INFERTILITY AND ADENOMYOSIS

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Abstract
The causes of adenomyosis, like other forms of endometriosis, remain unclear, despite numerous hypotheses, opinions, and debates on the subject. Crucially, when discussing its etiology, endometriosis is considered a single disease, focusing on the shared histological characteristics of its external and internal forms. At the same time, a growing number of advocates support a different understanding of adenomyosis—as a completely separate disease, unrelated etiologically and pathogenetically to the external forms of endometriosis. The first group of hypotheses (implantation, dissemination, dysontogenetic, and metaplastic) attempt to elucidate how endometrial elements arrive at their unusual locations; the second group (immune, hormonal, genetic, vascular, apoptosis-associated, and environmental) views endometriosis as a process associated with subtle mechanisms of dysregulation in a woman's body. Given that the uterine cavity is the natural habitat for the endometrium, its invasion of the myometrium is more likely explained by the second group of causes, although this is only speculative. Heterotopic lesions arising in adenomyosis become a source of pain, provoke heavy and prolonged menstrual periods, and reduce endometrial receptivity, contributing to the development of infertility.

Keywords: adenomyosis, infertility, diagnosis.

Recently, the number of endometriosis classifications continues to increase, reaching more than 10 [4–6]. The most common, including in our country, is the classification that distinguishes between genital (localization of the pathological process in the internal and external genitalia) and extragenital endometriosis (development of endometriotic implants in other organs and systems of the woman's body). Genital endometriosis is further divided into internal (uterine body, its isthmus, interstitial sections of the fallopian tubes) and external (external

genitalia, vagina and vaginal portion of the cervix, retrocervical region, ovaries, fallopian tubes, peritoneum lining the pelvic recesses).

In our country, in addition to morphological definitions of adenomyosis, there is a classification by Academician of the Russian Academy of Sciences L.V. Adamyan (1998) [7], which divides adenomyosis into stages IV:
Stage I – the pathological process is limited to the submucosa of the uterine body;
Stage II – the pathological process extends to the muscular layers;
Stage III – the pathological process extends throughout the entire thickness of the muscular wall of the uterus to its serous layer;
Stage IV – the pathological process involves, in addition to the uterus, the parietal peritoneum of the pelvis and adjacent organs. Clinical and Morphological Features of Adenomyosis
It is known that clinical definitions of various forms of endometriosis vary. Internal endometriosis (adenomyosis) is typically characterized by more pronounced clinical symptoms [1-3].

As early as 1908, T. Cullen described clinical symptoms such as uterine bleeding, dysmenorrhea, and changes in uterine size, which are characteristic of endometriotic uterine lesions (increase in size before menstruation and decrease after it). The clinical symptoms of adenomyosis are extensive. The results of many years of research have allowed us to formulate the main clinical symptoms, including menstrual irregularities, pain, psychoemotional disturbances, and infertility. However, experts emphasize the nonspecific clinical manifestations of adenomyosis and the widespread occurrence of these symptoms in other gynecological diseases [10, 17].

Adenomyosis and Infertility

The impact of adenomyosis on female reproductive function remains an unexplored issue, particularly in the early stages of adenomyosis [1, 8]. Some experts indicate that adenomyosis is diagnosed in 40–45% of women with unexplained primary infertility and 50–58% with secondary infertility of unknown origin. Others associate habitual miscarriages in 15.3% of women with endometrioid uterine lesions; however, whether these data are objective or a consequence of overdiagnosis of the pathology is highly debatable [9, 10].

Today, a number of international classifications define endometriosis as one of the leading causes of infertility; however, this generally applies to external genital endometriosis to a greater extent [2]. However, internal endometriosis—adenomyosis—remains outside the large pool of studies devoted to genital endometriosis.

The pathogenesis of subfertility in adenomyosis is the most controversial issue. Numerous factors, primarily related to impaired endometrial receptivity, are being considered. These include decreased receptivity due to aseptic inflammation, impaired secretory transformation of the endometrium [11–13], impaired expression of estrogen and progesterone receptors [14], increased local aromatase activity in endometriotic lesions [15], and impaired endometrial receptivity, resulting in a shift in the implantation window. N. Mahajan et al. demonstrated that the implantation window shifts significantly. The rate of IVF failure was 66.6% in patients with adenomyosis, compared to 34.9% in the control group. The pregnancy rate after personalized embryo transfer with implantation window assessment in the adenomyosis group was 62.5%, indicating a shift in the implantation window as a cause of ineffective IVF attempts in patients with adenomyosis [16].

However, a number of authors do not discount other possible causes: disruption of the hormonal regulation of the menstrual cycle with the development of chronic anovulation and insufficient function of the corpus luteum [1, 15]; sperm inactivation, impaired sexual function due to severe dyspareunia, which complicates regular sexual activity and ensuring full sexual intercourse [1]; embryo damage by peritoneal macrophages, which excessively increase their activity under the influence of paracrine regulators and cytokines produced in excess in the foci of chronic inflammation accompanying adenomyosis [17]; Increased uterine contractility (preventing blastocyst implantation) and dynamic tubal obstruction due to impaired peristalsis, caused by abnormalities in prostaglandin metabolism in heterotopic foci [14].

The numerous hypotheses put forward raise doubts about their objectivity and validity, further suggesting that adenomyosis remains a poorly understood pathology.

Thus, while external genital endometriosis, despite its recognized role in reproductive dysfunction, remains a mystery, adenomyosis can be considered an even more unexplored pathology in terms of its impact on reproductive function, as well as issues of objective diagnosis and rational patient management.

Diagnosis of Adenomyosis

Most studies by leading specialists in this field confirm that both overdiagnosis and delays in diagnosis of adenomyosis occur in the diagnosis of the disease, often amounting to several years. Unjustified overdiagnosis is often based solely on a single study and the subjective opinion of a single specialist. Clearly, a comprehensive approach is necessary to optimize the diagnosis of adenomyosis, especially in its early stages [28–31].

Obviously, the presence of adenomyosis can only be accurately confirmed, the stage of its spread in the diffuse form can be clarified, and the localization of endometrioid heterotopias in the uterus (diffuse, focal, nodular, and cystic adenomyosis) can be determined only after surgical removal of the uterus and histological examination [32, 33]. However, it is equally clear that such a diagnosis of adenomyosis is completely unacceptable for women planning to become fertile. This means that the diagnosis of adenomyosis can only be based on a combination of data obtained using standard clinical and noninvasive/minimally invasive instrumental examination methods: anamnesis, bimanual examination of the patient, along with consideration of the patient's history and clinical features. However, even significant anatomical changes are not always accompanied by any functional impairments [1].

There is no doubt about the need to use modern, highly informative instrumental methods: ultrasound, a widely available, non-invasive method, allows for the suspicion of pathology with varying degrees of certainty, as well as the determination of the extent of endometrial damage [35]. Magnetic resonance imaging is currently a fairly common technique, but whether this method can be used for screening or in cases of difficult diagnosis is a matter of debate [17].

Hysteroscopy is a diagnostically valuable and highly informative method for detecting intrauterine pathology, as indicated by numerous studies. However, the diagnostic value of this method, according to the same authors, varies widely – from 32.2% to 91.4% [7, 16].

The diagnostic value and necessity of laparoscopy for verifying the diagnosis of adenomyosis remains controversial, despite some authors emphasizing the diagnostic value of this method and proposing laparoscopic criteria for adenomyosis: a marbled uterine surface, diffuse enlargement, and a rounded shape [1, 7]. The diagnostic accuracy approaches 100% [7].

Nevertheless, despite the compelling nature of the published literature, the issues of diagnosing the early stages of adenomyosis, as well as the necessity and

methods of treatment, remain unresolved, especially in women of reproductive age seeking to achieve reproductive function, including through the use of assisted reproductive technologies.

Infertility Treatment in the Presence of Adenomyosis

Given that the significance of adenomyosis in the development of infertility remains an unresolved issue, infertility treatment in the presence of adenomyosis represents a significant clinical challenge.

Attempts to overcome infertility due to adenomyosis using various hormonal therapies, primarily antiestrogen therapy, often fail to achieve pregnancy, and patients seek IVF [3]. However, expert opinions on the impact of adenomyosis on IVF outcomes are quite contradictory and do not take into account the dependence of treatment results on the severity of the disease [3, 4].

In this regard, a key issue remains the rational classification of adenomyosis stages for women suffering from infertility and seeking pregnancy through IVF. The classification developed by K.V. Krasnopolskaya, which distinguishes the following forms of diffuse adenomyosis: mild, moderate, and severe, is most appropriate for the stated purposes [41].

There are various reports on the impact of adenomyosis on the success of IVF. Women with adenomyosis have a reduced pregnancy rate in IVF programs, as well as an increased incidence of preterm birth and premature rupture of membranes [5-9].

In a retrospective cohort study by S. Sharma et al., 973 women were divided into four groups: with endometriosis only (n=355); with endometriosis and adenomyosis (n=88); with adenomyosis only (n=64); and with tubal factor infertility as a control (n=466). Pregnancy outcome parameters (clinical pregnancy, miscarriage rate, live birth rate) were compared between these groups. The clinical pregnancy rate was 36.62% in women with endometriosis, 22.72% in women with endometriosis and adenomyosis, 23.44% in women with adenomyosis only, and 34.55% in the control group. The miscarriage rates were 14.62, 35, 40, and 13.04%, respectively. The live birth rate was 27.47% in the control group; 26.48% in women with endometriosis; 11.36% in women with endometriosis and adenomyosis, and 12.5% in women with adenomyosis only. There were fewer live births in the adenomyosis groups compared to the control group and women with endometriosis only. There were no significant differences in clinical pregnancy, miscarriage, or live birth rates between the control group

and women with endometriosis alone. Live birth rates differed significantly between the control group and women with adenomyosis (p=0.01) and between women with endometriosis and adenomyosis (p=0.002).

D. Mavrelos et al. [40] also confirmed that the clinical pregnancy rate after IVF was significantly lower in patients with adenomyosis. The severity of the condition, expressed as a number of morphological features on ultrasound scanning, increases the incidence of negative outcomes.

Given the low pregnancy rates associated with adenomyosis in IVF programs, early screening and preliminary preparation of this group of patients are necessary, according to some experts [44, 46].

The primary goal of various hormonal treatment regimens for endometriosis is to induce atrophy of heterotopic lesions by suppressing the function of the hypothalamic-pituitary-ovarian axis [6]. However, most authors emphasize that treatment is symptomatic, providing short-term relief of clinical symptoms, rather than a cure for the disease itself [1].

Treatment of Infertility Associated with Adenomyosis

Some researchers believe that suppressive therapy for stages I and II adenomyosis with hormonal drugs allows for the possibility of natural pregnancy. However, a Cochrane review by E. Hughes et al. demonstrated that this approach does not improve the prognosis for pregnancy.

The most common approach is medical suppression with gonadotropin-releasing hormone (GnRH) agonists before assisted reproductive technologies (ART).

G. Younes et al. [44] analyzed and pooled existing data on the impact of adenomyosis on fertility and IVF outcomes. An electronic patient search was conducted using the following databases: Pubmed, Embase, Ovid Medline, the Cochrane Central Register of Controlled Trials, and Google Scholar. As a result, all related articles were identified up to November 2016. Eleven comparative studies evaluating the clinical outcomes of IVF treatment in women with adenomyosis diagnosed by magnetic resonance imaging or transvaginal ultrasound (519 patients) and without it (1535 patients) were included. Fertility was compared in two groups of infertile patients with adenomyosis who did not receive treatment and those treated surgically or medically with GnRH agonists. The implementation of reproductive function in terms of implantation rate, clinical pregnancy per embryo transfer, ongoing pregnancy, and live birth in women with adenomyosis were significantly lower than in women without

adenomyosis. The miscarriage rate was higher in women with adenomyosis than in women without adenomyosis. It was concluded that treatment with GnRH agonists increases the pregnancy rate in women with adenomyosis. However, the authors noted an increase in the dose of gonadotropins per ART cycle after long-term suppression.

X. Hou et al. [45] conducted an observational cohort study of three groups of patients undergoing the first cycle of IVF treatment with normal ovarian reserve: (A) 362 patients with adenomyosis in the super-long protocol with GnRH agonists; (B) 127 patients with adenomyosis in the long protocol with GnRH agonists; (C) 3471 patients with tubal infertility who underwent an IVF program using a long protocol with GnRH agonists. According to the results of the study, the implantation rate and the live birth rate increased in the super-long protocol with GnRH agonists compared to the long protocol with GnRH agonists. Patients with adenomyosis in the super-long protocol with GnRH agonists had better pregnancy outcomes than patients in the long protocol with GnRH agonists. Therefore, it was concluded that adenomyosis can negatively impact IVF outcomes, regardless of the state of ovarian reserve.

A meta-analysis of three randomized controlled trials showed that the use of GnRH agonists for 3–6 months before ART in women with stage II–IV endometriosis significantly increased the pregnancy rate. These women also had a higher live birth rate. No increase in gonadotropin dosage was demonstrated during the stimulation cycle compared to the control group; however, these data were statistically inconsistent [17].

A study by J. Lin et al. [4-8] examined the role and significance of GnRH agonists in the treatment of adenomyosis in women with infertility. The authors described their effectiveness in reducing uterine size, increasing the receptivity of the uterus or endometrium to embryos, and improving the ability of the uterus to support pregnancy. It has been shown that treatment with GnRH agonists, rather than surgical removal of lesions located deep in the myometrium, is a priority for adenomyomas and infertility, as it can prevent uterine rupture during pregnancy. In infertility, treatment with GnRH agonists before laparoscopic surgery significantly reduces surgical complications and, in some cases, blood loss.

It would seem that the presented data clearly indicate the positive effects of GnRH agonists in women with adenomyosis and infertility, both as a pre-treatment and in IVF programs. However, these studies, like most others, focus on severe forms

of adenomyosis requiring treatment for medical reasons and do not address asymptomatic early-stage adenomyosis.

Other pharmacological suppression before ART. Z. Liang et al. [49] conducted a retrospective study that included 358 women with adenomyosis who underwent IVF. Of these, 134 women were assigned to the levonorgestrel-containing IUD group, and another 224 women were assigned to the control group. The results of this study revealed a positive effect of pre-treatment with a levonorgestrel-containing IUD on the outcomes of IVF programs in women with adenomyosis: the implantation rate was 32.1% versus 22.1%, and the clinical pregnancy rate was 44% versus 33.5% in the levonorgestrel-containing IUD group and in the control group, respectively.

An open-label, controlled study without randomization by D. de Ziegler et al. [50] demonstrated the efficacy of continuous combined oral contraceptive use for 6–8 weeks before ART in women with endometriosis; Results were comparable to those in women without this disease. A significant finding was that no reduction in gonadotropin dosage was observed during stimulation in patients taking combined oral contraceptives compared to the control group.

Conclusion:

In summary, the problems of adenomyosis, and especially infertility associated with adenomyosis, are extremely pressing. Many aspects of the disease's pathogenesis and its impact on reproductive function remain unclear. The role of various treatment and rehabilitation methods in restoring reproductive function and increasing the effectiveness of IVF programs also remains unresolved, necessitating further research.

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