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Endometriosis: Classification, Risk factors, Diagnosis and management - Review of Literature

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Abstract

Endometriosis is an oestrogen-dependent disease characterized by the presence of the endometrial tissue outside its normal location. Three types of endometriosis are distinguished: ovarian, peritoneal, and deeply infiltrating [1,2].

The literature reports that 6-15% of the general female population suffers from endometriosis. This disease occurs mainly in women of reproductive age, but also in young women and postmenopausal women [3]. Symptoms of endometriosis include periodic pain that becomes constant, very painful menstruation, painful intercourse, as well as painful micturition or defecation. Endometriosis is present in up to 35-50% of women diagnosed with infertility. In diagnosing endometriosis, laparoscopy is of utmost importance, as it allows for simultaneous treatment of the condition. Laparoscopy should be preceded by a thorough medical history and imaging diagnostics such as ultrasound or magnetic resonance imaging (MRI).
The treatment of endometriosis is divided into pharmacological and surgical methods, which can be either conservative or radical. The type of treatment used depends on the patient's age and reproductive desires, the symptoms present, and the form of the disease. A proper diet and lifestyle play a significant role in the treatment of endometriosis.

Keywords
endometriosis, endometriosis treatment, endometriosis diagnosis, infertility in endometriosis, pelvic pain.

Results
Laparoscopy is currently the gold standard in the diagnosis of endometriosis. Less invasive methods are still being sought to shorten the time to make an accurate diagnosis. Current treatment for endometriosis is limited to surgical, hormonal, and pain management therapies.

Introduction
Endometriosis is a disease that contributes to infertility in a large population of women. This condition is characterized by chronic pain, which leads to a decreased overall quality of life for women. Endometriosis lesions are mainly located in the pelvic area but can occur throughout the body. Late diagnosis is a major issue in the treatment of endometriosis. It has been proven that non-invasive tests have high potential in the diagnostic process of endometriosis; however, further analyses are needed before they can be used in everyday clinical practice. Future research should focus on thoroughly understanding the pathogenesis, identifying subtypes of endometriosis, and modern approaches to diagnosis. Most importantly, comprehensive treatment should consider the accompanying general symptoms.

Aim
To summarize the current state of knowledge on endometriosis, and to analyze topics such as classification, risk factors, diagnostic methods, the impact of endometriosis on fertility, and its treatment.

Methods and materials
A review of the literature available in the PubMed database, Medline and Google Scholar using the following keywords: endometriosis, endometriosis treatment, endometriosis diagnosis, infertility in endometriosis, pelvic pain.

Articles were considered for inclusion, with publication dates between 1986 and 2024 to ensure relevance to contemporary understanding and practice.

Types of Endometriosis

Endometriosis is a heterogeneous disease that manifests in three main phenotypes:

1. **Superficial/Peritoneal Endometriosis:** This type can be detected in 15-50% of all women diagnosed with endometriosis [4].
2. **Ovarian Endometrial Cysts (Endometriomas):** This type affects approximately 210% of women of reproductive age. It also occurs in over 50% of women treated for infertility [5].
3. **Deeply Infiltrating Endometriosis (DIE):** In this form of endometriosis, endometrial implants penetrate at least 5 millimeters beneath the peritoneal surface. These implants contribute to the fibromuscular proliferation surrounding the endometriosis foci. The prevalence of DIE among all patients with endometriosis is about 20%, corresponding to an overall prevalence of nearly 2% [6].

In rare cases, foci of endometriosis can be located in distant organs, most commonly the lungs, liver, and brain. A special variant of endometriosis is adenomyosis, where the changes are located within the uterine muscle [7,8].

Risk Factors for Endometriosis

Epidemiological studies analyzing the correlation between women's menstrual cycles and the incidence of endometriosis have shown that the onset of the first cycle before the age of 11 is associated with a high risk of developing endometriosis [9,10,11,12]. Women with menstrual cycles shorter than 27 days have an increased risk of endometriosis, although this is not related to the number or volume of bleeding [13].

Additional risk factors predisposing individuals to endometriosis include low Body Mass Index (BMI), low fertility, Caucasian race, age between 25 and 29 years, and daily alcohol consumption of at least 10 grams [14,15]. Proper nutrition plays a very important role in preventing the development of endometriosis. A daily intake of green vegetables and fresh fruits is considered extremely beneficial. Fruits and vegetables contain antioxidant substances that are crucial for the proper functioning of the immune system and the elimination of free radicals. Additionally, the fiber in vegetables helps regulate gut flora and contributes to hormonal balance [16].

Conversely, consuming red meat has an antagonistic effect on the development of endometriosis compared to fruits and vegetables. Red meat has a relatively high content of dioxins, fat, and hormones, resulting in an increase in oestrogen levels in the body [16]. A study conducted by Yamamoto et al. on a group of 81,908 women from 1991-2013 aimed to answer whether higher consumption of poultry, red meat, fish, and seafood correlates with the risk of laparoscopically confirmed endometriosis [17]. Diet was assessed using a specially prepared food questionnaire administered every 4 years. The study showed that women who reported consuming > 2 servings/day of red meat had a 56% higher risk of endometriosis compared to women who consumed ≤ 1 serving/week.

The study did not show a correlation between the consumption of fish, shellfish, poultry, and eggs and an increased risk of endometriosis [17].
Another prospective study demonstrated that the intake of fish oil, rich in omega-3 fatty acids, significantly reduced the risk of endometriosis recurrence [18]. The ratio of unsaturated to saturated fatty acids was crucial [18]. Vitamins A, C, E, and elements such as zinc and selenium also exhibit antioxidant properties. Vitamin D, in addition to its anti-inflammatory effects, also has immunomodulatory and antiproliferative properties [19].
A 2020 meta-analysis showed that low levels of vitamin D correlate with an increased risk of endometriosis and exacerbate its symptoms [20]. One study even demonstrated that vitamin D supplementation reduced pain symptoms [21,22,23], likely due to reduced histamine release. In a randomized, placebo-controlled trial conducted on women previously diagnosed with endometriosis, a dose of 50,000 IU of vitamin D every 2 weeks for 12 weeks reduced pelvic pain by 1.12 points in self-assessment [20].
An extremely important factor in preventing primary endometriosis is maintaining an appropriate lifestyle, in which rest and physical activity should be key aspects [24].

Diagnosis of Endometriosis

The fundamental element in the initial stage of diagnosing endometriosis is conducting a detailed interview with the patient. Studies have analyzed the clinical utility of a properly conducted medical interview and the pain symptoms reported by patients with endometriosis [Patient-Reported Outcome Measures in Endometriosis-PROME]. The studies described above have shown that PROME has high clinical utility [25].
PROME includes questions about symptoms such as quality of life, the nature of pain, gastrointestinal and urinary disorders, sexual life quality, fatigue, depressive disorders, and the impact of endometriosis on professional life [26]. Questions about the most characteristic symptoms of endometriosis, such as painful and/or heavy menstruation and painful intercourse, should be detailed by asking further questions about frequent and/or painful defecation or micturition. It is also essential to ask about symptoms like bloating, diarrhoea, constipation, urinary urgency, pain in the sacral and lower abdominal regions, sciatica-like pain, and bleeding from unusual locations. The likelihood of diagnosing endometriosis increases with the number of symptoms reported by the patient [21].
The interview should also pay special attention to a positive family history, as endometriosis in the mother increases the risk of the disease sevenfold in the daughter, fivefold in the sister, and about one and a half times in the cousin [27,28,29,30]. Interestingly, statistically, mothers of women with endometriosis smoked nicotine during pregnancy, were more likely to have preeclampsia, and the pregnancy ended prematurely. Low BMI or high BMI accompanied by infertility are also significant predispositions to endometriosis [22, 23].
Women with endometriosis are more likely to have autoimmune diseases such as Sjögren's syndrome, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, ulcerative colitis, celiac disease, or Crohn's disease compared to women without this condition [31,32,33,34,35]. Endometriosis is also more common in women with bronchial asthma, atopic diseases, and food or drug allergies [36,37, 38, 39, 40].

Symptoms such as painful menstruation or painful intercourse are common among the general female population, so when asking about these symptoms, it is essential to focus on their cyclic occurrence [41]. For patients not currently planning reproduction, where the only symptom is painful menstruation and can be effectively managed with hormonal contraception, endometriosis diagnosis is not absolutely indicated [42,43,44]. Targeted clinical examination should be conducted when symptoms suggesting endometriosis appear [44]. Such an examination should include inspection and palpation of the abdominal wall, a thorough examination of the vaginal fornices using a speculum, and a bimanual gynecological examination. The presence of endometriosis in the described examination may be indicated by bluish lesions in the posterior vaginal fornix, tense and tender sacro-uterine ligaments, adnexal masses, an immobile and retroverted uterus, palpable nodules in the Douglas pouch, on the sacro-uterine ligaments, or in the bowel wall, and pelvic pain during the examination. Conducting the clinical examination during menstruation increases the detection of endometriosis [45,46].

Even if no abnormalities are visible in the clinical examination, if the medical interview suggests the presence of endometriosis, imaging diagnostics must be implemented [43]. Imaging studies that visualise endometrial changes include transabdominal, transvaginal, and transrectal ultrasound, as well as magnetic resonance imaging (MRI) with contrast [47,48,49,50]. However, these techniques are usually ineffective in cases of peritoneal endometriosis [51].

In suspected endometriosis, the first-choice examination is transvaginal ultrasound [43,44,47]. However, this method does not benefit detecting small endometriosis lesions [52]. According to the International Ovarian Tumour Analysis guidelines, a typical endometrial cyst in an ultrasound should be unilocular, and its echogenicity should resemble a ground glass appearance [53]. Some cases require modifications to ultrasound techniques, such as performing transvaginal ultrasound with appropriate bowel preparation to visualise deep endometriosis in the recto-uterine pouch [54]. Water-contrast ultrasound in the vagina and rectum and 3D ultrasound are also applicable [55, 56].

According to the International Deep Endometriosis Analysis's proprietary scheme, expert transvaginal ultrasound can significantly assess the presence of adhesions in the pelvic area, changes in the bladder, bowel loops, or pelvic sections of the ureters [47]. MRI, while useful for diagnosing deep endometriosis extending beyond the pelvic area or involving the intestines, is not commonly used in routine clinical practice due to limited availability and high cost [49,57].

We cannot exclude superficial endometriosis lesions using tools like ultrasound or MRI if no clear abnormalities are detected in both clinical and ultrasound examination algorithms. When a clinical interview suggests endometriosis, but imaging studies cannot confirm it, continuous combined hormonal contraception or progestogens should be recommended for patients not planning pregnancy [42]. This pharmacotherapy aims to confirm or exclude endometriosis with high probability based on the relief or reduction of symptoms.

Unfortunately, a specific biological marker for endometriosis that can be detected in body fluids to confirm or exclude the diagnosis remains unavailable [58, 59].

Measuring Ca-125 levels in blood serum is erroneous, as low levels below 30 IU/ml do not exclude the disease, while elevated results may indicate endometriosis or other conditions, potentially leading to unjustified treatment [60].
Current clinical trials are investigating biomarkers such as brain-derived neurotrophic factor (BDNF) obtained from blood plasma using ELISA, expression of fucosyltransferase 4 (FUC4) from endometrial cells, and sequencing endometriosis-specific microRNA from patient saliva. Of the markers described, BDNF showed the greatest specificity for endometriosis. However, as of writing this article, the effectiveness of these tests, particularly for differentiating the aetiology of chronic pelvic pain, remains unconfirmed, preventing their recommendation for diagnosing endometriosis.

Pharmacological Treatment of Endometriosis

The treatment of endometriosis should focus on maximising long-term pharmacological therapy while minimising surgical interventions.
The following groups of drugs are distinguished in pharmacological treatment:

- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)
- COCs (Combined Oral Contraceptives)
- Progestogens
- Antiprogestogens
- GnRH Agonists
- GnRH Antagonists
- Aromatase Inhibitors
- Danazol
- Levonorgestrel-releasing intrauterine systems

Since no single type of pharmacological treatment has been shown to be superior to others, the choice of treatment should be based on individual effectiveness for the patient. Selection should be made based on the side effect profile, patient preferences, or therapy costs.
The primary goal of pharmacological treatment is to eliminate or reduce the chronic pain associated with endometriosis [63]. Pharmacotherapy can also reduce the likelihood of postoperative pain recurrence, the formation of new endometrial cysts, and tissue adhesions [64]. However, pharmacological treatment does not affect existing adhesions or endometrial cysts [65]. The goal of pharmacology is not to improve fertility in patients, as the hormonal medications used prevent pregnancy [43,66].
Over time, the effectiveness of pharmacological treatment for endometriosis diminishes, leading to the recurrence of symptoms similar to those observed after stopping treatment entirely [67].
Unfortunately, there is still a lack of sufficiently strong evidence to confirm the choice of an appropriate treatment regimen [43]. Literature suggests that for patients without endometrial cysts, where lower abdominal pain is mild to moderate and does not limit daily activities, a therapy based on NSAIDs and COCs is worth proposing [65]. For patients contraindicated for combined oral contraceptives, combining NSAIDs with a progestogen-only contraceptive is recommended [65]. For patients planning pregnancy, monotherapy with non-steroidal antiinflammatory drugs is advised to eliminate chronic pain associated with the disease [65].

In this context, selective cyclooxygenase-2 (COX-2) inhibitors should be excluded, as their action disrupts ovulation, hindering fertilisation [66].
Pharmacological treatment before the planned surgical removal of endometrial cysts can be used to alleviate pain. However, it is important to note that this treatment does not affect the effectiveness of the surgical procedure [43].
Pharmacological treatment should be administered after surgical treatment in cases of confirmed intraoperative diagnosis. The aim of pharmacotherapy is to reduce the risk of pain recurrence and the return of endometrial lesions for up to 12 months [68, 69, 70, 71]. It has been shown that the implementation of pharmacotherapy after surgical treatment results in increased pregnancy rates [67]. The most effective actions in preventing endometriosis recurrence have been demonstrated by continuous-use combined oral contraceptives and the insertion of a levonorgestrel-releasing intrauterine device [68]. Another study reports high efficacy of dydrogesterone used from day 5 to day 25 of the cycle to control pain after laparoscopy [69].

Proposed Stages of Pharmacological Treatment

Currently, in the treatment of endometriosis, there is a lack of algorithms based on strong evidence from randomised clinical trials. Existing therapy schemes are mainly based on expert opinions. The treatment of endometriosis can involve the following stages [63]:

1. Continuous therapy with combined oral contraceptives [COCs] in combination with NSAIDs.
2. Evaluation of the effectiveness of the above therapy after 3 months, and in cases where it is ineffective or poorly tolerated, it should not be discontinued but rather changed to another combination of COCs + NSAIDs. However, if the therapy yields positive results, it should be continued until plans for pregnancy or the average age of menopause onset. The described treatment should not be discontinued, and after breastfeeding, it should be reintroduced.
3. Combination of GnRH analog with oestrogen in a small dose in an add-back scheme, or surgical treatment will be applied if the new combination of COCs + NSAIDs is ineffective, or from the beginning of therapy if the patient reports severe exacerbation of pain preventing her from functioning in daily life. After surgical treatment of endometriosis, continuous oral contraception or other suppressive treatment should be introduced to reduce the risk of adhesions and recurrence of endometriosis lesions.
4. If none of the above-described treatment regimens for endometriosis is effective, it can be changed by using an intrauterine device with levonorgestrel or aromatase inhibitors. This treatment has been clinically proven to completely eliminate or alleviate painful and/or heavy menstrual bleeding.

Surgical treatment

Surgical treatment of endometriosis should be divided into conservative treatment for women of childbearing age who are planning a pregnancy and radical treatment for patients who are not planning a pregnancy and whose pain has not subsided despite pharmacotherapy.

The main indications for surgical treatment are pelvic pain, endometrial ovarian cysts and infertility [72].

Laparoscopy is the technique of choice for the surgical treatment of endometriosis. It has been shown to be superior to laparotomy due to less reported pain, reduced hospitalisation time and better cosmetic results.

In contrast, an analysis of the available studies showed no significant differences between conventional and robotic surgery. The exception is the longer procedure time for robotic surgery. Patients with deep infiltrating endometriosis, elevated BMI or a history of previous surgery may benefit more from robotic surgery in multidisciplinary long-term care centres [73]. It is recommended to avoid multiple reoperations due to the formation of adhesions and the negative effect of reducing ovarian reserve. Before surgery, pharmacological treatment is not recommended just to improve intraoperative conditions. Pharmacological treatment should be implemented immediately after surgery in patients undergoing surgery due to the presence of an endometrial cyst or complaints of pain who currently have no plans to become pregnant. With good tolerance, pharmacotherapy should be continued until the patient wishes to become pregnant or long-term in patients who do not plan to become pregnant in order to minimise the chances of recurrence with pain.

The surgical treatment of endometriosis in women of reproductive age involves the radical removal of endometriosis foci while leaving the uterine muscle and ovaries. It should be emphasised that surgical removal of endometrial ovarian cysts should be carried out with great precision with careful preservation of the ovarian cortex while resecting the obstructed fallopian tubes. Unfortunately, this treatment is an incomplete treatment due to the nature of the disease. Therefore, after the reproductive period is over, radical treatment is applied - removal of all endometriosis foci together with the uterus, leaving or not the ovaries. Surgical techniques make it possible to reduce pain in up to 50-80 % of affected women. However, relapse is observed in approximately 5-15 % of patients despite hysterectomy and ovariectomy [73].

Endometriosis and infertility

In a group of women suffering from infertility, the coexistence of endometriosis is found in up to 20-35%. In the case-control studies conducted, a history of endometriosis was confirmed up to six times more often. In these women, the percentage of pregnancies per natural monthly cycle is only 2-10%.

Anatomical abnormalities such as adhesions, damaged or obstructed fallopian tubes are a mechanical cause of infertility. In the case of an in vitro fertilization procedure, endometriosis can affect the quality of the embryo, the quality of the oocyte, the efficiency of fertilization, the environment of the peritoneal fluid and the normal process of embryogenesis [74].

Pharmacological treatment and fertility

No evidence has been described to support a beneficial effect of pharmacological treatment of endometriosis on increasing fertility parameters. Most of the pharmacological agents used cause inhibition of ovulation.

In the described meta-analysis of twelve randomized trials that compared pharmacological treatment with placebo, no positive effect of pharmacotherapy on achieving pregnancy was demonstrated. In contrast, a comparison of laparoscopic techniques for the treatment of endometriosis and the use of GnRH analogues to placebo showed a decisive advantage of the above-mentioned modalities over placebo in the number of pregnancies achieved. According to the guidelines of the European Society of Human Reproduction and Embryology [ESHRE], the postoperative use of pharmacology does not contribute to an adverse effect on pregnancy rates, and pharmacological treatment for pain relief should be offered to women who currently have no reproductive plans. In addition, randomized trials have also shown no positive effect of anti-estrogenic treatment with aromatase inhibitors and anti-inflammatory treatment with pentoxifylline on fertility in natural cycles [75].

Surgical treatment of endometriosis and fertility

For infertile patients with minimal or mild endometriosis, i.e. grade I and II according to the rASRM [The revised American Society for Reproductive Medicine] classification, performing laparoscopy with excision or ablation of endometrial foci is likely to significantly improve fertility compared to diagnostic laparoscopy. In the study by Garcia-Velasco et al., there was no evidence of a significant benefit after removal of an endometrial ovarian cyst in relation to the percentage of pregnancies achieved in patients undergoing in vitro fertilization, relative to patients who had cysts left behind [76]. In contrast, a large randomized multicenter study of 341 women found an almost twofold increase in the likelihood of pregnancy in women after surgical removal of endometriosis foci [OR=2.03 ;95%CI = 1.28-3.24] [77]. In advanced stages of endometriosis, surgical treatment can restore normal pelvic anatomy, but there is no reliable data on the effectiveness of these therapeutic interventions. According to a meta-analysis based on 19 studies published in 2020, it was found that surgical treatment of ovarian endometriosis was followed by a significant decrease in ovarian reserve [AMH-Anti-Mullerian hormone] at 3 and 6 months after intervention [78].

When planning surgical treatment for endometriosis, factors such as the patient's age, previous surgeries, pain, ovarian reserve, the speed at which the tumour grows and the overall prognosis should be taken into account. Prognosis can be assessed using, for example, the endometriosis fertility index [EFI- endometriosis fertility index]. This index is a validated indicator of the likelihood of spontaneous pregnancy within 3 years of surgical removal of endometriosis in women suffering from infertility. The EFI index consists of elements such as the patient's history, the severity of endometriosis in the intraoperative description of the lesions together with a qualitative assessment of the adnexa under visual inspection. According to the results of a systematic review and a meta-analysis in 2020, it was shown that the higher the EFI index, the higher the probability of pregnancy in women after surgical treatment of endometriosis. At 3 years, the probability of pregnancy for an EFI of 0-2 points was 10%, while for an EFI of 910 points it had already risen to 69% [79]. Given the study, it can be concluded that the EFI index is a good predictor of the chances of pregnancy after surgical treatment of endometriosis. The EFI index can also be a suitable tool for planning further treatment [80,81].

Removal of the endometrial cyst has not been shown to improve IVF success rates, and therefore the operation should only be considered in cases of severe pain or difficulty accessing the affected ovary during IVF-ET [In Vitro Fertilization- Embryo Transfer]. In contrast, in the case of natural conception, studies have shown that prior excision of an endometrial cyst with removal of its capsule results in better outcomes than merely emptying the cyst with ablation of its locus [82]. Cystectomy using a laparoscopic technique with removal of its capsule compared to coagulation of the locus with a CO2 laser results in a more than twofold higher chance of spontaneous pregnancy [82].

Because of the potential severe complications and the extent of surgical treatment of deep endometriosis, the implementation of this treatment should only be considered when very severe symptoms are present [43,83,84].

Aggravated pain complaints include dyschezia and VAS [Visual Analog Scale] dyspareunia >7. Additionally, surgical treatment should be indicated in patients presenting symptoms of bowel lumen narrowing and after unsuccessful IVF [In Vitro Fertilization] [85].

The literature reports that after at least 2 unsuccessful IVFs, surgical treatment of the deep form of endometriosis can have a positive effect on fertility [85].

Disclosure

Author's contribution Statement

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