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Adenomyosis as an Independent Unit of Dysfunction of the Endometrium and Uterine Myometrium

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Keywords: *Pathogenesis of adenomyosis According to one of the theories of the pathogenesis of adenomyosis, during the menstrual cycle, during periods of regeneration and epithelialization, the endometrium penetrates into the myometrium predisposed to such disorders or injured.*

ABSTRACT

In modern literature, adenomyosisis described as "benign invasion of the endometrium into the myometrium, leading to diffuse enlargement of the uterus. Microscopic examination reveals ectopic neoplasia of the endometrial glands and stroma surrounded by hypertrophied and hyperplastic myometrium" [1, 2]. In recent years, interest in the problem has increased significantly, since the disease violates the quality of a woman's life, encourages the doctor to resort to surgical treatment, including organ-bearing operations. The role of endomyometrial dysfunction characteristic of adenomyosis in the development of obstetric pathology cannot be overestimated. Based on visualization methods by C.M. Juang et al. [3] have shown that adenomyosis is an important risk factor for spontaneous premature birth. In addition, adenomyosis is associated with other obstetric complications, such as abnormal postpartum bleeding [4]. According to a systematic review and meta-analysis, adenomyosis has a negative impact on the results of infertility treatment when using assisted reproductive technologies due to a decrease in the likelihood of clinical pregnancy and implantation of the fetal egg, as well as an increase in the risk of early pregnancy loss [5].

The argument in support of this theory is data on an increase in the incidence of adenomyosis after repeated curettage of the uterine cavity due to termination of pregnancy, as a result of which the boundary between the endometrium and myometrium at the implantation site is violated and endometrial invasion occurs [6]. It is possible that changes in the intermediate layer of the myometrium (subendometrial myometrium) during pregnancy, such as increased angiogenesis and the introduction of trophoblast, can aggravate the manifestations of already existing adenomyosis. Interestingly, curettage of the uterine cavity in non-pregnant women does not increase the risk of this pathology. Among them are changes in the population of immunocompetent cells [7], pathological expression of the aromatase enzyme [8], a violation of the regulation of interleukin 6 synthesis [9], a functional violation of the cell adhesion protein integrin beta–3 [10] and homeobox-containing genes [11], as well as a decrease in the level of apoptosis, which contributes to increased viability and the invasiveness of endometrioid cells [12]. The role of the intermediate zone of the myometrium is expanded by magnetic resonance imaging (MRI) with high spatial and contrast resolution, which 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 [13] has been identified, which has received many definitions: intermediate zone, archimiometry, inner myometrium, transition zone, subendometrial myometrium. This intermediate or transitional zone is the basal layer of the myometrium and consists of longitudinally arranged smooth muscle fibers, usually its thickness in women of reproductive age does not exceed 2-8 mm. The main diagnostic MRI criteria for adenomyosis are two signs. The first is a focal or diffuse expansion of a low-intensity signal from a transition zone exceeding 12 mm. The second is an irregularly shaped myometrial thickening with a low-intensity signal. Additional signs of adenomyosis include small, high-intensity signal foci on T1-weighted images (hemorrhagic areas) and high-intensity signal lines from the endometrial surface on T2-weighted images, reflecting direct invasion of the basal layer of the endometrium into the underlying myometrium. However, not all abnormal presentations of the intermediate zone should be considered as adenomyosis. According to some researchers [14], "the pathology of the endometrial subendometrial region of the myometrium" (or the intermediate zone of the myometrium) may not always correspond to the diagnosis of "adenomyosis". To date, there is a significant need for a unified terminology and classification of myometrial transition zone disorders, as well as systematization of ideas about instrumental criteria for diagnosing adenomyosis [15].

Thus, the issue of the possibility of recognizing the existence of the "subendometrial-myometrial zone" as a new nosological unit, different from adenomyosis, is being discussed. Disturbances in this zone are associated with infertility and pregnancy complications, since not always with deviations of the transition zone of the myometrium detected by MRI, histologically confirmed adenomyosis is diagnosed [14]. The use of three-dimensional transvaginal ultrasound has expanded the possibilities of an objective assessment of the state of the intermediate zone [16]. For two-dimensional and three-dimensional transvaginal ultrasound diagnostic accuracy is 83 and 89%, sensitivity - 75 and 91%, specificity - 90 and 88%, positive predictive value - 86 and 85%, negative predictive value - 82 and 92%, respectively [17]. Thus, the diagnosis of adenomyosis can be instrumentally confirmed in the presence of the following ultrasound signs [18]: spherical uterus, poorly defined border between the myometrium and endometrium, subendometrial echogenic linear striation, asymmetry of the anterior and posterior myometrium, intramyometrial cysts, heterogeneous echotexturamyometry [19] .

Several studies have demonstrated comparable diagnostic value with MRI and transvaginal ultrasound. A systematic review and meta-analysis of data obtained using these two methods in women with histologically confirmed adenomyosis showed a similar high level of accuracy. However, MRI had the advantage of standardized images that are independent of the presence of fibroma [20]. Factors of increasing the invasive potential of endometrial cells. There is a lot of evidence of an increased invasive potential of endometrial cells in endometriosis, including due to insufficient expression of the main protein of intercellular contacts, E-cadherin [21]. The invasion of endometrial cells into the myometrium is mediated by disruption of the connections between smooth muscle cells of the myometrium, collagen, elastic fibers, and cellular elements of the connective tissue due to increased expression of mainly matrix metalloproteinases [22]. Endometrial stromal fibroblasts produce the antiadhesive protein tenascin, which is modulated by hormone-regulated growth factors and facilitates the migration of epithelial elements into the myometrium by inhibiting cell attachment to fibronectin [23]. The detection in some cases of endometrial cells in the intramyometrial lymphatic vessels [24] represents another possible route for invagination of both the basal endometrium and stromal cells into the myometrium [25].

Local hyperangiogenesis. In adenomyosis, an increase in endometrial vascularization is observed, and, according to H. Ota et al., the total surface area of capillaries was 11.6 times higher than that in the proliferative phase of the menstrual cycle [25]. Despite the fact that such a pronounced angiogenesis was not subsequently confirmed in other studies, the density of

microvessels in the endometrial tissue in patients with adenomyosis was significantly higher compared to women in the control group [24]. Data have been obtained on the relationship between increased angiogenesis and the activity of matrix metalloproteinases in adenomyosis. One molecular study demonstrated an increase in the expression of matrix metalloproteinases 2 and 9 in both eutopic endometrium and adenomyosis tissue, which correlated with an increase in microvascular density [21]. In a prospective study of patients with adenomyosis (n = 21), expression levels of matrix metalloproteinases 2 and tissue inhibitor of metalloproteinases type 1 were significantly increased in endometrial stromal cells with stem cell potential compared with healthy patients (n = 25), however, their invasive properties in both groups were similar [29].

When studying the prevalence of polymorphism of the matrix metalloproteinase 2 (1306C/T) gene, it was found that it occurs more often in women with adenomyosis (n = 180), therefore, it can be attributed to risk factors (relative risk 1.83 (95% confidence interval 1.13–2.96)) [30]. It has also been demonstrated that carriage of the 2578A or 1154A alleles of the gene encoding vascular endothelial factor is associated with a reduced risk of adenomyosis [23]. Disruption of hormonal regulation A lot of data have been obtained on the expression of both types of estrogen and progesterone receptors and their isoforms (A and B) in the endometrium and in the inner layer of the myometrium in women with adenomyosis, but not in its outer layer [21]. Steroid hormones play an important role in the pathogenesis of adenomyosis, with local hyperestrogenemia being one of the most significant pathogenetic factors [13].

An increase in estrogen levels at the local level can occur under the influence of hyperactivity of the aromatase enzyme [34] or estrone sulfatase, which converts estrone-3-sulfate to estrone [35]. There are also data on impaired function of type 2 17-beta-hydroxysteroid dehydrogenase in the endometrium in patients with adenomyosis, which leads to an increase in the conversion of E2 to estrone in the secretory phase of the cycle [36]. The decrease in the expression of estrogen receptors in the middle of the luteal phase of the menstrual cycle in the glands and stroma in adenomyosis is statistically significant ($p < 0.001$). However, no differences in the expression of estrogen receptors alpha in the internal and external myometrium were found, while the level of estrogen receptors beta in the endometrial glands in adenomyosis is increased throughout the entire menstrual cycle. In patients with adenomyosis, the levels of expression of progesterone receptors A and B were reduced in the stroma of the basal layer of the endometrium, in the inner and outer layers of the myometrium [22]. Cyclic changes in the intermediate zone, according to MRI, and peristaltic waves, recorded using ultrasound, also demonstrated the dependence of this layer on the influence of sex steroids [38]. Pathology of the myometrium More and more new data support the hypothesis that adenomyosis indicates a pathology not only of the glandular and stromal elements of the endometrium, but also of the stroma and smooth muscle cells of the inner layer of the myometrium. This can be explained by the peculiarities of embryogenesis: the endometrium and the inner layer of the myometrium develop from the paramesonephric (Müllerian) ducts, while the “outer” myometrium is of mesenchymal origin [39]. Although it is generally accepted that adenomyosis results from endometrial invasion into the myometrium, MRI studies suggest that proliferation and hyperplasia of smooth muscle cells in the intermediate zone may precede endometrial cell invasion [40]. G. Leyendecker believe that the disruption of the specific microenvironment in the basal layer of the endometrium can cause structural and functional disorders in the intermediate zone, such as hyperperistalsis and/or discoordination, disordered proliferation of smooth muscle cells, which is characteristic of endometriosis and adenomyosis. In smooth muscle cells in adenomyosis, numerous ultrastructural differences in cytoplasmic organelles, nuclear structures, endoplasmic reticulum and Golgi apparatus were revealed, as well as more active synthesis of proteins associated with cellular hypertrophy compared to those of healthy women.

The data obtained in the study of uterine embryogenesis indicate the interaction of the endo-

myometrium within the framework of the concept of epithelial-mesenchymal plasticity. The smooth muscle cells of the myometrium originate from undifferentiated mesenchymal cells , and during embryogenesis, cells morphologically similar to myocytes are found in the basal endometrium . These cells resemble myofibroblasts in the proliferative phase and immature smooth muscle cells in the secretory phase of the cycle. As already noted, in the epithelial cells of the endometrium during adenomyosis, the expression of cell adhesion proteins E-cadherin and vimentin decreases [21]. All of the above suggests that the epithelial-mesenchymal transition in the embryonic period may play an important role in the pathogenesis of this disease, when endometrial stem cells, under certain conditions, can begin to differentiate into endometrial cells in the myometrium, regardless of the cellular microenvironment [22, 24]. Association between endometriosis and adenomyosisToday, new data on the structural and functional characteristics of the endometrium and myometrium, the presence of the so-called intermediate zone (endomyometrium) in patients with adenomyosis and endometriosis provide more and more evidence in favor of the fact that these nosological forms are characterized by a combined pathology of the endo- and myometrium and represent two variants of the endomyometry dysfunction syndrome phenotype. Using the results of MRI, S. Kennedy et al. [25] found a high prevalence (six to nine times the population level) and a correlation between the presence of endometriosis and adenomyosis in first-degree relatives, concluding that this pathology is a difficultly inherited genetic disease.

Endometriosis of the pelvic organs, especially in severe form, is largely associated with compaction of the intermediate zone [16]. At present, a threshold value of the thickness of the intermediate zone, equal to 10 mm (with additional signs up to 12 mm), has been established, above which a diagnosis of adenomyosis can be made [17]. Traditionally, it was believed that adenomyosis develops in the fourth or fifth decade of a woman's life. However, according to recent studies based on MRI data, the disease can manifest much earlier, especially in infertile women with endometriosis. G. Kunz et al. established a positive correlation between the diameter of the posterior intermediate zone, the stage of the disease and the age of the patients. Signs of adenomyosis in women with endometriosis (n = 160) were detected in 79% of cases. In patients with endometriosis (n = 160) aged under 36 and infertile, the prevalence of adenomyosis was 90% ($p < 0.01$). This fact indicates that adenomyosis plays an important role in the occurrence of infertility in women with endometriosis [18]. Later, the same authors [19] performed MRI in 227 women of different age groups (starting from 17 years old) with and without endometriosis and showed that in patients with endometriosis, thickening of the posterior intermediate zone begins already in the third decade of life and progresses significantly during fourth decade. An increase in the incidence was registered in patients older than 34 years, depending on changes in the profile of expressed genes in different periods of life. In addition, in a prospective study by S. Kissler et al. [5] found that these pain symptoms in patients with severe dysmenorrhea (n = 70) who suffered from endometriosis for 11 years were largely associated with adenomyosis.

In the opinion of the authors, MRI should become the standard procedure in cases of severe dysmenorrhea associated with endometriosis, and the presence of this symptom should always raise suspicion for the possible presence of adenomyosis. S.B. Larsen et al. [5] found adenomyosis in 34.6% of women with endometriosis in 19.4% of women in the control group ($p < 0.05$). 39.9% of women with endometriosis had an abnormal intermediate zone of the myometrium (22.5% in the control group, $p < 0.01$). Although the majority of women with severe endometriosis (stage four according to the American Fertility Society classification) had a pathological process extending to the entire thickness of the muscular layer of the uterus up to its serous cover (stage three adenomyosis), the presence of deep infiltrative rectovaginal endometriosis and the degree of infiltration did not correlate with the presence of adenomyosis.

Thus, based on MRI data, the authors concluded that severe endometriosis in at least one third of cases is associated with adenomyosis [1]. Drug Therapy Speaking about the possibilities of drug effects on pathologically altered endomyometrium, gonadotropin-releasing hormone agonists can be considered as pathogenetic therapy today . It has been shown that as a result of the use of gonadotropin-releasing hormone agonists, the intensity of angiogenesis significantly decreases (the density of the vascular network decreases, the levels of expression of the angiogenesis factor MCP-1 (CCL2), etc.), the infiltration of tissues by immunocompetent cells decreases (the levels of expression of CD68-positive cells decrease).) and, conversely, the expression of apoptosis markers (for example, caspase 3) increases [13].

Of course, it is important for the clinician to evaluate the possibilities of drug therapy for adenomyosis for the most effective relief of the main symptoms of the disease. Thus, in 2010, the results of a prospective observational comparative study of the use of triptorelin in 70 women with adenomyosis and endometriosis were published, equally divided into two subgroups. The experimental group received an intramuscular injection of triptorelin at a dose of 3.75 mg with an extended interval of administration (once every six weeks), and the control group received an intramuscular injection at the same dose once every four weeks. Thus, the duration of therapy was 24 weeks. In total, patients in both groups received four doses of the drug. The following main indicators were evaluated: the disappearance and resumption of dysmenorrhea, the occurrence of menopausal symptoms associated with the treatment, a decrease in the volume of the uterus, and the determination of hormone levels. By the end of the treatment, the volume of the uterus in both groups significantly decreased by more than 30% (by 37.6% in the experimental group and by 39.2% in the control group, $p < 0.05$). The disappearance of dysmenorrhea was observed in all women of both groups within six months of therapy. During the first 12 weeks of therapy, no adverse events associated with menopausal symptoms (hot flashes, sweating, vaginal dryness) were recorded in any of the cases in both groups. It seems extremely important that the therapeutic effect of triptorelin persisted for another six weeks after the last injection of the drug (lowering the hormonal level to the limits required for treatment and reducing dysmenorrhea) [15].

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