Endometriosis

Learning Objectives:

By the end of this lecture, you need to:

1- Define endometriosis.
2- Demonstrate the most common site of its occurrence.
3- Enumerate the various presenting features of this gyn. problem.
4- Relate this disease with female infertility.
5- Know how to investigate women who suspect to have this disease.
6- Discuss the method of treatment of each type of this health problem.

Definitions:

■Endometriosis is the presence of endometrial glands and stroma (glandular and stromal elements of the endometrium, both must be present for the dx*)* outside the lining of the uterine cavity.

■ Endometriosis is primarily a pelvic disease with implants in the ovaries, the fallopian tubes, uterosacral ligaments, recto-sigmoid, bladder, and appendix. Less commonly, endometriosis can be found outside the pelvis, suggesting a metastatic spread.

■ It is one of the benign gynecological conditions. Generally benign disease usually affects women in their reproductive years. However, there have been several case reports of adenocarcinoma developing within foci of endometriosis.

Incidence:

- 10-15% of women presented with gynecological symptoms have the condition.

This estimate of prevalence is usually made on identifying the lesions at Laparoscopy undertaken for pain or subfertility investigations.

- Sometime seen in asymptomatic women at the time of laparoscopic sterilization.
- Can be seen in 30-40% of patients with infertility.
- Usually regresses following menopause and not usually found prior to menarche.
- No differences among ethnic groups.
- Genetic predisposition 6-7% increased risk with history of first degree relative**.**
- lesion can be very small 2-3 mm, or can be extensive, in some cases completely obliterating the normal anatomy of the pelvis.

Risk Factors for Endometriosis:

- Increasing age (up to menopause), but mostly seen between 20-40.
- Shorter menstrual cycle length (less than 27 days).
- Longer duration of menstrual flow (greater than 7 days).
- Heavy menstrual flow.
- Delayed childbirth.
- Low or no parity, the relation with fertility??? Pregnancy is protective.
- First-degree relative (mother, sister, daughter) with endometriosis, 7×Higher
- Social and economic factors

Pathogenesis:

- Cells exhibit a pattern of hormone responsiveness, has cyclical changes.
- Unlike the normal endometrium, they don't have an order blood supply, but there is an in-growth

of new capillaries. Cyclical bleeding can occur within, and from, the endometriotic deposits and this contribute to a local inflammatory reaction. With healing and subsequent fibrosis overlying peritoneal damage will lead to adhesions between associated organs.

- Ovarian implant lead to formation of chocolate cyst or endometrioma, where localized bleeding cannot be discharged from the body, continuous absorption of some of fluid content lead to tarry chocolate material.
- Rupture of the cyst lead to scattering of their contents and dissemination of endometrial cells. This lead to peritoneal reaction to the material with adhesion and fixation.
- Various forms include: lesions, nodules, polyps and cysts ranging in size from microscopic to >10cm.
- Common sites: ovaries, fallopian tubes, ligaments supporting the uterus and other surfaces of the uterus, cul-de-sac, uterosacral ligaments & broad ligaments.
- Less common sites: GI tract, urinary tract, external genitals and rarely disseminates to distant organs as CNS, extremities, skin, eye, nasal mucosa, episiotomy scars. It can occur in almost every organ.

Etiology:

The precise etiology remains unknown, several theories explain the process but no single one can explain the location of endometriotic deposits in all the sites reported.

Theories of pathogenesis:

- Transplant of endometrial tissue via retrograde menstruation: **(*Sampsons theory*)**

Retrograde flow of menstrual debris which contains viable endometrial glands and tissue through the fallopian tubes causes the endometrial cells to spread into the pelvis, form implants there.

■Clinical evidence: Endometriosis is commonly found in dependent portions of the pelvis, most frequently on the ovaries, cul-de-sac, and uterosacral ligaments. In addition, patients with outflow obstruction (e.g., mullerian anomalies) have a significantly increased risk of endometriosis.

- Coelemic metaplasia : transformation of embryonic tissue (Ivanoff &meyer theory). There is a common origin of the cells lining the Mullerian duct, the peritoneal cells and the cells of the ovaries. These cells may undergo de-differentiation back to their primitive origin and then transformed into endometrial cell.

The transformation of coelomic epithelium into endometrial cells results from some yet-unspecified stimuli may be hormonal stimuli of ovarian origin by as yet unidentified chemical substances liberated from uterine endometrium, or those produce from inflammatory irritation. This theory explains endometriosis reported in: Prepubertal girls, women who have never menstruated and men.

- Lymphatic or vascular transport:

Endometriosis at sites distant from the pelvis may be caused by vascular or lymphatic transport of endometrial fragments. This could explain the presence of endometriosis at distant sites such as the brain, joints, skin and lungs.

- Genetic and immunological factors:

The relative risk of endometriosis is 70% in siblings, compared with 1% in control groups. An altered immunologic response may be involved in the pathogenesis of endometriosis with racial difference as the incidence is more in oriental than Afro- Caribbean origin. Immune mechanisms supported by that not all women with seeding of menstrual debris into the pelvis develop endometriosis.

Environmental factors:

■ It has been suggested that the prevalence of the disease has been increased in the recent year which may be link to environmental pollution. A possible link between endometriosis and exposure to dioxin, an environmental toxin, found in humans through pesticides in diet, or airborne dioxin released by

certain types of waste incineration. It has been found that endometriosis increased in rhesus monkeys, the higher the dose of dioxin, the more severe the monkey's endometriosis.
However apparent increase of the disease may be reflect the greater use of diagnostic laparoscopy to investigate pain symptoms. There appear to be no relation between the extent of the disease process seen at laparoscopy and the patient's age or symptoms.

Histological subtypes:

Endometrial deposits-correlation between histological, morphological and functional activity:

Histological subtype	Components	Hormonal response	Laparoscopic appearance
Free (polypoidal cauliflower-like structure). Grow along the surface .Very sensitive to hormones suppressive therapy.	Surface epithelium glands and stroma	Proliferative, secretory& menstrual changes. Highly responsive to alteration in Oestrogen secretion.	Haemorrhagic vesicle/ bleb
Enclosed At this stage, the implant has been covered with a surface layer of peritoneum so located within the tissue. React in a similar way as basal endometrium and partly respond to hormonal treatment	glands and stroma	Proliferative,variable secretory changes , no menstruation	Papule & later nodule
Healed Have features of cystically dilated glands. Insensitive to hormonal therapy	Glands only	No response	White nodule or flattened fibrotic scar
Ovarian endometriosis Presented as superficial form with haemorrhagic lesion or as enclosed haemorrhagic cyst **Endometrioma**: means endometriotic or (Chocolate cyst) of the ovary. Formed by lesion from outer surface of the ovary and with growth, there is inversion of ovarian cortex and with increase inflammatory reaction it become occluded	Wide variation in the presence of endometriotic tissue, the cyst wall can be lined by free endometrial tissue. In long standing endometrioma, the cyst wall becomes covered only by thickened fibrotic reactive tissue, no specific features of glandular or stromal tissue.		Superficial haemorrhagic lesion, red vesicles, blue black (powder-burn) lesion with adhesion formation or endometrioma

ملاحظة : الجدول اعلاه للاطلاع

Diagnosis:

History and physical examination may be suggestive of endometriosis, but the only way to diagnose the condition is by visualization at surgery (usually laparoscopy) and by biopsy of implants. Clinical diagnosis is usually made following the laparoscopic observation of haemorrhagic or fibrotic lesions in the peritoneal or the serosal surface of various pelvic organs.

A. History. The patient might have one or more of the characteristic symptoms. A history of endometriosis in the patient's mother or sister is also important.

Symptoms: they are variable**,** depending on the site. But sometime there is a lack of correlation between apparent extent of the disease and the intensity of the symptoms.

1- Pain: three common types of pain in endometriosis:

a. Dysmenorrhoea. Spasmodic dysmenorrhoea (menstrual pain secondary to an anatomic pelvic abnormality) is the most common symptom of endometriosis. The painful menses usually develop after years of relatively pain-free menses.

b. Chronic pelvic pain. Pelvic pain for more than 6 months (diffuse or localized in the pelvis) is considered chronic. However, many women with endometriosis are asymptomatic, and the degree of endometriosis often does not correlate with the existing amount of pain, it also may associate with low backache &lower abdominal pain.

c. Dyspareunia. (Deep dyspareunia) Painful intercourse may be caused by:

i- Endometrial implants of the uterosacral ligaments.

ii- Endometriomas of the ovaries.

iii- Fixed retroversion of the uterus secondary to endometriosis and adhesions**.**

● **Pathogenesis of pain in endometriosis.**

a. Lesions of the peritoneum can cause scarring and retraction of the peritoneum. They may also transmit pain through somatic afferent pain fibers.

b. Pain may result from elevated prostaglandins and histamines in endometriotic tissues and peritoneal fluids. Use of prostaglandin synthetase inhibitors may help many women with endometriosis.

2- Infertility and endometriosis:

● Endometriosis has been demonstrated by laparoscopy in as many as 30 to 40% of women who are infertility. No sufficient evidence supports the fact that minimal endometriosis is associated with infertility and that treating minimal endometriosis laparoscopically enhances fertility. Exactly how minimal endometriosis causes infertility is still under investigations. How endomtetriosis could impaired fertility due to:

i. Ovarian function: Oocyte maturation defect, endocrinopathies, luteinized unruptured follicle syndrome (which the ovum is trapped in the follicle and not released with the luteinizing hormone (LH) surge), altered prolactin released & anovulation.

ii. Fallopian tubes: Impaired fimbrial oocyte pick-up, altered tubal motility & tubal blockage.

iii. Coital function: Deep dyspareunia – reduce coital frequency.

iv. Sperm function**:** Antibodies causing inactivation & Macrophage phagocytosis.

v. Early pregnancy failure: Prostaglandin induced, Immune reaction & luteal phase deficiency**.**

3- Associated Symptoms.

a. Urinary. Urinary symptoms are common in patients with endometriosis; as many as one third of patients with endometriosis have urinary tract involvement including, bladder, lower ureter, upper ureter, and kidney. Symptoms range from intermittent dysuria, frequency, and urgency to complete ureteral obstruction. Gross or microscope hematuria is present in many patients and frequently follows the menstrual cycle.

b. Gastrointestinal. 7-35% of all women with endometriosis have bowel involvement. Symptoms may vary from dyschezia (pain on defecation) and hematochezia (bloody bowel movements) to other symptoms of partial or complete bowel obstruction, may need radiographic evaluation of the bowel with barium contrast to exclude other causes.

B. Pelvic examination. The pelvic examination in minimal endometriosis is usually normal.

- Uterosacral ligament tenderness and nodularity is very specific to endometriosis

Nodularity and tenderness of the uterosacral ligaments are characteristic findings on rectovaginal examination.

- Tenderness/nodularity in cul-de-sac
- Adnexal tenderness : Endometriomas "chocolate cysts" are palpated as adnexal masses often fixed to the lateral pelvic walls or to the posterior cul-de-sac with tenderness.
- The uterus is often in a fixed retroverted position. (Obliteration of the cul-de-sac occurs with fixed uterine retroversion implying severe disease).
- Cervical excitation.

C. Laparoscopy and the classification of endometriosis:

Laparoscopy : is the golden standard mean of diagnosis and could be of help as therapeutic tool also.

1. Appearance:

- The classic endometriotic implant: is characterized as brown or black pigmentation (powder-burn lesion) and fibrosis.
- "Atypical" or "subtle" lesions: Lesions ranging from clear vesicular, white opacified, glandular, polypoid, or red hemorrhagic vesicles have been increasingly apparent on laparoscopy and confirmed by biopsy to be endometriosis. Recent studies also suggest that these early implants may be the most metabolically active.
- Tissue damage: Endometriosis may cause deep tissue damage, resulting in local scarring and reduplication of peritoneum and leading to surface peritoneal defects.

2. Staging of endometriosis:

The extent of formation of classic lesions, ovarian involvement, and adhesive disease is classified

First stage: Minimal disease --small amount of brownish, reddish,blue-black, white, or clear implants.

Second stage: Mild disease -- deeper and more numerous than stage one.

Third stage: Moderate disease -- many deep implants, small endometriomas on ovaries and some filmy adhesions.

Fourth stage: Severe disease -- many deep implants and dense adhesions, large endometriomas on ovaries, rectum may adhere to the back of the uterus.

D. Pelvic ultrasound: to detect endometrioma of the ovary.

E. CA 125: is a glycoprotein expressed on the cell surface of some coelomic epithelium (including endometrial tissue), elevated levels found in women with endometriosis, shouldn't be used for screening but may correlate with patient's response to treatment and its elevated in other benign conditions - early pregnancy, acute pelvic inflammatory disease, uterine fibroids, and menstruation. This test is useful as marker for response to treatment or recurrence but not as a diagnostic test because it lacks specificity

F. Other Imaging technique: include CT scan and MRI.

Differential diagnosis:

Chronic salpingo-oophoritis.
Corpus luteum cyst or neoplastic cyst.
Uterine leiomomas.
Malignant diseases of the ovary, or metastases on pelvic peritoneum.
Carcinomas of the cervix or vagina.
Bowel malignancy.
Any case of acute abdomen.
All cases of intestinal obstruction.
All tumour of umbilicus.

Hernia and any swelling in the inguinal canal.
All causes of haematuria.

Treatment:

a. General considerations. Age of the patient, extent of disease, duration of the infertility, and severity of symptoms are important considerations. The patient's reproductive plans should also be taken into account. Pregnancy tends to alleviate the symptoms of endometriosis.

b. Expectant treatment.

Expectant therapy may be appropriate in young women who have pelvic pain with apparent endometriosis on laparoscopy and no immediate interest in pregnancy. Goals are relief of the dysmenorrhea and prevention of further growth of endometriosis. So it's of help in cases of:

- Small multiple lesions with few symptom
- Newly married women
- Endometriosis with pregnancy

c. Medical therapy: Ectopic endometrium responds to cyclic hormone secretion in a fashion similar to normal endometrium. Hormonal suppression of menses constitutes the basis of medical therapy.

1- Nonsteroidal anti-inflammatory drugs (NSAIDs). The prostaglandin synthetase inhibitors are effective in controlling endometriosis-related dysmenorrhea. Women with endometriosis show increased concentrations of prostaglandins in the peritoneal fluid. When (oral contraceptive pills) OCPs and NSAIDs are administered simultaneously, they have a synergistic effect. NSAIDs, Inhibit prostaglandins produced by endometrial implants, Begin 1 to 2 days before the onset of menses and continue for the duration of menstrual cycle.

2- Oral contraceptive pills (OCPs). Continuously administered OCPs for up to 6 months are appropriate for mild disease because they reduce the amount of endometrial buildup and shedding, thereby preventing further growth of endometriosis, it produces a pseudopregnancy state with amenorrhea and causing decidualization and resorption of the ectopic endometrium. This treatment is appropriate only in mild endometriosis that does not produce much distortion of the pelvic anatomy by adhesions or endometriomas.

3- Progestins. Suppress ovarian function and cause atrophy of endometrial implants,
Depo-Provera –IM every 3 months, and dydrogesterone given on continues base to produce pseudo-decidualization of the endometrium and comparable changes in endometriotic lesion.

Visanne: it is a 2 mg dienogest, is a new drug for treatment of endometriosis for a period of around 15 months.

Side effects of progestins– Breakthrough bleeding, depression, nausea, bloating & breast tenderness.

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4- Danazol. synthetic isoxazol derivative of 17 alpha-ethinyl testosterone consistently improved symptoms of endometriosis. It has been now replaced by the GnRH agonists because of its side effects, it eliminates midcycle surge of LH and FSH, decreasing estrogen and progesterone; creates high androgen – low estrogen state Side effects –are androgenic type; weight gain, greasy skin and acne. Prolong use will affect lipid profile or liver function. Its use now had been restricted because of possible association with ovarian cancer.

5- Gestrinone: Synthetic trienic, 19 norsteroid with androgenic and antigonadotrophic effect, causing progressive endomometrial atrophy.

6- Gonadotropin-releasing hormone (GnRH) agonists. These agents are the most commonly used method for medical treatment of endometriosis:

a- Mode of action. GnRH is a decapeptide that controls the release of the anterior pituitary hormones (FSH & LH). Normally, the release of GnRH is pulsatile. Chemical alterations of the amino acids at positions 6 and 10 produce synthetic derivatives of GnRH (GnRH agonists) that

resist cleavage by endopeptidases but retain a high affinity for the pituitary GnRH receptor. If the gonadotrope is exposed to GnRH for a prolonged time, downregulation and desensitization occur, and gonadotropin secretion is suppressed.

b- Administration. GnRH agonists may be administered intranasally, subcutaneously, or intramuscularly daily or as a depot injunction every month or every 3 months.

c- Adverse effects. Menopausal-type symptoms (e.g., hot flashes, decreased libido, vaginal dryness, and headaches) occur because of the hypoestrogenic state. Prolonged use (more than 6 months) may result in significant bone loss, leading to osteoporosis. Using "add-back therapy" (estrogen and progestin) may minimize bone loss.

d- Prognosis. Amenorrhea and atrophic endometrial changes occur in most patients. Regression of endometriotic lesions occurs in 80% of cases, and symptomatic relief results in more than 50% of cases after 6 months of therapy. However, recurrence rates are 25 to 30% per year after therapy is discontinued.

d- Surgical therapy. It is used when medical therapy does not dissolve adhesions or eliminate endometriomas. The success of surgery in relieving infertility is directly related to the severity of the endometriosis.

- Conservative surgery involves the excision, fulguration, or laser vaporization of endometriotic tissue. The excision of ovarian endometriomas; and the resection of severely involved viscera.
- Radical surgery involves a total hysterectomy and bilateral salpingo-oophorectomy.

This approach is used in patients who do not desire future fertility or those whose endometriosis is so severe.

- Estrogen replacement therapy is important in patients who undergo radical surgery to prevent osteoporosis and premature aging of the cardiovascular system.
- Pre-sacral neurectomy has been used to treat severe dysmenorrhea.

Recurrences

- May recur with medical therapy or surgical therapy
- GnRH agonists or Danazol-Minimal disease – 37%, severe disease – 74%
- Surgery – 40% after 5 years
- 56% of all patients after 7 years
- Possibility of adenocarcinoma in endometriosis??

Adenomyosis: When the endometrial tissue present in the myometrium, response to ovarian hormones is limited, because the adenomyoma is composed of basal type of endometrium which is normally insensitive to an endocrine stimulus.

To be differentiated from fibromyoma, adenomyoma has no capsule and cause diffuse enlargement of the uterus; while the myoma is localized nodule.

■ Mechanism of origin:
- down growth from the basal layer of the endometrium
- venous and lymphatic spread can also explain

■Presentation:
- usually multiparous and diagnose in their late thirties or early forties
- menorrhagia 75%
- progressive enlargement of the uterus, diurnal frequency, heaviness in the pelvis
- dysmenorrhea 30%. Increasingly severe spasmodic dysmenorroea

■ O/ E:

- enlarge tender uterus, mobile, rarely the uterus more than 12-14 wks.

■ Investigations:

- US: may be helpful which show alteration in the echogenicity within the myometrium from the localized haemorrhage filled the distended endometrial glands.
- Hysteroscopy: may help in the diagnosis
- MRI: now have a role and regarded as the investigation of choice.

■Treatment:

- Occasionally hormonal treatment as Gestrinone, Danazol and GnRHa could be of help as any treatment which could induce amenorrhoea would be of help, but symptoms are returned rapidly once treatment stop.
- If symptomatic, surgery which is the only method making the diagnosis certain, hysterectomy is the method of choice (because we can't remove the mass alone).

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