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INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS – IS IT A "DILEMMA" OR ALL ABUNDANTLY CLEAR?

Abstract. Endometriosis is still a phenomenon that hides its true face and there is nothing surprising in the fact that this pathological condition is a "disease of mysteries and assumptions." "The problem is within the problem" is infertility on the background of endometriosis with radically different ways of its overcoming. The hypothesis that endometriosis causes infertility or reduces fertility remain controversial. The review deals with the pathogenesis, diagnosis and treatment of infertility, associated endometriosis.

Key words: infertility, endometriosis, in vitro fertilization (IVF).

Introduction. Regarding the causes of endometriosis, there are many theories, however, the true mechanisms of its occurrence are still a mystery. Existing theories of etiopathogenesis do not reveal the true essence of endometriosis-associated infertility. It is known that 176 million women of reproductive age suffer from endometriosis, of which only 15-20% have no fertility problems, but it is believed that in reality, this percentage is much lower (2-10%) [1]. In this regard, the problem of endometriosis-associated infertility is of particular relevance. At the same time, it is impossible to equate endometriosis with infertility.

It is believed that the key pathogenic links of endometriosis are closely interrelated and include excessive local production of estrogen, resistance to progesterone, inflammation and neoangiogenesis, which does not allow to inhibit the pathological process at the initial stages and explains infiltrative growth, invasion into the surrounding tissues with their subsequent destruction and the spread of lesions [2]. To explain the nature of endometriosis proposed many different theories, the most common of them is the hypothesis of J. A. Sampson on implantation of viable endometrial cells in the pelvic area during retrograde menstruation [1, 3, 4]. The most likely cause of reduced ability to conceive are anatomical changes in the pelvic organs, such as occlusion of the fallopian tubes, adhesive deformation of the fimbriae, complete isolation of the ovaries by periovarian adhesions, direct damage to ovarian tissue by endometrioid cysts[1, 3-5].

The mechanisms of the pathophysiology of endometriosis associated with infertility. Despite the large number of studies on the pathogenesis of endometriosis, which the authors are trying to reveal the most subtle, ultrastructural and biochemical the mechanisms of this disease are riddles, the reasons for the formation of both the disease and endometriosis-associated infertility still remain controversial.

In the literature you can find a description of various factors of infertility in endometriosis. **Tubal-peritoneal factor** of infertility in endometriosis is characterized by the germination of endometrioid heterotopias in their lumen, anatomical obstruction of the fallopian tubes is characterized by their obliteration against the background of adhesions in the pelvis[1, 3]. It is assumed that periovarian adhesions can complicate the rupture of the walls of the preovulatory follicle, prevent the passage of the egg from

the ovary to the ampullary part of the fallopian tube. In some cases, tubal obstruction in endometriosis may be purely functional. According to the observations, discoordinated contractile activity of the tubes was recorded in almost every second patient with endometriosis and anatomically passable tubes [1, 3]. The reason for this may be a violation of the balance of sex steroids, which is typical for endometriosis absolute or relative basal hyperestrogenia, as well as peak emissions of estradiol in the luteal phase in combination with progesterone insufficiency. Imbalance of sex hormones, causing functional tubal infertility, may be a consequence of violations of the level and secretion of gonadotropins. With endometriosis of different localizations, insufficient peak LH rises can be observed, as well as random emissions of LH and FSH into the luteal phase, accompanied by a violation of the normal dynamics of the formation of ovarian hormones with a predominance of estrogen production. An important role also belongs to the formation of local inflammation: imbalance in the formation of prostaglandins, exerts on the fallopian tubes as spastic (F2α), so and relaxing impact (E) [1, 3, 9]. The pathogenetic mechanism of formation of adhesions in endometriosis is an inflammatory reaction of the peritoneum caused by periodic menstrual-like hemorrhages in endometrioid heterotopy. Endometrioid implants have been found to secrete estradiol, progesterone, monocyte chemotactic protein (MCP-1), vascular endothelial growth factor, and proinflammatory cytokines such as interleukins (IL-1, IL-6, and IL-8) and tumor necrosis factor alpha (TNF-a) [10]. Secretion of these substances promotes proliferative and angiogenic activity, development and progression of endometriosis. Endometrial cells exposed to peritoneal fluid in patients with endometriosis have been shown to enhance expression of endothelial growth factor genes and plasminogen activator (10). Since fertilization takes place in the fallopian tube, changes in the composition of the abdominal fluid directly affect the fertilization process. As an example, these changes can disrupt sperm motility due to IL-1, IL-6 secreted by macrophages and a factor inhibiting macrophage migration (MIF) [11]. In addition, TNF-a can damage sperm DNA, due to apoptosis and the negative effects of oxidative stress [12].

Another pathogenetic mechanism in the development of infertility in endometriosis is a **violation of the receptivity of the endometrium.** In infertile patients with endometriosis revealed molecular defects associated with changes in the expression of a large number of cytokines and biologically active substances regulating the homeostasis of the endometrium, resistance to progesterone simulates the late secretory phase, leading to premature initiation of inflammation [13]. As a result, proinflammatory cytokines, chemokines and prostaglandins accumulate in the endometrium, and all these inflammatory mediators interact with each other. Abnormally elevated ER isoform, which occurs in patients with endometriosis in the secretory stage, can lead to implant failure [14]. Eutopic endometrium in women with endometriosis contains significant activity of the enzyme aromatase P450, which increases the local activity of estrogen [15]. Stromal cells obtained from the endometrium of a woman with endometriosis have a reduced ability to decidualize [16], which is probably due to resistance to progesterone and inflammatory cytokines TNF-a and IL-1 [17]. The receptivity of the endometrium is associated with expression of integrin of the endometrium, but women with endometriosis have a reduced expression of avb3, possibly due to the decrease in HOXA10 [18]. Other implantation-related biomarkers, such as glycodelin A, osteopontin,LIF, lysophosphatidic acid receptor 3 and insulin-like growth factor binding protein 1 (IGFBP1), are also addressed). As a result of the studies, the increased content of the EMX2 gene during the implantation window was revealed in patients with endometriosis, which may lead to a decrease in the frequency of implantation [19]. Unsuccessful implantation of blastocyst into the endometrium may be associated with the activation of contractile function of the myometrium caused by progesterone insufficiency, imbalance of prostaglandin production and oxidative stress, as well as exposure to autoantibodies by damage to the receptor apparatus of the endometrium [12].

Another pathogenetic link in the formation of infertility in endometriosis is the development of chronic anovulation and luteal phase insufficiency [1, 3]. One likely reason for this may be the basal hyperestrogenia, aromatase provoked by increased activity in endometriotic tissues. The relatively high level of estrogen in the proliferative phase of the menstrual cycle on the basis of feedback leads to either inhibition of production of FSH, thereby slowing down the maturation of the follicles, or contributes to a tendency to premature peak of LH occurs luteinization Novoulyanovsk of the follicle, or is accompanied by chaotic fluctuations of FSH and LH. Increased levels of estrogen in endometriosis can provoke hyperprolactinemia, which occurs in some patients with infertility. Under the influence of excess prolactin

inhibits the effect of gonadotropins on steroidogenesis in the ovaries due to the competitive binding of prolactin with receptors to FSH and LH. Increasing the level of prolactin inhibits gonadotropin secreting function of the pituitary gland, blocking the spontaneous peak of LH secretion. As a result of such changes, chronic anovulation is formed [1-3].

Often, the influence of endometrioma on the morphofunctional state of the ovary, including contralateral, which is due to the diffusion of the content of endometrioid cyst into the surrounding tissues [20]. The content of the endometrioma is a rich source of proinflammatory cytokines, iron, reactive oxygen species, and growth factors [20]. There are many publications on the negative effect of oxidative stress resulting from local inflammatory reactions on the ovarian structure adjacent to the endometrioma [21]. Both TGF-b1 and reactive oxygen species (ROS) promote fibrosis in ovarian tissue [21]. Structural changes, including loss of ovarian stroma, have a negative impact on folliculogenesis due to impaired blood supply to follicles and reduced growth factors secreted by stroma cells [22]. Reduction of ovarian reserve after surgery for ECI, especially with bilateral localization, plays an important role in reducing the reproductive potential of women with NGE. Obtaining a "poor" response may be due to reduced sensitivity to follicle stimulating hormone (FSH), including genetically determined in some infertile women with endometriosis [23]. Wnt4, FSHB and VEZT genes have been found to be the most consistently associated genes with endometriosis, but the search for mechanisms of infertility at the genetic level continues [44].

There are many reports that in endometriosis in some of the infertile patients there is a decrease in the quality of oocytes and embryos, respectively **(«embryonic factor of infertility»).** There are reports that endometriosis is a dysfunction of the mitochondria of granulosa cells, which is accompanied by a decrease in the formation of ATP. The resulting energy deficit contributes to the development of oxidative stress, resulting in damage to the genetic apparatus of oocytes, which causes a further decrease in the implantation potential of embryos [23, 45]. There are many reports of follicular fluid studies, elevated cytokine concentrations in combination with low levels of antioxidant and antiproliferative factors in some infertile patients. High levels of IL-1, IL-6, IL-8 and IL-18 were found in the evaluation of follicular fluid in patients undergoing IVF. It is shown that the presence of intrafollicular IL-1 and IL-6 can negatively affect the follicular apparatus [24], high levels of IL-8, IL-12 were negatively correlated with the number of Mature oocytes obtained and the quality of embryos [25].

In addition to the described probable mechanisms of infertility in endometriosis, some researchers also add an immune theory **(immune factor)**. Endometriosis is characterized by enhanced humoral immune response with an increase in the number of B-lymphocytes and production of autoantibodies [26]. Immunohistochemical analysis and evaluation of microarrays of gene expression showed that endometrioid heterotopias of infertile women contain an increased number of plasma cells and activated macrophages, and highly expressed stimulators of b-lymphocyte cytokines [27]. B-lymphocytes belong to the cytokine family of tumor necrosis factor, which plays a major role in the differentiation of B-lymphocytes, and its excessive expression is associated with autoimmune diseases [28]. High levels of B-lymphocytes lead to the production of large amounts of autoantibodies, which include antiendometrial, antiphospholipid and anti-nuclear antibodies. The formation of immunopathological processes is facilitated by the accumulation of tissue degradation products that are not completely eliminated from the body, but are phagocytized and resorbed by tissue macrophages surrounding the foci of endometriosis. Which contributes to the induction of autoimmune reactions against the tissues of the endometrium [1, 3, 28]. In conditions of inflammation, locally formed biologically active substances and cytokines activate peritoneal macrophages, which prevent the realization of sperm function due to their phagocytosis and/or inactivation by cytotoxic mediators.

M. T. Beste et al. it was shown that in patients with endometriosis, there were changes in the cytokine profile, revealed a significant content of interleukins (IL-1, IL-1b, IL-6, IL-8, IL-10, IL-16), hepatocyte growth factor (HGF), monocytic chemotoxic factor (MCP-1), interferon gamma (IFN-g), granulocytic-colony stimulating factor (G-CSF-granulocyte). colony stimulating factor), growth-regulated oncogenes and RANTES (regulated upon Activation, Normal T cell Expressed, and Secreted chemokine secreted by T-cells upon activation). The study found that the level of cytokines directly correlates with the process controlled by macrophages associated with proto-oncogenes (NFkB - nuclear factor kappa-light-chain-enhancer of activated B cells), Jun (c-Jun), Fos (c-Fos), activator protein 1 (AP-1) and mitogen-activated protein kinase (MAPK) [29].

In addition, infertility in endometriosis to some extent contributes to the **violation of sexual function** due to severe dyspareunia, complicating regular sexual life and/or ensuring full sexual intercourse [1-4].

Diagnostic algorithm of a patient. To date, none of the existing classifications of endometriosis is not recognized as universal. One of the most widely used in the world practice was the classification proposed in 1979 by the American fertility society (since 1995 – the American society for reproductive medicine) and revised in 1996, based on the calculation of the total area and depth of lesions of endometrioid heterotopias expressed in points [1-4]. However, this classification is not without drawbacks, the main of which is the frequent mismatch of the stage of distribution, determined by counting points, the true severity of the disease and the lack of proper, in particular, an objective assessment of infiltrative forms of the disease. Based on the assessment provided, depending on the degree of prevalence, endometriosis can be described as "minimal", "mild", "moderate" and "severe" or correspond to stage I, II, III, IV, respectively [1-4].

If NGE is suspected in patients with infertility, a comprehensive examination is indicated. In the process of diagnosis, it is mandatory to clarify the state of the ovarian reserve for choosing an individual plan of treatment for overcoming infertility. Assessment of ovarian reserve include: determination of the concentration of FSH, antimullerian of the hormone concentration of estradiol in serum, and ultrasound examination (sonography) of the ovaries on 2-3rd day of the menstrual cycle counting the number of antral follicles [1, 3, 30]. In women with endometriosis, attention is drawn to the poor quality of life, due to chronic pelvic pain, as well as a combination of symptoms such as dysmenorrhea, dyspareunia, dysuria and dyschesia. It is necessary to take into account the data of anamnesis, gynecological examination and the results of instrumental methods, including ultrasound, laparoscopy and hysteroscopy. As an additional examination can be used hardware imaging techniques such as Doppler, computer and magnetic resonance imaging. In case of suspicion of a deep invasive form of the disease (defeat of the intestine or bladder) , auxiliary examinations such as colonoscopy, cystoscopy, rectal ultrasonography may be required [1-4]. Laparoscopic visualization of foci with subsequent histological examination is the "gold" standard of endometriosis diagnosis in clinical practice [1-4].

Treatment of endometriosis - associated infertility. To date, there is no "ideal" operation or universal drug that would allow complete regression of endometriosis foci and thus eliminate the possibility of recurrence.

For many years, with the goal of hormone suppressive therapy was offered a different hormonal medication (combined oral contraceptives, progestogen, gestrinone, danazol or inrg) to reduce the severity of pain associated with endometriosis [30-33, 45]. Considering the recommendations of international societies on the effectiveness and appropriateness of hormonal therapy, it is known that the suppression of ovarian function in endometriosis as monotherapy to improve fertility with minimal or moderate endometriosis is ineffective (Ia). However, before art use inrg (Ia) increases the frequency of clinical pregnancy. At the same time, suppression of ovarian function in endometriosis after surgical treatment of endometriosis with subsequent wait-and-see therapy has no positive effect on the pregnancy rate (Ia) [34]. The combination of medical and surgical therapy certainly leads to a better outcome of the treatment of chronic pelvic pain [35].

The existing set of different surgical techniques and types of energies used in surgical treatment, such as CO 2 -laser ablation, resection or cystectomy, aspiration by ultrasound and drainage of the content of endometrioid cyst in laparoscopic access [36, 37], indicate the need for a personalized approach in each specific clinical situation [38, 39]. It should be borne in mind that the most common surgical complication, especially with endometrioma cystectomy, is a decrease in ovarian reserve of the ovary and, as a consequence, the appearance of iatrogenic infertility or premature ovarian depletion [38].

The question of tactics of management of patients with endometroid ovarian formations is debatable today. According to the clinical recommendations on endometriosis approved by the Ministry of health of Russia in 2013, surgical treatment with laparoscopic access is preferred for the diagnosis and treatment of newly diagnosed ECUS for the purpose of diagnosis verification [1]. Laparoscopic cystectomy in patients with infertility and ECA with the established diagnosis on the basis of pathomorphological conclusion is recommended for the size of cysts more than 3 cm in order to clarify the diagnosis, improve access to maturing follicles in IVF, exclude the negative impact of the contents of the cyst on the process of ovulation and fertilization; in order to exclude the malignant process – at any size of formation [1-4, 30].

In modern gynecology and Reproductology urgent task is the implementation and analysis of new high-tech methods of tissue during surgical guides on the ovaries for maximum recovery of reproductive function, reduce the risk of disease recurrence and improve the quality of life of patients undergoing such operations[40].

To date, laparoscopic ablation of endometrioid foci in combination with adhesion is an effective method of treating infertility in I–II stage of NGE, and is up to 20-40 % (Ia) [34]. The effectiveness of surgical treatment of moderate and severe forms of endometriosis to improve fertility is contradictory , it is proved that the natural fertility recovery does not exceed 10 % of cases [23]. Surgical treatment in patients with infertility and NGE of moderate and severe forms does not initially aim to achieve spontaneous pregnancy, but serves only as a preparatory procedure aimed at improving the therapeutic effectiveness of IVF. According to the existing international recommendations after surgical treatment of patients with stage III–IV NGE, regardless of the state of the fallopian tubes, ovarian reserve indicators, the age of the observed, IVF is an alternative method of overcoming infertility [4, 30].

Thus, the question of choosing the most effective method of treatment, the appropriateness of its combination in the management of patients with infertility associated with endometriosis, including the role and characteristics of art programs, ways to improve their effectiveness, is currently the subject of extensive discussions.

In the development of tactics for the management of patients with endometriosis-associated infertility should take into account the state of ovarian reserve, the age of the woman, the duration of infertility, the presence of pain and the stage of the disease [4, 23, 30].

If PE is suspected in patients with infertility, diagnostic laparoscopy should be performed to clarify the stage of the spread of the endometrioid process in the pelvic area and, subsequently, the removal or destruction of endometrioid foci. In the case of established I–II stage of endometriosis, according to the domestic clinical guidelines for the management of patients with infertility from 2019 and international ESHRE-2014, it is possible to conduct wait tactics from 6 to 12 months after surgery [4, 30].

In the absence of pregnancy within 6 months, it is advisable to perform IUI against the background of induction of ovulation with gonadotropins [4, 24, 30]. According to numerous studies, IUI combined with controlled ovarian stimulation (CBS) is the most effective method of overcoming infertility in women with minimal or mild endometriosis [4, 24, 30]. Induction of ovulation and intrauterine insemination with minimal and mild endometriosis increases the incidence of pregnancy (Ib). Total CNB in subfertile women with stage I–II NGE, according to E. Kemmann et al. that was 7.3% against KOS with agonists of gonadotropin releasing hormone (inrg) and IUI, during KOS clostilbegyt and IUI – 6.6%, and the lowest values were established in the group of patients with wait-and-see tactics and 2.8%, respectively [41]. Art in infertile patients with endometriosis is an alternative method of overcoming infertility in the presence of tubal, male factor, as well as in the age of the patient over 35 years [4, 23, 30].

In the absence of pregnancy within 1 year, the use of IVF is recommended [4, 23, 30]. In particular, IVF should be considered as the 1st line therapy in patients with low ovarian reserve, older reproductive age and infertility for more than 2 years, as well as low fertility of the partner's sperm [23,30]. Some advantage may have "supergranny" Protocol using agnrs with infiltrative, disseminated endometriosis [42].

According to experts of the American society for reproductive medicine (ASRM), endometriosis, accompanied by infertility, should be considered as a disease in which it is necessary to develop a plan for the long-term management of the patient using medical treatment (according to indications!) to exclude repeated surgical interventions [1, 4, 30]. Patients with relapse of ovarian endometriosis require a personalized approach when choosing management tactics in order to achieve the desired pregnancy.

in patients with infertility, a diagnostic laparoscopy should be performed to clarify the stage of the spread of the endometrioid process in the pelvic area and, subsequently, the removal or destruction of endometrioid foci. In the case of established I–II stage of endometriosis, according to the domestic clinical guidelines for the management of patients with infertility from 2019 and international ESHRE-2014, it is possible to conduct wait tactics from 6 to 12 months after surgery.

Conclusion. The high incidence of endometriosis and not encouraging epidemiological data explain the need to search for any opportunities that increase the effectiveness of endometriosis therapy. However, neither the pathogenesis nor the diagnostics do not give a clear answer.

Thus, the choice of treatment can not fully rely on pathogenesis, and patient care consists of a set of measures. The formation of such a complex from a variety of possibilities – surgical treatment, the use of drug therapy, finally, art – only an illustration of the impotence of doctors before the disease-a mystery.

Consequently, the problem of endometriosis is so great that in the modern medical community began to spread the term "management of endometriosis", replacing the usual medical hearing "treatment". Each of these methods has accumulated Pro - and contraversions. This suggests that the key task is still the selection of patients for the application of a particular treatment strategy. So far, this selection is speculative and does not have clear criteria. This means that there is still no satisfaction with the results of treatment of endometriosis and overcoming endometriosis-associated infertility neither in patients nor in doctors in patients with infertility, diagnostic laparoscopy should be performed to clarify the stage of the spread of the endometrioid process in the pelvic area and, subsequently, the removal or destruction of endometrioid foci. In the case of established I–II stage of endometriosis, according to the domestic clinical guidelines for the management of patients with infertility from 2019 and international ESHRE-2014, it is possible to conduct wait tactics from 6 to 12 months after surgery.

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ЭНДОМЕТРИОЗБЕН БАЙЛАНЫСҚАН БЕДЕУЛІК – "ДИЛЕММА" НЕМЕСЕ БӘРІ АНЫҚ?

Аннотация. Эндометриоз әлі де өзінің шынайы бет-әлпетін жасыратын феномен болып қалады және бұл патологиялық жағдайдың"жұмбақтар мен болжамдардың ауруы" екеніне таңқаларлық ештеңе жоқ. "Мәселенің ішіндегі – мәселе" бұл эндометриозбен байланысты бедеулікті әртүрлі тәсілдермен түбегейлі жеңу. Эндометриоз бедеулікке әкеледі немесе өсімталдықты төмендетеді деген гипотеза контроверсиялық болып қалады. Шолу эндометриозбен байланысқан бедеуліктің патогенезіне, диагностикасына және еміне арналған.

Түйін сөздер: бедеулік, эндометриоз, экстракорпоралдық ұрықтандыру (ЭКО).

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БЕСПЛОДИЕ, АССОЦИИРОВАННОЕ ЭНДОМЕТРИОЗОМ – «ДИЛЕММА» ИЛИ ВСЕ ПРЕДЕЛЬНО ЯСНО?

Аннотация. Эндометриоз все еще остается феноменом, скрывающим свое истинное лицо, и нет ничего удивительного в том, что это патологическое состояние является «болезнью загадок и предположений». «Проблемой – внутри проблемы» оказывается инфертильность на фоне эндометриоза с радикально многообразными путями ее преодоления. Гипотезы о том, что эндометриоз приводит к бесплодию или снижает фертильность, остаются контроверсионными. Обзор посвящен патогенезу, диагностике и лечению инфертильности, ассоциированной эндометриозом.

Ключевые слова: бесплодие, эндометриоз, экстракорпоральное оплодотворение (ЭКО).

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