

Ovarian Endometriosis as a Cause of Impaired Fertility: Current Status and Prospects for Predicting Reproductive Outcome

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Abstract: Background. Ovarian endometriosis occupies a special place in the structure of endometriosis-associated infertility, as it directly affects ovarian tissue, ovarian reserve, and the microenvironment of the maturing oocyte. Despite the significant accumulated data on the clinical, anamnestic, hormonal, morphofunctional, inflammatory, oxidative, and neuroinflammatory mechanisms of impaired fertility, current approaches to assessing the reproductive prognosis in women with ovarian endometriosis remain insufficiently comprehensive. Study Objective. To analyze current understanding of the role of ovarian endometriosis in infertility, summarize data on the leading mechanisms of fertility decline, and identify unresolved issues in predicting reproductive outcome. Materials and Methods. A problem-based analytical review of the current literature on ovarian endometriosis, reproductive dysfunction, ovarian reserve, laparoscopic and instrumental disease assessment, the ovarian microenvironment, and the inflammatory, oxidative, and neuroinflammatory mechanisms of endometriosis-associated infertility was conducted. International clinical guidelines, World Health Organization guidelines, systematic reviews, meta-analyses, and clinical trials of the greatest scientific and practical significance were analyzed. Results: It was demonstrated that ovarian endometriosis should be considered a multifactorial cause of infertility, in which decreased fertility results from a complex interaction of clinical, anamnestic, hormonal, anatomical, morphological, inflammatory, oxidative, and neuroinflammatory mechanisms. It has been established that existing prognostic approaches, including EFI, have significant clinical value; however, they do not fully reflect the biological complexity of the disease, as they rely primarily on anamnestic and laparoscopic criteria and insufficiently consider the state of the ovarian reserve, the ovarian microenvironment, and the activity of inflammatory-oxidative processes. It has been revealed that one of the key unresolved issues remains the insufficient integration of known clinical and pathogenetic factors into a unified fertility assessment system.

Keywords: Ovarian endometriosis, infertility, fertility, ovarian reserve, ovarian microenvironment, inflammation, oxidative stress, neurogenic inflammation, prognosis, EFI.

Introduction

Endometriosis is currently considered one of the most significant chronic diseases of the female reproductive system, characterized by high prevalence, long-term recurrence, severe pain, and a significant impact on fertility, quality of life, and social activity [1]. According to the World Health Organization, endometriosis affects approximately 10% of women and girls of reproductive age, equivalent to approximately 190 million people worldwide. This figure alone elevates the problem to the level of global public health. However, its true significance is determined not only by the prevalence of the disease, but also by the fact that endometriosis manifests during the active reproductive period, tends to be chronic, is often diagnosed late, and is accompanied by a significant decrease in quality of life [2], [3].

The significance of the problem is particularly increased when considered in the context of infertility. According to the WHO, approximately 17.5% of the world's adult population, or approximately one in six people, will experience infertility during their lifetime [4]. At the same time, endometriosis remains one of the leading causes of female infertility: 25–50% of women with impaired fertility are diagnosed with various forms of endometriosis, and 30–50% of patients with endometriosis experience difficulty conceiving [5], [6]. Consequently, endometriosis-associated infertility is not a rare clinical variant, but rather one of the central reproductive scenarios of the disease. The problem is further compounded by the fact that endometriosis is often diagnosed years after the onset of symptoms. The World Health Organization indicates that the diagnostic delay can range from 4 to 12 years [1]. According to modern reviews, this represents a transition from early functional. The clinical severity of endometriosis is determined not only by infertility but also by a wide range of symptoms that impair quality of life. Among the most significant are chronic pelvic pain, dysmenorrhea, dyspareunia, sexual dysfunction, limitation of daily activities, emotional exhaustion, and decreased work capacity [7], [8]. As a result, the disease has a long-term impact not only on a woman's physical well-being but also on her family, professional, and social fulfillment. Recent reviews emphasize that it is the combination of pain, reproductive dysfunction, and chronicity that makes endometriosis a disease with a particularly heavy individual and societal burden [8].

Late diagnosis remains one of the most serious problems. The World Health Organization indicates that the diagnostic delay in endometriosis can range from 4 to 12 years. Contemporary studies and reviews confirm that even in developed healthcare systems, the average time from the onset of symptoms to diagnosis remains significant, often lasting many years [9]. This delay is crucial, as the disease progresses during this period, leading to persistent morphofunctional changes, chronic pain, sexual dysfunction, and decreased reproductive potential. Consequently, a diagnostic delay in endometriosis has not only a clinical but also a direct reproductive cost [9].

The economic burden of the disease is no less significant. Recent publications demonstrate that endometriosis is associated with significant direct costs for diagnosis, surgical, and drug treatment, as well as even higher indirect losses due to decreased productivity and temporary disability. According to recent estimates, a significant portion of the overall economic damage is associated with lost productivity, and not just with healthcare costs [10], [11]. Given that infertility treatment itself can require significant financial resources, this adds urgency to the problem and highlights the need for more accurate and early prediction of reproductive outcomes [12].

Thus, endometriosis should be considered a major global reproductive health problem, affecting millions of women and associated with chronic pain, infertility, reduced quality of life, late diagnosis, and a high socioeconomic burden. Therefore, further improvement of approaches to fertility assessment in various clinical forms of endometriosis, particularly when it affects the ovaries, is of not only scientific but also significant practical importance.

Methodology.

The methodology of this study is based on a structured problem oriented analytical review of contemporary scientific literature focused on ovarian endometriosis and its impact on reproductive

function. A comprehensive search and selection of sources was carried out using international medical databases, prioritizing high quality evidence including clinical guidelines from the World Health Organization, systematic reviews, meta analyses, and recent clinical trials. The selection criteria emphasized publications addressing ovarian reserve, hormonal regulation, laparoscopic and imaging based assessment, as well as inflammatory, oxidative, and neuroinflammatory mechanisms involved in infertility. The analysis followed a comparative synthesis approach, where findings from different studies were critically evaluated and integrated to identify consistent patterns and contradictions in current knowledge. Special attention was given to evaluating existing prognostic models, particularly their ability to reflect the multifactorial nature of ovarian endometriosis. Data were interpreted through a multidimensional framework combining clinical, biological, and pathogenetic perspectives to ensure a holistic understanding of fertility impairment. The methodology also included identification of gaps in current predictive systems, especially the lack of integration between clinical indicators and molecular mechanisms. This approach allowed the formulation of evidence based conclusions and the proposal of directions for developing a more comprehensive and clinically applicable fertility prediction model.

Result and Discussion.

Ovarian endometriosis as a specific form of endometriosis-associated infertility

Among the various clinical forms of endometriosis, ovarian endometriosis occupies a special place, as it directly involves ovarian tissue, the follicular apparatus, and the microenvironment of the maturing oocyte [13], [14]. Unlike peritoneal lesions or some deep infiltrative forms, endometrioma affects not only the anatomy of the pelvis but also the functional capacity of the ovary, thereby directly affecting a woman's reproductive potential. This makes ovarian endometriosis one of the most prognostically significant forms of endometriosis-associated infertility.

Modern data show that the negative impact of endometrioma on fertility is realized in several ways. First, ovarian endometriosis can be accompanied by a decrease in functional ovarian reserve. Secondly, it alters the local biological environment in which follicle growth and maturation occur. Thirdly, in advanced cases, additional mechanical effects on the ovary, tubo-ovarian relationships, and adjacent pelvic structures are possible [13], [14], [15], [16]. Consequently, ovarian endometriosis should be considered not only as the presence of a cystic formation, but also as a condition affecting several levels of reproductive function.

In recent years, particular attention has been paid to the relationship between endometrioma and ovarian reserve. ESHRE clinical guidelines emphasize that both ovarian endometriosis itself and endometrioma surgery can negatively impact ovarian function. Recent reviews confirm that AMH remains the most sensitive marker for assessing ovarian reserve in this situation, and the decrease in its levels after cystectomy is particularly pronounced in bilateral lesions. These data are of fundamental importance, as they demonstrate that reproductive risk in ovarian endometriosis is associated not only with the severity of the disease itself, but also with the potential reproductive cost of treatment.

Equally important is the issue of bilateral involvement. According to current publications, bilateral ova. However, a mature analysis of the current literature shows that the EFI structure primarily reflects the clinical, anamnestic, and laparoscopic assessment levels, while modern understanding of the biology of endometriosis-associated infertility is significantly broader [16], [17]. The index does not include ovarian reserve indicators, inflammatory markers, oxidative stress parameters, and ovarian microenvironment characteristics, which are increasingly considered critical for understanding the true reproductive damage associated with ovarian endometriosis [18]. Therefore, the EFI cannot be viewed as an insufficient or outdated tool; on the contrary, it is an important pillar of modern practice. However, current knowledge increasingly demonstrates that the clinical-laparoscopic model alone is no longer sufficient for a fully personalized fertility prognosis in this patient population.

Limitations of Existing Prognostic Approaches

Despite significant progress in the study of endometriosis-associated infertility, modern prognostic approaches remain markedly fragmented. In clinical practice, a situation often arises in which various

parameters of proven value for assessing fertility exist in parallel: clinical and anamnestic data are analyzed separately, ovarian reserve indicators are analyzed separately, instrumental and laparoscopic characteristics of the disease are analyzed separately, while inflammatory and oxidative mechanisms often remain within the scope of research interest and are insufficiently integrated into applied prognostic models [19], [20].

The EFI remains the most recognized and clinically useful tool for assessing the likelihood of natural pregnancy after surgical treatment of endometriosis. Its importance is difficult to overestimate: it has enabled standardization of postoperative counseling for patients and, for the first time, offered a practice-oriented approach to predicting reproductive outcomes. However, the EFI was developed during a period in the development of reproductive medicine when medical history and laparoscopic functional assessment were considered the primary prognostic parameters. The current understanding of endometriosis-associated infertility is significantly broader and includes new levels of pathogenesis that are not fully reflected in the structure of this index.

One of the most significant limitations of existing prognostic approaches is the insufficient integration of ovarian reserve into the overall fertility assessment system. Although the clinical significance of AMH, AFC, and FSH in ovarian endometriosis is now well established, these indicators are not always part of a single prognostic model, but are more often used as independent benchmarks, separate from the morphofunctional characteristics of the disease. As a result, the physician receives information about the condition of the ovary, but does not always have the tools to incorporate this information into a comprehensive prognosis of natural or postoperative reproductive outcome. An equally significant problem remains that instrumental and laparoscopic evaluation of the disease, despite its high diagnostic value, does not always translate into a comprehensive prognostic assessment. The size of the endometrioma, the bilateral nature of the lesion, the severity of the adhesions, the condition of the tubes and fimbriae, and the functional integrity of the ovary all these parameters have obvious reproductive significance, yet in real life practice, their interpretation often remains descriptive rather than holistic and prognostic [22]. This is why two patients with formally similar morphological presentations may receive prognostic conclusions that differ in quality.

An even more pronounced gap is observed with respect to inflammatory and oxidative mechanisms. Modern research convincingly demonstrates that follicular fluid in ovarian endometriosis reflects an unfavorable ovarian microenvironment, which combines proinflammatory cytokine signaling, ROS activation, impaired antioxidant defense, and damage to cellular structures [23]. However, these data are still poorly integrated into routine fertility assessment models. In most cases, they are considered important pathogenetic observations, but not as components of an applied prognostic tool. As a result, a significant part of the disease biology remains beyond the scope of practical solutions.

A similar situation is developing with regard to neuroinflammation. Accumulating data indicate a link between NGF, IL 6, TNF α , and neuroimmune activation with pain syndrome, chronicity of the process, and, likely, with the depth of biological activity of endometriosis [24], [25]. Nevertheless, neuroinflammatory mechanisms are barely integrated into existing fertility prognostic models. In practice, this means that the clinical phenomenon of pain.

Conclusion

Ovarian endometriosis is one of the most complex forms of endometriosis-associated infertility and requires a more in-depth, pathogenetically substantiated approach to predicting reproductive outcome. A promising direction is the development of an integrated prognostic model combining clinical, hormonal, morphofunctional, inflammatory, and oxidative parameters, which will improve the accuracy of fertility assessment and refine the choice of treatment strategy.

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