

INFERTILITY AS A COMPLICATION OF ENDOMETRIOSIS

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ABSTRACT

Genital endometriosis among gynecological pathology takes third place after inflammatory diseases and uterine fibroids, and in specialized endoscopic clinics comes first. The frequency of endometriosis among operated patients is from 12% to 50%. Currently, about 176 million women aged 15 to 49 suffer from endometriosis. This causes significant damage to the reproductive health of patients. The question of the causes of endometriosis, as well as the real mechanisms of the development of infertility associated with this disease, is still unclear. There are many causes of infertility in the presence of endometriosis: decreased receptivity of the endometrium, impaired implantation processes, tubal and peritoneal disorders, decreased ovarian reserve, decreased intensity of crushing of embryos, impaired implantation.

KEYWORDS: endometriosis, infertility, endometrium, anovulation, implantation, tube movement, adhesions.

Relevance. In recent decades, the problem of maintaining reproductive function in patients with endometriosis has become increasingly important. Today, about 176 million women aged 15 to 49 years worldwide suffer from endometriosis.^[1,3,7] This indicates that there is a serious threat to the reproductive health of patients. The question of the causes of endometriosis, as well as the real mechanisms of the development of infertility associated with this disease, is still unclear.^[1,10] Therefore, the study of this mechanism based on the collection and analysis of available data is one of the urgent problems of modern medicine.

Purpose of the work. Analysis of complications of endometriosis. To study the complications of endometriosis as a cause of infertility based on available data. Reveal the latest views at the present stage.

The existing theory of the etiopathogenesis of infertility in endometriosis does not fully reveal the true nature of this process. However, possible causes of infertility in endometriosis include: a decrease in tubular and peritoneal factors associated with decreased susceptibility of the endometrium, impaired ovulation, "embryonic factor", adhesions and impaired tubal mobility. The main causes of infertility in endometriosis are anovulation, a decrease in the ovarian reserve, a deterioration in the quality of the egg, a decrease in the rate of fertilization of the egg, a decrease in the rate of

reproduction of the embryo, and impaired implantation.^[8,10]

Endometrial insufficiency plays a leading role in the development of infertility in patients with endometriosis. It is known that the receptor apparatus of the endometrium plays a crucial role in implantation. Bulun S.E. and others in their study, they observed that progesterone receptors appear in the endometrium of patients with endometriosis, thereby increasing their resistance to progesterone.^[10]

In modern conditions, according to the results of the work of E. Hausman and Hammual, it was proved that in patients with endometriosis - the rate of pregnancy with oocyte donors is much lower.^[2,5] In particular, high levels of antiendometrial antibodies in women with endometriosis may lead to implantation failure.^[1,6] There is ample evidence that infertility in endometriosis may be associated with decreased embryonic quality.^[10]

In endometriosis, tubal infertility occurs because it disrupts the anatomy of the fallopian tubes. This factor is specific to the abdominal cavity of endometriosis and is directly related to the severity of the process. The fall of heterotopia in the fallopian tubes leads to their obliteration (anatomical shape), which in turn creates a barrier that prevents the passage of germ cells and the fertilization process.

It is also indicated the presence of a patental dysfunction of the fallopian tubes when the peristalsis of the fallopian tubes is impaired. Discoordinated contractile activity is observed as a result of prolonged exposure to prostaglandins and other biologically active substances intensively generated in EGE heterotopias, as well as due to absolute or relative hyperestrogenism in combination with progesterone deficiency of the second stage of the menstrual cycle.^[8,10] In endometrioid heterotopias, intermittent menstrual bleeding and accumulation of serous-hemorrhagic exudate lead to accumulation of large amounts of fibrin. Disruption of microcirculation causes tissue hypoxia, enhances the formation of adhesions. In peritoneal infertility, local inflammation is also observed in the area of endometrioid heterotopia.^[10] Chronic inflammation in EGE occurs as a result of activation of T-cell immunity, an increase in inflammatory mediators in the abdominal cavity is detected.^[1,4,7]

In the first and second stages of endometriosis, if the gestational age in the first year is estimated to be 20% to 50%, then the cumulative rate of pregnancy decreases by 4% per year.^[1,6] A meta-analysis of 27 randomized controlled trials involving 8,984 infertile patients showed a clinical association between infertility and endometriosis.^[10] In stage I-II of endometriosis, the frequency of pregnancies is significantly reduced (relative risk = 93, confidence interval 95% - 0.87-0.99, $p = 0.03$). In stage III-IV of endometriosis, there is a decrease in the frequency of implantation (relative risk = 0.79, 95% confidence interval 0.67-0.93, $81 P = 0.006$) and a clinically confirmed pregnancy rate (relative risk 0.79, 95% confidence interval 0.69-0.91, $P = 0.0008$).

In 2015, the issue of patients with infertility problems with endometriosis was widely discussed at the annual conferences of the world's leading reproductive societies - ASRM (American Society of Reproductive Medicine), ESHRE (European Society of Human Reproductive and Embryology). During a special interactive session of the ASRM conference, the mechanisms of infertility in endometriosis and its impact on the results of in vitro fertilization were discussed.

According to various authors, the incidence of infertility in women with endometriosis can reach 55-75%.^[5] One in three patients who resorted to assisted reproductive technologies had external genital endometriosis.^[9] Because of the high frequency of recurrent ovarian endometrioid formation and the negative impact of surgical treatment on ovarian reserve status, most authors use IVF programs as first-line therapy to overcome endometriosis-related infertility.

Studies by P. Vercellini *et al* (2009) have shown that the rate of pregnancy is almost 2 times lower after repeated surgical interventions on recurrent ovarian endometrioid lesions (1, 5, 7). According to the recommendations of ESHRE (2014), repeated operations aimed at restoring

natural fertility in patients with recurrent ovarian endometriosis, in the absence of absolute indications, prolongation of the use of IVF is not justified.^[6,9] W. Xing (2016) did not find significant differences in the frequency of pregnancies when they previously operated on for IVF and were examined in IVF programs for the formation of recurrent endometriosis.^[10] However, the authors note that patients with EGE require an increase in the initial dose of gonadotropins, and that the stimulation itself is more stable than in the group of patients with EGE stage I-II. Regarding the possibility of conducting primary transvaginal aspiration in the presence of EGE in a recurrent state before the IVF program, there is no opinion in the literature. W. Xing *et al.* (2016) did not reveal a positive effect of the effectiveness of the program and HBK on the transvaginal aspiration of the presence of EGE before the IFV program.^[1,5,9]

A. Aflatunsky *et al.* (2013), in contrast, confirm the positive effect of primary ethanol sclerotherapy in the treatment of recurrent endometrioid ovarian cysts, especially before the IFV program.^[10] Polat and others (2015) noted in an analytical article that endometriosis alone does not adversely affect the results of the IFV program.^[1] A similar opinion is shared by a number of other scientists who argue that endometriosis does not reduce the frequency of live births, but that the number of oocytes obtained in one stimulation cycle is less.^[3,5] When performing repeated operations on the ovaries, it should be borne in mind that there is an increased risk of a certain decrease in ovarian reserves, which leads to certain difficulties in solving reproductive problems.

When deciding on a recurrent EGE in favor of surgical treatment, it is advisable to make a decision to create a bank of your own oocytes or embryos before surgical treatment. According to experts from the American Society of Reproductive Medicine (ASRM), endometriosis with infertility should be considered a disease in which the patient needs to develop a long-term plan using medication (if indicated) to exclude repeated surgical intervention.^[6,8,10]

Patients with EGE disease require an individualized approach in choosing management tactics to achieve the desired pregnancy. In patients with moderate to severe EGE, especially in the presence of recurrent EGE, IFV is the most effective method of overcoming infertility associated with endometriosis.

The role and characteristics of assisted reproductive technology (ART) programs in selecting the most effective method of treatment, its targeted implementation in patients with recurrent EGE, as well as ways to increase their effectiveness are still widely discussed. The status of ovarian reserve, age of the woman, duration of infertility, presence of pain syndrome and stage of the disease should be taken into account when developing tactics of treatment of patients

with infertility associated with endometriosis.^[1,3,7] If endometriosis is suspected in patients with infertility, diagnostic laparoscopy should be used to determine the stage of spread of the endometrioid process in the small pelvic area and then to remove or eliminate endometrioid foci using different energy types.

If stage I-II endometriosis is detected, it is possible to conduct a waiting tactic, probably 6–12 months after surgery, in accordance with the clinical guidelines for the treatment of ESHRE-2019 infertility patients.^[1,4,6,8] The effectiveness of surgical treatment as the only means of pregnancy recovery with a prevalence of I-II stages of EGE is 20–40%.^[2,5,8]

However, the abandonment of the tactics of expectation and intrauterine fertilization with the sperm of a husband or donor, especially the use of gonadotropins to stimulate ovulation, significantly increase the frequency of pregnancy and childbirth. If there is no pregnancy for 6 months, it is recommended to perform intrauterine insemination (IUI) against the background of the induction of ovulation with gonadotropins.^[2,3,6,10] According to many studies, IUI is the most effective way to overcome infertility in women with moderate or mild endometriosis in combination with controlled ovarian stimulation.^[5,6] I. Tummon and Gammal reported that the cumulative birth rate after IUI with controlled ovarian stimulation (KOS) was 5 times higher than the tactics of expectant therapy (3, 5, 7, 10).

According to the literature, against the background of induction of ovulation by clostilbegit, the frequency of pregnancy during IUI is lower compared to the stimulation of gonadotropins.^[10] Pregnancy in infertile women with stage I-II EGE, according to E. Kemmann, when using gonadotropin releasing hormone agonists (GnRH) with COS is -7.3%, when COS is performed against IUI with clostilbegit - 6.6% and the lowest rates were found in the group of patients with the tactics of expectation - 2.8%.^[1] In the absence of pregnancy for 1 year, the use of IVF was recommended.^[5,7] At the same time, it is advisable to consider IVF as the first line of treatment in patients with a low reserve of ovaries, older than 30 years and duration of infertility of more than 2 years.^[10]

In patients with PE in the preparation for IVF, the appointment of GnRH for 2-3 months and in diffuse infiltrative endometriosis for 3-6 months shows positive results of ART with a high degree of evidence, and the clinical gestational age is more than 4 times. Gives.^[1,2,5] H. Sallam *et al.* in their work, the appointment of GnRH prevents the premature release of luteinizing hormone, prevents the shift of the implantation window, increases the frequency of implantation, and focuses on the improvement of HBK indices.^[1,5]

In endometriosis, no significant difference in GnRH protocols in the IVF program and the effectiveness of

GnRH antagonists in IVF was detected.^[6,8] In infiltrative diffuse endometriosis, the “Super-long” protocol with GnRH may have a number of advantages.^[3,5] The “super-long” protocol is primarily hormonal suppressive therapy (HST), in which a long and deep hypoestrogenic state is formed; At the end of HST, gonadotropins are prescribed as an induction of superovulation.

However, it should be noted that long-term suppression of ovarian function leads to a decrease in ovarian reserve or unresponsiveness at the time of ovarian stimulation, and this may be particularly pronounced in patients with reduced ovarian reserve and older reproductive age. Provides 35-45% of pregnancies in a stimulated cycle initiated by the use of IVF in stages I-II of EGE.^[10]

In the case of recurrence of IVF, as well as the use of HST is recommended only for the treatment of pain, as most studies suggest that stage I-II of EGE HST does not increase the fertility rate in women with.^[6,10] The choice of drug (GnRH, combined oral contraceptives, progestogen) depends on the length of the period between IVF attempts, the state of ovarian reserve and age. It should be noted that combined oral contraceptives and progestins, particularly dienogest, serve as first-line drug therapy when ovarian reserve is depleted and in older reproductive age patients.

According to modern data, the comparative efficacy of pain relief against the background of dienogest treatment with GnRH has been identified, however, it has shown its advantage due to the long-term use of dienogest therapy and the lack of side effects.^[1,2,6] The appointment of HST relieves pain, can maintain the antinociceptive effect from 50% to 90%.^[10] To date, the role of surgical methods, ST, IFV in the treatment of patients with EGE, especially in the case of recurrence, is the subject of lively discussion. According to the clinical recommendations on endometriosis approved by the Russian Ministry of Health in 2013, the superiority of the laparoscopic surgical method in confirming the diagnosis, treatment and diagnosis of endometrioid ovarian cysts has been demonstrated.^[5,6]

When diagnosed on the basis of pathomorphological findings in patients with infertility and endometrioid ovarian cysts, the size of the cysts is 3 cm. improve access to mature follicles in IFV when exceeded; laparoscopic cystectomy is recommended to clarify the diagnosis to exclude adverse effects of cyst composition and dangerous processes - tumors of different sizes during ovulation and fertilization.^[1,5,10] In patients with moderate to severe forms of infertility and EGE, surgical treatment is not prescribed to achieve spontaneous pregnancy, but only serves as a preparatory process to increase the therapeutic efficacy of IFV.

According to existing international recommendations, in patients with stage III-IV EGE after surgery, the condition of the fallopian tubes, the state of the ovarian

reserve, an alternative way to overcome infertility when monitored by IFV, regardless of age not considered. This indicates that the chances of resuming a natural pregnancy in the postoperative period are very low. The use of IFV in stages III-IV of EGE ensures that the stimulation cycle of pregnancy is 8.3% to 14.9% of the onset of pregnancy.^[1,3,7] According to experts from the American Society of Reproductive Medicine (ASRM), infertility-induced endometriosis should be considered as a disease in which the patient has a long-term plan of medication (if indicated) to exclude repeated surgical intervention. development is expedient.^[6,8,10] An individual approach is required in selecting treatment tactics to achieve the desired pregnancy in patients with recurrent EGE.

In patients with moderate to severe forms of EGE, especially if there is a recurrence period of EGE, the most effective way to overcome infertility associated with endometriosis is IFV. The high prevalence of endometriosis, its negative impact on the reproductive functions of young women, requires a detailed study of this disease.

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