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In vitro fertilization for endometriosis-associated infertility: A literature review

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ABSTRACT

This article analyzed the work of Russian and international authors over the past 10 years on the effect of endometriosis on the development of infertility and evaluated studies on the analysis of in vitro fertilization procedures in patients with this condition. Every third patient who uses assisted reproductive technology (ART) suffers from endometriosis-associated infertility. Endometriosis is a significant cause of this disease, and its clinical forms and the degree of foci spread often limit doctors' choice of ART programs, which do not always result in pregnancy. Cystic ovarian endometriosis is one of the most common forms of endometriosis. Controversy surrounds the treatment of this form; some authors advocate hormonal therapy (to preserve the ovarian reserve), whereas others believe that more radical surgical treatment helps reduce relapses. In any case, several factors must be considered when choosing the optimal treatment approach for women with ovarian endometriosis and infertility, including the age of the patient, presence of pain, outcomes of previous surgeries, size and number of cysts, preserved ovarian reserve, and access to the follicles. These factors prove the relevance of this condition, which requires a modern approach to its diagnosis and treatment.

Keywords: endometriosis; infertility; assisted reproductive technologies (ART); ovarian reserve; antirelapse therapy; endometrioid cysts; literature review.

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Экстракорпоральное оплодотворение при эндометриоз-ассоциированном бесплодии (обзор литературы)

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АННОТАЦИЯ

В статье проанализированы работы отечественных и зарубежных авторов за последние 10 лет о влиянии эндометриоза на развитие бесплодия, выполнена оценка исследований, посвящённых изучению проведения процедуры экстракорпорального оплодотворения (ЭКО) у пациенток с данным заболеванием. Известно, что каждая третья пациентка, обращающаяся к вспомогательным репродуктивным технологиям (ВРТ), страдает ассоциированным с эндометриозом бесплодием. Эндометриоз занимает особое место в структуре этого заболевания: различные клинические формы и степень распространения очагов зачастую ограничивают врачей в выборе программ ВРТ, и они не всегда приводят к наступлению беременности. Одна из самых распространённых форм эндометриоза — эндометриоидная киста яичников. Существует множество споров, касающихся лечения данной патологии: одни авторы склоняются в сторону гормональной терапии (в целях сохранения овариального резерва), другие считают, что более радикальные хирургические методы лечения способствуют уменьшению частоты рецидивов. В любом случае, при выборе оптимальной тактики лечения женщин с эндометриозом яичников и бесплодием необходимо учитывать целый ряд факторов, включая возраст пациенток, наличие болевого синдрома, результаты предыдущих операций, размеры и количество кист, сохранённый овариальный резерв и доступ к фолликулам. Всё вышесказанное лишь доказывает, что проблема остаётся актуальной и требует современного подхода к диагностике и лечению данного заболевания.

Ключевые слова: эндометриоз; бесплодие; вспомогательные репродуктивные технологии (ВРТ); овариальный резерв; противорецидивная терапия; эндометриоидные кисты; обзор литературы.

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INTRODUCTION

In light of recent advancements in medical science, infertility is no longer regarded as a definitive diagnosis of sterility. Despite significant progress in the diagnosis and treatment of various types of infertility, including improvements in embryo culture, selection, and transfer techniques, it is evident that not all causes of infertility have been fully addressed.

Given the considerable variety of clinical forms and degrees of severity, endometriosis represents a significant risk factor for infertility. This often constrains the selection of assisted reproductive technologies (ARTs), with the risk of unsuccessful fertilization. The recent advancements in *in vitro* fertilization (IVF) as an effective treatment option for endometriosis-associated infertility have attracted considerable interest.

Although endometriosis is considered the most common benign disease, its diagnosis and treatment may become significantly more complicated in the presence of metastatic lesions and infiltrating growth. Endometriosis is estimated to affect 10% of women of reproductive age, with 40% being infertile as a result. A distinction has historically been made between genital and extragenital endometriosis based on the localization of the disease. Genital endometriosis is commonly present in the uterus, fallopian tubes, ovaries, pelvic peritoneum, and vagina. Extragenital endometriosis is observed outside the reproductive system, affecting the intestine, bladder, lungs, diaphragm and pleura, and scar tissue. Genital endometriosis can be further classified into two forms: internal (adenomyosis) and external. In the case of external genital endometriosis, the ovaries, fallopian tubes, peritoneum, vaginal portion of the cervix, and vagina are involved [1-3]. A consensus exists among researchers that cystic ovarian endometriosis is the most prevalent form of external endometriosis.

This disease is frequently associated with infertility, necessitating the involvement of fertility specialists to enhance the likelihood of pregnancy. Medical professionals have identified endometriosis as a significant factor of infertility, with a lower likelihood of success compared to other indications for IVF [4].

INFERTILITY AND CYSTIC OVARIAN ENDOMETRIOSIS

Although a number of theories have been proposed to explain the pathogenesis of endometriosis, the mechanisms underlying infertility associated with this disease remain poorly understood. [4]

Endometriosis is currently believed to be caused by increased local estrogen production, progesterone resistance, chronic inflammation, and neoangiogenesis. Collectively, these factors result in inability to suppress the initial pathological process, which causes infiltrative growth into adjacent organs and tissues, their destruction, and subsequent spread of lesions [5].

Recent epidemiological studies have demonstrated that the prevalence of external genital endometriosis (EGE) in women of reproductive age ranges from 5% to 10% [6]. However, some authors have reported a significantly higher incidence, up to 50%. [7, 8] The histological variants of endometrial infiltration display three common characteristics: infiltrating endometrial cells, persistent hemorrhages, and inflammation. Pathogenically, the inflammatory response is considered both as the cause of the disease and the factor determining the spread of lesions induced by interleukins, prostaglandins, and other pro-inflammatory mediators, which can contribute to ectopy and the proliferation of endometrial lesions. The adhesion of endometrial tissue to the peritoneum may be the result of elevated levels of cytokines and estrogens. These, in turn, enhance local prostaglandin secretion through constant stimulation, thereby increasing inflammation and creating a vicious cycle [6-9].

A number of authors consider endometriosis to be a chronic inflammatory disease. [6, 9] Prolonged inflammation reduces tissue sensitivity to progesterone, resulting in increased endometrial proliferation, prostaglandin production, and decreased anti-inflammatory activity. It appears that endometriosis is consistently associated with elevated pro-inflammatory activity, which is a primary contributor to infertility [9].

In 2021, Ershova et al. conducted a study in 142 patients with severe peritoneal endometriosis classified as stage III-IV EGE in accordance with the American Fertility Society (AFS) classification system. A total of 136 (96%) patients had bilateral endometrial lesions classified as cystic ovarian endometriosis. The authors found that in patients with severe peritoneal endometriosis, both ovaries are almost invariably involved in the pathological process. In many cases, surgical management of peritoneal endometriosis and bilateral cystectomy in infertile patients have proven ineffective in restoring fertility. Moreover, this approach may even result in recurrent endometriosis. According to a literature review, the majority (55%) of patients who had a history of bilateral ovarian endometriomas and sought assisted reproduction were diagnosed with recurrent cystic ovarian endometriosis (COE), affecting both ovaries in approximately 30% of cases [10].

Additionally, it is important to acknowledge that surgical management of COE has been shown to be ineffective in producing definitive recovery and often has the potential to negatively impact ovarian reserve [11-13]. Furthermore, there is currently no evidence that this approach can be relied upon to prevent recurrence of the disease. [11, 14] Postoperative hormone therapy to prevent recurrent COE was not consistently effective; there were cases of COE during treatment [11].

However, alternative recommendations may also be suggested. In particular, Annenkova (2019) reported that persistent COE can result in adhesions between the ovary,

fallopian tube, and the broad ligament of the uterus, a process which could also be a cause of infertility [14]. In this case, the benefits of COE surgery are evident, particularly in young, infertile females [16].

Given the chronic and recurrent nature of endometriosis, many researchers have sought to identify the risk of recurrence and to determine the recurrence-free time following surgical intervention. The recurrence rate of endometriomas in women with persistent infertility has been found to be impressively high in the first postoperative year, reaching 40%. This figure increased to 76% within one to three years post-surgery [10]. Unfortunately, surgical treatment is not a complete solution for endometrial infiltration, nor does it address all risk factors associated with cyst recurrence and further endometriosis progression. A statistical analysis of another study revealed that 15% of cysts recurred within a year, while 21.5% and 40–50% recurred within two and five years after surgery, respectively [17].

PRE-IVF TREATMENT OF FEMALES WITH ENDOMETRIOSIS

Over the past decade, there has been a notable advancement in the diagnosis and treatment of endometriosis, with the incorporation of the latest medical innovations. Assisted reproductive technologies are rapidly evolving, with a growing number of previously intractable causes of infertility being successfully addressed. Nevertheless, the efficacy of COE surgery in patients with diminished ovarian reserves remains debatable. There is no consensus regarding the efficacy of hormonal ovulation induction and the success of the IVF protocol for patients with no absolute indications for surgical treatment (pain syndrome, significant adhesions, cysts >4 cm, and stage III ovarian endometriosis).

The negative impact of endometriosis on the ART success rate has been reported in various studies. Zhang et al. (2021) demonstrated that even after multiple cycles of an ultra-long gonadotropin-releasing hormone agonist protocol, adenomyosis was still associated with poor IVF outcomes [18, 19].

Efforts to replace surgical treatment with pharmacotherapy have been employed for a long time, with varying success. One of the most effective agents is dienogest, an oral progestin that exerts a progestogenic effect and a moderate estrogen-suppressive action. In addition, it has anti-inflammatory, antiproliferative, and antiangiogenic effects that inhibit the growth of endometriosis [18, 19].

In 2021, Esedova et al. conducted a comparative study in 150 infertile women aged 24 to 38 years, with 120 of them diagnosed with endometriosis. Dienogest therapy increased the likelihood of getting pregnant by 1.5 and 1.4 times, respectively [19].

The study by Barra et al. (2020) is also worthy of note. It evaluated the use of dienogest prior to IVF in women with endometriosis who had previously failed one IVF cycle. The study demonstrated that the implantation, clinical pregnancy, and live birth rates were significantly higher in the dienogest-treated group than in the non-treated group [18, 19].

Those who advocate for surgical intervention believe that COE surgery is an essential component of the IVF preparation process. However, some authors suggested that surgical intervention should be withheld in cases of small, asymptomatic cysts.

Feskov et al. proposed that IVF programs should be considered for patients with COE up to 3 cm without prior surgical treatment [20].

A large three-year study conducted in Belarus included 179 infertile patients with COE (Zhukovskaya et al.) [21]. The study concluded that surgical treatment and delayed IVF are not advisable in endometriosis-associated infertility and stage II COE. Otherwise, this can have a significant negative effect on the ovarian reserve, with higher doses of hormonal induction and a lower likelihood of IVF pregnancy.

The guidelines do not present any clear criteria for surgical treatment of cystic ovarian endometriosis (3 or 4 cm). Furthermore, recurrence rates are high even with hormone therapy. Therefore, it is essential that each case be treated on an individual basis. As long as no treatment method can be identified that will result in complete recovery, with the exception of radical surgical treatments, there is still a lack of consensus regarding the most appropriate method (surgical or pharmaceutical) to be used as a first-line treatment [1].

COE has long been regarded as an absolute indication for surgical intervention. Surgical intervention remains the most efficacious and definitive treatment for COE. In recent years, patient management strategies and surgical indications for ovarian cysts have been largely revised. It is widely acknowledged among Russian and international surgeons that ovarian cystectomy should be the method of choice for large (>3 cm) and complex cysts with a high risk of malignancy. Surgical intervention may also be indicated in the treatment of severe pain syndromes, pelvic adhesions, and cases where hormone therapy has been unsuccessful. Surgical treatment of asymptomatic endometriosis prior to ART procedures remains controversial, as there is currently no strong evidence to suggest that surgery improves the success rate of IVF [21, 22].

In contrast, surgical treatment of stage III ovarian endometriosis with bilateral cysts >5–6 cm appears justified, as it eliminates the risk of cyst rupture or torsion during controlled ovarian induction, transvaginal follicle puncture, and pregnancy.

The published literature indicates that conservative treatment may be the preferred option for patients with small COE to avoid the risk of diminished ovarian reserve.

Following surgical treatment of cystic endometriosis in women planning to become pregnant, it is of great importance to ascertain the patient's reproductive function as rapidly as possible, as there is a significant risk of recurrence of

endometriomas. Repeated resections of recurrent COE have been found to diminish ovarian reserve and negatively impact IVF outcomes with autologous oocytes [23].

In their study, Fedorov et al. [24] investigated the impact of ovarian cystectomy using the stripping technique on the likelihood of natural conception and the outcomes of ART procedures. A pregnancy rate of greater than 50% was observed in infertile patients following COE surgeries.

A review of recently published European studies on reproductive medicine has yielded a somewhat divergent conclusion. Muzii et al. (2023) discuss the long-standing opinion that surgery is the "gold standard" in COE treatment, particularly for cysts >3 cm. However, recent evidence suggests that surgical procedures have a detrimental impact on the ovarian reserve, making conservative treatment a more viable option. Furthermore, numerous studies indicate that diminished ovarian reserve may be associated with COE. The 2023 Guidelines of the European Society of Human Reproduction and Embryology define surgical indications for endometriomas by emphasizing medication response and the presence of infertility, rather than focusing on cyst size [25]. A novel surgical stripping technique is gaining increasing popularity. It maintains the ovarian reserve at the highest possible level while reducing the recurrence rate [25]. Some studies have indicated that fenestration, drainage, and bipolar coagulation of cystic walls may be more effective than cyst excision [25]. Ultrasound-guided aspiration of ovarian endometriomas followed by sclerotherapy is another possibility. This technique offers improved ovarian reserve preservation; however, it is associated with higher recurrence rates. Endometriosis can also be eliminated by excision of a portion of the cyst wall followed by coagulation of the residual cystic envelope [25].

ASSISTED REPRODUCTIVE TECHNOLOGIES IN PATIENTS WITH CYSTIC OVARIAN ENDOMETRIOSIS

IVF has been historically considered the first-line therapy for patients with low ovarian reserve, advanced age, and prolonged infertility.

One-third of patients undergoing assisted reproductive treatment have been diagnosed with external genital endometriosis [26]. The high probability of recurrent COE and the known negative impact of surgical interventions on ovarian function indicate that IVF should be considered the first-line treatment of endometriosis-associated infertility [27].

The study by Shcherbakova et al. (2019) demonstrated that, despite a lower ovarian response to ovulation induction in patients with endometriosis, their pregnancy rates were comparable to those observed in patients with tubal or peritoneal factors of infertility. In patients with endometriosis, high-dose ovulation induction was found to result in the greatest number of follicles, thereby ensuring a sufficient number of high-quality embryos and a high clinical pregnancy rate [28].

A comparison between the IVF success rate and the prevalence of endometriosis in clinical practice revealed that pregnancy occurs more frequently in patients diagnosed with stage I or II endometriosis than in patients with tubal or peritoneal factors of infertility. However, deep infiltrative endometriosis is associated with the lowest IVF success rate [28]. Harb et al. reported similar findings in their meta-analysis, with lower implantation and clinical pregnancy rates among patients with severe endometriosis. In contrast, patients with mild endometriosis demonstrated comparable implantation, clinical pregnancy, and fertility success rates to those observed in patients with other infertility factors [29].

Krasilnikova et al. demonstrated that endometrial injury resulting from separate diagnostic scraping of the uterine cavity did not lead to significant improvement in local cytokine production. However, endometrial injury regardless of the technique employed may improve IVF outcomes in infertile women with "small" genital endometriosis [30].

A significant body of evidence indicates that a woman's gynecological history may influence both her ovarian reserve and her success in IVF treatments [31]. In 2014, Eliseenko reported that the incidence of premature depletion of the ovarian reserve had increased by 15–20% over the previous five years. A contributing factor was a significant increase in the number of ovarian surgeries performed in females of reproductive age. The prevalence of these surgeries varies considerably, with estimated rates ranging from 14% to 29% of all gynecological pelvic surgeries. The majority of these surgical procedures were performed for COE treatment [32]. The diminished ovarian reserve can result in a number of complications, including infertility, IVF failures, and premature ovarian depletion. It has been demonstrated that surgical interventions can have a negative impact on the population of oocytes capable of being fertilized. Consequently, timely ovarian reserve testing is of great significance [33].

Furthermore, the studies demonstrated that pelvic surgeries, diminished ovarian reserve, COE, and pelvic peritoneal endometriosis were more prevalent in women with prior IVF failures and a history of preeclampsia than in those who had become pregnant [31].

In recent years, scientists and clinicians have given considerable attention to the challenges posed by endometriosis. Despite the extensive research conducted to date, numerous questions remain unanswered. Numerous hypotheses have been proposed for the etiology of endometriosis; however, it is evident that individual predisposition remains a significant contributor due to genetic, anatomical, endocrine, and environmental factors [34, 35]. This renders the development of rigorous treatment algorithms unfeasible and requires a personalized approach to each patient with endometriosis-associated infertility.

A number of factors should be considered when determining the optimal therapeutic approach for women with COE and infertility, including the patient's age, the presence of pain syndrome, surgical outcomes, size and number of cysts, the ovarian reserve, and the availability of follicles. Advanced, effective methods for diagnosing and treating endometriosis have the potential to significantly increase the likelihood of pregnancy and reduce the risk of repeated surgical interventions, which may result in a reduction in ovarian reserve.

CONCLUSION

A literature review revealed that there is no consensus regarding the absolute surgical indications for COE. The opinions expressed by various researchers frequently diverge, with some reaching opposing conclusions. The development of surgical techniques aimed at minimizing ovarian tissue injury and preserving the ovarian reserve is a growing area of research internationally. In Russia, there has been a notable increase in the popularity of ART programs. Moreover, there is a growing emphasis on pharmaceuticals and classical surgical treatments, with ovarian resection being a particularly prevalent option. It is evident that endometriosis-associated infertility represents a significant challenge for current medicine. However, there is a reason to believe that a solution to this problem may be forthcoming as a result of the collaborative efforts of obstetricians, gynecologists, and fertility specialists.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. The concept and design of the study — Svidinskaya E.A., Ageev M.B.; collection and processing of the material — Sarkisyan E.A.; writing of the text — Svidinskaya E.A., Sarkisyan E.A.; editing — Sosnova E.A.

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