ОГЛЯД ЛІТЕРАТУРИ

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IMPACT OF ENDOMETRIOSIS ON OVARIAN RESERVE AND FEMALE REPRODUCTIVE FUNCTION: A REVIEW OF CURRENT EVIDENCE

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Objective. To evaluate the impact of endometriosis on ovarian reserve and to analyze the mechanisms underlying its detrimental effects on ovarian function based on current literature.

Materials and Methods. This review included original studies, systematic reviews, meta-analyses, and clinical guidelines published in Ukrainian and English. Relevant publications were identified by searching PubMed, Scopus, Google Scholar, and the Cochrane Library using keywords such as endometriosis, fertility, pathophysiology, endometrioma, ovarian reserve, and surgery.

Results and Discussion. The review summarizes current evidence on endometriosis-associated infertility, focusing on the impact of endometriomas on ovarian reserve. Ovarian endometriosis negatively affects ovarian reserve and reproductive outcomes. Anti-Müllerian hormone (AMH) is a key marker in clinical assessment. Most studies demonstrate reduced AMH levels in patients with endometriomas even before surgery, indicating primary ovarian damage caused by chronic inflammation, oxidative stress, fibrosis, and mechanical follicular loss. Comparative analyses show that combined surgical approaches are associated with lower recurrence rates and higher spontaneous pregnancy rates than ablative techniques. However, reproductive prognosis should not rely solely on AMH. Evidence suggests its limited predictive value for spontaneous conception, while a comprehensive assessment of infertility factors provides more accurate prediction of reproductive outcomes.

Conclusions. Endometriosis-associated infertility is multifactorial. Management should be individualized and based on an integrated evaluation of clinical, historical, hormonal, ultrasonographic, and surgical factors to improve reproductive outcomes.
Keywords: endometriosis, infertility, gynecologic surgery, gynecology, gynecological surgery.

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ВПЛИВ ЕНДОМЕТРІОЗУ НА ОВАРІАЛЬНИЙ РЕЗЕРВ І РЕПРОДУКТИВНУ ФУНКЦІЮ ЖІНОК: ОГЛЯД СУЧАСНИХ ДАНИХ
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Мета роботи – оцінити вплив ендометріозу на овариальний резерв і механізми впливу захворювання на стан яєчників за даними літератури. Проаналізовано оригінальні дослідження, огляди, метааналізи та клінічні настанови (PubMed, Scopus, Google Scholar та Cochrane). Результати дослідження показали, що ендометріоз яєчників негативно впливає на овариальний резерв і репродуктивні результати пацієнток із безпліддям. Рівень АМГ знижений у пацієнток з ендометріомами до оперативного втручання, що свідчить про ураження овариальної тканини через запалення, оксидативний стрес, фіброз тканини яєчника та його механічне руйнування. Комбіновані хірургічні технології мають кращі результати щодо рецидивів і вагітності. Прогноз настання спонтанної вагітності не слід базувати лише на показниках АМГ. Пацієнки з ендометріоз-асоційованим ендометріозом потребують мультифакторного підходу.
Ключові слова: ендометріоз, безпліддя, оперативна гінекологія, гінекологія, гінекологічна хірургія.

Introduction

Genital endometriosis is a disease characterized by the presence of endometrioid epithelium and/or stroma outside the endometrium and myometrium and is usually accompanied by an inflammatory process. Endometriosis affects approximately 10% of women of reproductive age and is known for its impact on women's quality of life. Approximately 25–50% of infertile women are affected by endometriosis. Endometriosis is one of the challenges of modern reproductive medicine. The causes of infertility can be explained by several mechanisms, including disruption of pelvic anatomy, impaired pelvic hemostasis, ovarian dysfunction, and impaired fertilization [1]. However, meta-analyses based on assisted reproductive technology (ART) have shown that, in general, ART outcomes are partially impaired in infertile women with endometriosis. It is important to note a consistent trend toward a higher cycle cancellation rate and a lower mean number of oocytes retrieved per cycle. Moreover, a recent ART-based study demonstrated that the difference in success rates between patients with and without endometriosis is limited or absent when comparing women according to the number and quality of embryos obtained [2]. Overall, these data suggest that, from a reproductive perspective, the most concerning aspect in patients with endometriosis may be ovarian dysfunction rather than endometrial abnormalities, which interfere not only with natural conception but also with conception via ART. The mechanisms of endometriosis-associated infertility are not yet fully understood. Of particular interest in this context is the investigation of the impact of endometriosis on healthy ovarian tissue and female reproductive function.

Objective. To investigate the effect of endometriosis on ovarian reserve and to evaluate the mechanisms of the disease's negative impact on ovarian function based on an analysis of current literature data.

Materials and Methods

The study included original research articles, systematic reviews and meta-analyses, as well as clinical guidelines in Ukrainian and English. A literature search was conducted in PubMed, Scopus, Google Scholar, and the Cochrane Library using the keywords: endometriosis, fertility, pathophysiology, endometrioma, ovarian reserve, surgery. The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" (Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009) and was approved by the Bioethics Commission of Odesa National Medical University (Protocol No. 18 dated 06.12.2023).

Research results and their discussion

Endometriosis predominantly develops in women of reproductive age and regresses after menopause or oophorectomy, indicating its estrogen-dependent growth. It is known that approximately 190 million women and adolescent girls worldwide are affected by this disease during their reproductive years, and in some women, clinical manifestations persist even after menopause [3].

The exact prevalence of endometriosis remains unclear; however, epidemiological data range from 2% to 10% in the general female population and up to 50% among women with a history of infertility, making genital endometriosis one of the leading causes of impaired conception in women. The etiology of endometriosis is still not fully understood. A considerable number of potential predictors of its pathogenesis have been proposed; however, no single triggering mechanism has been identified, suggesting a multifactorial nature of the disease. Among the factors increasing the risk of endometriosis, the following are commonly distinguished: genetic factors, hormonal imbalance, immune dysfunction, menstrual disorders (menstruation lasting more than 8 days, shortened menstrual cycles, early menarche), and gynecological procedures (diathermocoagulation, cesarean section, myomectomy, and induced abortion). There is still no consensus regarding the etiopathogenesis of endometriosis; therefore, several theories of its origin have been proposed [3; 4].

The theory of retrograde menstruation (implantation theory) was first described in 1921 by J. A. Sampson. It is the oldest hypothesis explaining the etiology of endometriosis. This theory suggests that endometriosis develops as a result of the retrograde flow of viable endometrial cells through the fallopian tubes into the peritoneal cavity during menstruation, provided that the fallopian tubes are patent [5]. Studies have shown that in non-human primate models, endometriosis can be induced by inoculating autologous menstrual endometrial tissue into the peritoneal cavity of baboons and macaques, mimicking retrograde menstruation. After a single inoculation of menstrual endometrial tissue into the pelvic cavity, up to 46% of animals developed pelvic endometriosis, whereas after two consecutive cycles of inoculation, peritoneal endometriotic lesions developed in 100% of animals. These lesions were histologically and clinically similar to ectopic endometriotic lesions in humans [6]. In humans, retrograde menstruation may be triggered by factors such as uterine retroversion, gynecological interventions and surgeries, childbirth, heavy physical activity, psychological and emotional stress, sexual intercourse during menstruation, and cervical canal atresia. The implantation theory is widely accepted but insufficiently supported, as studies show that retrograde menstruation occurs in 75–90% of women with patent fallopian tubes, while not all of these women are diagnosed with endometriosis [7].

The metaplastic theory suggests that endometriosis arises from ectopic cells that abnormally transdifferentiate or transform into endometrial-like cells. According to this theory, endometriosis develops as a result of metaplasia of specialized cells present in the mesothelial lining of the visceral and parietal peritoneum, pleura, endothelium of lymphatic vessels, renal tubular epithelium, and other tissues. It is assumed that hormonal or immunological factors stimulate the transformation of normal peritoneal tissue or cells into endometrioid tissue.

Ectopic endometrial tissue has also been detected in female fetuses, and it has been suggested that endometriosis may result from defective embryogenesis. According to this theory, residual embryonic cells from the Wolffian or Müllerian ducts persist and develop into estrogen-

producing endometriotic lesions. However, this theory is considered questionable, as endometriotic lesions are found in areas outside the Müllerian developmental pathway [8].

In most women with endometriosis (20–45%), the menstrual cycle remains regular. Sex hormone concentrations remain largely unchanged. However, a correlation between polycystic ovary syndrome and endometriosis has been reported. As a result, patients with endometriosis may exhibit disruption of the sequence of gonadotropin-releasing hormone secretion [9]. Estrogen exposure is believed to promote the development and growth of endometriotic lesions, as evidenced by the higher prevalence of endometriosis in women of reproductive age. It is known that endometrioid heterotopic cells are hormonally responsive, exhibiting proliferative and, to a lesser extent, secretory changes and desquamation, leading to hemorrhage and even cyst formation. It has also been demonstrated that hormones do not act directly on cells of hormone-dependent organs. Their effects are mediated through growth factors, gene expression, specific oncoproteins, cytokines, interleukins, and an imbalance between proliferation and apoptosis. Therefore, recent scientific studies consider endometriosis a pseudotumorous process that, under certain conditions, has the potential for malignant transformation [10].

A working hypothesis suggests that in women who develop endometriosis, the immune system is unable to recognize antigenic ectopic cells and mount an appropriate immune response. However, in response to the presence of gene fragments, the concentration and proportion of macrophages and neutrophils increase in the peritoneal fluid of women with endometriosis, and these cells are a major source of elevated pro-inflammatory and chemotactic cytokines. In addition, macrophages represent the main source of angiogenic mediators, including TNF-α and IL-8. It has been shown that neutrophils from healthy women, when incubated with plasma or peritoneal fluid from women with endometriosis, demonstrate a reduced rate of apoptosis compared with those from the control group [11]. This study clearly demonstrated the possible presence of anti-apoptotic factors in the plasma and peritoneal fluid of women with endometriosis, which are less concentrated in women without the disease. It also showed that neutrophils in women with endometriosis may be more resistant to spontaneous apoptosis than neutrophils from the control group. These findings further support the concept of a dysregulated immune response in women with endometriosis. In addition, conflicting results from two independent studies make it difficult to define the role of dendritic cells in the pathogenesis of endometriosis [12]. Further studies are required to clarify their function. A reduced cytotoxic activity of natural killer (NK) cells has also been observed in the peritoneal environment. Immunosuppression has been identified in both normal endometrial stromal cells and endometriotic stromal cells. This suggests that normal endometrium has an inherent immunosuppressive capacity against NK cell cytotoxicity, which may facilitate embryo implantation. In women with endometriosis, this immunosuppressive effect on NK cell cytotoxicity is enhanced, potentially creating favorable conditions in the peritoneal environment for the survival, adhesion, and subsequent growth of endometriotic lesions within the abdominal cavity [13]. Although the role of cytokines and chemokines in the development of endometriotic lesions has been established, it remains insufficiently studied. This is explained by the fact that these modulators are highly pleiotropic proteins exhibiting a wide range of functions. Since these aberrant immune responses are further influenced by the unique hormonal environment in which they develop, it is difficult to definitively determine their role in the pathogenesis of endometriosis. Indeed, endometriosis is sometimes classified as an autoimmune disease due to the detection of anti-endometrial antibodies in the serum of affected women. However, the role of adaptive immunity, including T-helper cells and B-cells, requires further investigation [14].

Although each theory has its relevance, endometriosis is a multifactorial disease characterized by a systemic inflammatory response and a chronic, often progressive course. Despite relatively high prevalence rates and increasing clinical relevance due to a rising incidence, the etiology and pathogenesis of this disease remain incompletely understood and are the subject of ongoing research.

The classification of endometriosis distinguishes three subtypes or forms based on localization and morphological characteristics (phenotypes): peritoneal (superficial) endometriosis, ovarian endometriosis (endometrioma), and deep infiltrating endometriosis, as well as possible combinations of these forms. Superficial peritoneal endometriosis rarely causes pronounced clinical symptoms, is located on the surface of pelvic organs and the parietal peritoneum, and in most cases corresponds to minimal or mild disease according to the revised American Society for Reproductive Medicine (rASRM) classification [15]. It is well known that, despite normal pelvic anatomy, superficial endometriosis may negatively affect female fertility [16]. However, it remains unclear whether superficial endometriosis is associated with a reduction in ovarian reserve.

Ovarian endometriomas, or so-called “chocolate cysts”, arise as a result of invagination of the ovarian surface epithelium and represent the most common form of ectopic endometrial tissue within the ovary. Ovarian endometriomas account for 35% of all benign ovarian cysts. In one-third of cases, endometriomas are bilateral, which significantly worsens reproductive prognosis. The origin of endometriomas and their negative impact on ovarian reserve are explained by a complex and heterogeneous pathogenesis. An endometrioma is a cystic ovarian lesion derived from endometrial glands and stroma containing thick, dark-brown fluid, commonly referred to as a “chocolate cyst” [17]. Although the exact pathogenesis of endometrioma remains unclear, three main theories have been proposed. According to Hughesdon’s study, endometriomas are pseudocysts formed from retained menstrual debris due to bleeding from active implants on the ovarian surface. Other theories describe coelomic metaplasia of the ovarian epithelium (the theories of Nisolle and Donnez) and invasion of endometrial implants into functional ovarian cysts with subsequent development of endometrioma; however, the

origin of the cyst fluid remains unclear (the theory of Jain and Dalton) [17; 18]. Numerous studies report an association between endometrioma and infertility, but a definitive causal relationship requires further investigation and confirmation. Increasing attention is being paid to the potentially deleterious effects of endometriomas on ovarian physiology. Long-standing ovarian endometriosis is associated with persistent inflammation leading to cortical ovarian fibrosis, resulting in follicular loss and smooth muscle cell metaplasia. It is also known that endometrioma fluid contains high concentrations of iron, reactive oxygen species (ROS), transforming growth factor beta (TGF-β), and proteolytic enzymes, which exert additional detrimental effects on ovarian tissue. These substances diffuse into surrounding tissues, further promoting fibrosis, smooth muscle metaplasia, and reduction of the ovarian cortical stroma, ultimately leading to follicular depletion. In addition, the endometrioma itself and its content exert a mechanical effect on the ovary by stretching its tissue, leading to impaired vascularization due to cortical compression [18; 19].

Several studies have demonstrated the negative impact of deep and ovarian endometriosis on ovarian reserve parameters. In a prospective cohort study, Uncu et al. reported that women with endometriomas had a lower ovarian reserve, as evidenced by lower anti-Müllerian hormone (AMH) levels and antral follicle count (AFC), compared with healthy women [20]. A more recent study from the same group also showed that women with ovarian endometriosis experienced a more rapid progressive decline in serum AMH levels compared with healthy control groups [21].

Deep infiltrating endometriosis is a rare form of the disease in which endometriotic lesions, morphologically similar to endometrium, infiltrate beneath the peritoneum and its surface, most often forming fibrotic nodules. These lesions are capable of invading adjacent structures and disrupting normal anatomy; therefore, they frequently require surgical treatment. Deep endometriosis combined with ovarian endometriomas represents one of the most severe forms of the disease, associated with significant adverse reproductive outcomes. Current evidence indicates that the combination of these pathological processes has a synergistically negative effect on female reproductive function, as it simultaneously affects both oocyte quality and the morphofunctional state of the pelvic organs [22]. The problem of ovarian reserve depletion in women of reproductive age with endometriosis is one of the most relevant issues in modern gynecology. According to many researchers, ovarian endometriomas pose a particular threat to ovarian reserve and are often associated with deep endometriosis, being diagnosed in 17–44% of all endometriosis cases. It has been shown that even small endometriomas are associated with reduced ovarian potential [23].

Diagnosis of endometriosis. In patients with different forms of endometriosis, conventional treatment methods are often insufficiently effective, requiring the use of modern multidisciplinary diagnostic and therapeutic approaches. The most important step is accurate determination of the localization and extent of the disease. According to recent guidelines from leading professional societies (ESHRE, ACOG, ESGE), laparoscopy is no longer considered the "gold standard" for diagnosis. The main currently used diagnostic tools include clinical assessment (medical history, evaluation of pain syndrome, menstrual and reproductive disorders), transvaginal ultrasound (TVUS), magnetic resonance imaging (MRI), laparoscopy, and assessment of ovarian reserve.

TVUS is one of the leading imaging methods for pelvic pathology. According to current recommendations (ESHRE 2022, ESGE 2022), it is recognized as a first-line diagnostic tool for endometriosis, as it allows detection of both ovarian endometriomas and deep infiltrating lesions. In contrast to laparoscopy, this method is non-invasive, accessible, safe, and reproducible.

MRI is considered the method of choice for diagnosing deep endometriosis, particularly in cases of extrapelvic involvement and when planning complex reconstructive surgery. It allows detailed assessment of the extent of infiltration of the bowel, bladder, and parametrial tissues. Laparoscopy with histological verification remains one of the most accurate diagnostic methods; however, it is no longer regarded as the "gold standard" and is now used primarily for therapeutic purposes.

Laboratory markers (CA-125, HE4) have an auxiliary role: they are useful for disease monitoring and assessment of disease course but are not specific. Assessment of ovarian reserve (AMH, AFC by ultrasound, inhibin B, FSH, estradiol) is mandatory in patients with reproductive plans [24].

For comprehensive evaluation of reproductive potential in women with endometriosis-associated infertility, modern clinical practice widely uses the concept of a fertility index. This parameter integrates patient history, age, duration of infertility, previous pregnancy outcomes, and the morphofunctional state of the pelvic organs, allowing prediction of the likelihood of spontaneous conception or conception via assisted reproductive technologies (ART). The endometriosis fertility index (EFI), developed by Adamson and Pasta in 2010, is particularly widely used in patients with deep endometriosis combined with ovarian endometriomas. The EFI allows standardized estimation of the probability of spontaneous pregnancy after surgical treatment. The index is calculated based on a combination of clinical and intraoperative findings: tubal status, ovarian reserve, presence of adhesions, and extent of endometriosis assessed using the r-ASRM classification. Each parameter is assigned a score, and the total score ranges from 0 to 10, where low values (0–3) indicate a poor fertility prognosis, and high values (7–10) indicate a high probability of pregnancy. The EFI has considerable clinical value [25]. It enables clinicians to make evidence-based decisions regarding treatment strategy, including the appropriateness of surgical intervention, prediction of spontaneous conception, or timely referral to in vitro fertilization (IVF). Thus, integration of EFI with AMH and ultrasound assessment of AFC represents a modern approach to comprehensive evaluation of reproductive potential. It combines morphological, functional, and clinical parameters, provides high prognostic accuracy, and allows personalized treatment strategies for patients with

severe forms of endometriosis and ovarian endometriomas.

The issue of reduced not only quantity but also quality of oocytes in patients with endometriosis remains unresolved. The first reports on the causes of altered reproductive function and the impact of endometriosis on follicular quality appeared in 1976. This study was the first to describe degenerative oocytes identified during morphological examination in patients with endometrioma [26]. The evaluation of the impact of endometriosis on oocyte quality, both from a clinical and biological perspective, is important, as to some extent this effect may be associated with adverse pregnancy outcomes, which are more frequently observed in patients with endometriosis [27].

Morphological changes in the ovaries associated with endometriosis-related fibrosis have attracted considerable attention from researchers. Fibrosis associated with endometrioma is characterized by hyperactivation of myofibroblasts and excessive deposition of extracellular matrix components. It has been shown that fibrosis induced by endometrioma promotes scar formation and damages the surrounding ovarian cortical tissue, leading to reduced ovarian reserve and dysmenorrhea [28]. The role of ectopic endometrial stromal cells in the development of endometrioma-associated fibrosis has been demonstrated. These cells act as precursors of myofibroblasts within endometrioma lesions. In another study, ovaries with endometriomas demonstrated increased fibrosis, loss of cortex-specific stroma, and lower follicular density compared with contralateral healthy ovaries ($6.3 \pm 4.1/mm^3$ versus $25.1 \pm 15.0/mm^3$) [29].

Takeuchi et al. identified excessive activation of primordial follicles and defined this process as a mechanism of follicular reserve depletion in ovarian endometriosis. Primordial follicle activation is considered an irreversible process and leads to depletion of the follicular reserve. The authors demonstrated that the number of primordial follicles decreases, whereas the number of primary, secondary, antral, and growing follicles increases in ovaries with endometrioma [30].

An increased level of granulosa cell apoptosis has also been observed in women with endometriosis; however, the possible mechanism leading to cell loss has not yet been established.

In addition to quantity, oocyte quality is of great importance in endometriosis. Oocyte quality is reflected in oocyte morphology and its ability to complete maturation and fertilization processes [31]. The method of assessing oocyte and embryo quality is based on morphological criteria, which are subjective and therefore insufficiently accurate. According to pathomorphological studies, women with endometriosis exhibit various oocyte dysmorphisms, including loss of cortical granules, thickening of the zona pellucida, reduction in the number and quality of cytoplasmic mitochondria, and chromatin decentralization. Wu Y. et al., in a retrospective cohort study, evaluated the impact of endometrioma on the quality and quantity of oocytes, embryo quality, and live birth rate during IVF/ICSI [31, 32]. It was found that women with endometrioma had significantly lower AFC, AMH levels, ovarian sensitivity index, oocyte maturation and fertilization rates, blastocyst formation rate, number of retrieved oocytes, and available embryos compared with the control group ($p < 0.05$). The findings of this study confirmed that ovarian endometrioma negatively affects both the quantity and quality of oocytes but does not influence overall pregnancy outcomes in women undergoing IVF/ICSI.

Some molecular studies confirm the negative impact of endometriosis on the growth, steroidogenic activity, and function of granulosa cells. Estradiol (E2) is crucial for follicular and oocyte development, allowing the oocyte to reach the mature metaphase II stage and become capable of fertilization. The negative impact of endometriosis on normal granulosa cell physiology has been extensively described by several researchers. For example, in a study by Shi et al. (2022), sequencing of granulosa cells from patients with endometrioma and from healthy women revealed increased gene expression in the WNT signaling pathway, which is associated with cell proliferation, death, and migration [33].

In addition to changes in E2 concentration, particular attention is given to impaired tissue response to progesterone. A study by Flores et al. showed that in patients with endometriosis who do not respond to progestin therapy, progesterone receptor levels are significantly lower than in patients who respond to such therapy. Reduced expression of progesterone receptors in endometriosis is considered both a marker and a cause of progesterone resistance [34].

Follicles are the main functional units responsible for the formation and development of oocytes. Follicular fluid (FF) is the fluid that fills the antral follicular cavity and provides the microenvironment for oocyte development and maturation. It contains important metabolites such as growth factors, cytokines, energy substrates, steroids, lipids, and cholesterol. These metabolites are crucial for oocyte growth and development. Numerous studies have been published on the effects of endometriosis on various growth factors present in FF [35].

Cytokines are small soluble signaling proteins best known for their immunoregulatory properties but increasingly recognized as growth factors regulating cell proliferation, differentiation, and function. Interleukins (ILs) are a subgroup of cytokines that exhibit an abnormal profile in endometriosis. Ovarian endometrioma may lead to follicular inflammation and oxidative stress. To date, several studies have investigated cytokine levels in FF of ovaries affected by endometrioma. For example, in 2020, Iland et al. found elevated levels of monocyte chemoattractant protein-1 (CCL2) and IL-8 in FF produced by ovaries affected by endometriosis. IL-8 is also a cytokine-chemokine; its main biological activity is the recruitment and activation of neutrophils, thereby inducing inflammation. The authors also determined that fewer oocytes were produced in ovaries affected by endometriosis (mean ± SD = 4.6 ± 2.3) compared with ovaries from the control group (7.9 ± 5.6). IL-6 is a pro-inflammatory cytokine that promotes the initiation and progression of endometriosis through a cytokine network and is predominantly produced by macrophages [43]. A significant number of studies have assessed the concentration of this cytokine and the number of macrophages in the peritoneal fluid of women with confirmed endometriosis. Researchers concluded that

elevated IL-6 concentration is a prognostically valuable biomarker of endometriosis. Godsi et al. demonstrated that IL-6 concentration is significantly increased in peritoneal fluid of women with endometriosis [36].

Oxidative stress can induce inflammation. At the same time, inflammation can lead to oxidative stress. Thus, the level of oxidative stress in the ovarian cortical tissue surrounding endometriotic cysts is significantly higher than in dermoid cysts. Kunitomi et al. demonstrated that endoplasmic reticulum dysfunction induced by high oxidative stress in granulosa cells of ovaries with endometrioma mediates apoptosis of these cells, leading to ovarian dysfunction in patients with endometriosis [37]. This suggests that endometriosis affects oocyte quality by inducing oxidative stress in granulosa cells. In addition to reduced oocyte quality, oxidative stress may also impair ovulation. Reactive oxygen species generated as a result of oxidative stress disrupt ovarian cortical vascularization and contribute to meiotic abnormalities and chromosomal instability, thereby reducing oocyte quality [38].

In patients with endometriosis, analysis of iron-related composition has revealed higher levels of oxidative substances such as 8-hydroxy-2-deoxyguanosine, ROS, peroxynitrite ion, nitric oxide, and malondialdehyde, and lower levels of antioxidant substances such as superoxide dismutase, catalase, vitamins A, C, and E, and reduced glutathione. Iron is an essential trace element in biological processes (oxygen transport and storage in tissues, hormone synthesis, mitochondrial energy metabolism, and adenosine triphosphate production), but iron overload may increase oxidative stress through the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$). This leads to damage of DNA, lipids, and proteins, and subsequently to cell death.

Iron overload may occur due to activated macrophages causing erythrocyte destruction, which in turn results from periodic bleeding from ectopic endometrial lesions and retrograde menstruation. Numerous studies on iron expression and hemoglobin variants have demonstrated the presence of hemoglobin, heme, or free iron in ovarian endometriotic cysts, peritoneal fluid, or follicular junctions in patients with endometriosis. Furthermore, it has been shown that iron content in follicles adjacent to endometriotic cysts is higher than in contralateral intact ovaries. The total iron content decreases in the following order: follicles proximal to the endometrioma, follicles distal to the endometrioma, and healthy ovarian follicles. These data suggest that iron contained within ovarian endometriomas may freely diffuse from the cyst wall and reach granulosa cells.

The concentration of transferrin, a protein required to maintain normal free iron levels, is reduced in follicular junctions in women with endometriosis-associated infertility. The authors also noted that iron overload and transferrin deficiency induce excess ROS, disrupt spindle integrity, and promote chromosomal instability, which may affect the number and maturation of oocytes retrieved from women with endometriosis. The authors further emphasized that iron overload and transferrin deficiency lead to ROS excess, disrupt spindle integrity, and promote chromosomal instability, which may affect both the number and maturation of oocytes obtained from women with endometriosis [39; 40].

Ferroptosis is a form of cell death at the intersection of iron regulation and ROS metabolism. Endometriosis is considered to be closely associated with ferroptosis mediated by iron-dependent oxidative stress. Granulosa cells in follicles play a key role in oocyte maturation, which depends on the intrafollicular microenvironment. Iron overload and transferrin deficiency have been detected in follicular fluid of women with both infertility and endometriosis. Ferroptosis of granulosa cells induced by an imbalance between iron concentration and transferrin impairs oocyte quality and negatively affects reproductive function. Ferroptosis is characterized not only by functional changes (e.g., increased lipid peroxide content) but also by morphological alterations. Mitochondria are considered important participants in iron metabolism and ROS production. Ferroptosis is accompanied by mitochondrial swelling and changes in mitochondrial cristae. Iron overload in endometriotic cysts decreases GPX4 expression and induces lipid peroxidation, which may trigger ferroptosis of granulosa cells, impair oocyte maturation and blastocyst formation, and consequently lead to infertility [41; 42].

MicroRNAs (miRNAs) are small non-coding RNAs capable of modulating gene expression. They interact with messenger RNA (mRNA), inhibiting translation or inducing its degradation. Increased miRNA expression suppresses translation via mRNA, whereas decreased miRNA expression may enhance the expression of genes encoded by the corresponding mRNA. Unlike other epigenetic mechanisms, miRNAs regulate gene expression at the post-transcriptional level and are detected both intracellularly and extracellularly.

Many studies have focused on the role of microRNAs in infertility caused by endometriosis. Over the past ten years, microarray analysis of endometrial tissue (ectopic and eutopic) has identified more than 20 microRNAs associated with endometriosis, the dysregulation of which leads to infertility. Thus, these microRNAs can be classified according to infertility-related processes. Dysregulation of miR-543 and miR-135a/b leads to impaired embryo implantation. Dysregulation of miR-2861, miR-488, miR-141-3p, miR-205-5p, miR-138, miR-370-3p, miR-34a/b/c, miR-9, miR-451, miR-210-3p, miR-27b-3p, miR-92a leads to increased proliferation of ectopic endometrium and decreased apoptosis of cells within endometriotic lesions. Altered expression of miR-29c, miR-194-3p, miR-34a/b/c, miR-196a, miR-125b, and miR-92a in endometrial cells leads to progesterone resistance, while miR-33b, miR-370-3p, miR-196a, and miR-194-3p prevent endometrial decidualization [43; 44]. However, further studies are required to confirm the role of microRNAs in the diagnosis of endometriosis.

Diagnostic and treatment approaches in patients with infertility associated with deep endometriosis combined with ovarian endometriomas. Deep endometriosis combined with ovarian endometriomas is one of the most complex forms of pathology, characterized by chronic pain, anatomical distortion of pelvic organs, and a significant reduction in reproductive potential. Further studies have shown that women with deep endometriosis may also

suffer from reduced ovarian reserve [45]. Pacchiarotti et al. compared AMH levels in women with stage III–IV endometriosis according to the rASRM classification and in fertile healthy women. In their study, women with stage III–IV rASRM endometriosis had significantly lower AMH levels, indicating a negative impact of deep lesions on ovarian reserve. Shebl et al. also demonstrated a negative correlation between the severity of endometriosis and serum AMH levels. It is important to note that in their study, women with minimal or mild endometriosis had AMH levels similar to those of the control group. A possible explanation for the negative impact of deep or severe endometriosis on ovarian reserve is significant pelvic inflammation, which may impair ovarian function. Laparoscopy alone does not take into account modern ovarian reserve biomarkers such as AMH and AFC and is therefore most often used in combination with other parameters for a more accurate assessment of reproductive potential [45; 46]. The endometriosis fertility index (EFI) does not directly include biochemical and morphological markers of ovarian reserve, which limits its accuracy in predicting fertility, especially in patients with combined forms of endometriosis and ovarian endometriomas.

AMH and AFC complement the EFI, allowing a more accurate assessment of ovarian reserve. AMH reflects the number of small preantral and early antral follicles in the growth phase and is a stable marker even within a single menstrual cycle. AFC, determined by TVUS in the early follicular phase, reflects the available antral follicles capable of responding to stimulation and allows assessment of the spatial distribution of follicles within the ovaries.

The integration of EFI with AMH and AFC enables more precise prediction of reproductive potential and the likelihood of spontaneous pregnancy or the effectiveness of ART. For example, a woman with a high EFI, normal AMH levels, and a sufficient number of antral follicles has a high probability of successful pregnancy, even in the presence of severe forms of endometriosis. Conversely, a low EFI combined with reduced AMH and low AFC indicates the need for rapid transition to ART, as spontaneous pregnancy is unlikely. A key aspect of integrated assessment is treatment personalization. The combined use of EFI, AMH, and AFC allows for: evidence-based planning of surgical interventions on the ovaries and pelvic organs, determination of optimal timing for transition to ART, prediction of ovarian stimulation and IVF outcomes, and reduction of unnecessary surgical procedures and ovarian reserve loss. However, current evidence indicates that AMH, although an important marker of quantitative ovarian reserve assessment, has limited predictive value for spontaneous pregnancy and live birth. Low AMH levels are not always associated with reduced natural fertility, as they do not reflect oocyte quality and other key factors of reproductive potential [47].

The choice of therapeutic strategy in endometriosis depends on age, duration of infertility, severity of symptoms, and reproductive plans. Medical therapy is an important component of comprehensive endometriosis management; however, current guidelines emphasize that it does not restore spontaneous fertility and is used primarily for symptom control and preparation for reproductive technologies. According to ESHRE (2022), ACOG (2023), and ESGE (2022) recommendations, medical treatment of patients with deep endometriosis combined with ovarian endometriomas should be individualized and include the following groups of drugs: progestins and progestin-containing agents, combined oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists and antagonists, other drugs, and experimental approaches. Medical therapy is not a method of improving fertility; therefore, in patients with reproductive intentions it is used only as an adjunct or as preparation for ART [48]. In women with severe pain syndrome, medical treatment may stabilize the condition and facilitate preparation for surgery or ovulation induction. The optimal approach is a combination of medical symptom control with individualized planning of surgical treatment and ART, ensuring the highest possible chance of achieving reproductive goals.

Surgical treatment remains a key component of comprehensive management of patients with severe forms of endometriosis, particularly when deep endometriosis is combined with ovarian endometriomas [48; 49]. The primary goal of the intervention is the removal of as many pathological lesions as possible while simultaneously restoring pelvic anatomy and preserving functional ovarian and fallopian tube tissue. Surgical treatment of endometriosis is used as part of infertility management protocols and yields favorable outcomes. It has been shown that 35–50% of infertile women have concomitant endometriosis. Laparoscopy remains the preferred method but is used for therapeutic rather than diagnostic purposes. The procedure is performed by a qualified multidisciplinary team (reproductive gynecologist, colorectal surgeon, urologist when the urinary system is involved) [49].

Surgical correction of adhesions involving the fallopian tubes and ovaries restores normal anatomy and helps improve fertility. Due to an excess of prostaglandins, proteases, and cytokines (inflammatory, angiogenic, and neurogenic) within endometriotic lesions, alterations in peritoneal fluid occur, which impair ciliary activity in the fallopian tubes and normal sperm function. Restoration of normal anatomy through adhesiolysis ensures adequate tubal patency and oocyte capture by the fimbriae [50].

Some studies emphasize that even after surgical treatment of deep endometriosis with endometriomas, the risk of reduced ovarian reserve remains high, since cyst removal is often accompanied by loss of a portion of functional ovarian tissue [50; 51]. This poses a complex clinical challenge of balancing the need to eliminate anatomical barriers while preserving ovarian potential. The decision regarding the extent of surgical intervention is based on disease severity and endometrioma size. Surgical treatment of ovarian endometriomas plays a leading role in the comprehensive management of patients with endometriosis-associated infertility. The aim of the intervention is removal of the pathological lesion, reduction of pain, and creation of conditions for restoration or preservation of reproductive function. At the same time, any ovarian manipulation is associated with a risk of diminished ovarian reserve; therefore, the choice of technique must be based on a balance between efficacy and safety.

In current practice, several main types of surgical interventions are used. Cystectomy is considered the "gold standard" for surgical treatment of endometriomas. This technique involves removal of the cyst capsule using blunt or sharp dissection, followed by coagulation of vessels in the cyst bed area. The advantages of this method include a low recurrence rate and long-term effectiveness; however, its disadvantage is the loss of a portion of healthy ovarian tissue, which may lead to a significant reduction in AMH levels and AFC, especially after repeated procedures [51; 52].

Ablation involves destruction of the inner cyst wall without complete removal of the capsule. Bipolar coagulation, laser energy (CO_2, diode), argon plasma, or plasma energy are used. The main advantage is reduced trauma to healthy ovarian tissue, allowing preservation of a larger proportion of ovarian reserve. The disadvantage is a significantly higher risk of endometrioma recurrence compared with cystectomy. A combined approach involves partial removal of the cyst capsule followed by ablation of the remaining wall. This strategy minimizes follicular loss while reducing recurrence rates, making it a promising option for women with reproductive plans [53].

Drainage and sclerotherapy are less commonly used methods that involve aspiration of cyst contents followed by injection of sclerosing agents (ethanol, tetracycline, etc.) or coagulation of the cyst wall. Advantages include minimal invasiveness and technical simplicity; however, the high recurrence rate limits its use. It may be considered as a temporary solution or in patients with high surgical risk. In a study involving 100 women who underwent laparoscopic cyst removal or drainage, recurrence rates were 4% and 84%, respectively. Cyst wall excision is superior to fenestration and ablation, as it reduces the risk of reoperation. It also reduces the severity of postoperative dysmenorrhea, dyspareunia, and non-cyclic pelvic pain [54].

Partial oophorectomy is indicated for large, multilocular, or recurrent endometriomas when preservation of intact ovarian tissue is not possible. The procedure allows radical removal of endometriotic lesions but is associated with a significant loss of ovarian reserve. It is mainly used in patients of advanced reproductive age or in the absence of prospects for natural conception. A radical method is applied in cases of extensive ovarian involvement, multiple recurrences, or suspicion of malignant transformation. It is rarely performed in women of reproductive age and is more commonly used in the perimenopausal period [55].

During surgical intervention for ovarian endometrioma removal, especially in young women, the issue of maximal preservation of healthy ovarian tissue remains highly relevant.

Research findings show that laparoscopic cystectomy for endometrioma reduces ovarian reserve regardless of hemostatic methods used after cyst removal.

After laparoscopic endometrioma excision, suturing demonstrated better outcomes in terms of ovarian reserve damage compared with bipolar electrocoagulation. Therefore, to prevent premature ovarian depletion, the use of hemostatic sutures is recommended, especially in young and infertile women.

The recurrence rate of ovarian endometriomas ranges from 9.6% to 45.5%. The surgeon must balance adequate lesion removal with iatrogenic reduction of ovarian reserve.

Analysis of AMH levels after surgical treatment of ovarian endometriosis showed a significant reduction in AMH concentration – by 24% after unilateral surgery and up to 67% after bilateral surgery.

The superiority of excision over electrocoagulation ablation was demonstrated in an interim meta-analysis of 7 studies, where excision was associated with a significantly lower risk of symptom recurrence and a significantly reduced recurrence rate (relative risk (RR) 0.50; 95% confidence interval (CI) 0.26–0.97; $p = 0.04$).

Recurrence rates after excision were also lower compared with laser vaporization (RR 0.33; 95% CI 0.12–0.88; $p = 0.03$). The rate of spontaneous pregnancy after excision was significantly higher compared with electrocoagulation (RR 2.64; 95% CI 1.49–4.69; $p < 0.001$) [56].

Thus, modern surgical management of ovarian endometriomas is based on an individualized approach with priority given to preservation of ovarian reserve.

Combined techniques are becoming increasingly popular, combining a relatively low recurrence rate with minimal damage to functional ovarian tissue. Personalized selection of surgical intervention based on patient age, AMH level, extent of disease, and reproductive plans is essential for optimal treatment outcomes [55, 56].

Conclusions

Despite the important role of AMH as a marker of the quantitative state of the follicular apparatus, current studies indicate its limited prognostic value for spontaneous pregnancy.

Therefore, assessment of reproductive potential should not rely solely on AMH levels but should be performed considering a combination of clinical, anamnesis-based, hormonal, ultrasound, and laparoscopic data.

Modern surgical management of endometriosis-associated infertility in combination with ovarian endometriomas should be based on a personalized approach with maximal emphasis on preservation of ovarian reserve.

A promising direction to achieve these goals is the use of combined surgical techniques that integrate a low recurrence rate with minimal negative impact on functional ovarian tissue.

Thus, the modern strategy for managing patients with endometriosis-associated infertility should be based on a multifactorial approach taking into account clinical, anamnesis-based, hormonal, ultrasound, and surgical parameters, which will improve reproductive outcomes in these patients.

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