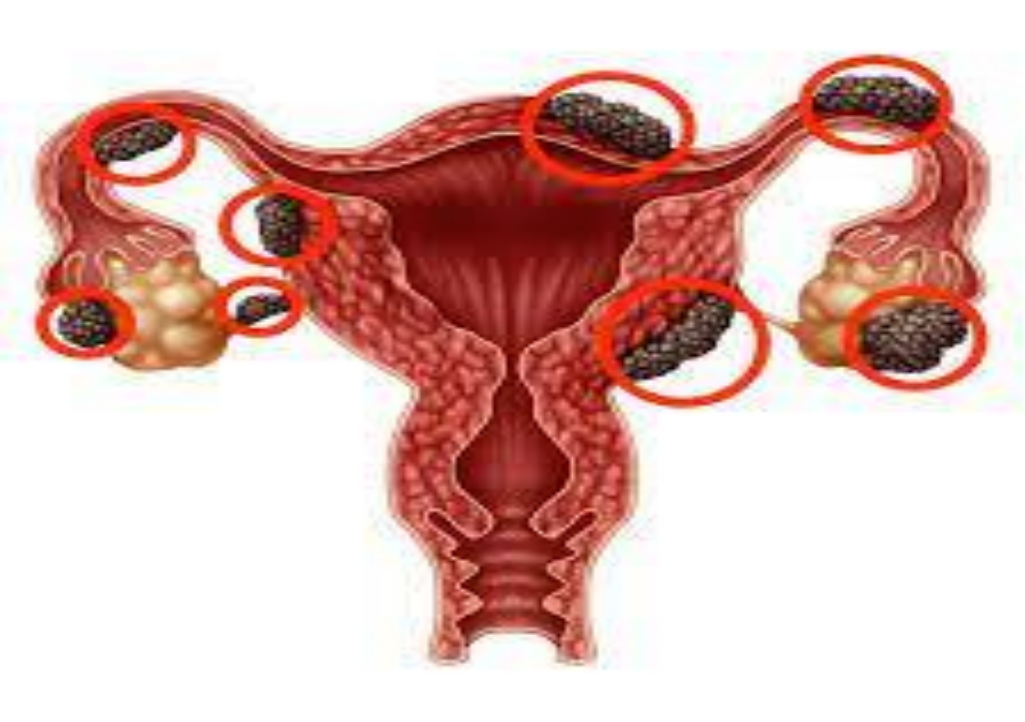
ENDOMETRIOSIS: EPIDEMIOLOGY, CLASSIFICATION, PATHOGENESIS



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Endometriosis—History

- Endometriosis is defined as the presence of the endometrium outside the uterine cavity accompanied by chronic inflammation.

Name of the Investigator	Year	Theory
Recklinghausen	1885	from Wolff wires
Cullen	1896	from Müller cables
Iwanhofen	1898	metaplasia theory—the assumption of the theory is the existence of cells capable of differentiating in the endometrium, and being precursors of the epithelium of the pelvic peritoneum
Meyer	1903	metaplasia theory—the assumption of the theory is the existence of cells capable of differentiating in the endometrium, and being precursors of the mesodermal epithelium of the ovary
Pick	1905	metaplasia theory; regarding the sexual epithelium of the ovary
Sampson	1927	"retrograde menstruation"
Halban	1924	endometrial elements can enter the peritoneal cavity by the blood or lymphatic route
Navrital i Kramer	1936	vascular spread
Javert	1949	a combination of implantation theory, transport by the blood and lymphatic routes, as well as the theory of direct penetration of the endometrium through the uterine muscle
Mc Weigh	1955	from the cells of the radial wreath of the egg
Weed i wsp	1980	failure of the immune system derived from the Müller ducts
Malick	1982	congenital or acquired weakened fibrinolytic activity of the peritoneum

Endometriosis—Epidemiology

Endometriosis is characterized by the presence of active foci of the endometrium (glandular cells and stroma) or endometrial tissue occurring outside its cavity, that is, in the muscular layer of the uterus, other genitals and their surroundings, and even in places distant from the genital organs of the body.

Endometrial foci outside the uterine cavity may appear, for example, in the peritoneal cavity, ovaries, bladder or ureters. The ectopic endometrium is functionally similar to the eutopic endometrium.

Endometriosis—Epidemiology

ENDOMETRIOSIS IS A BENIGN, ESTROGEN-DEPENDENT, GYNECOLOGICAL DISEASE; HOWEVER, DUE TO THE ACCOMPANYING AILMENTS AND CHRONIC NATURE, IT IS A VERY IMPORTANT MEDICAL, SOCIAL AND ECONOMIC PROBLEM. INFERTILITY IS A RELATIVELY COMMON SYMPTOM IN PATIENTS WITH ENDOMETRIOSIS.(UP TO 30% TO 50%)

ENDOMETRIOSIS CAN INFLUENCE FERTILITY IN SEVERAL WAYS:

DISTORTED ANATOMY OF THE PELVIS, ADHESIONS, SCARRED FALLOPIAN TUBES, INFLAMMATION OF THE PELVIC STRUCTURES, ALTERED IMMUNE SYSTEM FUNCTIONING, CHANGES IN THE HORMONAL ENVIRONMENT OF THE EGGS, IMPAIRED IMPLANTATION OF A PREGNANCY, AND ALTERED EGG QUALITY.

OFTEN, THIS INFERTILITY REMAINS UNEXPLAINED DUE TO A DELAY IN DIAGNOSIS, CAUSING SIGNIFICANT LEVELS OF STRESS.

Endometriosis—Epidemiology

Endometriosis is a common gynecological disease in the world. This disease affects from 10–15% of women of reproductive age and 35–50% of women with pelvic pain and/or infertility. , It should be noted that there are also cases of patients with endometriosis after menopause, and it also happens in adolescent women.

The vast majority of cases of endometriosis occur in women between menarche and menopause. The peak(25-45

Literature data indicate that endometriosis is found in 0.1–53% of women operated on laparoscopically or by laparotomy, of which 12–32% are women after diagnostic laparoscopy due to pelvic pain delays and 10–60% of the patient after diagnostic laparoscopy due to disability

Endometriosis—Epidemiology

Endometriosis in 7% of women is associated with their genetic predisposition in the family.

This disease was found in 2% of women undergoing tubal ligation and 17% of women after surgery to remove the ovaries.

World literature also reports the occurrence of foci of endometriosis in fetuses.

There have been isolated cases of endometriosis in men around the world who have been treated with hormones for prostate cancer.

The risk of developing endometriosis is the lowest in black women, the highest in Asian women.

▸ Endometriosis—Epidemiology

Caucasian women have a higher risk of getting sick than black women.

Endometriosis is a problem of enormous importance not only from the medical and social angles but also from an economic point of view.

The annual costs of endometriosis treatment in Europe range from 12.5 € billion to €12.5 billion depending on the country and are comparable to other chronic diseases such as diabetes.

Endometriosis—Epidemiology

Endometriosis has a significant negative impact on aspects of social life, family, and sexual, educational and professional life.

Pain and the associated dysfunction of the body worsen the quality of life and reduce professional productivity.

In cases where there is no clear cause or medication, the disease can be chronic and recurrent.

Due to its impact on sexuality and fertility, it can have a negative impact on partner relationships.

Endometriosis—Symptomatology

Endometriosis-related symptoms can affect a woman's overall health and mental and social well-being.

It causes a significant deterioration in the quality of life. In 66% of women with endometriosis, the first symptoms of the disease appear before the age of 20.

Symptoms of endometriosis include: gradually increasing acute premenstrual pain, pelvic pain, pain in the sacral region of the spine, dysmenorrhea, painful ovulation, pain during intercourse, pain when defecating, pain when urinating, pain radiating to the back, abundant irregular menstruation, blood in the stool, diarrhea or constipation, infertility and chronic fatigue.

▸ Endometriosis—Symptomatology

Patients may also experience uncharacteristic accompanying symptoms such as **sub febrile conditions, nausea, dizziness and headaches, symptoms of depression, anxiety, hypoglycemia, rectal bleeding, hematuria during menstruation or susceptibility to infections and allergies**.

The pain associated with endometriosis most often takes the form of painful menstruation. It precedes the appearance of bleeding; over time it intensifies and its location concerns the lower abdomen and deeper pelvic areas. Pain can radiate to the sacral region.

- **Endometriosis—Symptomatology**

The pain can extend beyond the bleeding period and also be present throughout the menstrual cycle.

There is a hypothesis that the intensification of menstruation soreness is associated with the involvement of the Douglas sinus and the formation of adhesions in it sometimes very advanced endometriosis may not cause any symptoms, and, paradoxically, small foci within the peritoneum can cause great pain.

Intraperitoneal adhesions or overgrowth of the fallopian gouges are the most common causes of the problem with the treatment of endometriosis.

- **Endometriosis—Symptomatology**

Sometimes foci of endometriosis produce antibodies to the eutopic endometrium, which can induce poor embryo implantation or spontaneous abortions.

Increased and profuse menstruation is one of the symptoms of endometriosis, In adenomyosis (so-called internal endometriosis).

Adenomyosis is defined as the occurrence of ectopic foci of the endometrium outside the uterine cavity.

Their effect is lower abdominal pain and abnormal menstrual bleeding. Due to its significant similarity to endometriosis, adenomyosis has so far been classified as endometriosis genitals internal, in which endometrial foci are located within the muscle membrane of the uterus.

In recent years, the distinctiveness of this disease entity has been proven, indicating differences in symptomatology, pathogenesis and treatment.

Endometriosis—Symptomatology

The cause of adenomyosis is still unknown.

This disease usually resolves after menopause.

The only effective treatment for adenomyosis remains surgery.

The range of diagnosis of adenomyosis varies between 5% and 70% of patients.

Adenomyosis is more common in multiparous women than in nulliparous women.

The average age of diagnosis of adenomyosis is between 40 and 50 years of age.

this disease can occur in young women as well as after menopause.

The pathogenesis of adenomyosis remains a mystery.

In addition to typical ailments such as menstrual pain, pain during intercourse or pain in the lower abdomen, there are also problems in partner relationships and symptoms of depressed mood .

- **Endometriosis—Symptomatology**

The time from the appearance of the first symptoms of the disease to the diagnosis is up to 8 to 10 years.

Deep infiltrating endometriosis (DIE) is defined as the presence of ectopic endometrial tissue infiltration under the peritoneum, pelvic structure, and organ walls, including the uterosacral ligaments, rectosigmoid colon, vagina, rectovaginal septum, bladder, ureter, and lateral parametrium (LP).

DIE may cause pelvic pain and thus negatively affect the function of different structures. Studies indicate that women with DIE may have dysfunctions of the pelvic floor muscles (pfms) and lower limb muscles (llms). Pain was associated with PFM hypertonia and difficulty in PFM relaxation .

Endometriosis—Symptomatology

The presence of lateral parametrial endometriosis (LPE) can be considered a reflection of a more severe disease, ureteral stenosis and dilatation, and voiding dysfunctions, mainly because of the involvement of the inferior hypogastric plexus.

Patients with LPE reported more frequent constipation and voiding symptoms. . Associations exist between lpe and straining to void, the feeling of incomplete emptying, intermittency, and abnormal residual urine and bladder outlet obstruction.

LPE might stimulate sympathetic fibers of the pelvic plexus, promoting an increase in urethral sphincter tone and thus leading to different degrees of outlet obstruction.

These findings emphasize the importance of obtaining a focused history and objective evaluations of urinary and rectal function in patients presenting with clinical or instrumental findings suggestive of DIE.

Risk Factors for Endometriosis

- **EARLY MENARCHE—EPIDEMIOLOGICAL** STUDIES ANALYZING THE CYCLE OF WOMEN WITH ENDOMETRIOSIS HAVE SHOWN THAT THE EARLY FIRST CYCLE (BEFORE THE AGE OF 11) IS ASSOCIATED WITH THE RISK OF ENDOMETRIOSIS.

  SHORTER THAN 27-DAY GENITAL CYCLES, GENITAL DEFECTS, INCLUDING HYMEN OVERGROWTH OR NARROWING OF THE CERVICAL CANALTHE RISK OF ENDOMETRIOSIS IS INCREASED IN WOMEN WITH SHORT CYCLES, I.E., LASTING LESS THAN 27 DAYS, BUT IS UNRELATED TO THE NUMBER OF BLEEDING DAYS AND THE VOLUME OF MENSTRUATION .

  LOW BMI

  SMALL NUMBER OF BIRTHS

  CAUCASIAN RACE

  AGE 25–29

  DAILY CONSUMPTION OF ALCOHOL IN THE AMOUNT OF AT LEAST 10 G PER DAY

  ENDOMETRIOSIS IS MORE OFTEN DIAGNOSED IN INFERTILE WOMEN WHO ARE ACTIVE SMOKERS AND WHOSE BODY MASS INDEX (BMI) IS NORMAL OR LOW

Theories of the Formation of Endometriosis

The theory of samson is more widespread. It says that the foci of endometriosis arise as a result of the displacement of menstrual blood into the peritoneal cavity through the fallopian tubes.

Mayer's theory, which says that peritoneal cells are transformed into muller-type cells under the influence of hormones .

the last theory is, in the light of two previous theories, that endogenous biochemical and immunological factors responsible for the non-functioning of endometrial factors are not being used for endometrial systems.

- **Cytokines associated with the development of endometriosis.**

Immune Factor	Role in Endometriosis
TNF-α	Increasing vascular permeability and transformation of inflammatory factors in the peritoneal cavity, which exacerbate peritonitis
NF-κB	Controlling gene expression associated with immune response, cellular proliferation, and cytokine production
MCP-1	Stimulation of monocytes to migrate from peripheral blood to the peritoneal cavity to turn into macrophages, leading to local inflammation
IL-1β	Induction of VEGF and COX-2 expression leading to the progression of endometriosis
IL-6	In the tide to impair the function of NK cells (natural *killer*) by regulating the protein expression of tyrosine phosphatase (SHP-2) in endometriosis
IL-10	In a mouse model with induced endometriosis, inhibition of IL-10 activity was found to be helpful in reducing lesions
IL-15	In normal endometrial cells, ovarian steroid hormones control the production of IL-15. Endometriotic cells in patients with endometriosis show higher concentrations of this cytokine in endometrial patients
IL-16	Higher concentrations of IL-16 in women with endometriosis are associated with the development of the disease by stimulating the secretion of IL-6, TNF-α and IL-1β. IL-16 polymorphisms are associated with women's susceptibility to the development of endometriosis and its severity
IL-17A	In endometriosis, IL-17A is expressed in endometrial lesions, and therefore the inflammatory environment of the peritoneal cavity of patients with endometriosis may be associated with the production of IL-17A

- **Cytokines associated with the development of endometriosis.**

Immune Factor	Role in Endometriosis
IL-18	IL-18 regulates the production of TNF-α and IL-8, acts as a potent angiogenic factor, and also regulates the intercellular expression of adhesion molecule 1 through NFκB and may increase MMP production. IL-18 is a major regulator of the immune response process in a wide range of cells that decreases in both eutopic and ectopic endometrium in endometriosis
IL-27	IL-10 + Th17 stimulate the proliferation and implantation of ectopic lesions and accelerate the progression of endometriosis, making IL-27 a key regulator in endometriotic lesions
IL-33	Member of the IL-1 family. IL-33 induces the synthesis of Th2-type cytokines through its orphan receptor ST2. Increased IL-33 expression has been correlated with fibrotic disorders such as skin scleroderma, liver and lung fibrosis, making IL-33 a key profibrotic mediator
IL-37	Increased levels of IL-37 expression in eutopic and ectopic endometrium in women with stage III-IV ovarian endometriosis may be involved in inflammatory processes leading to endometriosis

Another important factor in the pathogenesis of endometriosis is the disturbed balance between type 1 (th1) and type 2 (th2) helper lymphocytes.

Activated T cells differentiate into th1 lymphocytes and th2 lymphocytes. The main function of th1 is the production of cytokines and the promotion of cell-type responses, whereas th2 secretes cytokines involved in the differentiation of B lymphocytes, suppression of cell-type responses, as well as the severity of humoral type responses.

According to literature data, th2 lymphocytes gain an advantage in women with endometriosis.

PATHOGENESIS OF ENDOMETRIOSIS

IN WOMEN WITH ENDOMETRIOSIS, REDUCED NATURAL KILLER (NK) CELL ACTIVITY IS FOUND. THIS IS THE MAIN GROUP OF CELLS OF THE IMMUNE SYSTEM RESPONSIBLE FOR THE PHENOMENON OF NATURAL CYTOTOXICITY. IMPAIRED FUNCTION OF NK CELLS REDUCES THEIR ABILITY TO CLEANSE THE PERITONEAL CAVITY OF ENDOMETRIAL ELEMENTS AFTER RETROGRADE OUTFLOW OF MENSTRUAL BLOOD. THE FORMATION OF NEW VESSELS IS A NECESSARY CONDITION FOR THE DEVELOPMENT OF THE ECTOPIC ENDOMETRIUM, ESPECIALLY IN THE PERITONEAL MICROENVIRONMENT. NEO-ANGIOGENESIS IS ACCOMPANIED BY THE FORMATION OF NERVES, WHICH MAY EXPLAIN THE PAIN IN PATIENTS

Vascular endothelial growth factor (VEGF) is responsible for the formation and growth of new vessels. In women with endometriosis, elevated concentrations of VEGF in peritoneal fluid and its correlation with the stages of the disease were found

Types of Endometriosis

There are several types of endometriosis:

- ovarian endometriosis—occurs in the form of superficial lesions and as endometrial cysts,
- peritoneal—can occur in various forms: white raids on the peritoneum, peritoneal defects, red, brown, black-blue and black foci, colorless bright vesicles and focal dilated blood vessels and petechiae,
- deep infiltrating endometriosis—die,
- endometriosis of other locations.

▸Classifications of Endometriosis:

According to sampson
internal endometriosis affecting the uterine muscle
external endometriosis occurring outside the uterine muscle
divisions of endometriosis by location were developed according to the classification of martius and kistner

Types of divisions of endometriosis by location

According to the Classical Classification of Martius	According to Kistner's Classification
	1. Overlapping peritoneal endometriosis
	Ovaries
	serous membrane of the uterus
- endometriosis genitalis interna (adenomyosis) is present in the uterus or the Fallopian tube	uterine ligaments
	Fallopian tubes
- endometriosis genitalis externa (in the remaining parts of the reproductive organ)	large intestine, thin intestine, appendix
	2. Retroperitoneal endometriosis
- endometriosis extragenitalis (endometriotic lesions are present outside the reproductive organs)	inguinal regio
	neck, vagina, vulva, perineum
	drainage pathways
	pleural and lungs
	skin, skeletal muscles, limbs

▸Classifications of Endometriosis:

THE CLASSIFICATION DEVELOPED BY THE AMERICAN SOCIETY OF REPRODUCTIVE MEDICINE (ASRM), **BASED ON THE RESULTS OF LAPAROSCOPY OR LAPAROTOMY**, IT IS THE MOST COMMON SYSTEM USED IN CLINICAL PRACTICE.

THE MOST IMPORTANT GOAL OF CLASSIFYING AND DETERMINING THE SEVERITY OF ENDOMETRIOSIS IS TO PROPOSE AN EFFECTIVE TREATMENT PLAN FOR IT.

THE ENZIAN SCALE IN DEEPLY INFILTRATING ENDOMETRIOSIS IS A DESCRIPTIVE SCALE, CONSIDERING BOTH THE EXISTENCE OF THE LESION AND THE DEPTH OF THE INVASION. IN THE ENZIAN CLASSIFICATION, THE LOCATION OF FOCI WAS ASSIGNED TO SEPARATE ANATOMICAL COMPARTMENTS .

▸Classifications of Endometriosis:

- **Compartment a—foci** located in the vagina and the rectovaginal septum,

- **compartment b—foci** located in the sacro-uterine ligaments up to the pelvic walls

,

- **compartment c—foci** located in the sigmoid colon and rectum.

This classification also describes the foci of the ectopic endometrium depending on the place of their occurrence as: fa—adenomyosis, fb—urinary bladder endometriosis, fu—ureter endometriosis, fi—endometriosis of the bowel wall above the sigmoid colon, fo—infiltration of other anatomical structures, e.G., Abdominal integuments.

▸ Diagnostics

Histopathological examination clearly allows for the diagnosis of endometriosis.

a good medical history, gynaecological examination with specula, two-handed examination, additional diagnostic tests using imaging techniques, laparoscopy and biochemical tests are helpful in the initial diagnosis of the disease.

The basic examination in the diagnosis of endometriosis is an ultrasound examination.

Diagnostics

Ultrasound examination (ultrasonography, USG) is helpful in the diagnosis of **endometrial cysts of the ovary and of congenital defects of the reproductive organs** favoring the retrograde outflow of menstrual blood into the peritoneal cavity .

In the case of endometriosis infiltrating the urinary bladder or the large intestine, it is justified to perform cystoscopy, colonorectoscopy and transrectal ultrasound examination

.In the case of **deeply infiltrating endometriosis**, **the rectal water contrast transvaginal sonography** (RWC TVS) is also appropriate. The water contrast allows us to detect foci in the intestinal area and assess their progression.

Diagnostics

Transperineal ultrasound is a reliable and non-invasive tool for assessing pelvic floor morphometry

it is also helpful to have a magnetic resonance imaging (MRI) examination, but the ultrasound examination is the basic tool in the diagnosis of this disease.

, The gold standard in the diagnosis of endometriosis is laparoscopic surgery, with simultaneous confirmation in histopathological examination

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REVIEW

Endometriosis after menopause: physiopathology and management of an uncommon condition

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ABSTRACT

Endometriosis is a hormone-dependent inflammatory disease that is usually characterized by infertility and pain symptoms. This disease mainly occurs during the reproductive years and is rarely diagnosed after menopause. We discuss the physiopathology of this condition after menopause as well as treatment options and the risk of malignant transformation. Occurrence or progression of postmenopausal endometriosis lesions could be related to extra-ovarian production of estrogen by endometriosis lesions and adipose tissue, which becomes the major estrogen-producing tissue after menopause. Postmenopausal women with symptomatic endometriosis should be managed surgically because of the risk of malignancy; medical treatments can be used in cases of pain recurrence after surgery. Aromatase inhibitors act by decreasing extra-ovarian estrogen production and by blocking the feed-forward stimulation loop between inflammation and aromatase within endometriosis lesions. The evidence is currently insufficient to support a conclusion about the optimal hormone replacement therapy for women with endometriosis. The question of malignant transformation of endometriosis in response to hormone replacement therapy in women with a history of endometriosis remains unanswered and needs a long-term follow-up study to evaluate the risk of an adverse outcome. Further studies should be performed to determine the optimal management of menopausal women with endometriosis.

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