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Adenomyosis and Endometrioid Ovarian Cyst as a Cause of Infertility: *Real or Imaginary Connection?*

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Abstract The etiology of infertility and its association with adenomyosis and endometrioid ovarian cysts is controversial, and the exact mechanisms of infertility are unclear, as some women with endometriosis may become pregnant spontaneously, while others must resort to surgery and/or in vitro fertilization. others experience repeated failures when using assisted reproductive technologies. Unfortunately, infertility has a chance to become another pandemic of the modern world, so studying the causes of infertility is extremely important from the standpoint of both prevention and treatment of topical gynecological diseases. The effect on fertility of such a disease known to every gynecologist as endometriosis often causes many contradictions. Therefore, a review of modern research on this issue seems relevant.

Keywords Adenomyosis, Endometrioid ovarian cyst, Infertility, Endometrioid ovarian, Molecular mechanisms

The goal is, based on an analysis of scientific publications, to consider adenomyosis and endometrioid ovarian cyst as a cause of infertility from opposite points of view and describe the potential mechanisms for the formation of infertility.

Results. Despite some difficulties in studying the relationship between adenomyosis, as well as endometrioid ovarian cysts and infertility, the results of a meta-analysis have proven its negative impact on fertility. Adenomyosis, as well as the formation of infertility with endometrioid ovarian cysts, is based on 4 possible mechanisms: endometrial mobility, endometrial receptivity, implantation and association with chronic endometritis.

Conclusion. It is worth recognizing that there was earlier underdiagnosis adenomyosis, and therefore underestimating its potential impact on fertility. However, modern studies with a high degree of evidence indicate a negative effect of adenomyosis on reproduction, and it is based on endometrial dysfunction. Therefore, the previously seemingly imaginary connection between adenomyosis and infertility is now quite real.

Background. The etiology of infertility and its relationship to adenomyosis is controversial, and the exact mechanisms of infertility are unclear, since one part of women with endometriosis are capable of spontaneous conception, the second is forced to resort to surgery and/or in vitro fertilization, and the third undergo repeated failures when using assisted reproductive technologies. Unfortunately, infertility tends to be another pandemic in the modern world. Therefore, study of causes of infertility formation is extremely important both from the standpoint of prevention and treatment of topical gynecological diseases. The impact on fertility of such a disease known to every gynecologist as adenomyosis often causes a lot of controversy. Therefore, a review of modern research on this issue seems relevant.

The aim of the study was to consider adenomyosis as a cause of infertility from a controversial position based on the analysis of scientific publications and to describe the potential mechanisms for infertility formation.

Results. Despite some difficulties in studying the relationship between adenomyosis and infertility, according to meta-analyses, its negative impact on fertility has been proven. Four hypothesized mechanisms underlie the formation of infertility in adenomyosis: disorders of endo-myometrial peristalsis, endometrial receptivity, implantation, and association with chronic endometritis.

Conclusion. It is worth recognizing that earlier there was an underdiagnosis of adenomyosis, and therefore an underestimation of its potential impact on fertility. However, modern studies with a high degree of evidence indicate a negative effect of adenomyosis on reproduction. Therefore, the connection between adenomyosis and infertility, which previously seemed imaginary, is now quite real, and it is based on endometrial dysfunction.

The presence of endometrial glands in the myometrium was first described by Carl von Rokitansky in 1860 as internal endometriosis [1]. However, it was O. Frankl in 1925 who first named this disease, which has become familiar to all gynecologists with the term “adenomyosis” [2]. Despite significant scientific and technological progress, the definition of adenomyosis defined by S.S. is still relevant and widespread to this day. Bird et al. back in 1972 as “benign invasion of the endometrium into the myometrium, which morphologically represents ectopic endometrial glands and stroma surrounded by hyperplastic and hypertrophied

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smooth muscle cells, which together lead to diffuse enlargement of the uterus" [3].

Until relatively recently, adenomyosis could only be reliably diagnosed after a hysterectomy, so the disease was unfairly considered a disease exclusively of older, multiparous women. 40 years. However, advances in imaging techniques such as ultrasound, magnetic resonance imaging, and laparoscopy have provided tangible opportunities for early diagnosis of adenomyosis.

A number of modern studies have shown that adenomyosis can develop even in nulliparous young women, and in girls aged 10–20 years with complaints of chronic pelvic pain, the frequency of its detection can reach up to 46% [4,5]. Thus, it should be recognized that there was previously an underdiagnosis adenomyosis among women of reproductive age, and hence underestimation of its potentially negative impact on fertility.

The connection between adenomyosis and infertility

There are many known gynecological diseases that cause infertility. Among them, endometriosis occupies an "honorable" place, which is the cause of infertility in 25–50% of cases [6,7].

Adenomyosis and endometriosis have a number of common features in terms of clinical presentation, morphology, and molecular changes [8]. The two main differences between them are the origin tion of the ectopic endometrium (basal - with adenomyosis, functional - with endometriosis) and the anatomical location of the lesions (inside or outside the uterus, respectively) [9].

In most studies looking for a link between adenomyosis and infertility, there is a potential problem with its frequent association with diseases such as endometriosis and uterine fibroids, which themselves are also a cause of infertility. The combination of adeno- and endometriosis is especially common in clinical practice (54–90 %) [10,11]. Thus, it is difficult to avoid the prejudice that in such situations the primary cause of infertility can be considered endometriosis, and not adenomyosis. The counterbalance to this statement is an experiment conducted about 20 years ago by American scientists on baboons with a preliminary total exclusion of endometriosis. They demonstrated that histologically verified adenomyosis may be the only cause of infertility in primates [12].

G. Younes and T. Tulandi in a 2017 meta-analysis proved the detrimental effect of adenomyosis on the outcomes of assisted reproductive technologies [13]. In a comparative analysis of the effectiveness of in vitro fertilization (IVF) in 519 patients with adenomyosis and 1535 women without it, the rates of implantation, clinical pregnancy rates, progressive pregnancy and live births were statistically significantly lower in the group of patients with adenomyosis, and the rate of miscarriage was significantly higher [13]. In a meta-analysis published in 2022, M. Cozzolino et al. again there was convincing evidence of a reduction in pregnancy rates, clinical and progressive pregnancy, as well as an increase in miscarriage rates in adenomyosis [14].

Thus, modern studies with a high degree of evidence indicate the negative impact of adenomyosis on the results of IVF. Therefore, the previously seemingly imaginary connection between adenomyosis and infertility is now considered quite real.

Proposed mechanisms of infertility in adenomyosis and endometrioid ovarian cysts

Despite its long history, adenomyosis remains poorly understood, especially with regard to the ways in which associated infertility develops. Currently, there are 4 proposed mechanisms: disruption of endomyotrial peristalsis, endometrial receptivity, implantation and the occurrence of chronic endometritis (CE) [10].

Violation of endomyotrial peristalsis

Previously it was believed that, unlike other smooth muscle organs, the myometrium performs its contractile function only during a short period - childbirth. However, it has been demonstrated that even outside pregnancy, uterine contractions occur, which vary during the menstrual cycle and are influenced by sex steroids [15]. It is believed that invasion of the endometrium into the myometrium begins with the connecting zone (junctiale zone – JZ) – the internal hormone-dependent layer of the myometrium, which normally promotes the transport of sperm and embryos due to rhythmic contractions.

Histological abnormalities and functional defects in this area that occur during adenomyosis cause hyper or disperistalsis of the uterus, which can be a substrate for the formation of infertility, miscarriage and complications of pregnancy [16].

Adenomyosis currently dominates, according to which it occurs as a result of invagination of the basal layer of the endometrium in myometrium due to activation of the mechanism of tissue damage and repair (tissue injury and repair – TIAR) [10,17].

Steroid hormones are known to play a central role in the etiology of adenomyosis. Thus, supraphysiological production of estrogens (hyperestrogenism), resulting from local paracrine activity in both ectopic and eutopic endometrium, is a trigger of the disease. In turn, hyperestrogenism induces proliferation of the basal layer of the endometrium, tissue microtraumas occur in the JZ area, which leads to gradual invagination of the endometrium into the myometrium [10,18,19]. As a result of microtrauma, the TIAR mechanism is activated: increasing production of estrogen promotes hyperperistalsis of the uterus, causing increasing autotraumatization, the degree of lesions increases, active invagination of the endometrium into the myometrium occurs, and ultimately adenomyosis occurs [17]. Thus, based on the pathogenesis of this disease, the listed disorders certainly adversely affect the normal peristalsis of the uterus, which is so necessary to facilitate the transport of sperm and embryos.

It must be emphasized that successful spontaneous conception requires not only normal uterine peristalsis. Migration of sperm and embryos requires productive movements of microvilli located on the apical surface of the endometrial epithelium [20]. Their core consists of microtubules, which are extremely sensitive to environmental changes.

Local inflammation caused by adenomyosis is one of the biological basis of its negative impact on fertility. Various inflammatory mediators are able to diffuse into the apical cells of the endometrium and cause structural damage to microvilli and main microtubule bundles [20]. In an attempt to find a connection between endometrial inflammation, microvilli damage and axonemal changes, KN Khan (2021) conducted a prospective cohort study in which the study substrate was the endometrium of women with adenomyosis [21].

In-depth evaluation of the endometrium using transmission electron microscopy showed that, compared with a group of control samples without adenomyosis, the number of microvilli on the apical cells of endometrium obtained from women with focal or diffuse adenomyosis was significantly reduced, and this resulted in a noticeable abnormality in their axonemes [21]. In addition, the authors of this study often observed more abnormal axonemes in women with clinical adenomyosis compared to the control group [21]. Interestingly, according to L. Benaglia et al. (2014), clinical pregnancy rates, implantation rates and birth rates in IVF cycles in women with asymptomatic adenomyosis do not deteriorate compared to patients without adenomyosis [22]. At the same time, in a systematic review and meta-analysis of IVF outcomes, P. Vercellini et al. (2014) showed that in women with symptoms of adenomyosis, the likelihood of clinical pregnancy is reduced by 28% [23].

Considering the diversity of adenomyosis, the data presented above indicate that the presence of characteristic complaints may be one of the markers of infertility associated with adenomyosis.

Endometrial receptivity and implantation disorders

In the endometrium of infertile women with adenomyosis [24,25]. Endometrial dysfunction in adenomyosis may be a consequence of changes in the structure of the endometrium, for example, thickening of its stroma due to increased vascularization. According to a systematic review by MJ Harmsen et al. (2019), with adenomyosis, antiangiogenic activity decreases and overexpression of angiogenic markers such as vascular endothelial growth factor (VEGF) occurs, which leads to abnormal angiogenesis and is a possible cause of implantation disorders [26]. A few years later, a group of the same authors, using multiplex immunohistochemistry, demonstrated an abnormally high density of blood vessels in the ectopic endometrium of patients with adenomyosis [27]. Interestingly, members of the VEGF family stimulate not only angio-, but also lymphoangiogenesis [28]. An increase in the density of lymphatic vessels was found in the ectopic endometrium, and some researchers consider impaired lymphatic drainage to be one of the reasons for implantation failure in adenomyosis [26]. This statement is based on the observation of WX Zhang et al. (2021), who observed that pregnancy rates after IVF were significantly lower in women with uterine fluid. The authors of this study suggest that this fluid is present precisely because of impaired lymphatic drainage [29]. Thus, angio- and lymphangiogenesis play an important role in the pathogenesis of implantation disorders in adenomyosis.

Currently, the number of studies devoted to the effect of adenomyosis on the expression of biologically active factors that play an important role in endometrial receptivity has grown. It has been demonstrated that the expression of a key gene involved in implantation, *HOXA-10* [30], both in a mouse model of modulated adenomyosis and in the secretory phase endometrium of women with adenomyosis, is significantly reduced [31,32].

At the same time, in adenomyosis, a violation of expression was found during the "implantation window"; this is no less important. a significant marker of endometrial -embryonic interaction as a leukemia inhibitory factor (LIF) [33]. Decidualization disorders were also identified endometrial stromal cells, which is controlled by nuclear receptors NR4A through transcriptional activation of FOXO1A.

Their expression was decreased in adenomyosis [34]. In addition, an increase in the number of NK cells, macrophages and the cytokines they produce has been described, which also negatively affects implantation [35-37].

Thus, when analyzing modern studies in adenomyosis, disturbances in endometrial receptivity are noted, associated with changes in the expression of enzymes, cytokines, growth factors, adhesion molecules and various genes such as hypoxia-inducible factor 1 α (HIF1 α), interleukins (IL- 6, IL-8, IL-10, IL-II), chemokines (CXCR1, CXCR2), matrix metalloproteinases (MMP2 and MMP9), VEGF, LIF, LIF α receptor, *HOXA-10* gene, cytochrome P450, aromatase activity, receptors estrogens and progesterone, cell adhesion molecules (integrins, MUC1, pinopodia and L- selectin) [38-40].

Association of adenomyosis and chronic endometritis

It is known that CE can cause reproductive dysfunctions such as repeated implantation failures in IVF and embryo transfer cycles, miscarriage and infertility [41]. Considering the asymptomatic course of CE in most cases, it often goes unnoticed by patients and/or ignored by doctors.

At the morphological level, CE is characterized by edema, focal or diffuse hyperemia, endometrial micropolyps and infiltration of its stroma with plasma cells [42].

Immunohistochemical staining of the endometrium with syndecan-1 (CD138) is widely used in routine clinical practice, which allows easy and reliable identification of plasma cells, i.e. verify the diagnosis [42,43]. However, discussions regarding CD138 reference values continue.

Most researchers consider microbial infection to be the main cause of CE. This is confirmed by the fact that antibacterial treatment is quite effective in eliminating plasma cells from the endometrial stroma [43]. In a series of scientific studies, KN Khan et al. (2014) presented many facts regarding the association of endometriosis with CE and described their relationship with adverse reproductive outcomes [44,45].

However, information on the occurrence of CE in women with adenomyosis is extremely scarce. A Japanese multicenter cohort study found a higher incidence of endometrial

infection in women with adenomyosis, implying an increased risk of developing CE [46]. However, a new study by KN Khan et al. (2021) provided the first clinical evidence that CE is associated with adenomyosis in ~60% of cases [47]. Thus, along with the negative impact of adenomyosis itself on the implantation potential of the endometrium, described above, concomitant diseases such as CE and endometriosis aggravate an already difficult situation.

Conclusions

It seems reasonable to assume a causal relationship between adenomyosis and infertility. However, there are a number of factors that make it difficult to study the relationship between them: the incidence rate adenomyosis is not precisely known, consensus on diagnostic criteria has not yet been adopted, and adenomyosis is rarely an isolated gynecological disease. Despite the above difficulties, the knowledge accumulated to date indicates that the biological basis of the negative effect of adenomyosis on fertility is local inflammation, disturbances in the uterine-tubal transport of sperm and embryos due to uterine hyperperistalsis and changes in endometrial microvilli, its receptivity and the implantation process, and also a change in the regulation of local hormonal metabolism, leading to hyperestrogenism. At the same time, diseases often associated with it such as endometriosis and CE, which should not be underestimated, contribute to the implementation of implantation failure of the endometrium in adenomyosis.

Thus, further research is needed to elucidate in more detail the molecular mechanisms underlying the implementation of adenomyosis -associated infertility.

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