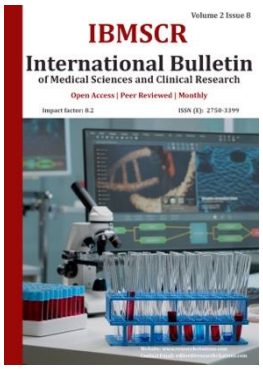


# PROSPECTS FOR THE TREATMENT OF ENDOMETRIOSIS AT THE PRESENT STAGE

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**Annotation:** Today, endometriosis affects about 176 million women aged 15 to 49 years worldwide. 20-50% of women suffer from infertility. Purpose of the study: to compare various modern treatment methods to identify the most effective way to overcome infertility due to endometriosis. Materials and methods: The study included 100 women with infertility due to endometriosis, divided into two groups according to the method of treatment. Results: the use of drug treatment and stimulation of ovulation in group A was 48% effective, and when combined with a surgical method and repeated stimulation, the effectiveness increased by another 16%. In group B, the effectiveness was 52%. Conclusion: when taking into account all factors and dividing patients by treatment method depending on the condition, the overall effectiveness of the two methods was 58% of patients in both groups.

**Keywords:** endometriosis, external genital endometriosis (EGE), infertility, endometrium, anovulation, implantation, adhesions, surgical treatment, conservative treatment.

**Relevance.** In recent decades, the problem of preserving reproductive function in patients with endometriosis has become increasingly important. Today, endometriosis affects about 176 million women aged 15 to 49 years worldwide [1, 3, 7, 12, 16, 20]. This indicates 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, still remains unclear [5, 9, 11, 13]. Therefore, the study of this mechanism based on the collection and analysis of available data for the treatment of endometriosis and its complications is one of the urgent tasks of modern medicine.

Existing theories of the etiopathogenesis of infertility in endometriosis cannot fully explain the true nature of infertility due to endometriosis. The main causes of infertility in endometriosis are anovulation, decreased ovarian reserve, deterioration in egg quality, decreased rate of egg fertilization, decreased rate of embryo reproduction, and impaired implantation [4, 6, 10].

Endometrial insufficiency plays a leading role in the development of infertility in patients with endometriosis. It is known that the endometrial receptor apparatus plays a decisive role in implantation. Bulun S.E. et al. in their study observed that progesterone receptors appear in the endometrium of patients with endometriosis, thereby increasing their resistance to progesterone.

With endometriosis, tubal infertility occurs due to disruption of the anatomy of the fallopian tubes. This factor is specific to abdominal endometriosis and is directly related to the severity of the process. The loss of heterotopias into the fallopian tubes leads to their

obliteration (anatomical form), which in turn creates a barrier that prevents the passage of germ cells and the fertilization process [2, 5, 8, 14].

Discoordinated contractile activity of the uterine tubes is observed as a result of prolonged exposure to prostaglandins and other biologically active substances intensively formed in heterotopias of external genital endometriosis, as well as due to absolute or relative hyperestrogenism in combination with progesterone deficiency of the second stage of the menstrual cycle [8, 10]. With endometrioid heterotopias, periodic menstrual bleeding and the accumulation of serous-hemorrhagic exudate lead to the accumulation of large amounts of fibrin. Impaired microcirculation causes tissue hypoxia and increases the formation of adhesions. With perinoneal infertility, local inflammation is also observed in the area of endometrioid heterotopia [10]. Chronic inflammation in external genital endometriosis occurs as a result of activation of T-cell immunity; an increase in inflammatory mediators in the abdominal cavity is detected [1, 4, 17].

In the first and second stages of endometriosis, if fertility in the first year is estimated at 20-50%, then the cumulative pregnancy rate decreases by 4% per year [1, 6]. A meta-analysis of 27 randomized controlled trials involving 8984 infertile patients showed a clinical association between infertility and endometriosis [10]. With I-II stages of endometriosis, the pregnancy rate significantly decreases (relative risk = 93, 95% confidence interval - 0.87-0.99, p = 0.03). With stage III-IV endometriosis, there is a decrease in the implantation rate (relative risk = 0.79, 95% confidence interval 0.67-0.93, 81 P = 0.006) and the frequency of clinically confirmed pregnancies (relative risk 0.79, 95% confidence interval). interval 0.69-0.91, p = 0.0008).

According to various authors, the incidence of infertility in women with endometriosis can reach 55-75% [4,5,8,11]. Every third patient who resorted to assisted reproductive technologies had external genital endometriosis [3,5,9,12,14]. Due to the high incidence of recurrent ovarian endometrioid formation and the negative impact of surgical treatment on the state of ovarian reserve, most authors use IVF programs as first-line therapy to overcome infertility associated with endometriosis. What relatively not every patient can afford, even though IVF is allowed in our country and there are already IVF centers both in the capital - Tashkent, and in other regions, including Samarkand.

In a study by P. Vercellini et al. (2009) one can see that the pregnancy rate decreases by almost 2 times after repeated surgical interventions for recurrent endometrioid lesions of the ovaries, and their attempt at successful IVF also decreases. W. Xing (2016) did not find significant differences in the pregnancy rate between patients who had previously been operated on and those who had not been operated on for IVF. However, the authors note that in patients with recurrent EGE it is necessary to increase the initial dose of gonadotropins, and the stimulation itself is more stable than in the group of patients with stage I-II EGE.

According to specialists from the American Society for Reproductive Medicine (ASRM), endometriosis with infertility should be considered as a disease in which the patient needs to develop a long-term plan using drug treatment (as indicated) to avoid repeated surgery [2, 6, 8, 11, 14, 15].

Patients with EGE disease require an individualized approach in choosing management tactics to achieve the desired pregnancy.

The role and features of assisted reproductive technology (ART) programs in choosing the most effective treatment method, its targeted implementation in patients with recurrent EGE,

as well as ways to improve their effectiveness are still widely discussed. The state of the ovarian reserve, the woman's age, the duration of infertility, the presence of pain and the stage of the disease must be taken into account when developing treatment tactics for patients with infertility associated with endometriosis [2, 3, 7, 11, 12, 15].

According to the authors, 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 pelvic area and subsequent removal or elimination of endometrioid lesions using various types of energy.

If stage I-II endometriosis is detected, it is possible to carry out expectant management; probably, 6-12 months after surgery, in accordance with clinical recommendations for the treatment of patients with infertility ESHRE-2019, spontaneous pregnancy will occur [1, 4, 6, 8]. The effectiveness of surgical treatment as the only way to restore pregnancy when stages I-II of EGE predominate, according to foreign authors, is 20-40% [13, 16, 17].

However, abandoning the tactics of waiting and intrauterine insemination with the sperm of the husband or donor, especially the use of gonadotropins to stimulate ovulation, significantly increases the incidence of pregnancy and childbirth. In the absence of pregnancy for 6 months, intrauterine insemination is recommended against the background of ovulation induction with gonadotropins with low ovarian reserve and taking into account the patient's age.

According to the literature, against the background of ovulation induction with clostilbegit, the pregnancy rate is lower compared to stimulation with gonadotropins [16,17]. In the absence of pregnancy within 1 year, the use of IVF was recommended [2, 5, 9, 11, 13]. At the same time, it is advisable to consider IVF as the first line of treatment in patients with low ovarian reserve, over 30 years of age and a duration of infertility of more than 2 years [2, 10, 11, 14, 17].

In patients with GE, when preparing for IVF, prescribing GnRH for 2-3 months and with diffuse infiltrative endometriosis for 3-6 months, positive results of ART with a high degree of evidence are shown, and the clinical gestational age is more than 4 times [1, 2, 5].

In infiltrative diffuse endometriosis, the "Ultra-long" protocol with GnRH may have a number of advantages [3, 5]. The "ultra-long" protocol is primarily hormonal suppressive therapy (HST), in which a long-term and deep hypoestrogenic state is formed; At the end of HST, gonadotropins are prescribed to induce superovulation.

However, it should be noted that long-term suppression of ovarian function leads to a decrease in ovarian reserve or non-responsiveness at the time of ovarian stimulation, and this may be especially pronounced in patients with reduced ovarian reserve and of advanced reproductive age.

It should be noted that combined oral contraceptives and gestagens, especially dienogest, serve as first-line drugs for depletion of the ovarian reserve and are recommended for patients of advanced reproductive age.

According to some scientists, in patients with moderate and severe forms of NGE and infertility, surgical treatment is not prescribed to achieve spontaneous pregnancy, but serves only as a preparatory process to increase therapeutic effectiveness and reduce pain symptoms in patients [6, 14, 17, 22].

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

improves and serves as an alternative way to overcome infertility. This indicates that the chances of resumption of natural fertility in the postoperative period increase.

According to scientists, in patients with moderate and severe forms of EGE, especially in the presence of a recurrent period of EGE, the most effective way to overcome infertility associated with endometriosis is laparoscopy and IVF.

Today, the role of surgical methods, medications and IVF in the treatment of patients with EGE, especially in case of relapse, is the subject of lively debate. The high prevalence of endometriosis and its negative impact on the reproductive function of young women requires a detailed study of this disease and the development of innovative treatment tactics.

**Purpose of the study.** To compare different treatment methods at the current level to identify the most effective way to overcome infertility due to endometriosis.

**Materials and methods of research.** The study was conducted based on the gynecological department of clinic No. 1 of Samarkand State Medical University and the Perinatal Center of the city of Samarkand for the years 2020-2022. The study included 100 women with endometriosis who suffered from infertility; they were divided according to the method of treatment into 2 groups: 50 of them were patients who underwent conservative treatment of endometriosis and restoration of fertility (group A), only after which laparoscopic treatment was recommended if ineffective, and 50 patients who underwent surgical treatment of endometriosis at the first stage, after which drug therapy was used (group B).

Clinical examination of the patients included anamnesis, initial examination, gynecological examination, ultrasound of the pelvic organs, hormonal examination, as well as a physician's opinion. The examination of men included a spermogram examination 2 times with an interval of 2-3 weeks, when assessing fertility, the corresponding WHO standards were used.

Surgical treatment of patients in group B included endoscopic laparoscopy, which was performed using KARL STORZ equipment by generally accepted techniques.

To diagnose pregnancy, the concentration of the hCG subunit was determined and ultrasound was performed.

In the first stage, patients received corrective therapy, and patients from group B received preparatory therapy for surgery.

Obese women (BMI>30) were prescribed diet therapy in combination with physical activity to reduce weight. Patients with high levels of LH and testosterone were prescribed low doses of oral contraceptives (3-6 months), for hyperprolactinemia - Dostinex and hypothyroidism - L-thyroxine preparations. Treatment was started before surgery and continued in the postoperative period. Correction of hormonal disorders was carried out under the supervision of endocrinologists.

Patients in group A were prescribed laparoscopy only after drug treatment (correction of hormonal disorders, elimination of factors of cervical dysfunction, restoration of vaginal microcenosis) and confirmation of the ineffectiveness of attempts to restore natural fertility using ovulation inducers.

When performing laparoscopy in cases of detection of pelvic pathology, appropriate surgical treatment was performed - the destruction of endometrioid heterotopia. All patients underwent chromopertubation to assess tubal patency. After endoscopic operations, to

prevent infectious complications, broad-spectrum antibacterial drugs were prescribed in recommended daily and course doses, as well as infusion therapy.

Ovulation induction was carried out according to the following scheme:

1) Treatment cycles using clomiphene citrate (CC).

a) As the first stage of infertility treatment, CC was prescribed to patients without signs of hypothalamic-pituitary insufficiency (FSH ranging from 3 to 12 IU/l, E2 > 100 pmol/l).

b) In group B, clomiphene citrate was used after endoscopic treatment.

In each of the two listed clinical situations, CC was administered in three (maximum) cycles of 5 days (from 5 to 9 days of the cycle) at a dose of 100 mg/day.

When CC was stimulated, the adequacy of the ovarian response began to be assessed from the 9th to the 10th day of the cycle, determining the size of growing follicles during folliculometry and determining the concentration of E2 in the blood. In the presence of a mature follicle measuring 18 mm, E2 concentration = 500-2000 pmol/l, an ovulatory dose of hCG of 5-10 thousand units was administered. 36-48 hours after administration, ovulation was confirmed using ultrasound.

In patients with anovulatory infertility, with early detection of resistance to CC, a combination of CC + rFSH was used to stimulate ovulation.

**Results**. The average age of patients in both groups was 24.7±1.6 years. The duration of infertility was more than 2 years. Treatment of infertility in patients with NGE with signs of endocrine infertility in group A gave the following results: all 50 patients in this group received ovulation inducers. In 10 (20%) patients with signs of hypothalamic-pituitary insufficiency (FSH <3 IU, E2 <100 pmol/l), drug hormone replacement therapy with estrogen-gestagen drugs was carried out before ovulation stimulation.

The first series of controlled stimulation of ovulation included the sequential use of folliculogenesis inducers in three cycles. After this, 10 (20%) of the women experienced intrauterine pregnancy during this series of ovulation stimulation.

The second series of ovulation stimulation was carried out in 40 (84%) patients, which was accompanied by the onset of intrauterine pregnancy in 14 patients (35% of the number of patients with the second series of ovulation therapy or 28% of all patients in group A).

In 26 (52%) of 50 patients with persistent infertility, after two series (6 cycles) of ovulation stimulation, laparoscopy was prescribed to identify and treat endometriosis, as well as concomitant peritoneal factors of tubal infertility.

According to the results of laparoscopy, 24 out of 26 examined patients had one or more pathological manifestations requiring surgical correction to restore fertility. Multiple heterotopias of EGE occurred with the highest frequency (in 92.3% of laparoscopies performed, 48% of the total number of patients in group A), adhesions of varying severity were present in 19 (38%), and functional ovarian cysts were identified in 10 (20 %). In these 26 patients, ovulation stimulation was repeated in three consecutive cycles. Inducers of folliculogenesis during repeated stimulation of ovulation in patients of this group began immediately after surgical endoscopy, that is, in group A, unlike group B, no effect was expected from the surgical treatment itself, which suggests a 6-month passive wait for the onset of “spontaneous” pregnancy. As a result of repeated stimulation of ovulation, intrauterine pregnancy occurred in 8 (16%) patients, and ectopic pregnancy in 1 (2%) woman.

Assessing the overall effectiveness of the treatment algorithm used in patients with EGE and signs of anovulatory (endocrine) infertility, we can conclude that the consistent use of the methods of ovulation stimulation described above ensured the onset of intrauterine pregnancy in 32 (64%) women from group A.

For patients in group B with preserved ovulatory and menstrual functions, the "first line" of treatment in all cases was the endoscopic method (laparoscopy). After endosurgical treatment of the identified pathology, a specific drug for the treatment of endometriosis, Visanne (2.0 mg dienogest), was prescribed for 6 months. At this time, spontaneous intrauterine pregnancy occurred in 18 (36%) patients. In cases of absence of pregnancy, they switched to the use of ovulation inducers. In general, ovulation induction using CC in this group was performed in 25 (50%) patients; As a result, intrauterine pregnancy occurred in 8 out of 25 patients (16%). Ovarian hyperstimulation syndrome was observed in 1 patient (2%). In 26 registered pregnancies, the proportion of ectopic pregnancy was 2% of the total number of patients in the group.

Thus, restoration of reproductive function in patients with EGE without signs of anovulatory (endocrine) infertility ensured the onset of intrauterine pregnancy in 52% (26 out of 50).

**Conclusion**. Based on the results of the study, we made the following conclusions:

1. In patients with EGE and an anovulatory cycle, rational drug treatment and stimulation of ovulation can naturally restore fertility in 48% of cases. When combined with the surgical method and repeated stimulation, the effectiveness increases by another 16%, amounting to a total of 64%.
2. Laparoscopy remains the "gold standard" for diagnosing EGE and concomitant diseases resulting from it: 48% of patients in group A were diagnosed with EGE and adhesions, and cysts during laparoscopy for infertility after unsuccessful conservative therapy for 6 cycles.

In patients with preserved ovulatory and menstrual functions (group B), intrauterine pregnancy occurs after laparoscopic treatment and a 6-month wait in 52% of cases

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