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ENDOMETRIOSIS: ETIOPATHOGENESIS, EPIDEMIOLOGY, DIAGNOSIS AND THE CURRENT STATE OF TREATMENT (LITERATURE REVIEW AND STATISTICAL ANALYSIS)

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Abstract. This article provides a systematic review and statistical analysis of contemporary scientific data on endometriosis, covering its epidemiology, etiopathogenetic theories, diagnostic approaches and treatment strategies. Statistical evidence from the Global Burden of Disease (GBD) studies, meta-analyses and major clinical trials is synthesized. Endometriosis affects approximately 10% of women of reproductive age, with a mean diagnostic delay of 6.6–9.7 years, and infertility observed in 30–40% of patients. The efficacy and limitations of hormonal therapy (progestins, GnRH agonists and antagonists), surgery and assisted reproductive technologies are compared. The detrimental impact of the disease on quality of life and the economy is substantiated by statistical data.

Keywords: endometriosis, retrograde menstruation, chronic pelvic pain, infertility, laparoscopy, rASRM classification, hormonal therapy, GnRH antagonists, quality of life, disease burden.

Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disease characterized by the growth of endometrium-like tissue outside the uterine cavity, and is considered one of the most pressing problems of modern gynecology. Although the disease is mainly located in the pelvic peritoneum, ovaries, uterosacral ligaments and the pouch of Douglas, in rare cases it is also found in the gastrointestinal tract, the urinary tract, and even the thoracic cavity. Owing to its chronic course, pain syndrome, association with infertility and the significant reduction it causes in quality of life, endometriosis has become a problem of not only medical but also socio-economic importance.

The relevance of the topic lies in the fact that, despite the wide prevalence of the disease, its etiopathogenesis has not been fully studied, diagnosis is often made with considerable delay, and the available treatment methods, while controlling symptoms, cannot fully cure the disease. The aim of this article is to systematically analyze the current state of the epidemiology, pathogenesis, diagnosis and treatment of the disease on the basis of scientific articles, meta-analyses and global statistical studies published in recent years, and to summarize the main statistical indicators.

Materials and Methods

The study was carried out in the form of a literature review and statistical analysis. Data were collected from PubMed, ScienceDirect, Wiley Online Library, Frontiers and other international scientific databases, mainly from articles, systematic reviews and meta-analyses published in 2017–2025. In analyzing the statistical indicators, results from the Global Burden of Disease (GBD) studies, multicenter clinical trials (including the “Elaris EM-I/II” trials) and large population-based studies were used. As a selection criterion, sources reporting numerical (statistical) data on the epidemiology, etiopathogenesis, diagnosis or treatment of endometriosis were included. The data obtained were grouped by topic and summarized comparatively.

1. Epidemiology and Statistical Analysis

According to the literature, endometriosis affects approximately 6–10% of women of reproductive age, that is, more than 190 million women worldwide [4]. The prevalence rate varies sharply depending on the group studied: 2–11% among asymptomatic women, 5–21% among those hospitalized with chronic pelvic pain, and up to 25–50% among infertile women [1]. A 2025 meta-analysis covering 127 studies and more than 198 million women estimated the prevalence of endometriosis in the general population at 5% (95% confidence interval 2–9%), while in women with gynecological complaints this figure approached 50% [3].

Global Burden of Disease (GBD) studies have clarified the age distribution of the disease. According to GBD-2021 data, the incidence of endometriosis reaches its highest level in women aged 20–24 (304.3 cases per 100,000 women in 2021), while prevalence is highest at 25–29 years [19, 20]. It should be especially noted that these indicators do not fully reflect the real situation, because the disease often remains undetected or is misdiagnosed. A number of researchers, when taking confirmed and suspected cases together, have shown that the true prevalence reaches up to 11.4% (95% confidence interval 11.10–11.70%) [16].

Table 1. Main statistical indicators of endometriosis

Indicator	Value	Source
Prevalence in women of reproductive age	6–10% (190 M+)	[4]
Prevalence among infertile women	25–50%	[1, 47]
Infertility in patients with endometriosis	30–40%	[42, 47]
Mean diagnostic delay	6.6–9.7 years	[24, 28]
Longest reported delay	up to 27 years	[24]
Age of highest incidence	20–24 years	[19]
Prevalence of retrograde menstruation	~90%	[37]
Postoperative recurrence (5 years)	up to 40–50%	[44]
Pregnancy after surgery (3 years)	~47%	[46]
IVF success (per transfer)	50–60%	[49]
Annual economic cost (per patient)	~27,855 USD	[53]

2. Etiology and Pathogenesis

Several theories have been put forward to explain the origin of endometriosis, none of which can fully account for all forms of the disease. The most widespread and best-evidenced theory is the theory of retrograde menstruation, proposed by J. Sampson in 1927 [6]. According to it, during menstruation, blood containing viable endometrial cells flows in a reverse direction through the fallopian tubes into the pelvic cavity, where it implants and proliferates. In recent years this theory has also been confirmed at the molecular level: in hundreds of patients, DNA mutations in the epithelial cells of the endometrium were found to be identical to mutations in the ectopic foci [35].

However, the theory of retrograde menstruation has an important limitation: this phenomenon is observed in approximately 90% of women of reproductive age, yet endometriosis develops in only a small proportion of them [37]. This means that additional factors are also involved in the formation of the disease. For this reason, other theories have also been advanced: coelomic metaplasia (transformation of peritoneal cells into endometrium-like tissue), the theory of embryonic Müllerian remnants, spread via blood and lymph (the metastatic theory), and mechanisms involving stem cells. Modern studies show that immune system dysregulation, chronic inflammation, estrogen dependence, progesterone resistance, and genetic and epigenetic changes play an important role in the pathogenesis of the disease [37, 39]. Endometriosis is therefore regarded as a multifactorial, multifaceted systemic disease [4].

At the molecular level, a number of disturbances have been identified in endometriotic foci. These include enhanced local estrogen synthesis resulting from increased aromatase enzyme activity, progesterone resistance, high levels of prostaglandins and inflammatory cytokines (IL-1, IL-6, TNF-α), activation of angiogenesis (the formation of new blood vessels), and a decrease in apoptosis (programmed cell death) [37, 39]. It is precisely these mechanisms that enable the survival and growth of the ectopic tissue and the persistence of chronic inflammation and pain. These molecular data serve as a basis for the search for new treatment targets.

3. Clinical-Morphological Forms of the Disease

According to their location and morphological features, three main forms of endometriosis are distinguished. The first is superficial peritoneal endometriosis, in which the foci are located superficially on the pelvic peritoneum. The second is ovarian endometrioma (the “chocolate cyst”), which manifests as a cyst in the ovary filled with old blood and adversely affects the ovarian reserve. The third is deep infiltrating endometriosis (DIE), in which the foci penetrate more than 5 mm beneath the peritoneum and may affect the uterosacral ligaments, rectum, bladder or urinary tract. It is precisely the deep infiltrating form that is associated with the most severe pain and surgical difficulties, and it is often detected in patients at rASRM stages II–III [64]. In addition, in rare cases extra-pelvic endometriosis (outside the pelvic cavity) — in the thoracic cavity, the umbilicus or in surgical-scar areas — also occurs.

4. Clinical Picture and Symptoms

The clinical presentation of endometriosis is diverse, with the pain syndrome occupying the leading position. The most common symptoms include dysmenorrhea (painful menstruation), chronic pelvic pain, dyspareunia (pain during sexual intercourse), dyschezia (pain during defecation), dysuria and infertility. An important feature is that the severity of the symptoms does not always correspond to the size and spread of the foci: minimal foci may cause severe pain, whereas a widespread process may run almost asymptomatically. In addition, endometriosis often coexists with chronic fatigue, anxiety and depression, and certain autoimmune diseases, which once again confirms its systemic nature.

Endometriosis has also been found to be associated with a number of comorbid conditions. Patients more frequently experience chronic fatigue, migraine, irritable bowel syndrome, some autoimmune diseases, as well as anxiety and depression. Epidemiological studies indicate that the relative risk of certain types of ovarian cancer may be somewhat higher in women with endometriosis, but the absolute risk remains low, and it has not yet been clearly proven that this association is causal. These observations once again emphasize the need to regard endometriosis not as a local gynecological problem but as a chronic systemic disease affecting the entire organism [4].

5. Classification

The most widely used system for classifying endometriosis is the revised classification of the American Society for Reproductive Medicine (rASRM, 1996). This system defines four stages based on the sum of scores according to the number, size and location of the foci and the degree of adhesions: stage I — minimal (1–5 points), stage II — mild (6–15 points), stage III — moderate (16–40 points), and stage IV — severe (more than 40 points) [62]. However, the rASRM classification does not adequately reflect the severity of the pain syndrome or the prognosis of the disease, especially in cases of deep infiltrating endometriosis. For this reason, additional systems have been developed — the ENZIAN classification, which describes deep infiltrating foci in detail, as well as staging systems based on ultrasound and MRI — and these are considered more effective in predicting surgical complexity and the risk of complications [63, 64].

6. Diagnosis and the Problem of Diagnostic Delay

Traditionally, the definitive diagnosis of endometriosis was considered to be the visualization of the foci by laparoscopy and their histological confirmation by biopsy. However, according to the 2022 guidelines of ESHRE (the European Society of Human Reproduction and Embryology), thanks to improvements in imaging methods endometriosis can now be diagnosed without laparoscopy [9]. Transvaginal ultrasound examination is recommended as the first-line imaging method; magnetic resonance imaging (MRI) has high accuracy in assessing deep infiltrating forms. When there is clinical suspicion, empirical hormonal treatment may also be initiated.

In laboratory diagnosis, the level of the CA-125 tumor marker is often elevated in endometriosis, especially in severe forms, but because of its low sensitivity and specificity it is not recommended as a screening or definitive diagnostic method. The very absence of a reliable, noninvasive biomarker remains one of the important causes of diagnostic delay. For this reason, recent studies have focused on the search for new biomarkers based on molecular, epigenetic and microbiome approaches [5].

One of the most serious problems of endometriosis is the considerable delay in diagnosis. According to a review by researchers at the University of York covering 22 studies, an average of 6.6 years passes from the appearance of symptoms to diagnosis, and in some cases this period stretched to as long as 27 years [24]. Other systematic analyses estimate the average delay to be in the range of 6.8–10 years: 1.5 years in Australia, up to 11 years in the USA, and 9.7±7.1 years in New Zealand [25, 28]. Before a diagnosis is made, patients consult on average 4–7 physicians [32]. The main causes of the delay are cited as the perception of symptoms as “normal menstrual pain,” insufficient awareness of the disease among women and medical staff, and the absence of objective biomarkers. It is noteworthy that studies published in recent years observe a reduction of the average delay to 4.4 years, which testifies to increasing awareness [27].

7. Endometriosis and Infertility

Endometriosis is one of the leading causes of infertility. According to statistical data, infertility is observed in 30–40% of patients with endometriosis, while among infertile women the prevalence of the disease is 25–40% [42, 47]. The mechanisms of infertility are multifaceted: a decline in ovarian reserve and oocyte quality, disruption of pelvic anatomy as a result of adhesions and fibrosis, a reduction in endometrial receptivity (its readiness for embryo implantation), and chronic inflammation [45, 48]. Endometriosis thus adversely affects the reproductive system at several stages.

8. Modern Treatment Methods and Their Efficacy

Hormonal therapy. The main direction of treatment is to inhibit the growth of ectopic tissue by suppressing the effect of estrogen. As first-line agents, combined hormonal contraceptives and

progestins (in particular dienogest) are used. Although gonadotropin-releasing hormone (GnRH) agonists are highly effective, they have side effects such as a decrease in bone density due to profound hypoestrogenism, and once treatment is stopped the recurrence rate may reach up to 50% within five years [44].

GnRH antagonists — new-generation agents. In recent years, oral GnRH antagonists (elagolix, relugolix, linzagolix) have been recognized as a promising class for the treatment of endometriosis-associated pain. The efficacy of elagolix has been confirmed in two phase III randomized controlled trials, "Elaris EM-I" and "Elaris EM-II" [8, 51]. The main advantage of these agents over the agonists is that they do not produce an initial "flare-up" effect (a temporary intensification of symptoms) and allow estrogen levels to be controlled in a dose-dependent manner. Meta-analyses have shown that GnRH antagonists are most effective in reducing non-menstrual pelvic pain, while dienogest is preferable for alleviating dyspareunia [57, 59].

Surgical treatment. Laparoscopic excision or ablation of the foci is effective in reducing pain and restoring anatomy. However, surgery also has its limitations: it may adversely affect the ovarian reserve, and recurrence is high. According to the literature, within five years after laparotomy up to 40% of patients require repeat surgery [44]. In infertile patients, the cumulative probability of pregnancy within three years after surgery averaged 47% [46].

Assisted reproductive technologies (ART). In infertility-related cases it is recognized that hormonal therapy alone does not increase pregnancy rates, and therefore in vitro fertilization (IVF) plays an important role. In severe endometriosis, IVF can provide a success rate of approximately 50–60% per embryo transfer, and the combination of surgery and IVF improves the outcome [49]. The treatment strategy is individualized, taking into account the patient's goal (pain control or pregnancy), the stage of the disease and the patient's age.

9. Quality of Life and Economic Burden

Endometriosis has a serious adverse effect on quality of life. Studies have shown that patients' physical, mental and social well-being is lower than that of healthy groups and of patients with other chronic diseases; medical and surgical interventions significantly improve these indicators [52, 56]. From an economic point of view, the disease represents a major burden: according to US data, the annual cost per patient is approximately 27,855 US dollars, while women lose on average 11 working hours per week because of endometriosis [53, 59]. A large part of the costs is generated by reduced labor productivity (indirect costs). At the same time, the scientific funding allocated to gynecological diseases remains relatively low, which constitutes an important obstacle to studying and treating the disease [18].

10. Current Trends and Prospects

At present, several promising directions of endometriosis research are taking shape. These include the search for reliable biomarkers for noninvasive diagnosis, the study of the genetic and epigenetic foundations of the disease, new treatment targets aimed at the immune system and at neuro-immune interaction, as well as approaches affecting ferroptosis, the microbiome and metabolic factors [45]. The need to develop non-hormonal treatment agents — especially drugs that control pain while preserving fertility — remains high. In addition, as emphasized in the ESHRE guidelines, a multidisciplinary approach — the collaboration of a gynecologist, a reproductive specialist, a pain specialist and a psychologist — is of key importance in improving treatment outcomes.

Conclusion

Endometriosis is a chronic, estrogen-dependent, multifactorial systemic disease that affects approximately 10% of women of reproductive age. The analysis of the literature and the statistical

data allow the following main conclusions to be drawn. First, the true prevalence of the disease may be higher than the available indicators suggest, because diagnosis is often delayed (on average 6.6–9.7 years). Second, although the theory of retrograde menstruation is the best founded, the pathogenesis of the disease is determined by the complex interaction of immune, genetic, epigenetic and inflammatory factors. Third, infertility is observed in 30–40% of patients, which demonstrates the serious impact of the disease on reproductive health.

Fourth, although the available treatment methods (hormonal therapy, surgery and ART) are effective in controlling symptoms and supporting fertility, they cannot fully cure the disease, and the recurrence rate remains high. New-generation agents such as the GnRH antagonists are expanding treatment possibilities. Fifth, endometriosis imposes a significant burden on quality of life and on the economy, and therefore early diagnosis, increased awareness and a personalized, multidisciplinary approach are of great practical importance. It is advisable that future research be directed toward developing noninvasive diagnostic methods and non-hormonal treatment strategies.

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