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## Endometriosis: Pathogenesis, diagnosis, treatment and the role of gut microbiota

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## **Abstract**

### **Purpose**

The first aim of this review is to provide an overview of existing literature and current knowledge of endometriosis pathogenesis, diagnosis and recommended forms of treatment. The second aim of this article is to emphasize the role of the microbiota on the pathogenesis and treatment of endometriosis

Endometriosis is a common disease. It affects 5-10% of women of reproductive age worldwide. However, despite its prevalence, diagnosis is typically delayed by years, misdiagnosis is common, and effective treatment takes years to achieve. Determining the mechanisms involved in its pathogenesis is vital, not only to pave the way for early identification, but also for disease management and development of less invasive but successful treatment strategies. Three main types of endometriosis have been described in literature: peritoneal, ovarian and deep infiltrative. This is mainly due to the most common locations of ectopic endometrium. Determining the precise pathogenesis of endometriosis has proved challenging and controversial for gynecologists, endocrinologists and researchers, but recent studies have focused on finding answers. A number of pathogenic mechanisms have been suggested to be involved in the development of endometriosis, and a large number of studies have investigated the causes of its pathogenesis. This disease is often asymptomatic and diagnosed incidentally during various surgical interventions or follow-up gynecological examinations. Women with this pathology report exhaustion and depression, as with other chronic pain conditions. However, the severity of pain doesn't always reflect the severity of endometriosis. Epidemiological research reports that women with this disease are more vulnerable to ovarian and breast cancer, asthma, skin cancer such as melanoma, cardiovascular disease and inflammatory joint diseases like rheumatoid arthritis. Due to the lack of specific symptoms diagnosis is often delayed about 6-10 years from the first symptoms. According to current gynecological recommendations, the clinical examination of patients with a suspicion of endometriosis should include inspection and palpation of the abdominal cavity, vaginal speculum, vaginal vault and a two-handed gynecological examination, best complemented by a composite study. Nowadays, geneticists are in complete agreement about the primary goals of endometriosis treatment. The most important of these are the relief or complete elimination of pain, the removal of endometriosis foci, and the fight against fertility. To date, the most commonly used therapy is combination therapy,

which consists of surgical procedures such as laparoscopy, laparotomy, or cryosurgery, and adjuvant hormonal therapy, which has significantly reduced the risk of recurrence

The microbiota is a diverse ecosystem of microorganisms that reside in various parts of the human organism. Specific microbiomes can be distinguished for the oral cavity, nasal cavity, ears, vagina, gastrointestinal tract, respiratory system, hair and skin. The connection between the gut microbiota and endometriosis is nowadays highly suspected to exist. Scientists are focused on the influence of the microbiome on estrogens, estrogens-dependent disorders, immune system, and inflammation. It is strongly believed that the correction of the gut microbiota with antibiotics, probiotics, or fecal bacterial transplantation is a hopeful method for improving the clinical management of endometriosis.

**Key words:** endometriosis; microbiome; hormone therapy; surgery; chronic pain; inflammation; dienogest; endometriosis pathogenesis; endometriosis diagnosis; infertility in endometriosis; endometriosis treatment

## **Introduction**

Endometriosis is a chronic non-cancerous disease affecting women, defined as the presence of foci of endometrial tissue, both glandular and endometrial, outside its physiological location, i.e. within the uterine cavity. [1,3,4,5] Endometriosis resembles malignancies in some ways: progressive and invasive growth, estrogen-dependent growth, recurrence and metastatic tendency. It can occur as seemingly straightforward endometrial cysts, but also as deep nodular infiltrates and peritoneal implants. [3,29]. The association of endometriosis with pelvic pain and impaired fertility has been recognized since the 1920s. Three main types of endometriosis have been described in literature: peritoneal, ovarian and deep infiltrative [5].

This is mainly due to the most common locations of ectopic endometrium, which include the peritoneum of the sinus of Douglas and the vesico-uterine fold, the sacro-uterine ligament, the surface of the ovary, the rectovaginal septum and the fallopian tubes. [3, 2]. These are not the only locations of the endometrium, it can also occur in rarer locations such as the surface of the colon, bladder, uterine obturator and broad ligament, caesarean scar, upper abdomen, lungs and even the brain. [2,3,4,7] In the general population, the prevalence of this disease is between 6-15%, mainly in women of reproductive age, but also in adolescents and in 3% of postmenopausal women. Endometriosis sometimes appears in women without endometrium [22,23] and in men [22,23,24]. Endometriosis is a disease that is inherited. The risk of developing endometriosis is 6-9% greater in first-degree relatives of women with endometriosis and 15% greater if the women have severe endometriosis [25,26]. Recently, hereditary factors have been reported to account for 50% of cases of endometriosis [22,27].. Among patients, 60% have a pain syndrome and between 35-50% suffer from infertility. [2,1,4,5]. Endometriosis can lead to infertility as a result of the changes that occur in the microenvironment of the fallopian tubes and pelvis, as well as in its anatomical structure. This results in impaired oocyte development and subsequently embryo development and implantation[2,16]. In addition, 20% of women have co-existing conditions such as irritable bowel syndrome, fibromyalgia, migraine, or interstitial cystitis. [4,8] Endometriosis appears as white, red, blue, brown or black nodules, the colour of which depends on hemosiderin deposition and intrauterine bleeding. Foci of endometriosis may also be devoid of pigmentation with peripheral fibrosis, petechiae, or window-like peritoneal defects. [2,3] Increased knowledge of the physiomy of foci has resulted in an up to 2-fold increase in the diagnosis of this disease compared to recent years.

## **State of knowledge**

### **Pathogenesis and symptoms**

Determining the precise pathogenesis of endometriosis has proved challenging and controversial for gynaecologists, endocrinologists and researchers, but recent studies have focused on finding answers. Sampson's theory of retrograde menstruation is one of the most important hypotheses regarding the pathogenesis of endometriosis [17]. Endometrial cells that have been depleted migrate through the fallopian tubes into the peritoneal cavity and

adhere. Another hypothesis that is compatible with the hereditary aspects is that the endometriotic cell has undergone genetic or epigenetic changes and these specific changes determine the development of deep endometriosis. As the pathogenesis of this disorder seems to involve a number of features, including ectopic endometrial tissue, altered immunity, imbalanced cell proliferation and apoptosis, aberrant endocrine signaling and genetic factors, there is a plethora of articles reporting multifactorial causes for the development of endometriosis. Therefore, to characterize the origins and evolution of the disease, a very thorough and extensive understanding of the physiology, cytology and immunology of the uterine microenvironment is required. [18,19,28]

A number of pathogenic mechanisms have been suggested to be involved in the development of endometriosis, and a large number of studies have investigated the causes of its pathogenesis. These include physical factors such as uterine tissue damage or scarring, residual cells from menstrual blood, stem cells, the uterine microenvironment and biochemical factors such as oxidative stress, inflammation, hormones, tumor-promoting genes proteins, and vascularization [20]. Estrogen receptors have been shown to be present on the surface of ectopic endometrium and to promote endometriosis through hyperestrogenism-related conditions [3,4,13,16]. However, there are other predisposing factors for the disease, most notably age between 25 and 35 years, Caucasian race, early menarche and short and heavy menstrual cycles. [1,4,9,10] In addition, macrophages attracted by haem-shedding create a pathologic environment that can promote both endometriosis, pre-cancer and cancer lesions [9]. Autoimmune diseases may result from the prolonged stimulation of immunological factors. Although these are frequently seen in women with endometriosis, the role of autoimmunity has not been proven [21]. According to the various reports published so far, these factors, alone or combined, are considered to be causative for the development of endometriosis. Endometriosis is usually associated with symptoms such as pelvic pain, painful menstruation, pain during urination and bowel movements, abdominal and sacral pains. Moreover women may complain of cyclical sciatica-like pain in the lower limb and bleeding from the rectum or genital tract. Diarrhea alternating with constipation and frequent urination are less common but equally troublesome. This disease is often asymptomatic and diagnosed incidentally during various surgical interventions or follow-up gynecological examinations. [30,31] Up to 50% of women seeking treatment for infertility are found to have endometriosis. Women with this pathology report exhaustion and depression, as with other chronic pain conditions. However, the severity of pain doesn't always reflect the severity of endometriosis. Epidemiological research reports that women with this disease are more

vulnerable to ovarian and breast cancer, asthma, skin cancer such as melanoma, cardiovascular disease and inflammatory joint diseases like rheumatoid arthritis. [32]

## **Diagnosis**

The non-specificity of the symptoms leads to a delay in diagnosis of about 6-10 years from the first symptoms. [3, 2, 10] The diagnostic sequence begins with a detailed patient history using the Endometriosis Questionnaire and physical examination. According to current gynecological recommendations, the clinical examination of patients with a suspicion of endometriosis should include inspection and palpation of the abdominal cavity, vaginal speculum, vaginal vault and a two-handed gynecological examination, preferably supplemented by a collation [15,10]. When assessing the pelvis, the clinician should pay particular attention to the adnexa, the sinus of Douglas and the sacro-uterine ligaments. The level of pain on physical examination provides a criterion for assessing the progression of the patient's disease without the additional cost of further investigations. At the time of surgery, medical imaging should be performed, primarily transvaginal ultrasound. However, after a vaginal ultrasound scan, if there is a suspicion of deep endometriosis, a transrectal ultrasound scan, a transabdominal ultrasound scan or an MRI scan can be performed. The typical ultrasound findings are endometrial cysts with hyperechoic contents, usually with thickened walls. Cystoscopy, colonorectoscopy and transrectal ultrasonography (TRUS) are used the depth of infiltration of colorectal or bladder endometriosis in DIE [10,2,5,3]. We use TRUS when the patient is struggling with indicative symptoms such as occurring lower gastrointestinal bleeding, recurrent pain during menstruation together with functional bowel disorders, a focal lesion reaching more than 3 cm located on the posterior vaginal vault [5]. Currently, MRI has the greatest role in the diagnosis of extraperitoneal endometriosis, particularly of the rectovaginal septum, due to the high resolution and its specificity to the endometrial cysts [10,2,3,5]. We use it to determine the progression and spread of the disease process. The use of MRI in preoperative qualification allows patients to preserve a greater ovarian reserve compared with other medical imaging. However, consistently the gold standard for the diagnosis of endometriosis remains laparoscopy, which is both a therapeutic procedure and has enabled a 2-fold increase in the diagnosis of endometriosis in recent years. From the characteristic endometrial implants visible on imaging, a biopsy of the tissue should be taken for subsequent histopathological evaluation. This provides increased opportunities to

assess the degree of malignancy of the lesions as well as an unequivocal diagnosis can be made [2,5,10,3]. For this invasive diagnosis we qualify women with dyspepsia, dyschezia, painful menstruation and chronic pain when the pharmacological treatment was unsuccessful or is contraindicated. Laparoscopy is useful also in patients when the torsion or rupture of cyst of the adnexa is suspected or diagnosed with a nodular lesion of the adnexa. Moreover, one of the most important reason to qualify women to laparoscopy is infertility that is not explained by gynecological examination and medical imaging. Unfortunately, still unsatisfactory results were obtained in the study of a specific and sensitive biomarker of endometriosis, extracted from plasma, blood or urine, which in a simple and non-invasive way to make a diagnosis. In contrast, the determination of protein concentrations such as chromogranin A, interleukin-6, interleukin-8, Ca-125 and Ca 19-9 would guide further management.

## **Treatment**

Nowadays, geneticists are in complete agreement about the primary goals of endometriosis treatment. The most important of these are the relief or complete elimination of pain, the removal of endometriosis foci, and the fight against infertility. When choosing a treatment method, special attention is paid to the progression of the disease process. Taking into account the data available in the literature, it seems that the best results in the treatment of endometriosis are achieved with a combined therapy consisting of surgical laparoscopy and adjuvant hormonal therapy. Nowadays there is a wide range of hormone therapy such as gonadoliberin analogues, selective progesterone receptor modulators, aromatase inhibitors, progestogens, levonorgestrel-releasing intrauterine formulation, danazol, estrogen-progesterone preparations and progestogens Gonadoliberin is a neurohormone produced by the hypothalamus that stimulates the secretion of the It is strongly believed that the correction folitropin (FSH) and lutropin (LH). Surgical treatment may include laparoscopy, classical laparotomy or cryosurgery. The implementation of a combined method makes it possible to take advantage of the positive aspects of both treatment modalities. In patients suffering from infertility, laparoscopy has an invaluable advantage over the other methods. [33,34,35,36]

## **Surgery**

The goal of surgery is to excise or coagulate all visible lesions of peritoneal endometriosis, ovarian endometriosis cysts, deep rectovaginal endometriosis, and to restore the anatomy.

The choice of surgical treatment depends on the severity of the disease. Patients with minimal lesions and mild symptoms will be treated differently than patients with advanced endometriosis. The aspect of pain and infertility is also very important. It also needs to be considered that patients are often asymptomatic, or the pain is caused by other conditions such as irritable bowel syndrome or cystitis. [ 33,37] Surgical treatment may be divided into laparoscopy with the use of ablation or excision, classical laparotomy or cryosurgery. Ablation methods include carbon dioxide laser ablation, bipolar diathermy, and monopolar electrosurgery. Randomized controlled research have demonstrated the efficacy of ablative surgery in the treatment of peritoneal disease. Sutton et al. randomized women with stage first and second disease to either laparoscopic ablation or diagnostic laparoscopy alone. After 6 months, 62% of the laser group had an improvement in pelvic pain compared to only 22% of the control group. Patients with minimal disease had the least benefit from ablative treatment. Up to 73% of patients with mild to moderate disease achieved adequate pain relief. [38,39] Laparoscopy is a diagnostic and therapeutic method to diagnose or confirm the presence of endometriosis and is extremely useful in the diagnosis and treatment of ovarian and peritoneal endometriosis. It provides an excellent view of the pelvic cavity and allows a section to be taken for histopathologic examination. Laparoscopy is also the method of choice when endometrial cysts are found, as pharmacological treatment for this form of endometriosis is ineffective, as well as intraperitoneal adhesions that cause pelvic pain. Endometrioma is also an indication for laparoscopic ovarian cystectomy with a significantly reduced risk of recurrence. Laparoscopic surgical treatment of benign endometriosis (stage 1-2), whether by ablation or excision, has been shown to be effective in improving fertility in comparison with diagnostic laparoscopy alone. The procedure is also effective in reducing pain. Lack of improvement after removal of endometrial cysts, excision of deep foci, and removal of adhesions is an indication for anterolateral neurectomy. [34,38,40] A laparotomy is most often performed in patients who have undergone multiple surgeries in the abdominal cavity. Hysterectomy is performed mainly in patients who no longer plan to have children and whose pain, which does not respond to other treatments, significantly reduces their quality of life. Typically, the operation includes removal of all endometriosis foci and the uterus with the adnexa. Patients who have a partial hysterectomy (with preservation of the adnexa) have a higher risk of recurrence than those who have a total hysterectomy. Patients are often treated with adjuvant hormone therapy, which significantly reduces the risk of recurrence. [34,41,42]



## **Medical treatment**

The pharmacological treatment of endometriosis can be used as an adjunct to the surgical treatment. When used as the primary method of therapy, its main goal is to treat chronic pain by suppressing the inflammatory response, suppressing follicular growth to induce amenorrhea, and thereby inhibiting the development and growth of endometriosis lesions. Pharmacologic treatment includes hormone therapy and pain management. Nonsteroidal anti-inflammatory drugs are the most commonly used. Hormonal drugs suppress ovarian function and cause atrophy of ectopic endometrial lesions. Danazol, gonadotropin-releasing hormone (aGnRH) analogues, progestins, estrogen-progestin preparations, levonorgestrel-releasing endometrial formulations, gestrinone, aromatase inhibitors, selective progesterone receptor modulators are among the most commonly used hormonal preparations. [33,43,44,45]

## **The role of gut microbiota in endometriosis**

The microbiota is a diverse ecosystem of microorganisms that reside in various parts of the human organism. Specific microbiomes can be distinguished for the oral cavity, nasal cavity, ears, vagina, gastrointestinal tract, respiratory system, hair and skin. The connection between the gut microbiota and endometriosis is nowadays highly suspected to exist. Scientists are focused on the influence of the microbiome on estrogens, estrogens-dependent disorders, immune system, and inflammation. Systemic levels of estrogen in post-menopausal women have been associated with fecal microbiome richness and levels of fecal Clostridia taxa. Moreover, epithelial proliferation is highly dependent of the estrogen level, and it's proven to have an impact on incidence of endometriosis, and endometrial cancer. Gut microbiota is reported to have an significant influence on the inflammation in human body, regulator of the mediators of inflammation and apoptosis. Proteins that are involved in apoptosis are biomarkers for endometriosis. Some serum/urinary diagnostic markers, and other body fluids of women with endometriosis have been demonstrated. The aim of using these markers is to provide noninvasive diagnosis and has become an important way to diagnose the disease. The inflammatory microenvironment is closely associated with the occurrence of endometriosis. Increasing levels of inflammatory markers can lead to tissue remodeling, fibrosis, and are

responsible for increased pain, and have a strong connection to fertility. A number of changes in cytokines, chemokines and other inflammatory regulators within the peritoneum and at the lesion site have been reported in patients with endometriosis. Macrophages play an important role in the inflammatory process. Therefore, it can't be overlooked when discussing the pathogenesis of endometriosis. Researchers have established a correlation between lipopolysaccharide and macrophage stimulation, thereby promoting the angiogenesis and proliferation seen in endometriosis. [46,47,48] Yu et al. Examined the connection of the profile of the gut microbiota in patients with stage 3/4 endometriosis. They determined that the variety of the gut microbiota decreased in patients with endometriosis and the ratio of bacteria increased. *Prevotella\_7* was the most prevalent taxon in patients with endometriosis. Furthermore, the abundances of Saccharibacteria, Actinobacteria, Fusobacteria Cyanobacteria, were highly increased in patients suffering from endometriosis.[47,52] The treatment of endometriosis is a great challenge for gynecologists. Combination therapy consisting of surgery and adjuvant hormone therapy is the most effective to date, but it still doesn't minimize the overall risk of recurrence. Endometriosis leads to emotional exhaustion and impaired functioning in daily life. That's why it's so important to find a safe and effective way to prevent the disease in women. For many diseases, including endometriosis, rebalancing the gut microbiota appears to be a potential beneficial treatment. To date, correction of the gut microbiota with antibiotics, probiotics, or fecal bacterial transplantation is a hopeful method for improving the clinical management of endometriosis. [49,50,51]

#### **Authors Contribution:**

Conceptualization, HS, AM, AS; methodology, PG; check, KL and ZM; formal analysis, PG; writing - rough preparation, ZM, PB and AS; writing - review and editing, AM, PB; supervision, HS, KL, ; project administration, HS; receiving funding, AS,AM,HS,PG,PB,KL,ZM, All authors have read and agreed with the published version of the manuscript.

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