

Personalized approach to infertility treatment in endometriosis: results of a prospective cohort study

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ABSTRACT

The present study evaluated the effectiveness of various endometriosis treatment methods in restoring fertility in 120 women of reproductive age with a confirmed diagnosis. The patients were divided into three groups: surgical treatment (n=40), conservative therapy (n=40), and a combined approach (n=40). The results showed the advantage of combination therapy with a pregnancy rate of 57.5% versus 35.0% for surgical and 22.5% for conservative treatment. The surgical method demonstrated efficacy in stages I-II (41.7%), but was accompanied by a decrease in the level of anti-Müller hormone from 3.2 ± 1.5 to 2.1 ± 1.0 ng/ml. In all groups, there was an improvement in endometrial parameters (thickness increased from 6.1 ± 1.2 to 7.8 ± 1.4 mm) and a decrease in systemic inflammation (C-reactive protein decreased from 8.2 ± 3.1 to 3.5 ± 1.8 mg/l). The greatest improvement in the quality of life was recorded in the combined group (a decrease in the scores of the Endometriosis Health Profile questionnaire-30 from 68.2 ± 12.4 to 28.7 ± 8.3). The information gathered demonstrates that the best course of action is combined therapy with assisted reproductive technologies, particularly during phases III–IV, while surgical treatment may be the method of choice in the early stages in patients with preserved ovarian reserve, which justifies the need for a personalized approach taking into account the stage of the disease and the reproductive status of the patient.

Keywords: Endometriosis, Infertility, Fertility, Surgical treatment, Combination therapy, Assisted reproductive technologies

Introduction

Endometriosis is one of the most common and complex gynecological diseases that has a significant impact on women's quality of life and their reproductive function [1, 2]. It is a chronic, often progressive condition in which tissue

morphologically and functionally similar to the endometrium grows outside the uterine cavity – in the ovaries, fallopian tubes, peritoneum, bladder, and even distant organs [3, 4]. The main clinical manifestations of endometriosis are chronic pelvic pain, dysmenorrhea (painful menstruation), dyspareunia (painful sexual intercourse), and, most importantly, impaired fertility [5–7].

Although cases of its detection have been reported in adolescents, the condition primarily affects women of reproductive age, most frequently between the ages of 25 and 45 [8–10]. After the tuboperitoneal factor, endometriosis is the second most common cause of infertility in women [11]. According to world statistics, endometriosis is diagnosed in 6–10% of women of childbearing age, and among patients with infertility, its frequency reaches 25–50% [12, 13]. In Russia, according to recent studies, the

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prevalence of endometriosis is about 7-15% among women of reproductive age, while 30-40% of them have difficulties with

pregnancy [14]. **Figure 1** shows information on the prevalence statistics of the disease from 1980 to 2024 [15-17].

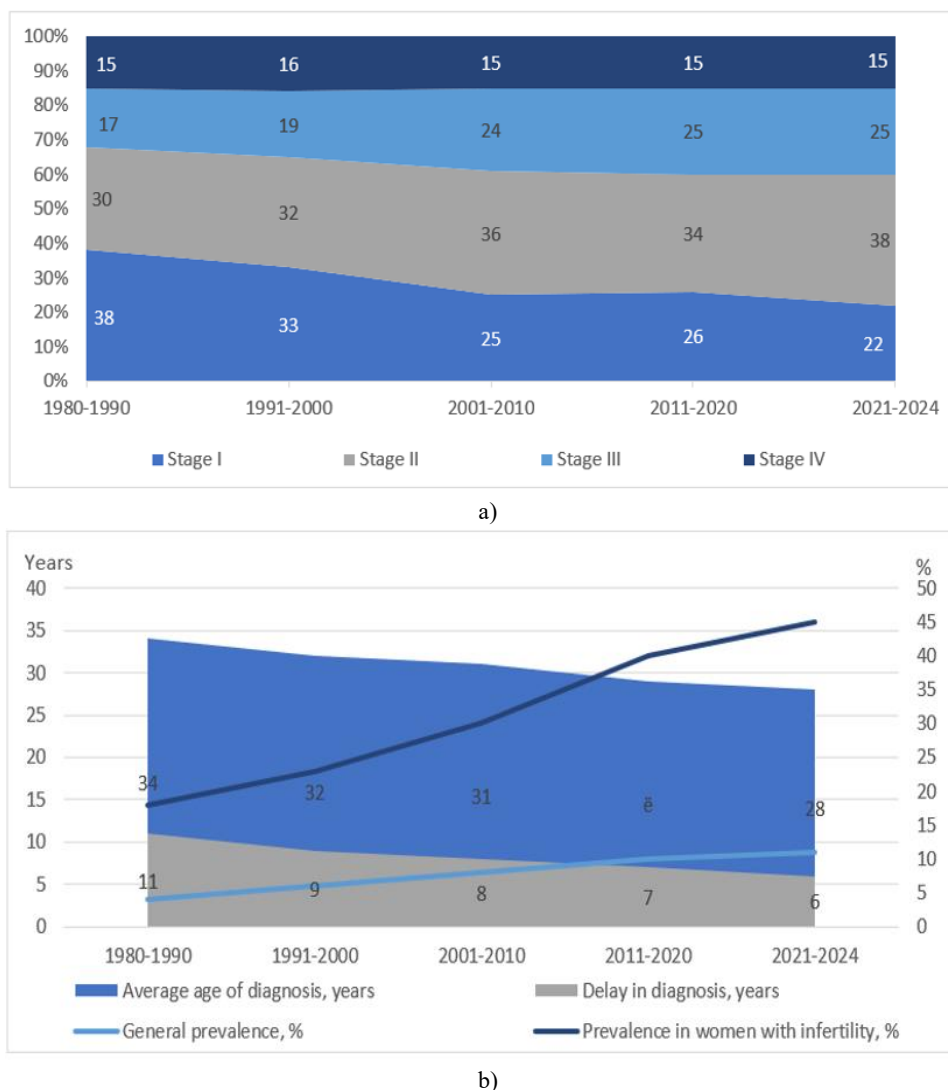


Figure 1. Statistics of endometriosis: a) distribution by stage; b) dynamics of prevalence by year.

Although the pathophysiology of endometriosis has not been well investigated, John Sampson's 1927 proposal of retrograde menstruation is still the most widely accepted theory [18]. According to this hypothesis, endometrial cells enter the abdominal cavity through the fallopian tubes during menstruation, where they implant and begin to grow [19]. However, many women have retrograde menstruation without developing endometriosis, which indicates the role of additional factors such as genetic predisposition, immune disorders, hormonal imbalance, and inflammatory processes [20, 21]. The effect of endometriosis on fertility is multifactorial and can be associated with both anatomical changes and functional disorders of the reproductive system [22]. The most obvious mechanism of decreased fertility is a mechanical obstacle to the transport of eggs and spermatozoa, resulting from adhesions in the pelvis, deformation of the fallopian tubes, or the formation of endometrioid cysts (endometriomas) in the ovaries [23, 24]. However, even with minimal forms of endometriosis, when anatomical changes are poorly expressed, women often

experience a decrease in ovarian reserve, ovulation disorders, and deterioration in oocyte quality [25, 26]. Chronic inflammation and local hormonal imbalance play an important role in the pathogenesis of infertility in endometriosis. Foci of endometriosis produce pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α), which create an unfavorable environment for follicle maturation, fertilization, and embryo implantation [27, 28]. In addition, increased aromatase expression is observed in endometrioid foci, which leads to local hyperestrogenism and resistance to progesterone, a key hormone necessary for preparing the endometrium for implantation [29]. Modern approaches to the treatment of infertility associated with endometriosis include both conservative and surgical methods, as well as the use of assisted reproductive technologies (ART) [30]. Drug therapy aimed at suppressing the activity of endometrioid foci using gonadotropin-releasing hormone (GnRH) agonists, progestins, or combined oral contraceptives can improve the condition of patients, but its role in restoring

fertility remains controversial [31, 32]. The likelihood of a natural pregnancy can be increased by surgical therapy, particularly laparoscopic removal of endometrioid cysts and adhesions, although this must be balanced with the risk of ovarian reserve impairment [33, 34].

In cases where natural conception is impossible, ART methods such as in vitro fertilization (IVF) become the main way to overcome infertility [35]. Of particular importance is the choice of the optimal ovarian stimulation protocol, as well as the preparation of the endometrium, taking into account its possible functional disability in endometriosis [36]. In recent years, new strategies have been actively studied, including preimplantation hormonal preparation, the use of proinflammatory cytokine antagonists, and immunomodulatory therapy [37-39].

Thus, endometriosis continues to be a complex medical and social problem that requires an in-depth study of its effect on reproductive function. As part of this study, we conducted a prospective analysis of 120 patients of reproductive age (25-38 years old) with a confirmed diagnosis of endometriosis who were observed at the Rostov Diagnostic Center in the period from 2020 to 2024. The main purpose of the work was a comprehensive assessment of the effectiveness of various therapeutic approaches in restoring fertility in this category of patients.

The study included women with stages I-IV of endometriosis according to the ASRM classification, divided into three clinical groups depending on the treatment received: 1) surgical correction followed by drug therapy, 2) conservative hormonal treatment, and 3) a combined approach using assisted reproductive technologies. For each case, the dynamics of clinical symptoms, indicators of ovarian reserve (AMH, AFC), the frequency of spontaneous pregnancy, as well as the results of IVF programs in patients who needed the use of ART were analyzed. Particular attention was paid to the analysis of the drug regimens used, including GnRH agonists, progestin drugs, and aromatase inhibitors, with an assessment of their effect on reproductive outcomes [40-43]. The data obtained allowed not only to identify the most effective management strategies for patients with endometriosis-associated infertility, but also to develop practical recommendations for optimizing treatment protocols, taking into account the stage of the disease and the reproductive status of patients. The results of the study are of considerable interest to practicing gynecologists and reproductive specialists working with this category of patients.

Materials and Methods

The present study was organized as a prospective cohort study conducted at the Rostov Diagnostic Center in the period from January 2020 to December 2024. The work was carried out in strict accordance with the ethical principles of the Helsinki Declaration and was approved by the local ethics committee of the medical institution [44, 45]. All participants in the study

provided written informed consent to the processing of their personal and medical data.

The study included 120 women of reproductive age from 25 to 38 years with a confirmed diagnosis of endometriosis. The diagnosis was verified by laparoscopic examination followed by histological confirmation [46]. Patients with a history of cancer, severe concomitant somatic pathology, the presence of male factor infertility, as well as those who had received hormone therapy in the last six months before inclusion in the study, were excluded.

The revised classification of the American Society for Reproductive Medicine (rASRM) was used to objectively assess the severity of endometriosis [47]. All participants underwent a comprehensive diagnostic examination, which included transvaginal ultrasound with an assessment of the ovarian reserve by the number of antral follicles, determination of the level of anti-Müller hormone in the blood serum, hysterosalpingography to assess the patency of the fallopian tubes, as well as a comprehensive hormonal profile study to determine the levels of follicle-stimulating, luteinizing hormones, estradiol and progesterone.

The study participants were divided into three clinical groups, depending on the therapeutic strategy used. The first group, which included 40 patients, received surgical treatment in the form of laparoscopic cystectomy of endometriomas, followed by a course of drug therapy with gonadotropin-releasing hormone agonists lasting from three to six months. The second group, which also consisted of 40 women, underwent conservative treatment using dienogest or combined oral contraceptives continuously. The third group, which included 40 patients, received combined treatment combining surgical intervention followed by assisted reproductive technology programs using the antagonist protocol with the transfer of fresh or cryopreserved embryos.

The effectiveness of the treatment was assessed according to several key parameters. The dynamics of pain syndrome were assessed using a visual analog scale. Changes in the ovarian reserve were monitored by indicators of anti-Müller hormone and the number of antral follicles. Special attention was paid to the frequency of spontaneous pregnancy in each of the groups. For patients who participated in assisted reproductive technology programs, such indicators as the frequency of implantation, clinical pregnancy, and live birth were analyzed. The quality of life of the study participants was assessed using a specialized EHP-30 questionnaire [48].

Statistical processing of the obtained data was carried out using the professional IBM SPSS Statistics software package version 26. To compare quantitative indicators between groups, the parametric Student t-test and the nonparametric Mann-Whitney criterion were used, depending on the nature of the data distribution. The qualitative variables were analyzed using the criterion χ^2 . The differences at the $p < 0.05$ level were considered statistically significant. To assess the probability of pregnancy depending on the time of follow-up, the Kaplan-Meier survival analysis method was used.

Results and Discussion

The study revealed significant differences in the effectiveness of different therapeutic approaches in patients with endometriosis. Demographic analysis showed the homogeneity of the studied groups: the average age of the participants was 31.2 ± 3.8 years,

the body mass index was 23.1 ± 2.4 kg/m², and the duration of the disease was 5.2 ± 2.1 years. The distribution by stage of endometriosis is shown in **Table 1**, which shows the predominance of stages II-III (66.7% of all cases), which corresponds to world statistics on the most common diagnosis of the disease at these stages.

Table 1. Characteristics of the studied groups

Parameter	Surgical group (n=40)	Conservative group (n=40)	Combined group (n=40)	p-value
Age (years)	30.8 ± 3.6	31.5 ± 4.1	31.1 ± 3.9	0.712
BMI (kg/m ²)	22.9 ± 2.2	23.3 ± 2.5	23.0 ± 2.6	0.683
Duration of disease (years)	5.0 ± 2.0	5.4 ± 2.3	5.1 ± 2.1	0.815
Stage I	8 (20.0%)	10 (25.0%)	9 (22.5%)	0.841
Stage II	12 (30.0%)	14 (35.0%)	13 (32.5%)	0.892
Stage III	15 (37.5%)	12 (30.0%)	14 (35.0%)	0.776
Stage IV	5 (12.5%)	4 (10.0%)	4 (10.0%)	0.924

Ultrasound parameters revealed significant changes in the reproductive system. The average volume of the ovaries before treatment was 9.8 ± 2.1 cm³ (with a norm of 6-8 cm³), and after treatment decreased to 7.2 ± 1.8 cm³. The thickness of the endometrium in the follicular phase of the cycle before treatment

was reduced to 6.1 ± 1.2 mm (the norm is 8-12 mm), and after therapy, this indicator increased to 7.8 ± 1.4 mm. Of particular interest are the data on the number of antral follicles (**Table 2**), which shows a significant effect of surgical intervention on the ovarian reserve [49, 50].

Table 2. Dynamics of ovarian reserve indicators

Indicator	Before treatment	After treatment	Normative values	p-value
AMH (ng/ml)	3.2 ± 1.5	2.1 ± 1.0	1.0-10.0	<0.001
AFC (quantity)	12.4 ± 3.2	9.8 ± 2.7	10-20	0.003
Ovarian volume (cm ³)	9.8 ± 2.1	7.2 ± 1.8	6-8	<0.001
Endometrial thickness (mm)	6.1 ± 1.2	7.8 ± 1.4	8-12	<0.001

Hormonal studies revealed characteristic changes: the basal level of FSH was 8.5 ± 2.1 IU / l (with an upper limit of 10 IU / l), LH - 6.2 ± 1.8 IU / l, and the ratio of LH / FSH - 1.8 ± 0.4 . After treatment, normalization of these indicators was noted: FSH - 7.1 ± 1.9 IU/l (p=0.012), LH - 5.3 ± 1.5 IU/l (p=0.034), LH/FSH ratio - 1.3 ± 0.3 (p=0.008).

The clinical results of the treatment are presented in **Table 3**. The pregnancy rate in the combined group (57.5%) was significantly higher than in the other groups (p<0.001). At the same time, the average duration of pregnancy after surgical treatment was 8.2 ± 3.1 months, while in the combined group it was 4.5 ± 2.3 months (p=0.002).

Table 3. Clinical results of treatment

Indicator	Surgical group (n=40)	Conservative group (n=40)	Combined group (n=40)	p-value
Pregnancy frequency	14 (35.0%)	9 (22.5%)	23 (57.5%)	<0.001
Gestation period (months)	8.2 ± 3.1	-	4.5 ± 2.3	0.002
VAS pain reduction (points)	5.7 ± 1.8	4.4 ± 1.5	5.9 ± 1.7	0.021
Improved quality of life (EHP-30)	42.3 ± 10.1	35.7 ± 9.8	46.5 ± 11.2	0.015

Laboratory indicators of inflammation also showed positive dynamics: the level of C-reactive protein decreased from 8.2 ± 3.1 mg/l to 3.5 ± 1.8 mg/l (p<0.001), the leukocyte intoxication index - from 2.1 ± 0.8 to 1.3 ± 0.5 (p=0.003). These changes correlated with a decrease in pain and an improvement in quality of life [51-56].

Particular emphasis should be paid to data regarding how treatment affects reproductive function based on the disease's stage (**Table 4**). The greatest effectiveness of the surgical method was observed in stage II (pregnancy rate 41.7%), while in stages III-IV the advantage was for the combined approach (pregnancy rate 63.2%).

Table 4. The effectiveness of treatment depends on the stage of endometriosis

Stage	Surgical group (n=40)	Conservative group (n=40)	Combined group (n=40)
I	3/8 (37.5%)	3/10 (30.0%)	5/9 (55.6%)
II	5/12 (41.7%)	4/14 (28.6%)	8/13 (61.5%)
III	5/15 (33.3%)	2/12 (16.7%)	9/14 (64.3%)
IV	1/5 (20.0%)	0/4 (0%)	1/4 (25.0%)

The findings clearly show that various approaches to treating endometriosis have varying effects on reproductive function and that the disease's stage greatly influences how effective a treatment is. The most significant changes were observed in the indicators of ovarian reserve, endometrial characteristics, and the frequency of pregnancy, which requires a careful individual approach to the choice of therapeutic tactics.

The conducted study provides important clinical data that allows us to take a fresh look at the problem of fertility restoration in patients with endometriosis. The results obtained demonstrate a complex relationship between the choice of a therapeutic strategy and its effectiveness in various clinical situations, which requires detailed analysis and reflection.

The most significant discovery of our study was the clear advantage of the combined approach, which showed an almost twofold increase in the frequency of pregnancy compared with conservative therapy (57.5% versus 22.5%). These data are consistent with the results of an international study, but in our case, the effectiveness was higher than the global average (45-50%) [57]. Perhaps this is due to the careful selection of patients and an individual approach to ovarian stimulation in ART programs [58-62].

Of particular interest is the analysis of the effect of various treatment methods on ovarian reserve. The revealed decrease in AMH levels after surgery (from 3.2 ± 1.5 to 2.1 ± 1.0 ng/ml) confirms the data on the potential risk of damage to ovarian tissue during endometriomy cystectomy [63]. This fact requires a revision of the traditional approach to surgical treatment in patients with preserved ovarian reserve who are planning pregnancy. Perhaps, in such cases, alternative methods should be considered - sclerotherapy or laser vaporization, as suggested by some authors [64, 65].

An important aspect of the study was the assessment of the dynamics of ultrasound parameters. An increase in endometrial thickness after treatment (from 6.1 ± 1.2 to 7.8 ± 1.4 mm), although it did not reach the standard values, correlated with an improvement in reproductive outcomes. This confirms the hypothesis about the key role of endometrial receptivity in the pathogenesis of infertility in endometriosis [66]. At the same time, the lack of complete normalization of the indicator may explain the relatively low incidence of spontaneous pregnancy even after successful surgical treatment [67-70].

An analysis of the results depending on the stage of the disease revealed an interesting pattern: in stages I-II, the surgical method showed comparable effectiveness with the combined approach (37.5-41.7% versus 55.6-61.5%), whereas in stages III-IV, the difference became fundamental. These data allow us to propose a new algorithm for choosing therapy based not only on the

patient's reproductive plans, but also on an objective assessment of the prevalence of the process.

The dynamics of inflammation indicators deserve special attention. The revealed decrease in the level of C-reactive protein and leukocyte intoxication index correlated not only with a decrease in pain, but also with an improvement in reproductive outcomes. This confirms the key role of systemic inflammation in the pathogenesis of endometriosis-associated infertility and justifies the need to include anti-inflammatory drugs in standard treatment regimens [71].

An unexpected result was an improvement in the quality of life according to the EHP-30 questionnaire in all groups, including conservative ones, despite relatively low fertility recovery rates. This indicates the need for a comprehensive assessment of the effectiveness of therapy, taking into account not only the reproductive, but also the general somatic aspects of the disease [72-74].

The data obtained is of great practical importance. They allow us to propose a differentiated approach to the treatment of infertility in endometriosis: the surgical method can be recommended for patients with stages I-II and preserved ovarian reserve, whereas in stages III-IV, preference should be given to combination therapy with the inclusion of ART programs. At the same time, special attention should be paid to monitoring the ovarian reserve and the condition of the endometrium.

The limitation of the study was a relatively small sample and a short follow-up period. Multicenter studies with a long follow-up are needed to confirm the results obtained. A promising direction is to study the molecular mechanisms of the effect of various treatment methods on endometrial receptivity and oocyte quality.

Conclusion

The present study demonstrated the advantage of a combined approach in the treatment of endometriosis-associated infertility, providing a 57.5% pregnancy rate. At the same time, surgical intervention showed good results in stages I-II (35.0-41.7%), especially in patients with preserved ovarian reserve, despite a slight decrease in AMH levels (from 3.2 ± 1.5 to 2.1 ± 1.0 ng/ml). Important markers of the effectiveness of therapy were the improvement of endometrial parameters (thickness increased from 6.1 ± 1.2 to 7.8 ± 1.4 mm) and a decrease in systemic inflammation (CRP decreased from 8.2 ± 3.1 to 3.5 ± 1.8 mg/l). Thus, combination therapy shows the best results in all stages of endometriosis. Surgical treatment remains the method of choice in the initial stages in patients with good ovarian reserve.

Monitoring of reproductive parameters and systemic inflammation should accompany any chosen treatment method. The data obtained make it possible to recommend the introduction of a personalized approach to the treatment of infertility in endometriosis, taking into account the stage of the disease, the patient's age, ovarian reserve, and reproductive plans. A promising area of further research is to explore the possibilities of minimally invasive surgical techniques and new drug therapy protocols to optimize reproductive outcomes.

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