

# New Approaches to Diagnosis and Management of Women with Adenomyosis

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**Abstract** Despite the fact that there is currently a large number of observations, the frequency of adenomyosis is increasing from year to year, while the disease is diagnosed mainly in late stages. This study will help to predict adenomyosis in the early stages and prevent severe disease. At the same time, female reproductive function is preserved.

**Keywords** Adenomyosis, Sexually transmitted infections, Vaginal ozone therapy

## 1. Introduction

There are many hypotheses trying to explain the pathogenesis of adenomyosis. The disease can manifest itself as damage to any one zone, or combined damage, including damage to the internal myometrium (subendometrial zone), middle and outer myometrium adjacent to the serosa of the uterus. These changes can be focal or diffuse in nature [3,4]. Different manifestations of the disease may reflect different pathogenetic mechanisms:

- 1 – damage to the internal myometrium may occur due to the “invasion” of the endometrium into the subendometrial zone;
- 2 – damage to the outer myometrium may be associated with the presence of remnants of the Müllerian duct and pluripotent cells that turn into localized areas of adenomyosis.

The subendometrial zone is a layer of the myometrium adjacent to the endometrium up to 5 mm in size (age-related changes up to 8 mm). According to the widespread theory, the development of the disease occurs during menstruation against the background of the processes of regeneration and re-epithelialization of the endometrium. At this moment, endometrial cells may invade the transitional a zone that has structural and functional differences compared to the rest of the myometrium. This process can be activated by disordinated contractions of the transition zone. An increase in the subendometrial zone of more than 12 mm according to magnetic resonance imaging (MRI) is a characteristic sign of uterine endometriosis. In a patient with adenomyosis, several mechanisms of its development can be realized. Modern classification systems are based on two categories: pathological examination data and imaging

systems (ultrasound, MRI). Depending on the degree of spread of internal endometriosis, according to the histological report, the following stages of the process are distinguished [11]:

stage I – the pathological process is limited to the submucous membrane of the uterine body;

stage II – the pathological process moves to the muscle layers;

stage III – spread of the pathological process throughout the entire thickness of the muscular lining of the uterus to its serous cover;

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

**Forms of the disease: diffuse, focal, nodular.**

Expanding the capabilities of MRI with high spatial and contrast resolution has made it possible to study the zonal anatomy of the uterus. An area in the inner layer of the myometrium with a distinct signal density on T2-weighted images has been identified, which has received many definitions: “intermediate zone”, “archmyometrium”, “inner myometrium”, “transition zone”, “subendometrial myometrium”. This intermediate, or transitional, zone is the basal layer of the myometrium, consisting of longitudinally located smooth muscle fibers, the thickness of which in women of reproductive age does not exceed 8 mm.

Homogeneous thickening of the “transition zone” is a standard indicator in the diagnosis of adenomyosis. Prognostic signs of histologically confirmed adenomyosis are: the thickness of the “transition zone” is 12 mm with hemorrhagic inclusions having a high MR signal intensity; local thickening of the “transition zone” or the appearance of myometrial nodules with low signal intensity on a T2-weighted image [1]. In their study, C. Reinhold (1999) et al. [4,6] concluded that adenomyosis can be diagnosed with a high degree of accuracy when the thickness of the transition zone is 12 mm or more. A transition zone thickness of 8 mm or less usually

excludes uterine endometriosis. Kishi Y *et al.* 4 types of adenomyosis were identified depending on MRI data:

1. Subtype I (internal) adenomyosis develops in direct connection with the subendometrial zone and is a classic type and can be explained by direct invasion of the endometrium into the myometrium. Previous surgical interventions and childbirth are predisposing factors in the development of the disease. However, according to the authors, a number of patients did not have intrauterine interventions and childbirth.
2. Subtype II (external) adenomyosis was localized in the outer layer of the myometrium and was often found in patients with external peritoneal endometriosis, rectovaginal endometriosis and is presumably the result of direct and indirect inflammatory effects from pelvic endometriosis. The presence of such a localization is difficult to explain in terms of endometrial invasion, while the transition zone remained intact without aberrations, and healthy muscle structures were present between the adenomyosis and the connecting zone.
3. Subtype III (intramural) adenomyosis group was composed of those patients in whom MR adenomyosis occurred in isolation, without any connection with the functional zone or serosa.
4. Patients who previously did not have clear classification criteria (localization of the MRI lesion was unclear and uncertain) were classified as subtype IV (uncertain) adenomyosis [7,8].

**Hysteroscopy** is a method for direct visualization of abdominal pathology and facilitates direct biopsy. Hysteroscopy can be performed on an outpatient basis with or without anesthesia or in the operating room under local or general anesthesia. Characteristic signs of adenomyosis are: deformation of the uterine cavity, unevenness, roughness of the walls, relief, rigidity when dilating with a perfusion medium.

#### CLINIC:

1. Asymptomatic.
2. Abnormal uterine bleeding (AUB) of various types.
3. Pain (dysmenorrhea, dyspareunia, chronic pelvic pain).
4. Infertility.

In 2011, the FIGO expert group proposed a fairly simple PALM-COEIN classification system, which distinguishes two main groups of AUB, associated and not associated with organic pathology of the uterus [6]. The first group (PALM) includes four categories of disorders determined using visual diagnostic methods: polyp, adenomyosis, leiomyoma and malignancy/hyperplasia, the second group (COEIN) also includes four categories of disorders caused by coagulopathy, ovulatory dysfunction, endometrial changes of a functional nature or iatrogenic, as well as a category that includes as yet unclassified disorders [9].

Treatment of adenomyosis involves drug therapy, surgical treatments (endometrial ablation, myometrectomy, myolysis, uterine artery embolization, hysterectomy), as well as MRgFUS technology [2].

The main groups of drugs used for drug therapy of adenomyosis:

1. Progestins
2. Levonorgestrel-containing intrauterine system (LNG-IUD)
3. Gonadotropin-releasing hormone agonists (GnRH agonists)
4. Combined oral contraceptives (COCs)
5. Danazol
6. Selective progesterone receptor modulators (SPRMs)
7. Aromatase inhibitors.

## 2. Purpose of the Study

Improving the quality of life of women through the development of new criteria for early diagnosis and treatment of the disease by studying the results of clinical, instrumental and morphological studies of adenomyosis in women.

## 3. Material and Research Methods

The study was conducted in 2021-2023 on the basis of the Department of Obstetrics and Gynecology of the Urgench branch of the Tashkent Medical Academy in the gynecological departments of the Regional Perinatal Center of the Khorezm region.

The research took place in two stages. At stage I, during 2018-2020, 60 patients were examined and sent for surgical treatment to the gynecological departments of the Regional Perinatal Center of the Khorezm region for hysterectomy with a diagnosis of adenomyosis. The indication for surgical treatment was the severity of the clinical picture: pain in the lower abdomen during and outside of menstruation, heavy menstrual bleeding, ineffectiveness of hormonal therapy, decreased quality of life.

At stage II, 156 patients were examined.

The main group consisted of 106 women with adenomyosis. The control group consisted of 50 practically healthy women. The main group was further divided into 2 subgroups depending on the type of treatment: in group 1 - the combination of dienogest + vaginal ozone therapy + intrauterine plasma lifting was used  $n = 62$ ; in group 2 - treatment was carried out according to standard therapy  $n=44$ .

All patients underwent clinical, laboratory and functional research methods: clinical (traditional gynecological examinations); functional diagnostic methods (ultrasound); clinical and laboratory (general and biochemical blood tests); analysis of the hormonal status of women (TSH, LH, FSH, testosterone, AMH, prolactin and progesterone), anthropometry (measurement of height, body weight and determination of BMI), indicators of the evening and daytime levels of melatonin in the blood and saliva. Information on sleep disturbances, psychoemotional status and pain was collected from all women using the improved questionnaire to assess health-related quality of life in women with adenomyosis.

## 4. Research Results

The age of women in all groups ranged from 17 to 42 years. The average age of women in group I was  $29.8 \pm 0.2$  years, and for women in the control group –  $29.3 \pm 0.2$  years. Thus, according to the age of the patients taken into the study, the clinical groups were comparable.

The average age of onset of menstruation in women of group I was  $13.8 \pm 0.12$  years, in group II –  $13.6 \pm 0.1$  years. Thus, there were no differences in the average age of menarche between patients with adenomyosis and the control group.

Primary infertility occurred in 40.3% (47) of patients with adenomyosis. Secondary infertility was found in 7.5% (8) of patients with adenomyosis.

One woman in the control group underwent sterilization (2%), primary infertility was detected in 2 (4%) patients.

Diseases suffered by patients are divided into gynecological and extragenital to assess their structure.

In patients with adenomyosis (group I), sexually transmitted infections occurred in 33.9% (36), chronic inflammatory processes - in 64.2% (68) of patients, while in group II, sexually transmitted infections were found in 10 % (5), and inflammatory diseases of the pelvic organs – in 14% (7) of women, which is statistically significantly higher compared to the control group ( $p < 0.05$ ). At the same time, ovarian hypofunction developed in 1.9% (2) of patients with minimal manifestations of the disease. Background diseases of the cervix were detected in 11.3% (12) of patients with adenomyosis, while cervical dysplasia was found in 22.6% (24) of patients in group I.

In patients of the control group, no background pathology of the cervix was detected, and cervical dysplasia was detected in 6% (3) of women. Taking into account the above, we can say that a history of sexually transmitted infections and inflammatory diseases of the pelvic organs in patients with adenomyosis are an unfavorable background that contributes to the development of the disease.

In the structure of infectious diseases suffered by patients, against the background of identified sexually transmitted infections, there was often diagnosed chlamydia in group I in 15% (16), which is statistically significantly higher ( $p < 0.01$ ) compared to the control group - 2% (1); 7.5% (8) of group I patients had trichomoniasis in the past. Dysbiosis occurred in 14.1% (15) of patients in group I, while in the control group only in 2 (4%) patients; A history of urea and mycoplasmosis was present in 42.4% (45) of patients with minimal forms of the disease, while in group II these diseases were detected in 4% (2) of patients.

After treatment, negative controls for cure were obtained. Such a high level of past diseases and sexually transmitted infections may confirm the role of the inflammatory process in the pathogenesis of adenomyosis.

A history of laparotomy was present in 14.1% (15) of women in clinical group I and in 4% (2) of patients in group II. In 7.5% (8) of cases, laparoscopy was performed, including 2.8% (3) of women who underwent cystectomy, and in 1.9% (2) of patients, ovarian resection, tubectomy, and uterine

plastic surgery were performed in equal proportions. tubes, ovarian cauterization and conservative myomectomy. This is statistically significantly higher compared to the control group ( $p < 0.05$ ), where such an operation was not performed.

Thus, all of the above indicates a high level of factors aggravating the gynecological history of patients with adenomyosis compared to women from the control group.

In clinical groups of patients with adenomyosis, 15% (16) women had a history of urinary system diseases, which is statistically significantly higher compared to the control group ( $p < 0.05$ ). Gastrointestinal tract diseases occur in 22.6% (24) of women with adenomyosis. Chronic tonsillitis was noted in 7.5% (8) of patients in group I and in 4% (2) of the control group. Diseases of the cardiovascular system were detected in 5.6% (6) of group I patients. Endocrinopathies were detected in 30.1% (32) of patients in group I, which was significantly ( $p \leq 0.05$ ) higher when compared with group I.

An important role in the regulation of intracellular metabolism belongs to biologically active polypeptides - growth factors that stimulate or inhibit angiogenesis, as well as regulating cellular mitogenic effects. This refers to TGF $\beta$ 1. According to the results of a study at the systemic and local levels, we found deviations in the production of TGF $\beta$ 1 with severe symptoms of adenomyosis. Physiological serum TGF $\beta$ 1 levels support the notion that adenomyosis is a tumor-like process without atypical heterotopic changes.

TGF $\beta$ 1 inhibits proliferation and induces differentiation of most cell types studied to date. The biological action of TGF $\beta$ 1 is realized through two types of receptors - TGF $\beta$ 1RI (betaglin) and TGF $\beta$ 1RII (endoglin). Premature expression or overexpression of receptors on the membrane of granulosa cells has a negative effect on them (Shyamal K. et al., 1998). Matrix metalloproteinase-9 controls the availability of growth factor and, by cleaving decorin, releases TGF $\beta$ . Its action requires a receptor that is common to this growth factor and epidermal growth factor.

Cellular and intercellular bioregulators are represented by a twofold increase, in particular, TGF $\beta$ 1 at the local level (peritoneal fluid) in adenomyosis. No changes in the activity of the specific receptor for this growth factor endoglin were detected, which indicates the influence of a high level of TGF $\beta$ 1 on a significant increase in the activity of arginase in the blood serum at stages I-II and III-IV, and at the local level at stages III-IV adenomyosis, ensuring the formation adhesive process, due to increased synthesis of proline, the main substance of connective tissue.

The severity of clinical symptoms of adenomyosis, the verification information content of ultrasound and hysteroscopy increase as the degree of spread of adenomyosis increases. Adenomyosis degree is characterized by minimal non-pathognomonic symptoms; standard ultrasound and hysteroscopy do not have sufficient diagnostic sensitivity and specificity.

Ultrasound visualization of a “transition zone” more than 5 mm thick and a statistically significant increase in resistance to blood flow in the uterine artery basin are among the echographic signs of grade 1 adenomyosis. The use of a

functional stress test during Doppler measurements in the uterine vessels increases the specificity and sensitivity of early ultrasound diagnosis.

The ozonizer operates in two modes: the ozone gas production mode and the air flow mode. Ozone output increases with increasing switch button number. In the air passing mode, gas is passed through the arrester.

After complex treatment and ozone therapy, when assessing the nature and severity of pain using a visual analogue scale (VAS) in women of group 1 compared with condition 2, a decrease in the intensity of pain, cramps before menstruation, pain during menstruation, pain during sexual activity, pain in the mid-cycle, pressure on the bladder.

## 5. Conclusions

Adenomyosis, the studied microorganisms (*Chlamydia trachomatis*, *Ureaplasma* spp., *Mycoplasma genitalium*, HSV 1-2, CMV, HPV of high carcinogenic risk) are detected in the endometrium in 40.5%.

The most frequently reported are *Ureaplasma* spp. and HPV of high carcinogenic risk. Thus, after complex therapy of adenomyosis using medical ozone using the vaginal method, a significant improvement in the quality of life was revealed by reducing the severity of pain and anxiety-depression, especially in women with chronic endometritis. Medical ozone used vaginally is prescribed once a day for 7 days with an exposure of 20 minutes (mode 5-6) against the background of hormonal therapy with gestagens.

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