectomy stage alone or with uterine artery embolization (UAE). The advantages of UAE over myomectomy are evident: shorter manipulation time ($p<0.05$) and shorter hospital stay ($p<0.05$), no need for anesthesia, and no intraoperative complications. The duration of surgery was 45-115 minutes, with an average of 80 minutes. Depending on the size and number of the excised nodules, blood loss ranged from 95 to 350 ml, with an average of 180 ml.

Hormonal therapy (gonadotropin agonists, ulipristal) prior to surgery resulted in a decrease in blood loss compared to when adenomyosis was associated with smaller fibroid sizes and isolated tumor growth. During laparoscopic approaches, the duration of the intervention and the thermal effects on the uterine tissue, as well as the consistency of postoperative scars, are significant factors for pregnancy planning. In the LSM group and in cases with combined adenomyosis, complaints of lower abdominal pain and weakness persisted for 5-7 days, whereas after LSM (1-2 days later), a more favorable postoperative course and earlier activation of the women were observed. The temperature reaction after LSM occurred earlier than in the LTM group ($p<0.05$).

The significant frequency of complications such as hyperthermia, stitch infiltration, bleeding, and long-term pain syndrome after LTM and UAE reflects the inadequacy of preoperative examination and lack of preventive health measures rather than the technical complexity of the interventions. To assess the location, size, and condition of the endometrium, preoperative Doppler ultrasound, hysteroscopy, and diagnostic curettage of the cervical canal and uterine cavity should be performed to select the appropriate surgical method and entry.

Thus, modern three-dimensional echography allows for layer-by-layer analysis, multi-dimensional reconstruction, and retrospective assessment of the obtained data. Additionally, Doppler ultrasound helps in obtaining information on blood circulation in the nodule and predicting its growth dynamics. In proliferating nodules, according to color Doppler, intratumoral blood flow was observed along the peripheral capsule and within the nodule center with moderate color signals.

The next step in surgical treatment primarily aims to ensure a favorable postoperative course, determined by the extent of the surgical intervention and the method of entry and technique used. Minimal trauma, clear tissue visualization, shortened hospitalization, and a reduced risk of postoperative adhesions allow for widespread use of laparoscopic intervention in women of reproductive age. However, the unavoidable use of coagulation causes thermal damage to the myometrium, which may lead to fistulas, separation of the uterine stitches, and excessive postoperative adhesions.

The main goal of the performed surgeries is to restore fertility. Laparoscopic intervention is avoided for patients with fibroids located in the lower or cervical-isthmic region, interstitial nodules with centrifugal growth, or with severe adhesive disease of the abdominal cavity and small pelvis. Laparoscopic myomectomy followed the generally accepted technique in four technical stages. To restore the integrity of the uterine wall effectively, new suture material – a unidirectional self-locking thread – was used, allowing for smooth sliding along the suture without moving in the opposite direction.

Laparotomy was performed for patients with multiple myomatous nodules, large nodules, interstitial nodules with centrifugal growth, and subserosal nodules. When choosing the direction of the incision, the number, location, depth of penetration, and architecture of the myometrium and blood vessels were considered. Cross-sectional incisions were preferred when enucleating myomatous nodules, considering the muscle fibers' dominant transverse orientation in all layers of the myometrium and the similar direction of relatively large secondary arterial vessels, which surround the strongest vascular layer of the myometrium. The nodule beds were restored with two rows of absorbable sutures.

Therefore, the selection of surgical tactics for adenomyosis should depend on the size and number of nodules, the expected blood loss, and the surgeon's proficiency with a given surgical approach. The sooner the surgical intervention is performed, the more favorable the prognosis for fertility restoration. The treatment strategy chosen by the physician for each patient depends on their age, location, number, and morphological type of the nodules. When selecting the surgical approach, it is essential to evaluate the technical feasibility, safety, and clinical efficacy of each method.

In the postoperative period, regardless of the approach, it is advisable to administer GnRH agonists to prevent recurrence. To date, there are no unified recommendations regarding the use of specific treatment methods to prevent recurrence. None of the existing treatment options are considered etiopathogenic. The criteria for treatment effectiveness remain the elimination of clinical signs of the disease, absence of recurrences, and the restoration of reproductive function in patients of reproductive age. Furthermore, the quality of life of women significantly improves. Therefore, the treatment of uterine adenomyosis presents challenges in achieving long-term therapeutic effects, which requires the search for new treatment methods involving an optimal combination of minimally invasive surgery and medication.

## RESULTS

1.Clinical-laboratory and diagnostic examination of the women surveyed made it possible to identify different forms of adenomyosis: diffuse form – 47.32±3.3% (106 women), nodular form – 52.68±3.3% (118 women). Overall, 152 women (67.9±3.1%) with the diffuse form of adenomyosis were of reproductive age, while 72 women (32.1±3.1%) were in the premenopausal stage [4, 6, 9].

2. In women with adenomyosis who participated in the survey, the following risk factors for adenomyosis were identified: hyperpolymenorrhea – 58.61±3.9%, algomenorrhea – 77.0±4.8%, menorrhagia – 55.37±3.3%, proliferative endometrium – 27.55±4.5%, glandular cystic hyperplasia of the endometrium – 21.49±4.2%, secretory endo-

metrium – 20.41±4.1%, glandular hyperplasia of the endometrium – 16.27±3.7%, diagnostic curettage performed once – 37.50±3.2%, and two or more times – 6.25±1.7% [3, 10].

3. The algorithm for the clinical and anamnestic diagnosis of adenomyosis includes a personal and family medical history, pain not related to menstruation evaluated using a Visual Analog Scale, expression of clinical symptoms, and severity of dysmenorrhea. In all stages of adenomyosis, levels of IL-2 (60.5±1.23 pg/ml), IL-4 (3.5±0.02 pg/ml), and IL-6 (12.1±0.18 pg/ml) exceeded reference values and did not significantly change during disease progression. After treatment, a reduction in these cytokine levels was observed, but they remained elevated. Notably, IL-2 in serum increased significantly after treatment (83.9±0.75 pg/ml) [7, 13].

4. In patients at early stages of diffuse adenomyosis, it is advisable to perform genotyping of the functional alleles of the MMP1 gene. Genotype frequencies among examined patients were as follows: 1G/1G – 34.4%, 1G/2G – 43.8%, and 2G/2G – 21.8%. For choosing the correct follow-up strategy, the role of immune system cells as primary biomarkers in diagnosing adenomyosis in women of reproductive age was assessed. Dopplerometry using color Doppler mapping (a non-invasive method for assessing uterine blood flow) was considered appropriate for diagnosing early-stage adenomyosis and differentiating it from more severe pathological spread in the myometrium [11, 13, 14].

5. Compared to reference values, all T-helper/inducer markers (CD3+CD4+CD45+) and the immunoregulatory index CD3+CD4+/CD3+CD8+ (T-helper/STL) showed significant increases during adenomyosis (pre-treatment index: 1.85±0.009, post-treatment: 1.41±0.09, reference range: 0.30–0.90). Conversely, the number of NK cells expressing the alpha chain of the CD8 antigen (CD3-CD8+CD45+), CD8+ receptor-expressing blood cells with high proliferative activity, and CD45+ lymphocytes decreased [3, 7, 9].

6. Analysis of uterine blood flow Doppler parameters in patients with various forms of adenomyosis revealed that in the follicular phase of the menstrual cycle (days 3–5), the importance of end-diastolic

blood flow velocity was greater than in the luteal phase (days 20–23). Compared to the first phase, values were approximately twice as high: uterine artery index in Group I – 0.84±0.02, in Group II – 0.43±0.01. In the second phase, reduced blood flow resistance was observed, demonstrated by a significant decrease in Systolic-diastolic approach (Group I – 4.76±0.02, Group II – 3.52±0.01) and PI (Group I – 1.91±0.02, Group II – 1.42±0.01) [6, 20].

7. Results of pathomorphological studies confirmed the need for high-quality diagnostics using high-performance equipment. This approach allows for accurate diagnosis, selection of conservative treatment methods, and reduction in the frequency of radical surgeries (such as hysterectomy). Compared to radical surgery, conservative myomectomy led to reduced hospital stays and fewer lost workdays post-operation, resulting in an economic benefit [11, 17].

8. The treatment strategy for patients with adenomyosis depended on clinical manifestations, age, reproductive plans, and the presence of comorbidities. Concurrent occurrence of adenomyosis with external genital endometriosis of various localizations was noted in 54.0±3.3% of cases. After organ-preserving surgical treatment, hormone therapy was administered depending on the extent of the surgery, patient age, and reproductive goals. The greatest improvement in symptoms (heavy and painful menstruation) was observed when LNG-IUD was used post-surgery compared to surgery alone [16, 17].

9. Proposals to study the quality of life of women with adenomyosis aim to characterize new treatment approaches and support the development of informed and timely interventions. Data showed that adenomyosis negatively affects multiple aspects of quality of life in women of reproductive age. In most patients with pain syndrome, psychological features such as anxiety-phobic and depressive disorders, affective tension, obsessive and anankastic disorders were dominant. Applying these findings in practice can reduce the negative impacts of adenomyosis and guide future research for more effective treatment and services for affected women [15, 18].

## PRACTICAL RECOMMENDATIONS

1.To increase the effectiveness of diagnosis and identify combined forms, ultrasound examination using expert-class devices is necessary. As the degree of adenomyosis increases, the severity of clinical symptoms and the informative value of ultrasound and hysteroscopy verification also increase. Grade I adenomyosis is characterized by minimal non-pathognomonic symptoms, and standard ultrasound and hysteroscopy do not have sufficient diagnostic sensitivity and specificity.

2. In the absence of ultrasound markers of endometrial hyperplasia, it is not advisable to perform hysteroscopy to confirm Grade I adenomyosis. When the above-mentioned ultrasound criteria for adenomyosis are present, to clarify the diagnosis in patients with Grade I adenomyosis, VEGF-A should additionally be determined in the central nervous system. A transition zone thickness greater than 5 mm, uterine artery functional test coefficient (FTC) greater than 1.2, and VEGF-A level above 70 pg/ml—if these signs are jointly present—confirm Grade I adenomyosis.

3. The choice of treatment method for adenomyosis depends on age, the severity of the disease, and the patient's interest in preserving reproductive function. It is recommended to determine the promoter polymorphism of the MMP1 (1G/2G), MMP3 (5A/6A), and PAI-1 (4G/5G) genes using allele-specific PCR. Therefore, identifying different gene expression profiles is of great importance for a better understanding of the pathogenesis of adenomyosis. The presence of the 2G allele of the MMP1 gene in heterozygous (1G/2G) or homozygous (2G/2G) form makes it possible to predict the progression of the disease, which helps select an appropriate treatment strategy for the patient.

4. In women diagnosed with adenomyosis who plan to maintain reproductive function, it is recommended to perform a 3D ultrasound examination to determine the form, size, and boundaries of the pathological process. This helps in selecting the appropriate treatment strategy and assessing the feasibility of organ-preserving therapy.

5. In the surgical treatment of patients with adenomyosis, laparoscopy is considered the preferred approach. In organ-preserving treatment, nodular adenomyosis involves laparoscopic excision of the nodules, while in diffuse forms, excision of the affected myometrium is performed. The integrity of the uterine wall is restored in all cases using a two-layer suture technique.

6**.** During the comprehensive outpatient examination of patients with adenomyosis, a psychotherapeutic consultation using psychological testing is also conducted.

## LIST OF SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION


1. Азизова М.Э Диагностическая эффективность определения опухолевого антигена CA-125 при аденомиозе // - Bakı: «Azərbaycan təbabətinin müasir nailiyyətləri», Elmi-praktik jurnal. № 3, 2021, - s.135-137
2. Азизова М.Э. Состав микробиоты влагалища у женщин репродуктивного возраста с аденомиозом / Материалы международной конференции «Достижения современной медицины в изучении эпидемиологии инфекционных болезней», Фергана, 10 июня, 2021, с.76-80
3. Азизова М.Э. Эпидемиология и факторы риска развития аденомиоза // - Bakı «Sağlamlıq» jurnalı, 2021, №1 cild 27 s.172-177
4. Əzizova M.E. Adenomioz diaqnozu olan qadınların xəstəliyin klinik markerləri // "ELMİ İŞ" Beynəlxalq elmi jurnal, 2022, Cild 2, sayı 3, s. 30-31
5. Азизова М.Э. Ведущие факторы риска развития аденомиоза у женщин репродуктивного возраста г.Баку / Материалы Международного научно-методического журнала «Global science and innovations 2022: Central Asia», Нур-Султан, Казахстан, 2022, № 3(17), с.26-28
6. Азизова М.Э. Определение уровня показателя онкомаркера яичников CA-125 при аденомиозе // Актуальные проблемы эпидемиологии инфекционных и неинфекционных болезней" Материалы международной научно-практической конференции с участием международных партнерских вузов 12-апреля 2022 года, Фергана, с.11-12
7. Əzizova M.E. Reproduktiv yaşlı qadınlarda adenomiozun inkişafinin risk amilləri // - Bakı: Cerrahiyye Elmi-praktiki jurnal. III cərrahi xəstəliklər kafedrasının 100 illiyinə həsr olunmuş "Cərrahi xəstəliklərin diaqnostika və müalicəsində yeni üsullar" mövzusunda Beynəlxalq konfransın materialları, № 4(2), 2022, s.36-37
8. Əzizova M.E. "Adenomiozun patogenezində immunoloji amillərin rolu" / Ümummilli Lider Heydər Əliyevin anadan olanasının

100 illiyinə həsr olunmuş “Təbabətin aktual problemləri” Beynəlxalq elmi-praktiki konqres, 3-6 may 2023, s.41

9. Əzizova M.E. İzoləedilmiş adenomiozla xəstələrdə əsas klinik əlamətlər // Zərifə Zeynalova 90 illik yubileyinə həsr olunmuş elmi konfransın materialları, Bakı, 2023, s.51-53

10. Азизова М.Э. Frequency and clinical anamnestic features of patients with adenomyosis // - Poltava: World of Medicine and biology. Ukraine. 2023, № 4 (86), p.11-15

11. Əzizova M.E. Adenomiozun patogenezində apoptozun və proliferasiyanin rolu / “Biokimya və təbabətin aktual problemləri” Professor A.M. Əfəndiyevin 80-illik yubileyinə həsr edilmiş elmi-praktik konfransın materialları,2023 Bakı, s. 45-46

12. Azizova M.E, Bagirova H.F Features of the vagina microbiotope in patients with adenomyosis // - Kiev: Reproductive health of woman scientific-practical journal, Ukraine 1(72), 2024,c.48-51

13. Азизова М.Э. Клетки иммунной системы как биомаркеры в диагностике аденомиоза // - Минск: Reproductive health of woman Eastern Europe, Беларусь, 2024, том 14, № 4, с.458-466

14. Azizova M.E, Magalov I. Sh Features of doppler indicators of uterine blood flow in patients with adenomyosis // -Poltava: World of Medicine and biology. Ukraine, 2024, № 1(87) p.11-15

15. Azizova M.E. Psychomatic status of women of reproductive age with adenomyosis // - Kiev: Reproductive health of woman Reproductive health of woman scientific-practical journal, Ukraine 2024, № 3(74), p. 41-46

16. Azizova M.E. Pathomorphological and clinical characteristics of the uterus in combined adenomyosis and myoma // - Тблиси-New York: Georgian Medical News, 2024, №-10 (355), p.123-127

17. Азизова М. Э Качество жизни и психоматический статус женщин репродуктивного возраста с аденомиозом // - Москва: Российский Вестник Акушера, Россия, 2024, Том 24, № 5, с.83-85

18. Əzizova M.E. Adenomiozun diffuz və düyünlü formalarının qadınların reproduktiv funksiyasına təsiri // - Bakı: Müasir ginekologiya və perinatologiyanın aktual məsələləri. 2024, Cild 11, № 3, s.44-49

19. Əzizova M.E. Reproduktiv yaşda olan qadınlarda adenomiozun xarakterik ultrasəs əlamətlər // - Bakı «Sağlamlıq» jurnalı, 2024, № 3, s.47-53

20. Азизова М.Э Определение степени агрегации тромбоцитов у женщин репродуктивного возраста с аденомиозом // - Bakı: «Azərbaycan təbabətinin müasir nailiyyətləri», Elmi-praktik jurnal, 2024, № 2, s. 96-100

21. Əzizova M.E. Adenomiyozlu xəstələrdə endometriumda patoloji prosesin inkişafinin nisbi risk faktorları // - Bakı: Nəzəri, Klinik və Eksperemantal Morfologiya jurnalı Cild 5, № 1, 2025(əlavə), s.209-210

22. Əzizova M.E. Adenomiozun müxtəlif formaları olan xəstələrdə sonsuzluğun tezliyi // Ümummilli lider Heydər Əliyevin 102 illiyinə və 95 Azərbaycan Tibb Universitetinin illiyinə həsr olunmuş Tibb Festivalı tezislər toplusu. Bakı , Azərbaycan, 6-8 may 2025, s.157-158

23. Азизова М. Э. Влияния аденомиоза на качество жизни женщин репродуктивного возраста // Central Asian medical university.Acta CAMU. Сборник материалов международной научно-практической конференции на тему - Стратегия окружающий среды, интеграция здравоохранения и зеленой экономики-основа устойчивого будущего. Фергана, Узбекистан 14-15 мая, 2025

## List of Abbreviations:

| | | |
|---|---|---|
| ADF | – | Diffuse form of adenomyosis |
| AM | – | Adenomyosis |
| AUQ | – | Abnormal uterine bleeding |
| JZ | – | Junctional zone |
| BMI | – | Body mass index (BMI) |
| CA-125 | – | Carbohydrate antigen 125 |
| 3D TVE | – | Three-dimensional transvaginal exography |
| EuESC | – | Eutopic endometrial stromal cells |
| EESCs | – | Ectopic endometrial stromal cells |
| Fas-L | – | Fas ligand for membrane molecule |
| GnRH | – | Gonadotropin-releasing hormone |
| G | – | Gene allele |
| HK | – | Quality of life |
| HSG | – | Hysterosalpingography |
| XGE | – | External genital endometriosis |
| IL | – | Interleukin |
| KRT | – | Assisted reproductive therapy |
| KOK | – | Combined oral contraceptive |
| LSM | – | Laparoscopic myomectomy |
| LUAO | – | Laparoscopic occlusion of uterine arteries |
| LNG-UDV | – | Levonorgestrel intrauterine device |
| UDK | – | Intrauterine contraceptive device |
| UPA | – | Ulipristal acetate |
| MMP1 | – | Matrix metalloproteinase 1 |
| MRT | – | Magnetic resonance tomography (MRI) |
| TNF | – | Tumor necrosis factor |
| TVUM | – | Transvaginal ultrasound examination |
| TVE | – | Transvaginal exography |
| IUD | – | Intrauterine contraceptive device (IUD) |
| SDA | – | Systolic-diastolic approach |

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