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Fertility and Adenomyosis. Solved and Unresolved Problems

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Abstract Adenomyosis is a common condition in modern gynecology and does not tend to increase, which prompts gynecologists to continue studying this problem. Uterine endometriosis, or adenomyosis, is a distinct pathology that differs from external and extragenital endometriosis in its pathogenesis and morphological structure. Questions regarding pathogenesis, uniform terminology, classification, diagnosis, and treatment remain unresolved.

Keywords Adenomyosis, Dienogest, Ultrasound

Adenomyosis is a benign condition characterized by the spread of ectopic tissue, similar in morphological and functional properties to the endometrium, at varying depths within the myometrium (more than 2.5 mm below the basal layer of the endometrium), often surrounded by hypertrophic and hyperplastic smooth muscle cells [1-3].

Risk factors for the development of adenomyosis include early menarche, short menstrual cycles, increased body mass index, and a history of depression [4]. Surgical injury to the endometrium and myometrium during pregnancy, including cesarean section, is the most well-known risk factor for adenomyosis [5]. For a long time, the diagnosis of adenomyosis was based on histological examination of the uterus after hysterectomy. Therefore, adenomyosis was believed to occur in multiparous women aged 40–50 years and was associated with early menarche, high parity, and a history of miscarriages [1,6,7].

The incidence of adenomyosis has not been precisely established due to the lack of uniform diagnostic criteria. In publications, the prevalence of adenomyosis based on the results of histological analysis of postoperative material from the removed uterus varies widely: from 5–8 to 40–70% (on average 20–25%) [8]. Adenomyosis is increasingly being detected in young women with pain syndrome: in 30–50% – with infertility, in 30% it is asymptomatic, which was shown using imaging methods: transvaginal ultrasonography and magnetic resonance imaging (MRI) [9]. In a recent cross-sectional in-depth study of patients suffering from infertility, the prevalence of adenomyosis was 24.4% in women aged 40 years and older and 22% in women under 40 years. This percentage increased to 38.2% in cases of repeated pregnancy loss and to 34.7% in cases of previous failures of assisted reproductive technologies [10].

It is important to consider that adenomyosis is often combined with other gynecological diseases: in four-fifths of adenomyosis cases, uterine myoma and endometriosis are concomitant diseases [13]. J. Kitawaki showed that adenomyosis and leiomyoma coexist in 35–55% of cases, and adenomyosis and endometriosis coexist in 70% of cases [11]. It was also noted that endometrial polyps, typical and atypical endometrial hyperplasia, and endometrial carcinoma are more often combined with adenomyosis than detected in isolation [10].

The etiology of adenomyosis remains unclear. Of all the theories of pathogenesis, two are considered the most popular. The first theory is based on the assumption that the basal glands of the endometrium and stroma penetrate (invaginate) into the underlying myometrium, causing the development of internal adenomyosis. It has been established that in adenomyosis, more pronounced and asynchronous contractions of the uterus are observed. These contractions can cause microdestruction in the endometrial-myometrial junction zone (JZ), which leads to the displacement of the endometrium into the surrounding myometrium, where myometrial cells proliferate and undergo metaplasia, which contributes to thickening. Traumatization of the transition zone is aggravated by the development of inflammation, hyperestrogenism and progesterone resistance, thereby facilitating the stimulation of pathological proliferation of the endometrium. In 1983, H. Hricak et al. first described the functional zone of the uterus, which is the junction between the endometrium and the internal myometrium. In the literature it is designated by different names: archiometrium, basal layer, internal myometrium, myometrium of the junctional zone, endometriomyometrium interface, transition zone and subendometrial myometrium [1].

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The second theory suggests that adenomyosis is a de novo formation by metaplasia of embryonic pluripotent remnants of Müllerian ducts or adult stem cells [11]. Alternative theories include endometrial intussusception along lymph nodes within the myometrium, platelet aggregation and activation as possible causes of adenomyosis induction [7]. Furthermore, a higher risk of adenomyosis has been reported in women carrying MMP-1-1607 1G/2G and MMP-2-1306 C/T polymorphisms in their promoter region [8].

Adenomyosis can present in various forms, ranging from simple thickening of the JZ to focal, cystic, and diffuse lesions. However, thickening of the JZ should be interpreted correctly, since it is known that changes in this zone can be caused by cyclic hormonal changes. Typically, the JZ thickness is 5 mm or less, with a tendency to increase with age in women, normally reaching 8 mm. Changes in the size and characteristics of the JZ (>12 mm, hemorrhagic spots of the myometrium with a high signal level) indicate the development of adenomyosis [1]. M. Bazot and E. Darai [10] suggested that adenomyosis has a heterogeneous nature and proposed to distinguish internal and external types of adenomyosis. Based on clinical experience, evaluation of MRI and histological results, researchers consider internal adenomyosis to be the result of direct invasion of the endometrium involving the internal (subendothelial) and middle myometrium, and external adenomyosis to be a lesion of endometriosis originating from outside the uterus [12].

Clinical symptoms of adenomyosis include progressive dysmenorrhea, chronic pelvic pain, dyspareunia, and abnormal uterine bleeding (AUB). The disease significantly reduces quality of life. The severity and frequency of symptoms correlate with the extent and depth of ectopic endometrial invasion into the myometrium [13].

Currently, the problem of adenomyosis has become even more significant due to evidence of the negative impact of the disease on fertility and pregnancy outcomes. In a case-control study of women undergoing in vitro fertilization (IVF), the implantation rate was slightly lower in patients diagnosed with adenomyosis compared to patients without adenomyosis [14-18]. In a multicenter prospective study, D. Mavrelos et al. showed that the probability of clinical pregnancy decreases from 42.7% in women without adenomyosis, to 22.9% in patients with four ultrasound signs of adenomyosis, and to 13.0% in patients with all seven ultrasound signs [4]. This suggests that the severity of the condition, expressed as the number of morphological features on ultrasound examination (US), worsens reproductive outcomes. The results of a systematic review and meta-analysis of the outcomes of IVF treatment for adenomyosis, including 11 studies and 519 patients diagnosed with adenomyosis by ultrasound or MRI, confirmed the negative impact of adenomyosis on reproductive outcomes. Implantation rate, clinical pregnancy rate per cycle, clinical pregnancy rate per embryo transfer, ongoing pregnancy, and live birth rate were lower among women with adenomyosis, whereas miscarriage rate was significantly higher [26]. In a recent retrospective study of women who underwent IVF, the presence of adenomyosis affected clinical pregnancy rate, live birth rate, and miscarriage rate. When comparing women diagnosed with endometriosis, patients with adenomyosis had significantly lower clinical pregnancy rates (26.4% vs. 12.5%) and live birth rates (26.4% vs. 12.5%) [19]. Regarding the association between endometriosis, adenomyosis, and fertility, a 2014 systematic review and meta-analysis reported a 68% reduction in pregnancy rates in patients after surgery for rectocervical and colorectal endometriosis [11].

Several theories have been proposed to explain the mechanisms underlying infertility [20-25]. One factor in the development of infertility is considered to be abnormal utero-tubal transport due to anatomical deformation of the uterine cavity, disrupting its peristalsis and, consequently, sperm transport. Damage to the inner layer of the myometrium leads to dysfunctional hyperperistalsis and increased intrauterine pressure, and uterine contractility is impaired [26-29]. In infertility associated with adenomyosis, significant molecular changes leading to altered receptivity have been identified in the eutopic endometrium. Altered synthesis of sex hormones, elevated markers of inflammation and oxidative stress, decreased expression of implantation markers and adhesion molecules, and altered function of the embryonic development gene (HOXA 10 gene) cause impaired implantation [7].

Adenomyosis is known to affect not only reproductive function but also pregnancy outcomes. In a published meta-analysis, R. Vercellini et al. The miscarriage rate in women with adenomyosis was 31%, compared to 14.1% in healthy women. A recent retrospective case-control study showed that adenomyosis is associated with an increased risk of second-trimester miscarriage, preeclampsia, and abnormal placental location. An increased risk of preterm labor and premature rupture of membranes has been demonstrated in patients with adenomyosis. These results were obtained in a small cohort of patients with a diagnosis of adenomyosis confirmed before pregnancy by ultrasound or MRI. This cohort of patients had a significantly higher risk of cesarean section, small-for-gestational-age fetuses, postpartum hemorrhage, and fetal malpresentation. The type of adenomyosis has been shown to influence pregnancy outcomes: higher rates of pregnancy-induced hypertension and intrauterine infection were recorded in patients with diffuse adenomyosis compared to those with focal adenomyosis. Furthermore, the risk of developing cervical insufficiency increased with the prevalence of adenomyosis [30].

Regarding the pathogenetic mechanisms involved in the development of obstetric complications in adenomyosis, inflammation, increased prostaglandin production in the myometrium, impaired uterine contractility, and impaired intrauterine pressure hypothetically explain the association with preterm labor. In adenomyosis, activation of the local and systemic inflammatory response influences the interaction of the decidua with the trophoblast in early pregnancy, as well as the interaction of the chorion-decidua,

which leads to the initiation of mechanisms for preterm labor in late pregnancy. Disruption of the modeling of the spiral arteries of the myometrium and deep placentation can be attributed to the main causes of obstetric complications in adenomyosis [7].

The "gold standard" for diagnosing adenomyosis is histopathological confirmation of the presence of ectopic endometrium within the myometrium. Imaging techniques such as transvaginal ultrasound (TVUS) and MRI have revolutionized the diagnosis of adenomyosis in women with an intact uterus. TVUS is considered the first-line diagnostic tool for adenomyosis due to its availability, rapidity, and low cost. If adenomyosis is suspected, ultrasound is performed during the second phase of the menstrual cycle, a few days before menstruation [9].

The presence of one or more of the following features on 2D TVUS (two-dimensional TVUS) allows for diagnosis:

1) spherical uterine configuration;
2) anteroposterior asymmetry of the uterine walls not associated with leiomyoma;
3) heterogeneous echostructure of the myometrium;
4) poorly defined border between the endometrium and myometrium;
5) echogenic linear striations of the myometrium (acoustic shadows not originating from a leiomyoma or other echogenic lesion);
6) myometrial cysts;
7) diffuse proliferation of small vessels in the myometrium.

Ultrasound has a sensitivity of 72% (95% CI 65–79%) and a specificity of 81% (95% CI 77–85%) in diagnosing adenomyosis. However, diagnostic accuracy depends on the experience of the physician performing the examination [6].

Another ultrasound sign was recently added by an Italian research group: "the body of the uterus is curved posteriorly, the fundus of the uterus is directed posteriorly, and the cervix is directed frontally toward the bladder." A sign called the "question mark of the uterus" has demonstrated high sensitivity and specificity (92% and 75%, respectively) [1,12].

3D-TVUS (three-dimensional TVUS) allows for direct visualization of endometrial invasion into the myometrium. Furthermore, the use of 3D-TVUS with color Doppler helps in the differential diagnosis of adenomyosis and leiomyoma, as well as other common gynecological diseases with similar clinical symptoms [34]. A recent study evaluated the resistance index around and within pathological lesions. The presence of "central vascularization" and "ill-defined transition zone" on 3D-TVUS demonstrated high sensitivity and specificity (95.6% and 93.4%, respectively) in the diagnosis of adenomyosis foci. MRI is traditionally considered a more accurate diagnostic method for adenomyosis than TVUS (sensitivity 77%, 95% CI 67–85%; specificity 89%). However, a later meta-analysis found no statistically significant difference between the diagnostic performance of MRI and TVUS. The advantage of MRI is that the result is less dependent on the experience of the examiner. Given the high cost of the method, it is often performed in selected cases (e.g., concomitant fibroids, polyps, endometriosis). MRI allows identification of the transition zone as a band of low signal intensity in T2-weighted images compared to the myometrium or endometrium [31]. In 2001, M. Bazot et al. proposed several diagnostic criteria that are still used today:

1) foci of high signal intensity in the myometrium;
2) transition zone thickness >12 mm (diffuse or focal) and/or poorly defined lesions with low signal intensity;
3) transition zone thickness/myometrial thickness >40% [13].

The role of hysteroscopy in the diagnosis of adenomyosis is currently unclear. Indirect signs of adenomyosis include endometrioid tracts (pinpoint dark red openings that may bleed), difficulty in dilating the uterine cavity, and deformation of one of the uterine walls. During hysteroscopy, an endometrial biopsy can be taken for histological verification of the diagnosis [30]. However, after curettage of the uterine cavity, damage to the vessels of the basal layer occurs, which can produce a similar picture.

Treatment of adenomyosis requires the development of a lifelong management strategy, as the disease negatively impacts quality of life. The choice of treatment depends on the woman's age, reproductive plans, and clinical symptoms [1]. The main indication for the treatment of adenomyosis is the presence of symptoms that negatively impact the daily life of women. Nonsteroidal anti-inflammatory drugs, hormonal therapy, including oral progestins, levonorgestrel-containing intrauterine system (IUS), combined oral contraceptives (COCs), and gonadotropin-releasing hormone (GnRH) analogues, are currently used to relieve pain and treat abnormal uterine bleeding in adenomyosis.

If drug therapy is ineffective or contraindicated, surgical treatment is performed, which can be divided into conservative (organ-preserving) and radical. Conservative surgical procedures include endometrial ablation/resection, myometrial electrocoagulation, and uterine artery ligation. However, these methods are not considered highly effective. Myometrial removal/reduction surgeries, including the Osada technique, are currently not widely used, and indications for them are not standardized. Hysterectomy is the last line of treatment for adenomyosis [1].

Currently, there are no data on randomized controlled trials on the effectiveness of nonsteroidal anti-inflammatory drugs and combined oral contraceptives (COCs) in treating adenomyosis [12]. COCs are not included in recommendations for the treatment of endometriosis in the Russian Federation.

GnRH analogs have shown a significant reduction in uterine volume with relief of severe symptoms of pelvic pain and uterine bleeding [1,7]. However, the use of GnRH analogues is associated with hypoestrogenic effects, including the development of vasomotor symptoms, decreased bone mineral density, genital atrophy, and mood instability, which limits the duration of their use. Therefore, treatment

with GnRH analogues is usually limited to women refractory to other types of drug therapy or is considered as an alternative to hysterectomy [32].

Dienogest, a 19-nortestosterone derivative, is a progestin with high selectivity for progesterone receptors (PR) [6,7]. Dienogest suppresses ovarian function with a slight hypoestrogenic effect, which has an antiproliferative effect on the endometrium. Cell proliferation is also inhibited by inducing apoptosis [8]. In uterine tissue obtained after hysterectomy in women receiving dienogest, significant histological changes were observed, including decreased cell proliferation, nerve growth factor expression, and nerve fiber density. These data explain the clinical effect achieved in the treatment of pain associated with adenomyosis.

The results of the study by S. Prathoomthong et al. [13] showed that oral use of dienogest resulted in increased NK cell infiltration in the glandular structure of the eutopic endometrium. This confirms that dienogest has a direct effect on the endometrium in addition to its systemic effect, which contributes to improved local immunity in the endometrium.

No effect of dienogest on macrophage infiltration in the eutopic and ectopic endometrium or in the myometrium in patients with adenomyosis was detected. The effect of dienogest on macrophage infiltration differed from the effect of GnRH shown by Khan et al.. GnRH agonists (GnRH a) reduced the infiltration of CD68-expressing cells in the endometrium of women with endometriosis and adenomyosis. It is possible that the local effects of dienogest and GnRH a) on the endometrium differ in endometriosis and adenomyosis.

Mehasseb et al. studied the expression pattern of PR-A and PR-B using immunohistochemistry in women with focal adenomyosis and in the control group. PR expression in adenomyosis was lower in the endometrial stroma, as well as in the inner and outer myometrium, compared with the level of receptor expression in the glands. Therefore, dienogest has a differentiated effect on different uterine tissues, reducing bleeding and pain [11]. The first pilot study of dienogest included 17 premenopausal women with symptomatic adenomyosis. The drug was effective in reducing pain, although some women experienced menorrhagia [2]. A multicenter, randomized, double-blind, placebo-controlled study showed that daily administration of dienogest to women with adenomyosis for 16 weeks resulted in a significant reduction in pain as measured by a visual analog scale [4,6]. The drug was well tolerated, although irregular uterine bleeding was reported during treatment. Another recent study assessed the safety and efficacy of long-term use of dienogest (52 weeks) [19]. Dienogest was effective in reducing dysmenorrhea and pelvic pain, and the need for analgesics was reduced. A reduction in pain parameters after 24 and 52 weeks of treatment contributed to an improvement in the quality of life of patients, with the analgesic effect lasting up to 104 months after discontinuation with a duration of use of 24 weeks. 67% of patients who received dienogest before menopause avoided hysterectomy [4,11].

Dienogest and GnRH analogues demonstrated similar efficacy in relieving pain associated with adenomyosis. Furthermore, treatment with GnRH analogues resulted in more rapid resolution of AUB and a reduction in uterine volume, as measured by ultrasound [7]. Meanwhile, estradiol levels with dienogest, unlike with GnRH agonists, were maintained at the lower end of the physiological range, without causing hypoestrogenic effects. Treatment of adenomyosis requires lifelong use, as discontinuation of treatment leads to recurrence of symptoms. Therefore, dienogest is the drug of choice when long-term therapy is required [19].

For women with infertility, organ-preserving therapy is crucial. Currently, there are few publications on the treatment of adenomyosis in infertility. Achieving pregnancy in this cohort of women further indirectly confirms the impact of adenomyosis on fertility. However, there are no recommendations for treating infertility in adenomyosis [2,9]. Surgical treatments include adenomyoma excision and hysteroplasty using a laparoscopic or laparotomic approach. When assessing the onset of spontaneous pregnancy, the overall rate was very low (18.2%). However, with the use of GnRH analogs for 24 weeks after surgery, the overall pregnancy rate was higher (40.7% versus 15.0%; p=0.002) [30]. Live births were recorded in 36.2% of women who underwent surgery [12].

Several studies have shown that the use of GnRH analogs can improve reproductive function by increasing the receptivity of the uterus and endometrium during the implantation period when using assisted reproductive technologies [5,33]. A long-term stimulation protocol in women with adenomyosis was more effective than a short-term protocol in terms of pregnancy rate (43.3% vs. 31.8%; p=0.0001), live birth rate (43.0% vs. 23.1%; p=0.005), and reduction in miscarriage rate (18.5% vs. 31.1%; p<0.0001) [10].

In Verto fertilization (IVF) can overcome many factors of infertility associated with genital endometriosis; however, impaired endometrial receptivity in the case of adenomyosis becomes an insurmountable factor in infertility when using this procedure. It is known that with adenomyosis, pathological changes are detected in the endometrium at the microscopic level - decreased development of pinopodia. Molecular pathological changes in the endometrium are also observed, namely decreased expression of the HOXA-10 gene, integrin 3, L-selectin, mucin MUC-1, leukemia inhibitory factor, impaired expression of cytochrome P450 aromatase, and changes in the ratio of progesterone and estrogen receptor isoforms [6,31]. Increased expression of oxytocin receptors is also observed in the non-pregnant uterus. All this leads to impaired blastocyst nidation, inadequate trophoblast invasion, and ultimately infertility and miscarriages in early gestation.

A recent study by S. Prathoomthong et al. [5] revealed that dienogest administration causes an increase in mature NK cells in the glandular structure of the eutopic endometrium in patients with adenomyosis. The authors suggested that the immunomodulatory effect of progestin in adenomyosis may be beneficial for implantation and fetal protection

during pregnancy that occurs after treatment.

It is suggested that the milder ovarian suppression regimen during dienogest treatment, compared to GnRH agonists, may create adequate uterine blood flow conditions prior to pregnancy planning [33]. E.V. Vartanyan et al. [34] demonstrated that dienogest therapy increases the effectiveness of IVF cycles in patients with varying degrees of adenomyosis severity (combined with external forms of endometriosis), including in patients with long-term infertility and a history of IVF failures. The effectiveness of IVF in patients using dienogest increased twofold, reaching 48.6%. Menstrual patterns returned to normal in more than half of the patients after dienogest therapy, and a reduction in pain was noted in 74.3%. The authors proposed to conduct conservative therapy of adenomyosis with dienogest for 4–6 months at the stage of preparation for IVF: for adenomyosis of 1–2 degrees of severity for 4 months, and for adenomyosis of 3 degrees – 6 months.

For long-term conservative treatment of adenomyosis, it is desirable for medications to be affordable and accessible, yet of high quality.

In 2019, the generic drug Alvovisan, containing 2 mg dienogest, entered the Russian pharmaceutical market. A bioequivalence study showed that both the generic and original drug exhibited a high degree of similarity in pharmacokinetic parameters, with pharmacokinetic curve profiles of similar shapes. The compared drugs were characterized by similar values for relative bioavailability, maximum concentration, and relative absorption rate. The CIs for AUC (area under the curve), Cmax (maximum drug concentration in the blood), and Cmax/AUC correspond to acceptable limits of 80–125% [11].

Thus, the problem of adenomyosis cannot currently be considered resolved. Adenomyosis negatively impacts fertility, pregnancy outcomes, and reduces women's quality of life. It is important to begin treatment at the first clinical manifestations of the disease, and this treatment should be long-term, effective, and safe.

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