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MODERN POSSIBILITIES FOR THE DIAGNOSIS OF ADENOMYOSIS

© M.A. Shalina[1], M.I. Yarmolinskaya[1, 2], E.I. Abashova

[1] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia;
[2] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

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▪ This review article presents modern data on the diagnosis and pathogenesis of adenomyosis, various classifications of the disease being highlighted. The role of genetic and immunological factors in the development of internal endometriosis is discussed. The results of domestic and foreign studies are presented, with the most informative non-invasive markers for the diagnosis of adenomyosis described.

▪ **Keywords:** adenomyosis; genital endometriosis; transition zone; junctional zone; oxytocin receptor expression.

СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ДИАГНОСТИКИ АДЕНОМИОЗА

© М.А. Шалина[1], М.И. Ярмолинская[1, 2], Е.И. Абашова[1]

[1] Федеральное государственное бюджетное научное учреждение «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта», Санкт-Петербург;
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации, Санкт-Петербург

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▪ В статье представлены современные данные о диагностике и патогенетических механизмах развития аденомиоза. Освещены различные классификации заболевания. Отражена роль генетических и иммунологических факторов в развитии внутреннего эндометриоза. Приведены результаты отечественных и зарубежных исследований и описаны наиболее информативные неинвазивные маркеры диагностики аденомиоза.

▪ **Ключевые слова:** аденомиоз; генитальный эндометриоз; переходная зона; соединительная зона; экспрессия окситоциновых рецепторов.

Adenomyosis occupies one of the leading positions in the structure of gynecological diseases. Adenomyosis is often combined with external genital endometriosis (EGE), which indicates the generality of pathological processes [1]. Despite various theories of disease occurrence as well as the discovery of new pathogenetic mechanisms, adenomyosis can be distinguished as a separate pathology [2–4]. The prevalence of this disease in the women of reproductive age is 5%–10% [5–7]. A wider verification of adenomyosis is associated with the use of various diagnostic methods and criteria along with the absence of a specific clinical picture. There are difficulties in diagnosis because of the combination of adenomyosis with other hyperplastic diseases such as uterine myoma, endometrial hyperplasia [8, 9]. The detection frequency of internal endometriosis in the preoperative period is 2.6%–26.0%. Its diagnosis is based on the clinical picture and data obtained from the use of non-invasive examination methods [10]. The clinical appearances of adenomyosis are various variants of abnormal uterine bleeding, pain syndrome, and dyspareunia that lead to

a significant decrease in the quality of life [11–15]. Recent studies have shown that young women with diseases associated with infertility and miscarriage are also susceptible to adenomyosis [13, 16, 17].

There are several classifications of adenomyosis. The generally accepted classification of this disease is based on the prevalence of endometrioid heterotopias that distinguish adenomyosis into diffuse, nodular, and focal forms. At the Congress of The Society of Endometriosis and Uterine Disorders in 2016, the sclerotic form was decided to be added to these classic forms of adenomyosis [18]. In Russia, clinical and anatomical classifications of endometriosis of the uterus body, endometrioid ovarian cysts, and retrocervical endometriosis are widely employed in practice [19, 20]. The clinical classification of adenomyosis provides four stages of the spread of the pathological process [19]:

- Stage I — adenomyosis heterotopias are located only in the submucosal layer;
- Stage II — the pathological process extends to the muscle layer;
- Stage III — the pathological process inhabits the entire thickness of the myometrium, further reaching the serous cover of the uterus;
- Stage IV — in addition to the uterus, the parietal peritoneum and nearby organs are involved in the pathological process.

The ultrasound method is widely used in the diagnosis of adenomyosis; however, various authors have stated that the accuracy of detecting this disease via ultrasound ranges from 20 to 86% [18, 20]. Ultrasound examination of the myometrium reveals the following changes: hyperechogenic inclusions in the walls of the uterus with a diffuse and chaotic location, reduced echogenicity, thickening of the subendometrial zone, blurring or absence of a clear line, pitted projection of the basal layer, asymmetry in the uterine walls is more than 3 mm, local thickening of the uterine wall, and the effect of vertical stripes [21]. The latest FIGO recommendations (2018) proposed the assessment of the state of the transition zone between the endometrium and myometrium for the diagnosis of adenomyosis during the ultrasound of the uterus [22]. The sensitivity of transvaginal echography depends on the degree of disease prevalence and is maximal at grade III (92%), whereas the average accuracy of the ultrasound diagnosis of adenomyosis is 88.7%, with sensitivity and specificity of 91.5% and 86%, respectively [23].

Currently, not only ultrasound and hysteroscopy are used for the diagnosis of endometriosis of the uterus, but also a magnetic resonance imaging (MRI) scan because of its noninvasiveness and high information content. The sensitivity, specificity, and accuracy of MRI diagnostics of adenomyosis reach up to 95% [20]. The advantage of this method is the standardization of images, precise localization, shape and distribution process, and the possibility of differential diagnosis between the nodular form of adenomyosis with the deformation of uterine cavity and submucous myomatous node [20]. Accurate information about the location of the node, its size, and blood supply allows you to perform organ-preserving surgical treatment with maximum efficiency. The high cost and inaccessibility, which do not allow using the method as a routine screening in the diagnosis of the disease, can be noted among the disadvantages of MRI.

The use of MRI paves the way for the clearest identification of the changes in the structure of the transition zone between the endometrium and myometrium, which is the characteristic of adenomyosis. The term “transition zone” of the uterus first appeared in 1983 [24]. In a study using MRI, the authors found a region with a low echo signal between the endometrium and myometrium. This are was later called as the transition zone (junctional zone [JZ]) [22, 25–28]. The transition zone plays a significant role in the pathogenesis of adenomyosis. Normally, its thickness lies in the range of 2.0–5.0 mm [29], and changes in the different periods of life under the influence of various drugs [25].

The increase in JZ is significant in the development of adenomyosis as it serves as a predictor of the disease [24, 30]. In the diffuse form of adenomyosis, there is an uneven thickening of JZ because of the local hyperplasia of myocytes surrounding the endometrioid heterotopias. Back in 1999, C. Reinhold et al. found that adenomyosis is diagnosed when the thickness of transition zone is 12 mm or more [3]. Additionally, the thickness of the JZ is increased in the area of the uterine floor as compared to the walls [25]. The study of JZ contractions in the unchanged uterus and in adenomyosis in the different phases of the menstrual cycle revealed significant differences

in the amplitude, frequency, and direction of contractions [31]. Thus, the frequency of peristaltic activity in the follicular phase of the menstrual cycle is twice as higher for women with adenomyosis than for the patients without this disease [31]. X. Shen et al. [26] studied the expressions of type I and II of cannabinoid receptors of JZ for women with and without adenomyosis, along with the relationship between their expression levels and clinical appearances of the disease. Scientists have found that the expression of types I and II of cannabinoid receptors of women with adenomyosis is significantly higher. There was a positive correlation between the level of expression of type II cannabinoid receptors in the transition zone and the severity of dysmenorrhea. Based on the obtained data, it can be assumed that the cannabinoid receptors contribute to the pathogenesis of dysmenorrhea in adenomyosis, and they can be considered as a potential therapeutic target [26].

According to MRI data, the diagnosis of adenomyosis is established in accordance with the following criteria [32]. With grade I adenomyosis, there is a thickening and "notching" of the transition zone up to 0.5–0.8 cm, tubular formations and/or cystic cavities in the transition zone of up to 2 mm in diameter, separate small foci or zones of heterogeneous structure in the myometrium, along with small cysts located directly near the transition zone without clear contours. With grade II adenomyosis, the above changes are supplemented by an increase in the uterus because of the anterior size with a difference in the wall thickness of more than 5 mm, penetration of the basal layer of the endometrium into the myometrium by more than half of the thickness of the myometrium, along with an increase in the number and size of heterogeneous and cystic inclusions in the transition zone. There are also multiple foci and cystic cavities in the myometrium according to the MRI characteristics as well as in the basal layer of the endometrium. Cysts with hemorrhagic contents are detected at the different stages of hemoglobin breakdown in a T1-weighted image. According to MRI, adenomyosis of III degree shows an even greater increase in the size of the uterus, endometrial penetration of the full thickness of the myometrium, the formation of heterogeneous zones and pockets of various shapes and sizes, as well as the formation of multiple small cysts and cavities with a diameter of 2 mm or more in the transition zone with hemorrhagic content or signs of calcification of blood clots. At the IV degree of the prevalence of adenomyosis, the visceral and parietal peritoneums are involved in the pathological process with the formation of an expressed adhesive process. The uterus has uneven, bumpy contours due to endometrioid heterotopias on its surface (foci of different densities of the MR signal), which are hypointensively heterogeneous, coinciding in the density with the endometrium and the transition zone. The cysts are identified with an increased MR signal on the T2-weighted images, and cavities of different diameters are filled with heterogeneous hemorrhagic content.

Nowadays, many researchers agree on the need to create a unified systematic classification of adenomyosis, which include the use of various imaging methods [12–14]. The search for new pathogenetic mechanisms of a disease development to predict the rate, nature, and severity of clinical appearances has reinvigorated the scientific and practical interests. The development of common criteria for the disease, possibly correlating with the different phenotypes of patients, will lead to a greater understanding of the pathological process and the application of a personalized approach for the treatment of this disease.

A histological research distinguishes four morphofunctional forms of adenomyosis; growing, stable, regressing, and mixed; which allows us to assess the features of each case and adenomyosis as a whole [18]. Growing adenomyosis is represented by two morphofunctional variants: proliferating (24%) and secreting (up to 2%). Mixed adenomyosis is characterized by the simultaneous existence of endometrioid heterotopias with different morphofunctional states and occurs in about 60% of patients. The histological appearances of various trends in the evolution of adenomyosis can be detected even within a single focus, thus reflecting its undulating course [18].

Present studies are focused on the immunological as well as immunohistochemical aspects and the role of angiogenesis factors in the pathogenesis of adenomyosis. The composition of peripheral blood mononuclear cells changes with endometriosis of the uterus body. Several studies have detected the activation of B cells against the background

of the decreased activity of T-cell immunity and the suppression of the function of natural killers ($CD16^+$, $CD56^+$) [33–35]. Studies evaluating the levels of IL-6, IL-16, TNF-alpha, and LIF in peripheral blood and peritoneal fluid, as well as their expression in the endometrial samples, in women with adenomyosis and EGE did not show any specific results, possibly due to a small sample [36].

Contemporary studies are primarily concentrated on the role of genetic factors in the development of adenomyosis [33, 37–39]. Thus, a high incidence of the disease was found for the first-line relatives and monozygotic twins. Many factors of the receptor status of ectopic endometrium and genetic abnormalities of cells have been studied, but no convincing data on the role of a specific gene in the formation of ad enomyosis had been obtained. The expression of the phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) gene has shown an interesting feature. The product of this gene is a phosphatase with double substrate specificity, which is characterized by an anti-oncogenic activity. Mutations in the *PTEN* gene lead to the development of hereditary syndromes with the manifestations of multiple benign tumors in various organs and tissues [37]. Expression of the *PTEN* gene is reduced during the development of the tumor process, as well as in endometrioid heterotopias [40] and ectopic endometrium in adenomyosis [17, 40]. A decrease of *PTEN* expression may be associated with a mutation both in the gene itself and in the promoter region [41]. Results of the study by H. Hu et al. [42] showed that miR-17 expression was significantly increased in the endometrial tissues of patients with adenomyosis ($p < 0.05$). The expression of matrix ribonucleic acid (RNA) and PTEN protein was significantly lower in patients with adenomyosis as compared to those in the control group ($p < 0.05$). When the expression was suppressed in the miR-17 cells, there was a significant increase in the PTEN expression ($p < 0.05$). Thus, PTEN expression in the ectopic endometrium is reduced in endometriosis. However, we were not able to find any data in the literature on the level of expression of this anti-oncogen in the different forms of adenomyosis.

Changes in the expressions of RAS and RAS-association domain family genes contribute to the development of adenomyosis. The mechanism of their actions is associated with a violation of the cell cycle, uncontrolled cell proliferation, and influence on the mechanisms of apoptosis. Programmed cell death plays an important role in the development of adenomyosis. The violation of apoptosis processes due to the changes in the functioning of various markers leads to the survival of endometrial cells in the myometrium, myometrial hyperplasia, and the development of various forms of adenomyosis [43]. The regulators of apoptosis involved in the development of the disease are Bcl-2, Ki-67, etc. An increased expression of Bcl-2 leads to cell resistance to apoptosis. The Ki-67 marker is expressed in the nuclei of proliferating cells; therefore, its expression is higher in the functional layer of the endometrium than in the basal one. An increased production of Ki-67 is significantly more often detected in adenomyosis, which serves as a kind of indicator of the pathological process [9, 17, 43]. Moreover, because Ki-67 is a marker of dividing cells, it can be used to predict the risk of recurrence of various cancers.

The expression of oxytocin receptors (OXTR) is of great interest. It is known that oxytocin is one of the most important mediators of the regulation of contractile activity of the uterus, which is not only restricted during pregnancy. Outside of pregnancy, contractions spread from the transition zone. Additionally, the amplification, frequency, and direction of contractions correlate with the phase of the menstrual cycle [44, 45]. The distribution of oxytocin receptors themselves may change during the menstrual cycle [28]. Y. Zhang et al. studied the expression of oxytocin receptors of the transition zone in the region of the bottom and in the area of the isthmus of the uterus in the different phases of the menstrual cycle of women with and without adenomyosis. Researchers have identified a violation of the expression of oxytocin receptors in adenomyosis in the various parts of the uterus in both the proliferative and secretory phases of the menstrual cycle [28, 46]. The evaluation of OXTR expression in the various parts of the uterus revealed an increased expression in the isthmus, which leads to an increase in contractility in the proliferation phase. This increased expression reaches a maximum in the preovulatory period of the follicular phase [47], and it ensures the transport of spermatozoa

to the cervical canal and further into the uterine cavity while maintaining pressure in the isthmic part of the fallopian tubes for fertilization [47]. In contrast, the lower expression of OXTR was detected in the isthmus of the uterus during the secretion phase, which is exhibited by less frequent and weaker contractions during this period. By the end of the menstrual cycle, only one quarter of each new contraction reaches the bottom of the uterus, thereby causing minimal contractile activity of the myometrium in response to embryo implantation.

Currently, it is important not only to use non-invasive tests, but also search for new markers of both EGE and adenomyosis [5, 36, 48, 49]. New highly effective minimally invasive tests, such as imaging, genetic studies, biomarkers, or microRNAs, can serve as the foundations for making a diagnosis without using any invasive methods to diagnose the disease. Even though some non-invasive tests, having a promising diagnostic potential and including modern methods such as the use of tandem mass spectrometry [5], are currently widely studied in the clinical practice, no specific indicators have yet been identified for the accurate diagnosis of external and internal endometriosis.

A systematic review was conducted that included a large number of individual studies and meta-analysis data to identify the role of individual factors and their combination in the development of adenomyosis [48]. The review studied angiogenesis and growth factors; cell adhesion molecules; DNA repair molecules; hormonal, myogenic, neuronal and tumor markers; and inflammatory markers. However, the results of the review showed that none of the indicators had sufficient accuracy and correlation with the development of the disease for use in practice and clinical works.

Another review [50] analyzed the databases and studies with an assessment of more than 140 sources, including about 16,000 surveyed women. The significance of various factors in the development of EGE and adenomyosis, such as angiogenesis/growth factors, apoptosis markers, cell adhesion molecules, hormonal markers, markers of the immune system and inflammation, oxidative stress, microRNAs, tumor markers, and other proteins, was assessed and determined in that review. However, none of the many biomarkers correlated with the development of diseases [50].

Thus, conducting a new research, searching for the most sensitive, specific genetic, immunological, and immunohistochemical markers of adenomyosis will allow for a more accurate diagnosis of the disease and will contribute to the development of new directions in the targeted therapy of the disease.

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Information about the authors *(Информация об авторах)*

Maria A. Shalina — MD, PhD, Senior Researcher. The Department of Gynecology and Endocrinology, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. https://orcid.org/0000-0002-5921-3217. SPIN-code: 6673-2660. **E-mail:** amarus@inbox.ru.

Maria I. Yarmolinskaya — MD, PhD, DSci (Medicine), Professor of the Russian Academy of Sciences, Head of the Department of Gynecology and Endocrinology, Head of the Diagnostics and Treatment of Endometriosis Center. The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia; Professor. The Department of Obstetrics and Gynecology, North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia. https://orcid.org/0000-0002-6551-4147. SPIN-code: 3686-3605. Scopus Author ID: 7801562649. **E-mail:** m.yarmolinskaya@gmail.com.

Elena I. Abashova — MD, PhD, Senior Researcher. The Department of Gynecology and Endocrinology, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. https://orcid.org/0000-0003-2399-3108. SPIN-code: 2133-0310. **E-mail:** abashova@yandex.ru.

Мария Александровна Шалина — канд. мед. наук, старший научный сотрудник отдела гинекологии и эндокринологии. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. https://orcid.org/0000-0002-5921-3217. SPIN-код: 6673-2660. **E-mail:** amarus@inbox.ru.

Мария Игоревна Ярмолинская — д-р мед. наук, профессор РАН, руководитель отдела гинекологии и эндокринологии, руководитель центра «Диагностика и лечение эндометриоза». ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург; профессор кафедры акушерства и гинекологии. ФГБОУ ВО «СЗГМУ им. И.И. Мечникова» Минздрава России, Санкт-Петербург. https://orcid.org/0000-0002-6551-4147. SPIN-код: 3686-3605. Scopus Author ID: 7801562649. **E-mail:** m.yarmolinskaya@gmail.com.

Елена Ивановна Абашова — канд. мед. наук, старший научный сотрудник отдела гинекологии и эндокринологии. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. https://orcid.org/0000-0003-2399-3108. SPIN-код: 2133-0310. **E-mail:** abashova@yandex.ru.