25

Endometriosis and Adenomyosis

ENDOMETRIOSIS

Endometriosis is a common benign gynecological disease affecting women of reproductive age group. It causes pelvic pain and infertility.

DEFINITION

Endometriosis is defined as the presence of functional endometrium (both endometrial glands and stroma) outside the uterus. It was described for the first time by von Rokitansky in 1860.

Prevalence: The prevalence varies form 5–20% (average 10%) in women of reproductive age group but is much higher, being 30%, in women with infertility and 15–30% in women with chronic pelvic pain. Incidence seems to be rising probably due to more use of laparoscopy which detects early cases too.

ETIOLOGY

Endometriosis is an enigmatic disorder which is also called disease of theories as no one theory can explain all cases. The following theories have been proposed to explain its etiology.

1. **Sampson's theory of retrograde menstruation:** John Sampson from USA after pioneering work on endometriosis (he operated his patients during menstruation and saw blood coming out through fimbrial ends) postulated in 1927 that endometriosis occurs due to retrograde flow of fragments of endometrial tissue through the Fallopian tubes into the peritoneal cavity. These refluxed endometrial fragments are viable, and invade the peritoneal mesothelium and develop a blood supply for their survival and growth. The supporting evidence comes from experiments in baboons, where surgical obstruction of outflow tract induces endometriosis and from the high prevalence of endometriosis in women with outflow tract obstruction (cervical atresia or vaginal agenesis) retrograde menstruation occurs. The theory also explains the presence of endometriosis in dependant parts of pelvis (the ovaries, pouch of Douglas, uterovesical peritoneum, uterosacral ligaments, posterior surface of uterus, posterior leaf of broad ligaments and rectosigmoid). However, retrograde menstruation can be observed in 90% women with patent tubes if laparoscopy is performed during menstrual time but only 5–10% develop endometriosis. Hence, other factors play a role in its etiology.
2. **Coelomic Metaplasia Theory:** This theory was proposed by Meyer and Ivanoff in 1919. It suggests that parietal peritoneum being pluripotent can undergo metaplastic transformation to functional endometrial tissue on repeated exposure to hormonal or infectious stimuli. Epithelium of the ovary, endometrium and peritoneum all arise from the same totipotent coelomic epithelium. This theory explains the development of endometriosis at unusual sites and in women with primary amenorrhea with absence of functional uterus, and in premenarchal girls.
3. **Stem cell theory:** According to this theory, undifferentiated endometrial cells which initially are present in the basalis layer of endometrium may give rise to endometriosis when displaced to an ectopic location (e.g. peritoneum). These cells have the potential to develop into epithelial, stromal or vascular cells causing endometriosis.
4. **Lymphatic and vascular spread (metastasis) theory (Halban's theory):** According to Halban (1924), menstrual fragments with endometrial cells enter the lymphatic and vascular channels and can implant in distant organs and sites. This theory can explain the presence of endometriosis at distant and unusual

sites like skin, umbilicus, bowel wall, pleura, lungs, ovaries, endocardium, pelvic lymph nodes and retroperitoneum.

5. **Immunological theory:** Retrograde menstruation is very common (90%) but only few women (< 10%) develop endometriosis. Normally refluxed menstrual endometrium is cleared from peritoneal cavity by macrophages, natural killer (NK) cells and lymphocytes preventing development of endometriosis in majority of cases. However, in some women with immune system dysfunction (decreased NK cells and macrophages), there is reduced immunological clearance of refluxed endometrium from peritoneal cavity, causing endometriosis.

6. **Genetic theory:** Although there is no genetic inheritance pattern of endometriosis, it tends to be much more common in first-degree relatives of endometriosis patients (6 times more).

7. **Inflammation theory:** There occurs subclinical peritoneal inflammation in women with endometriosis with increased peritoneal fluid volume, macrophages, cytokines, growth factors and angiogenesis promoting substances. Increase in prostaglandin E2 (PGE2) induces aromatase activity in endometrial stromal cells with increased estradiol production and increased PGE2 production with inflammation and pain.

8. **Hormonal influence:** Estrogen (from ovaries and extragonadal tissues) has a role in causation of endometriosis while progesterone has endometriosis inhibiting effect. In women with endometriosis, estrogen synthesis is increased and inactivation enzymes are decreased leading onto excess estrogen levels stimulating endometriosis. The endometriotic implants develop resistance to progesterone leading onto its progress.

9. **Current thinking:** In genetically predisposed women and with retrograde menstruation, the refluxed endometrium escapes from immune clearance (due to defective immune system). Due to environment of estrogen dominance and dependence, and progesterone resistance in endometriotic implants, there occurs local invasion, growth and neovascularization of the ectopic endometrium in the peritoneal cavity causing endometriosis as shown in Flow Chart 25.1. Various biologically active chemical substances help in the development and growth of endometriosis as shown in Flow Chart 25.1.

SITES (ANATOMICAL LOCATIONS) OF ENDOMETRIOSIS

Endometriosis can involve pelvic sites (more common) as well as extragenital sites as shown in Table 25.1.

PREDISPOSING (RISK) FACTORS FOR ENDOMETRIOSIS

The predisposing factors associated with endometriosis are poorly understood and are as follows:

1. Factors related to menstruation
   (i) Early menarche
   (ii) Heavy menstrual bleeding
   (iii) Frequent menstruation
2. Factors related to pregnancy
   (i) Late first pregnancy (delayed childbirth)
   (ii) No or few pregnancies (nulliparity or low parity)
   (iii) Absent or less breastfeeding
3. Familial predisposition - It is 6-7 times more prevalent among first degree relatives

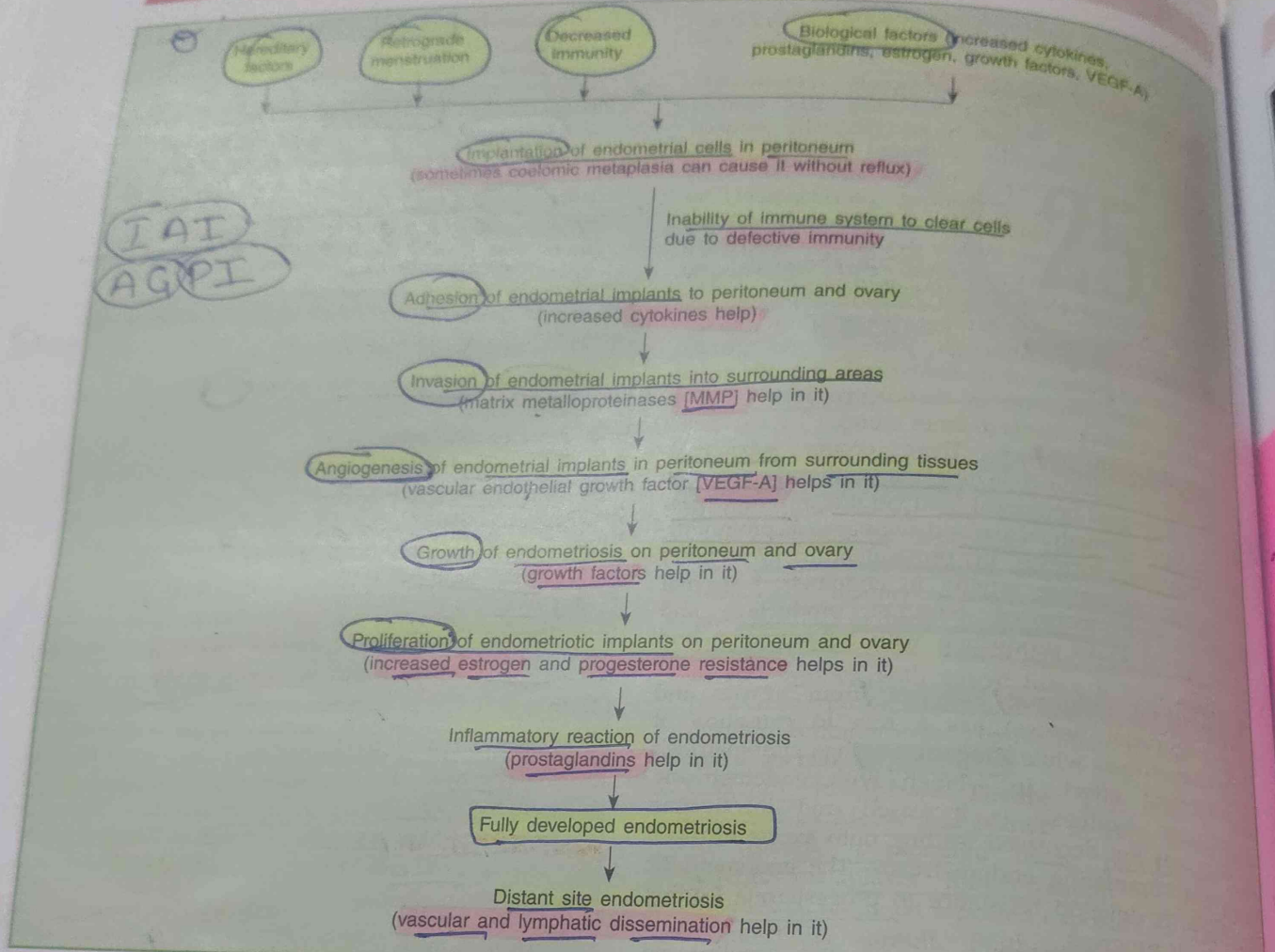
Table 25.1: Genital and extragenital sites of endometriosis

I. Genital sites of endometriosis

1. *Ovaries*: Most common site (almost 80% being bilateral in 50% cases
2. Pelvic peritoneum
3. Rectovaginal septum
4. Uterosacral ligaments
5. Uterine surface
6. Round ligaments
7. Ovarian ligaments
8. Cervix
9. Vagina
10. Vulva

II. Extragenital sites of endometriosis

1. *Gastrointestinal tract*
   (i) Rectum
   (ii) Sigmoid colon
   (iii) Vermiform appendix
   (iv) Ileocecal area
   (v) Small intestine
2. *Urinary tract*
   (i) Urinary bladder
   (ii) Ureters
3. *Surgical scars*
   (i) Hysterotomy scar (most common), it is on anterior abdominal wall
   (ii) Cesarean section scar
   (iii) Episiotomy scar
4. *Chest and lungs*
   (i) Pleura
   (ii) Lungs
   (iii) Rarely pericardium
5. *Distant sites and miscellaneous*
   (i) Extremities
   (ii) Meninges
   (iii) Lymph nodes
   (iv) Nasal mucosa
   (v) Hernial sac
   (vi) Eyes



Flow Chart 25.1 Pathophysiology of development of endometriosis

4. Higher social class
5. Lean and thin body habitus
6. Genital outflow obstruction
7. Environmental factors, like exposure to estrogen-like substances

PATHOLOGY

Endometriosis is of three types. They are superficial, ovarian and deep infiltrating endometriosis.

1. **Superficial (or peritoneal) endometriosis:** The lesions are usually observed in the dependent parts of the pelvis and are present on surface of ovaries (often both ovaries), posterior surface of uterus, pouch of Douglas, uterovesical pouch and uterosacral ligaments, but may involve other parts of pelvis.

Gross appearance: It depends upon the age of lesions.

(*i*) **Early lesions** are usually papular or vesicular but can also be red or pink vesicles full of hemorrhagic fluid. Such lesions also look like red-flame shaped lesions.

(*ii*) **Intermediate lesions:** The lesions become brown, bluish or black with time.

(*iii*) **Late lesions:** With time, the lesions appear white due to disappearance of discoloration. They may be nonpigmented or yellowish white with scarring and fibrosis.

Diagnosis: Superficial lesions are not palpable on vaginal examination nor can they be diagnosed by imaging (ultrasound, CT scan, MRI). They can only be diagnosed by laparoscopy.

2. **Ovarian endometrioma (endometriosis)** (Fig. 25.1): It is a deep type of endometriosis and is different from superficial ovarian endometriosis in which superficial endometriotic lesions are localized to the ovarian surface only. Deep ovarian endometriosis (endometrioma) develops due to inversion and

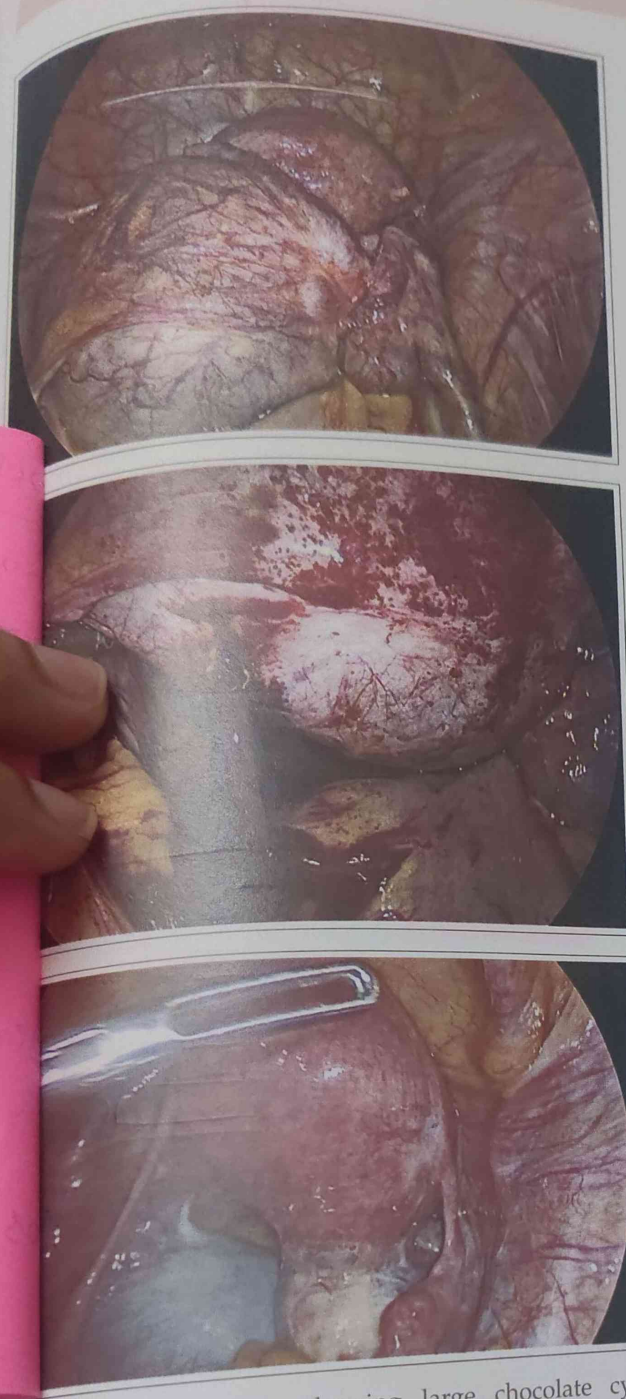


Fig. 25.1 **(A)** Laparoscopy showing large chocolate cyst (endometrioma) of ovary with white capsule; **(B)** Laproscopy showing thick chocolate fluid coming out of endometrioma; **(C)** Laparoscopy showing bilateral large endometriomas touching each other (kissing ovaries) (*Kind courtesy:* Prof. Alka Kriplani, AIIMS, New Delhi)

invagination of ovarian cortex implants or secondary to involvement of functional ovarian cysts by endometriotic implants from ovarian surface or rarely due to coelomic metaplasia. There occurs formation of single or multiple, unilateral or bilateral endometriotic cysts also called 'chocolate cysts' or endometrioma.

On gross examination (laparoscopy or laparotomy), they are situated on antimesenteric surface of the ovary causing adhesions to surrounding structures, like uterus and broad ligament. The cyst wall of endometrioma is white or yellow (Fig. 25.1 A) and is full of thick chocolate fluid from past blood secreted by endometrial cells of endometrium (Fig. 25.1 B). Sometimes the ovarian endometriomas (chocolate cysts) are bilateral and may be fused to each other (kissing ovaries) (Fig. 25.1 C). Large endometriomas can be felt by vaginal examination as adnexal mass and can be diagnosed by ultrasound, CT scan, MRI or by laparoscopy and laparotomy during which they can also be surgically managed. There may be associated endometriosis of uterosacral ligaments or other adjacent areas.

3. **Deep endometriotic lesions (deep infiltrating endometriosis):** These lesions usually involve rectovaginal septum, bowel, ureters, bladder, rectum, cervix and uterosacral ligaments. By definition, they are more than 5 mm deep underneath the peritoneum. These lesions may involve wall and lumen of rectum and other bowel parts causing luminal constriction and rectal bleeding.
   Diagnosis is by bimanual examination (tender nodules felt in pouch of Douglas and on uterosacral ligaments). They can also be detected on imaging modalities (ultrasound, CT scan and MRI). Laparotomy can visualize them but cannot assess their depth.
4. Extra pelvic endometriosis may occur at distant sites (urinary tract, GIT, thorax, etc.). It may be superficial or deep.

HISTOLOGICAL (MICROSCOPIC) APPEARANCE OF ENDOMETRIOSIS

Definite diagnosis of endometriosis is made by histologically detecting endometrial tissue (both endometrial glands and stroma) in the endometriotic lesions. On microscopic examination, the endometriotic implants consist of endometrial glands and stroma with or without hemosiderin laden macrophages (Fig. 25.2). The endometrial glands may have proliferative or secretory glandular activity with increased vascularization. Deep infiltrating endometriosis usually demonstrates proliferative glands and stroma in dense fibrous and smooth muscle tissue. Sometimes, endometrial glands and stroma may not be visible in endometrioma but hemosiderin laden phagocytic cells may be seen.

MALIGNANT CHANGE IN ENDOMETRIOSIS

Malignant change in endometriosis is rare and is typically low grade ovarian adenocarcinoma with better prognosis. They are estrogen dependeant. Ovarian clear cell carcinoma and endometrioid carcinoma can rarely develop in long-standing endometriosis. Hence, complete excision of endometriosis and total hysterectomy and bilateral salpingo-oophorectomy are usually performed in perimenopausal women.

Fig. 25.2 Microscopic appearance of endometriosis showing both endometrial glands (single arrow) and endometrial stroma (double arrows) (*Kind courtesy:* Prof. Sandeep Mathur, AIIMS, New Delhi)

Endometriosis is associated with a higher risk of ovarian, breast, and thyroid cancers, but the increase in risk is low. General cancer prevention measures like avoiding smoking, maintaining a healthy weight, exercising regularly, having a balanced diet with high intakes of fruits and vegetables and low intakes of alcohol, and using sun protection should be followed.

CLINICAL FEATURES OF ENDOMETRIOSIS

Endometriosis is usually observed in women of reproductive age group and is rare before menarche or after menopause. The patients are usually an educated, affluent and intelligent women who are career oriented, postponing marriage and childbearing till late.

Symptoms

Endometriosis (especially mild or moderate) may be asymptomatic. Various symptoms are as follows:

1. **Pain:** Various types of pains are common and are as given below.
   - (i) Chronic pelvic pain which may radiate to rectum or lower back
   - (ii) Secondary dysmenorrhea (severe and starts 1–2 days before onset of menses and does not respond to NSAIDs or OC pills)
   - (iii) Dyspareunia (especially deep dyspareunia) (usually due to endometriosis of rectovaginal septum, peritoneum, pouch of Douglas and uterosacral ligaments)
   - (iv) Dyschezia (painful defecation) (due to involvement of rectovaginal septum)
   - (v) Dysuria (painful micturition)
   - (vi) Abdominal wall pain
   - (vii) Sciatica (pain radiating to legs due to sciatic nerve involvement)
2. **Infertility:** It is common in endometriosis due to various factors described later.
3. **Menstrual symptoms**
   - (i) Heavy menstrual bleeding
   - (ii) Premenstrual spotting
4. **Gastrointestinal symptoms**
   (Usually in endometriosis of intestines)
   - (i) Constipation
   - (ii) Diarrhea
   - (iii) Rectal tenesmus (rectovaginal septal or rectal endometriosis)
   - (iv) Dyschezia (painful defecation)
   - (v) Hematochezia (blood in stools)
   - (vi) Vomiting
   - (vii) Colicky abdominal pain
5. **Urinary symptoms**
   (Usually in endometriosis of bladder and ureters)
   - (i) Loin pain
   - (ii) Backache
   - (iii) Abdominal pain (may occur in abdominal wall endometriosis)
   - (iv) Urinary frequency
   - (v) Urgency
   - (vi) Hematuria
   - (vii) Suprapubic pain
6. **Chronic fatigue**
7. **Respiratory and chest symptoms**
   (Usually in thoracic endometriosis)
   - (i) Cyclic (catamenial) chest pain during menstruation
   - (ii) Hemoptysis
   - (iii) Pneumothorax
   - (iv) Dyspnea
8. **Acute abdomen:** Sudden acute abdominal pain with shock or low blood pressure can occur if chocolate cyst ruptures.
9. **Miscellaneous:** Depending upon site of endometriosis various symptoms can occur. Author has seen blood oozing from eyes of a patient during menstruation in eye endometriosis.

The **classical terrible triad** of symptoms of endometriosis includes **dysmenorrhea**, **dyspareunia** and **infertility**.

CAUSES OF PAIN IN ENDOMETRIOSIS

Pain is most important and common symptom of endometriosis and can be dysmenorrhea (painful menstruation), dyspareunia (painful intercourse), chronic pelvic pain or abdominal pain, painful micturition (dysuria) and painful defecation (dyschezia). The severity of endometriosis may not be related to severity of pain. The pain may radiate to back or legs. The exact cause of pain is unclear. The various causes of pain are as follows:

1. Release of proinflammatory cytokines by the endometriotic implants
2. Release of proinflammatory prostaglandins by the endometriotic implants
3. Nerve growth into endometriotic implants has been observed by experimental studies. The exposure of these nerves to the inflammatory environment within the implants can cause chronic pelvic pain.
4. Involvement of rectovaginal septum and uterosacral ligaments in endometriosis can cause deep pelvic pain and deep dyspareunia.

5. Peritoneal inflammation in endometriosis may cause pain.
6. Stimulation and activation of pain receptors in peritoneum
7. Tissue damage due to endometriosis can cause pain.
8. Adhesion formation in peritoneal cavity can cause pain.
9. Accumulation of blood in endometriotic implants also causes pain.

CAUSES OF INFERTILITY IN ENDOMETRIOSIS

Endometriosis is a common cause of infertility and infertility is observed in 20–40% cases of endometriosis. Although moderate and severe endometriosis is often associated with infertility, link between mild endometriosis and infertility is not proven. Various causes of infertility in endometriosis especially in severe endometriosis are as follows:

1. **Mechanical (anatomical) factors**
   - (i) Distortion of tubo-ovarian relations
   - (ii) Defective oocyte pickup
   - (iii) Impaired tubal motility
   - (iv) Pelvic and peritubal adhesions
   - (v) Chronic salpingitis
2. **Ovulatory dysfunction**
   - (i) Defective folliculogenesis
   - (ii) Defective ovulation or anovulation
   - (iii) Luteinized unruptured follicle (LUF) syndrome
   - (iv) Hyperprolactinemia
   - (v) Luteal phase defects
3. **Biochemical changes in peritoneal fluid**
   - (i) Increased production of cytokines
   - (ii) Increased production of prostaglandins
   - (iii) Increased local activated macrophages
   - (iv) Peritoneal inflammation
   - (v) Increased phagocytosis of spermatozoa
4. **Immunological factors**
   - (i) Increased production of autoantibodies
   - (ii) Increased cell mediated gamete injury causing inactivation of spermatozoa
   - (iii) Increased antiendometrial antibody production
5. Defective fertilization
6. Implantation failure
7. Infrequent coitus due to dyspareunia
8. Increased risk of spontaneous miscarriage
9. Increased risk of pregnancy complications, like preterm delivery, fetal growth restriction and preeclampsia

CLINICAL EXAMINATION

1. There may be no abnormalities on clinical examination in patients with mild and moderate endometriosis.
2. General physical examination is usually normal.
3. Abdominal examination may reveal a pelvic mass extending into lower abdomen (in ovarian endometriosis). The mass is in one or both adnexal regions, and is usually fixed and tender.
4. Local genital examination and speculum examination should be carefully performed to detect any bluish or black puckered endometriotic lesions on vulva, vagina and cervix.
5. Bimanual vaginal examination may demonstrate fixed retroverted uterus. There may be tenderness and nodularity (cobblestone feel) in pouch of Douglas and on uterosacral ligaments. There may be tenderness, fullness and adnexal mass in ovarian endometrioma. There may be scarring in adnexa and pouch of Douglas.
6. Rectal examination may reveal tenderness and nodules in pouch of Douglas especially in endometriosis of uterosacral ligaments and pouch of Douglas.

DIFFERENTIAL DIAGNOSIS

Due to varied clinical presentation, there may be diagnostic dilemma in diagnosis of endometriosis, especially on clinical examination. Various differential diagnoses are as follows:

1. **Chronic pelvic inflammatory disease (PID):** It is the main differential diagnosis producing signs and symptoms similar to endometriosis. On clinical examination in PID, uterus may be fixed and retroverted with tubo-ovarian masses in both adnexa. Diagnostic laparoscopy can differentiate between the two conditions (typical lesions of endometriosis with patent tubes are seen in endometriosis, whereas inflamed and blocked tubes are seen in chronic PID). Hormonal therapy relieves endometriosis while antibiotics relieve PID.
2. **Leiomyoma uterus with degeneration** is usually painless and not fixed. But if associated with PID, it can produce symptoms and signs similar to endometriosis. Ultrasound and laparoscopy can help to differentiate the two conditions.
3. **Ovarian cancer** with metastatic deposits in pouch of Douglas may simulate endometriotic nodules but are painless and non-tender. Age of patients is usually more in ovarian cancer but is young in endometriosis. Levels of CA 125 are slightly raised in endometriosis but are significantly raised in ovarian cancer.
4. **Rectal cancer:** Endometriosis involving rectovaginal septum or rectal endometriosis may resemble rectal cancer. Rectal cancer is usually painless while endometriosis is painful and tender. Sigmoidoscopy and biopsy may be performed to differentiate between the two conditions.
5. **Chronic ectopic pregnancy** may produce similar symptoms and signs but causes more physical symptoms (low blood pressure and tachycardia). Urine pregnancy test, serum β-hCG and transvaginal ultrasound may differentiate the two conditions.
6. **Ruptured chocolate cyst** may cause acute abdomen mimicking acute appendicitis or ectopic pregnancy. Laparoscopy or laparotomy may clinch the diagnosis. Definitive surgery can also be performed in the same sitting.

7. **Pelvic congestion syndrome** may cause pain and tenderness in both adnexa. Ultrasound, CT scan or laparoscopy may differentiate the two conditions.
8. **Postoperative adhesions:** There is history of prior surgery.
9. **Gastrointestinal conditions**
   (i) **Ulcerative colitis:** There are abdominal pain with diarrhea and rectal bleeding.
   (ii) Crohn's disease
   (iii) Diverticulitis
   (iv) Irritable bowel syndrome

These conditions usually cause gastrointestinal symptoms and have chronic history. Diagnosis can be made by barium meal, barium enema or endoscopy and biopsy.

INVESTIGATIONS

After history taking and clinical examination, diagnosis of endometriosis is suspected. It is then confirmed with investigations as follows. Various investigations used in endometriosis are shown in Table 25.2. All tests are not needed for all patients.

1. **Laboratory testing:** Various blood tests, urine test, swabs are shown in Table 25.2. Out of all biomarkers only CA 125 (a glycoprotein and cell surface antigen) is useful in diagnosis of endometriosis, and its levels correlate with severity of endometriosis. There is moderate rise in levels (upto 200 U/mL) (normal < 35 U/mL). It can also be used for detection of recurrence. However, it is a nonspecific test which is mainly raised in epithelial ovarian cancer (levels are very high > 1000 U/mL) and is also raised in abdominopelvic tuberculosis Anti-endometrial antibodies are observed in blood, peritoneal and abdominal fluid, but are not routinely tested.

   European Society of Human Reproduction and Embryology (ESHRE) 2022 and RCOG 2018 do not recommend use of biomarkers to diagnose endometriosis. Recently, it has been found that miRNAs are aberrantly regulated in endometriosis. Measurement of these miRNAs as a non-invasive diagnostic test for early detection and intervention is under development.

2. **Diagnostic imaging**
   (i) Ultrasound especially transvaginal ultrasound, can pickup rectovaginal nodules. Both abdominal and vaginal ultrasound can detect ovarian endometrioma. In ovarian endometrioma, the mass is cystic with homogenous low level internal echoes (ground glass echogenicity) (Fig. 25.3). TVS has 65–90% sensitivity and 22–100% specificity for diagnosis of endometriosis.

   Colour Doppler can be used to detect increased blood flow in endometriosis. It can detect deep infiltrating endometriosis but is operator dependant and is less accurate than MRI.

   (ii) **CT scan:** It is not a useful modality for endometriosis and has poor sensitivity. However, it can be useful to detect thoracic endometriosis (chest CT scan is done).

   (iii) **Magnetic resonance imaging (MRI)** (Fig. 25.4): It is a very useful modality to detect endometrioma of more than 1 cm. It has better resolution and can detect ovarian endometrioma, deep infiltrating endometriosis and rectovaginal nodules of endometriosis. Low

Table 25.2: Various investigations for diagnosis of endometriosis

1. **Blood tests**
   (i) Complete blood count
   (ii) Serum β-hCG (to rule out ectopic pregnancy)
   (iii) Total and differential leukocyte count (to rule out infection)
   (iv) Erythrocyte sedimentation rate (ESR) (to rule out TB)
   (v) CA 125 levels: Moderate rise (upto 200 U/mL) in endometriosis
2. **Urine analysis and culture (to rule out urinary tract infection)**
3. **Vaginal and cervical swab and culture (to rule out pelvic inflammatory disease and sexually transmitted infections)**
4. **Diagnostic imaging:** More useful in endometrioma and deep endometriosis
   (i) ***Ultrasound* (transabdominal and transvaginal):** It can detect ovarian endometrioma. It can also detect hydroureteronephrosis if ureters are blocked by endometriosis. Not useful in superficial and deep infiltrating endometriosis.
   (ii) ***Magnetic resonance imaging* (MRI):** It has better accuracy and resolution than ultrasound. It can detect even smaller ovarian endometriomas (> 1 cm). It is also useful in rectovaginal endometriosis with higher accuracy than ultrasound. However, it can also miss superficial endometriosis.
   (iii) Doppler ultrasound can see blood flow of lesions but is not very useful.
5. **Barium swallow and enema for intestinal endometriosis**
6. **Intravenous urography:** It is mainly useful to detect severe endometriosis, ureteral endometriosis and to detect renal function due to compression of ureters in endometriosis
7. **Cystoscopy to detect bladder involvement**
8. **Sigmoidoscopy and biopsy to detect colorectal and colonic endometriosis**
9. **Laparoscopy:** It is the most important modality to diagnose, quantify, classify and to operate endometriosis. It is the only modality to pick superficial lesions. Biopsy can also be done to confirm histopathology of endometriosis.

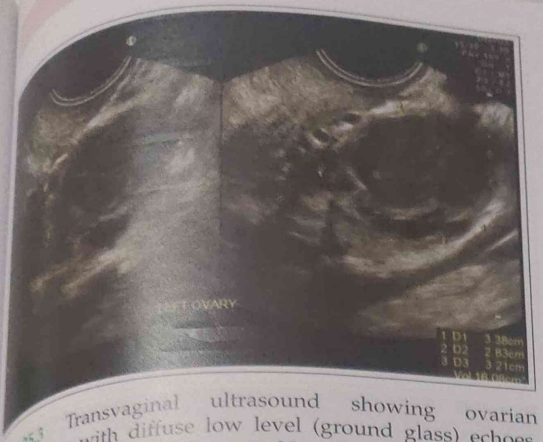


Fig. 25.3 Transvaginal ultrasound showing ovarian endometrioma with diffuse low level (ground glass) echoes. (*Kind courtesy:* Dr. Ashok Khurana, New Delhi)

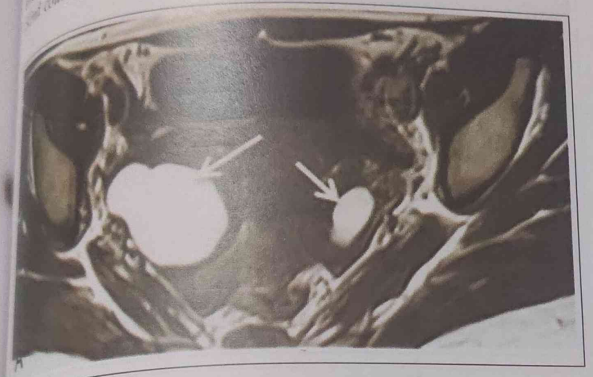


Fig. 25.4 MRI showing endometrioma (*Kind courtesy:* Dr. Smita Manchanda, AIIMS, New Delhi)

intensity signals are observed in T2 weighted image while high intensity signals are observed on T1 weighted images in endometrioma. MRI should not be used as the primary tool to diagnose. When done, pelvic MRI is done and specialist with adequate expertise is essential.

3. **Endoscopy** (Fig. 25.5)

(*i*) **Diagnostic laparoscopy:** Both diagnostic laparoscopy and imaging combined with empirical treatment (hormonal contraceptives or progesterone) can be considered in a suspected case. Laparoscopy is no longer the diagnostic gold standard and is recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate (ESHRE 2022). It is the only modality which can detect superficial endometriosis. The following findings can be observed depending upon the type and severity of endometriosis.

- Endometrioma
- Superficial endometriosis on ovaries
  - Red lesions (Fig. 25.5 A)
  - Red pink or pink lesions
  - Clear lesions
  - White lesions
  - Yellow-brown or only brown lesions (Fig. 25.5 B)
  - Black lesions (Fig. 25.5 C)
  - Black-blue lesions
  - Smooth blebs on peritoneal surface (Fig. 25.5 D)
  - Holes or defects in the peritoneum
  - Flat stellate lesions
- Frozen pelvis or obliterated pouch of Douglas is seen in rectovaginal endometriosis or deep infiltrating endometriosis

White and red lesions, if biopsied, usually show histopathologic picture of endometriosis (endometrial glands and stroma). Dark lesions (black or brown) usually show hemosiderin deposits due to accumulated menstrual debris. Laparoscopy has 97% sensitivity and 95% specificity to diagnose endometriosis. Another advantage is that treatment can be done in the same sitting (laser, cautery and biopsy can be done on peritoneal lesions).

(*ii*) ***Hysteroscopy*** is not usually performed in endometriosis.

(*iii*) ***Sigmoidoscopy*** for rectal or sigmoid endometriosis, biopsy can be taken to confirm diagnosis and to rule out cancer.

(*iv*) ***Cystoscopy:*** It is only performed for bladder endometriosis. Biopsy can be taken to confirm diagnosis but is not essential.

4. **Histopathological analysis:** The current guidelines do not require biopsy and histological evidence to diagnose endometriosis. If endometriosis is visible on laparoscopy, it can be taken as diagnosis of endometriosis. If biopsy is taken, it shows endometrial glands and stroma in the lesion. There may be hemosiderin deposition in the lesions.

CLASSIFICATION AND STAGING OF ENDOMETRIOSIS

The classification used is that of American Society for Reproductive Medicine (ASRM) revised classification of endometriosis (1997) also called Revised American Fertility Society Classification (R-AFS) which depends upon visualization of endometriotic lesions on laparoscopy with or without biopsy for histopathological diagnosis. In this classification Fig. 25.6, endometriosis on peritoneum, ovaries, fallopian tubes and pouch of Douglas (cul-de-sac) is scored at surgery (laparoscopy or laparotomy). In 2005, ENZIAN staging system was introduced which added information about retroperitoneal structures and lesions localized to other organs. The Endometriosis Fertility Index (EFI) was developed in 2010, to predict pregnancy rates in patients with surgically documented endometriosis who attempt

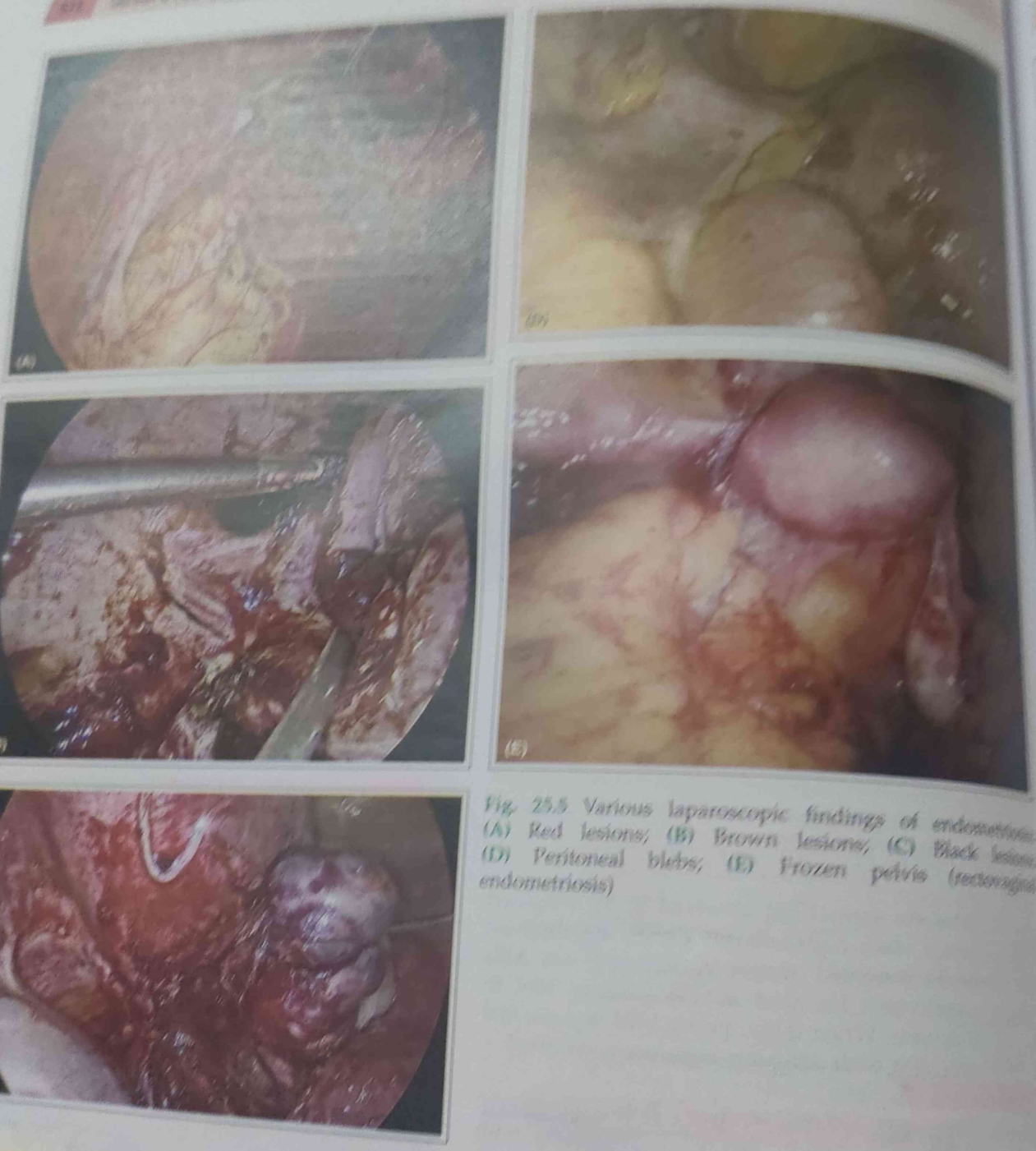


Fig. 25.5 Various laparoscopic findings of endometriosis: (A) Red lesions; (B) Brown lesions; (C) Black lesions; (D) Peritoneal blebs; (E) Frozen pelvis (rectovaginal endometriosis)

non-IVF conception. There are many classification systems proposed but these three are commonly used and will be discussed in detail here.

1. rASRM Classification 1997 (Revised American Society for Reproductive Medicine Classification) (Fig. 25.6 A)

This system is based on intraoperative disease findings, and takes into account peritoneal endometriosis, ovarian endometriosis, posterior cul de sac obliteration, ovarian adhesions and tubal adhesions. The points are assigned on the basis of surface area of disease, degree of invasion, morphology and associated adhesions (Fig. 25.6A). The disease is then classified as:

A. Stage 1 (Minimal Endometriosis): 1–5 points
B. Stage 2 (Mild Endometriosis): 6–15 points
C. Stage 3 (Moderate Endometriosis): 16–40 points
D. Stage 4 (Severe Endometriosis): > 40 points

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS (1997)

ASRM

R-AFS

Patient's Name _____ Date _____

Stage I	(Minimal)	1-5
Stage II	(Mild)	6-15
Stage III	(Moderate)	16-40
Stage IV	(Severe)	> 40

Total _____

Laparoscopy _____ Laparotomy _____ Photography _____

Recommended Treatment _____

Prognosis _____

			< 1 cm	1–3 cm	> 3 cm
Peritoneum	Endometriosis	Superficial	1	(2)	4
		Deep	(2)	4	6
Ovary	R	Superficial	1	(2)	4
		Deep	4	16	20
	L	Superficial	1	(2)	4
		Deep	4	16	20

		Partial	Complete
Posterior cul-de-sac obliteration		4	40

			< 1/3 Enclosure	1/3–2/3 Enclosure	> 2/3 Enclosure
Ovary	Adhesions				
	R	Flimsy	1	2	4
		Dense	4	(8)	(16)
	L	Flimsy	1	2	4
		Dense	4	(8)	(16)
Tube	R	Flimsy	1	2	4
		Dense	4*	(8*)	(16)
	L	Flimsy	1	2	4
		Dense	4*	(8*)	(16)

4 8 16

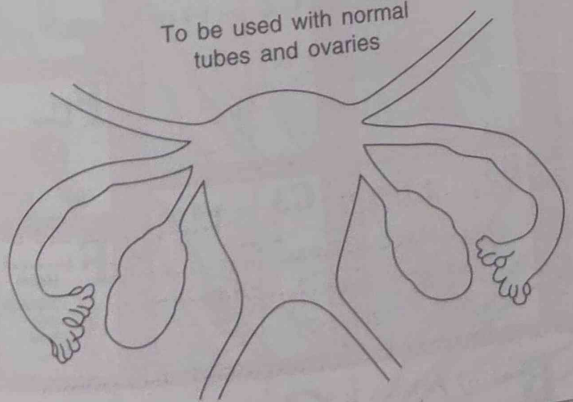
* If the fimbriated end of the Fallopian tube is completely enclosed, change the point assignment to 16.

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular bleds, clear vesicles], white [W], opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R ____%, W ____% and B____%. Total should equal 100%.

Additional Endometriosis: _____

Associated Pathology: _____

To be used with normal tubes and ovaries



To be used with abnormal tubes and/or ovaries

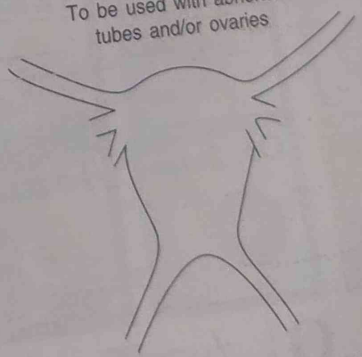


Fig. 25.6A Revised American Society for Reproductive Medicine Classification of Endometriosis

2. #ENZIAN Classification (2020) (Fig. 25.6 B)

The ENZIAN classification was developed as a supplement to rASRM by providing morphologically descriptive classification of Deep Invasive Endometriosis, but does not include peritoneal or ovarian disease or adhesions. In 2020, the #ENZIAN classification has been proposed, which is a comprehensive non-invasive and surgical descriptive system for endometriosis. It involves complete mapping of endometriosis, including anatomical location, size of lesions, adhesions and degree of involvement of the adjacent organs.

- It consists of following compartments and identified in this order (POTABCF):

P – Peritoneum
O – Ovary
T – Tubo-ovarian unit
A – Vagina/Rectovaginal Space (RVS)
B – Uterosacral ligaments (USL)/Cardinal Ligaments/ Pelvic sidewall
C – Rectum
F – Far locations
FA – Adenomyosis
FB – Urinary Bladder
FU – Ureters
FI – Intestinal locations (sigmoid colon, small bowel)
FO – Other extragenital lesions

- The extent of endometriosis is represented as 1, 2 and 3 in POTABC
- Paired organs are represented as R/L separately
- The diameter (> 3 cm and > 7 cm was adapted in line with the rASRM classification (< 3 cms – not treated surgically, > 7 cms – critical limit for organ preserving surgery.

3. The Endometriosis Fertility Index (EFI) (Fig. 25.6 C)

It includes assessment of historical factors at the time of surgery, of adnexal function at conclusion of surgery, and of the extension of endometriosis, each having an allotted score. Scores range from 0 to 10, with 0 representing the poor prognosis and 10 best prognosis. It gives an estimate of reproductive functionality after surgical intervention.

A comparison of these three system is given in Table 25.3.

TREATMENT

Endometriosis need shared decision-making approach and should take into consideration the individual preferences, side effects, individual efficacy, costs, and availability, when choosing between medical and surgical treatments' for pain. However, for severe pain

Fig. 25.6B ENZIAN Classification - Overview

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description
4	= Normal
3	= Mild Dysfunction
2	= Moderate Dysfunction
1	= Severe Dysfunction
0	= Absent or Nonfunctional

	Left	Right
Fallopian Tube		
Fimbria		
Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score	Left	+	Right	=	LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors

Factor	Description	Points
Age	If age is ≤ 35 years	2
	If age is 36 to 39 years	1
	If age is ≥ 40 years	0
Years Infertile	If years infertile is ≤ 3	2
	If years infertile is > 3	0
Prior Pregnancy	If there is a history of a prior pregnancy	1
	If there is no history of prior pregnancy	0
Total Historical Factors		

Surgical Factors

Factor	Description	Points
LF Score	If LF Score = 7 to 8 (high score)	3
	If LF Score = 4 to 6 (moderate score)	2
	If LF Score = 1 to 3 (low score)	0
AFS Endometriosis Score	If AFS Endometriosis Lesion Score is < 16	1
	If AFS Endometriosis Lesion Score is ≥ 16	0
AFS Total Score	If AFS total score is < 71	1
	If AFS total score is ≥ 71	0
Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical + Surgical = EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE

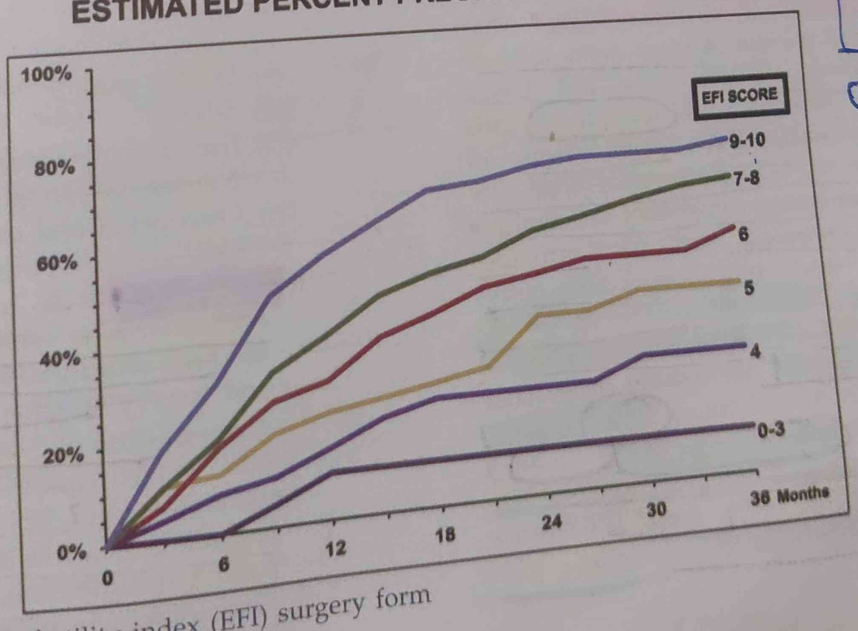


Fig. 25.6C Endometriosis fertility index (EFI) surgery form

Table 29.8: Comparison of the three classification systems

	ASRM	#ENZIAN	EFI
Strengths	Easy to use, widely used and simple to understand	Complete description of Deep Infiltrating Endometriosis, anatomically logical and easy to use	Useful in developing treatment plans for infertile women with endometriosis
Limitations	Incomplete description of Deep Infiltrating Endometriosis	Further studies are needed to provide proof for the applicability, reproducibility, and accuracy	Does not consider uterine abnormalities
Prognostic value	No correlation with symptoms, QOL and infertility outcome with treatment	Poor correlation with symptoms, QOL and infertility outcome with treatment	Predicts fertility outcome in women with previous surgical staging of endometriosis but no correlation with pain symptoms

not responding to medical treatment after childbearing, definitive surgery (total abdominal hysterectomy with bilateral salpingo-oophorectomy and excision of all endometriotic lesions) is recommended. For infertility, fertility preserving treatment is required.

1. **Expectant treatment:** For minimal and mild endometriosis inadvertantly detected on laparoscopy without any symptoms, expectant treatment is given and patients follow up. If they develop are asked to symptoms, than medical treatment can be given.

2. **Medical treatment of pain**

(*i*) ***Nonsteroidal anti-inflammatory drugs (NSAIDs):*** The pain and inflammation seen in endometriosis is caused by prostaglandins (synthesized by cyclooxygenase enzyme [COX] 1 and 2). Hence COX 1 and 2 inhibitors (NSAIDS) are usually the first line of therapy in women of endometriosis with dysmenorrhea and pelvic pain. Due to cardiovascular risk as a result of long-term COX-2 inhibitors, COX-1 inhibitors are more commonly used. A short trial of 3 months with Paracetamol or NSAID alone or in combination with hormones is tried initially. Ibuprofen 400 mg thrice daily and mefenamic acid 500 mg thrice daily are used during pain (during 5–7 days of menstruation).

(*ii*) ***Combined hormonal contraception:*** They are mainly of use for women with mild to moderate symptoms who are not trying to conceive (suitable for unmarried girls with endometriosis). They inhibit release of gonadotropins and reduce menstrual blood flow and their progesterone component decidualizes endometriotic implants and also provides contraception and other noncontraceptive benefits. Combination pill containing 30 µg ethinyl estradiol with 0.5 mg levonorgestrel or 0.15 mg of desogestrel are usually used. They can be given in a traditional cyclic regimen or may also be used continuously without a break. The continuous regimen is more effective in control of chronic pelvic pain. They cause atrophy of endometriotic lesions, relieve pain and other symptoms and induce amenorrhea (continous use). They are usually given for 6–12 months. Contraceptive patch or combined ring is also effective. However, their long-term use can cause side effects and thromboembolism (see Chapter 11 for detail).

(*iii*) ***Progestogens (progestins):*** Historically progestogens have been used frequently for the treatment of endometriosis. They antagonize the estrogenic effects on endometriosis causing initial decidualization and later atrophy of endometriotic implants.

They produce a pseudopregnancy state

They are usually given for 6–9 months at one time.

(*a*) Tab. medroxyprogesterone acetate is given in dose of 20–100 mg daily for 6–9 months causing 60% relief in peritoneal implants.

(*b*) Tab. Norethindrone acetate (Norethisterone) 5–20 mg daily

(*c*) Tab. Dydrogesterone 10–30 mg daily

(*d*) Inj. depot medroxyprogesterone acetate (Depo-Provera) can also be given intramuscularly as 150 mg every 3 months for 6–12 months

Side effects:

(*i*) Acne
(*ii*) Weight gain
(*iii*) Edema
(*iv*) Irregular menstrual bleeding
(*v*) Nausea, vomiting
(*vi*) Osteopenia and osteoporosis on long-term use.

(*e*) ***Dienogest:*** It is a fourth generation 19 nortestosterone synthetic progestogen which has high selectivity for progesterone receptor and is very suitable for endometriosis. It is given in dose of 2 mg daily for 6–9 months. Randomized controlled trials have observed dienogest to be equally effective to leuprolide (GnRH analogues) in relieving pain but with much lower incidence of vasomotor symptoms and lower effect on

bone metabolism (osteopenia) as compared to GnRH analogues. Currently dienogest is the treatment of choice for endometriosis. However, it is expensive (about ₹ 45 rupees a tablet). Long-term administration of dienogest (2 mg/day) reduces recurrence of endometriosis after excision of endometrioma.

(*f*) ***Levonorgestrel intrauterine system (LNG-IUS) (Mirena):*** It contains 52 mg levonorgestrel and is effective for 5 years, delivering 20 µg levonorgestrel per day to the endometrium. It causes suppression of menstruation and significant relief of pain, dysmenorrhea and dyspareunia. ESHRE 2022 recommends using LNG-IUS or an etonogestrel releasing subdermal implants to reduce endometriosis associated pain. Studies have found it to be effective for rectovaginal endometriosis after surgery. It has also been found to be effective in preventing the recurrence of endometriosis after surgical treatment.

(*iv*) ***GnRH agonists:*** Their use causes pituitary desensitization and inhibition of ovarian steroidogenesis.

Hence they produce pseudomenopause.

The hypoestrogenic environment caused by them leads to atrophy of endometriotic implants. They also reduce cyclooxygenase-2 (COX-2) levels. Any of the following depot preparations can be used (also see Chapter 9 for detail).

(*a*) Goserelin 3.6 mg subcutaneously monthly (or 10.8 mg 3 monthly)
(*b*) Leuprolide acetate 3.75 mg intramuscularly monthly (preferably every 28 days) or 11.25 mg 3 monthly
(*c*) Triptorelin 3.75 mg intramuscularly monthly
(*d*) Nafarelin 200 µg twice daily intranasally

Most of them (except Triptorelin) have been approved by US FDA (Food and Drug Administration) for use in endometriosis. They are given for about 3–6 months (6 months produce greater relief). Various studies have proven their efficacy in relieving symptoms of endometriosis, especially pain.

Side effects

(*a*) Vasomotor symptoms (hot flushes)
(*b*) Insomnia
(*c*) Reduced libido
(*d*) Vaginal dryness
(*e*) Headache
(*f*) Decreased bone mineral density (BMD)

To avoid decrease in BMD, they are usually not given for more than 6 months.

Add-back therapy: If GnRH agonist is given for more than 6 months, add-back therapy with low dose estrogen to supply enough estrogen to minimize hypoestrogenic side effects and prevent bone loss but still low enough to suppress endometriosis, is added. Norethisterone acetate 5 mg with conjugated equine estrogen 625 µg daily is given for the duration of GnRH agonist (upto 6 months). It prevents osteopenia. Calcium in dose of 1000 mg daily is also given along with add-back therapy.

(*v*) ***GnRH anatogonists:*** They do not produce flare-up effect and cause immediate gonadotropin suppression and hypoestrogenism. As there is partial dose-dependent reduction in estradiol levels, there is no need for add back therapy.

Advantages:

(*a*) Rapid onset
(*b*) Oral administration
(*c*) Absence of flare effect
(*d*) Available as two doses

Dose: Elagolix - Low dose (150 mg/day) and high dose (200 mg/day)

Side effects:

(*a*) Vasomotor symptoms - generally mild
(*b*) High dose - changes in bone mineral density, add-back therapy may be needed after 6 months
(*c*) Decreased Endometrial thickness
(*d*) Amenorrhea

They are second line of treatment after hormonal contraceptives and progestogens.

(*vi*) ***Aromatase inhibitors:*** Endometriosis can be caused by estrogen produced from ovaries as well as from other sources (peripheral aromatization of circulating androgens). Traditional hormone treatment targets estrogen produced from ovaries but not from other sources. ESHRE 2022, recommends them in endometriosis-associated pain refractory to other medical or surgical treatment. They should always be administered with an agent that down regulates the ovaries. Aromatase inhibitors can inhibit both production from ovaries and extraovarian estrogens. This produces hypoestrogenism which is responsible for their efficacy in endometriosis. Anastrozole (2 mg) and letrozole (2.5 mg) orally once daily are used for 6 months.

Side effects

(*a*) Nausea
(*b*) Vomiting
(*c*) Diarrhea
(*d*) Antiestrogenic side effects (hot flushes)
(*e*) Osteopenia and osteoporosis on long-term use. Calcium 1 g with Vitamin D (400 IU) should be given daily to prevent osteoporosis.

(*vii*) ***Selective progesterone receptor modulators (SPRMs):*** These drugs bind to progesterone

receptors, but have varying effects on different target tissues being agonist at some tissues and antagonistic at other tissues. Ulipristal acetate has been tried but is still experimental. Mifepristone (RU486) in dose of 10–25 mg daily for 3–6 months has been tried for endometriosis. However, their role in endometriosis is still experimental.

(viii) **Androgens:** These drugs were very popular in the past but are second-line drugs in current practice due to their androgenic side effects and due to availability of safer and more effective medication. They are as follows:

(a) **Danazol:** It is a synthetic 17 α-ethinyl testosterone derivative which suppresses midcycle LH surge (antigonadotropic action). It has mild antiestrogenic and antiprogestational actions. It decreases levels of SHBG (sex hormone binding globulin) and thus increases serum testosterone levels. It also directly binds to androgen and progesterone receptors. Danazol thus causes endometrial atrophy in the endometriotic implants through its hypoestrogenic and hyperandrogenic states.

Dose: Danazol is given in dose of 200 mg 2–3 times daily for 3–6 months (see Chapter 9 for detail). Upto 80% endometriotic implants resolve with use of danazol. There is 30% recurrence after stopping the medicine. Pregnancy rate after danazol treatment is upto 30–40%.

Side effects: They are common and are androgenic.
- Weight gain
- Hirsutism
- Acne
- Hot flushes
- Muscle cramps
- Breast atrophy
- Adverse lipid profile
- Elevated liver enzyme
- Deepening of voice
- Teratogenicity (effective contraception should be used with it)

(b) **Gestrinone:** It is also a 19-nortestosterone derivative with similar efficacy and side effects as danazol. It has long half-life and has fewer side effects.

Dose: 2.5–3 mg twice weekly for 3–6 months. It has been observed to be effective in treating moderate and severe pain in endometriosis. Side effects are similar to danazol but less. It can lower HDL levels.

(ix) **Newer medicines:** Cabergoline 0.5 mg twice a week for 3 months and antiprogesterone mifepristone in dose of 10–25 mg daily for 6 months have also been found effective. They are still experimental but may have a role in treatment of endometriosis in the future. They are as follows:
(a) Tumor necrosis factor alpha (TNF α) inhibitors
(b) Angiogenesis inhibitors
(c) Matrix metalloproteinase inhibitors
(d) Immunomodulators, like pentoxifylline
(e) Estrogen receptor antagonists
(f) Selective estrogen receptor modulators, like raloxifene
(g) Complementary medicine [herbal, homeopathy, neuromodulators, reflexology and acupuncture (TENS)] are not recommended to treat pain or infertility caused by endometriosis.

3. Surgical treatment

In cases of suspected endometriosis, surgery is done laparoscopically unless there are contraindications. During laparoscopy, consider surgical treatment if:
(a) Peritoneal endometriosis not involving the bowel, bladder or ureter.
(b) Uncomplicated ovarian endometriomas. The main role of surgery in endometriosis is to relieve pain in women not responding to medical treatment and also to improve fertility. At the time of surgery, all the visible lesions are excised rather than ablated.

Surgery can be performed laparoscopically (preferred method) or by laparotomy. Surgery may be conservative (preservation of ovaries and uterus) or radical when hysterectomy and bilateral salpingo-oophorectomy are performed. Type of surgery depends on age of patient, fertility status and disease stage. Surgery is usually performed for more severe lesions. There is no definite evidence that surgery helps in stages I and II.

Superficial Endometriosis

Superficial endometriosis It is amenable to laparoscopic treatment. Laparoscopy can diagnose and stage the extent of disease. Surgical treatment can be performed in the same sitting. All lesions are either excised or ablated. Adhesiolysis is performed for adhesions using laser or cautery. Laparoscopic uterine nerve ablation (LUNA) can be performed along with excision of all endometriotic implants. It can relieve pain of endometriosis.

Surgery for Ovarian Endometrioma

Laparoscopic surgery is the treatment of choice. Endometrioma is also treated to exclude cancer and to treat pain. After making an incision over the endometrium, the cyst is removed in totality. Cyst wall should be removed completely. Cautery or laser ablation can be done to the bleeding areas and to the cyst wall. Cystectomy is done and not drainage and coagulation as it reduces the recurrence of endometrioma and associated pain. Caution is to be taken to minimize ovarian damage.

Repeat transvaginal scan is performed after 3 months to exclude any recurrence.

SURGICAL TREATMENT OF DEEP INFILTRATING ENDOMETRIOSIS AND ADVANCED DISEASE

Preoperative evaluation with MRI or ultrasound is useful to quantify the disease and to see the involvement of gastrointestinal and urinary tract. Surgical removal of deep endometriosis reduces the associated pain and improves quality of life. Such cases are to be referred to a centre of expertise. The patients should be adequately counselled regarding the potential risks, benefits, long-term effect on quality of life and the long-term consequences of early menopause and possible need for hormone replacement therapy if ovaries are removed per op.

When opting for hysterectomy, the need for the procedure, risks and benefits, role of oophorectomy and risk of recurrence all needs to be discussed in detail.

Usually when indicated, laparotomy followed by radical surgery (total abdominal hysterectomy with bilateral salpingo-oophorectomy and complete removal and excision of all endometriotic lesions including deep-seated endometriosis) is performed. It may include bowel resection (removal of part of bowel with endometriosis in its wall), ureteric resection and reimplantation (for ureteric endometriosis). Surgery can also be performed laparoscopically or robotically or by using laparoscopic-assisted vaginal technique.

Presacral neurectomy: In this operation, transection of presacral nerves present in presacral space is performed. It can be performed laparoscopically (more challenging) or by laparotomy. However, being a major operation and less effective, it is rarely performed in current practice.

PRE AND POSTOPERATIVE HORMONE REPLACEMENT

Preoperative therapy with GnRH agonists or danazol or progesterone may reduce size and extent of endometriosis and may make surgery easier but does not change the result of surgery.

Postoperative therapy with GnRH agonists can be given for 3–6 months if complete removal could not be done at time of surgery. Hormone replacement therapy (only estrogen-like conjugated equine estrogen) can be given alone to prevent osteoporosis.

TREATMENT OF INFERTILITY IN ENDOMETRIOSIS

When treating infertility with endometriosis, post-operative hormonal suppression should not be done. Operative laparoscopy can be offered in rASRM stage I/II, endometrioma and also in deep endometriosis. They need to be counselled about the chances of becoming pregnant after surgery and impact on ovarian reserve. Endometriosis Fertility Index (EFI) should be used to identify patients that may benefit from ART after surgery, as it is validated, reproducible and cost-effective. If the patient is to undergo IVF, GnRH agonist suppression with addback for 3 to 6 months before IVF is associated with an improved pregnancy rate. Various effective treatments for infertility in endometriosis are as follows:

1. Ovulation induction
2. Controlled ovarian hyperstimulation
3. Intrauterine insemination
4. In vitro fertilization and embryo transfer. It has high success in endometriosis.
5. Intracytoplasmic sperm injection (ICSI)

An algorithm for diagnosis and treatment of endometriosis is given in Fig. 25.7.

RECURRENCE OF ENDOMETRIOSIS

Recurrence rate of endometriosis is very high after medical therapy or conservative surgery, being 5–20% per year and by 5 years 40–50% cases have recurrence. The severity of endometriosis and completeness of primary surgery are the determining factors for recurrence. Thus recurrence is more common in severe disease (stages III and IV) and if all endometriotic implants could not be removed at primary surgery.

Postoperative use of a levonorgestrel-releasing intrauterine system (52 mg LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months is recommended for the secondary prevention of endometriosis-associated dysmenorrhea.

Long term post-operative hormone treatment - considered to prevent recurrence of deep endometriosis and in women not seeking conception immediately.

Treatment

(*i*) Medical treatment with dienogest 2 mg once daily orally for 4–6 months can be given.
(*ii*) GnRH agonists (leuprolide or goserelin) once a month can be given for 3–6 months.
(*iii*) In vitro fertilization for infertility can be tried.
(*iv*) Usually repeat conservative surgery is avoided unless patient is infertile as it is more difficult, hazardous and less successful.
(*v*) Complete surgery in the form of total hysterectomy with bilateral salpingo-oophorectomy with removal of all endometriotic implants is usually the treatment of choice for recurrent endometriosis.

ENDOMETRIOSIS IN ADOLESCENCE (ESHRE 2022)

- Endometriosis is also seen is adolescents and possible risk factors should be searched for, like- positive family history, obstructive genital malformations, early menarche, or short menstrual cycle.
- They present with chronic or acyclical pelvic pain, nausea, dysmenorrhea, dyschezia, dysuria, dyspareunia or cyclical pelvic pain.
- Transvaginal ultrasound is recommended as it is effective in diagnosing ovarian endometriosis.
- If not appropriate, MRI, transabdominal, trans perineal, or transrectal scan may be done.

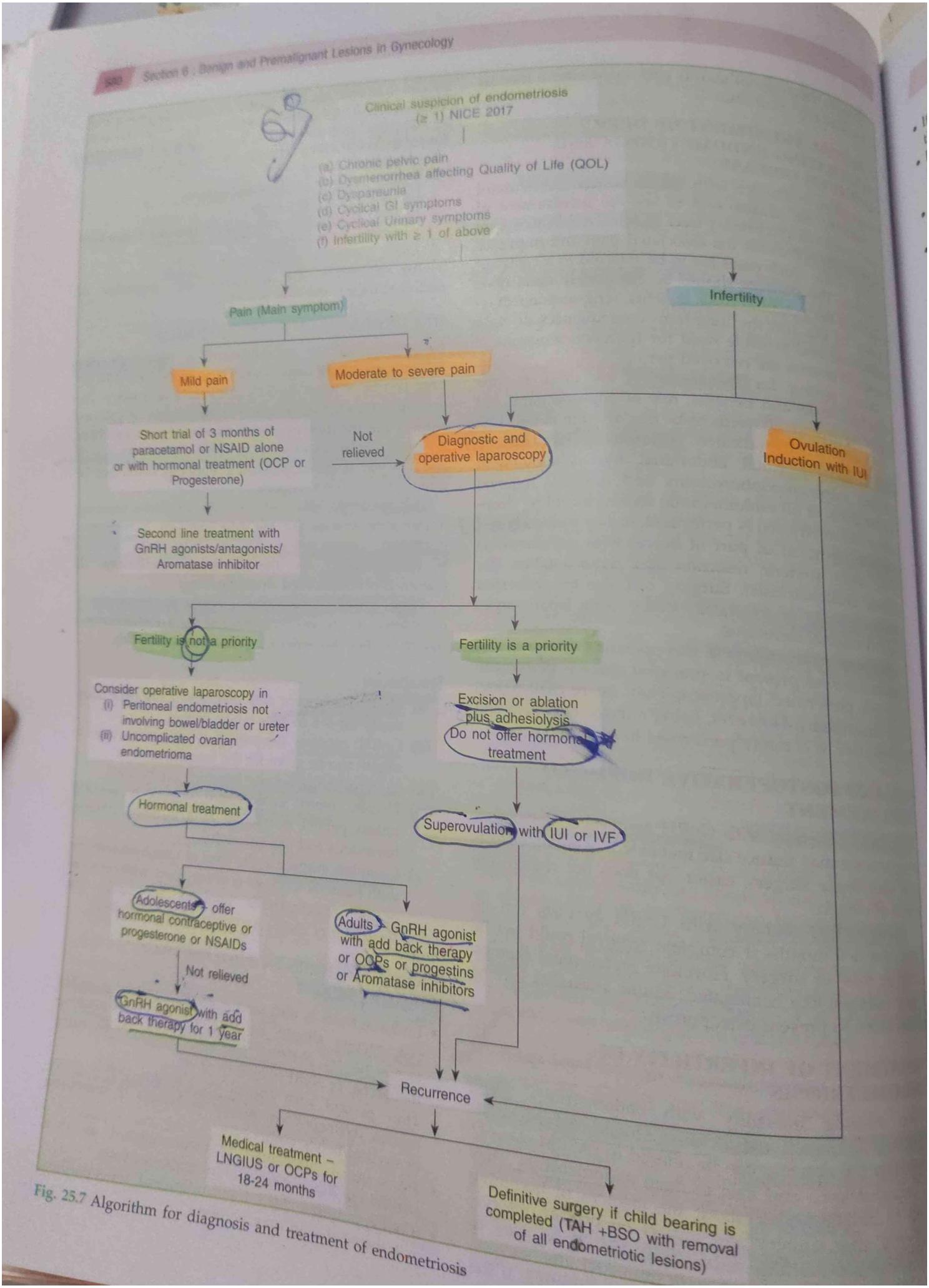


Fig. 25.7 Algorithm for diagnosis and treatment of endometriosis

- If laparoscopy is done, biopsies are taken to confirm the diagnosis histologically.
- Hormonal contraceptives or progestogens are first line hormonal hormone therapy because they may be effective and safe.
- NSAIDs is used as treatment for pain especially if first line hormone treatment is not an option.
- GnRH agonist treatment with add back therapy is the last resort after careful consideration.

SCAR ENDOMETRIOSIS (Fig. 25.8)

Surgical scar can sometimes be a site of endometriotic implantation. It usually follows hysterotomy (1% incidence) but can occur after cesarean section with implantation of endometrial cells (decidua) in the abdominal wall. There is history of delayed wound healing. There is a subcutaneous nodule or deep lying mass in anterior abdominal wall with cyclical local pain tenderness and discoloration (Fig. 25.8). Prevention is proper cleaning and proper closure of uterine and abdominal incision at time of cesarean or hysterotomy to prevent contamination.

Treatment is usually surgical wide excision of scar endometriosis under anesthesia and sending for histopathological examination. Dienogest 2 mg twice daily for 3–6 months or GnRh agonist for 3–6 months can be tried but are less effective.

NEW ADVANCES

Laparoscopic helium plasma coagulation: It is a minimally invasive procedure involving directly an ionised beam of helium gas, used to vaporise endometrial deposits. It causes less lateral burning then diathermy. It can be done on day care basis. Adverse events expected are injury to normal tissue, haemorrhage, infection and helium embolization.

ADENOMYOSIS

Adenomyosis is defined as the presence of endometrial tissue (both glands and stroma) within the myometrium at least 1 high-power field (2.5 mm) from the basal layer of the endometrium. It was called 'endometriosis interna' in older terminology (not used now) in contrast to the term 'endometriosis externa' for endometriosis. It was first described by Rokitansky in 1860.

Incidence: Exact incidence is not known but it is seen in about 10% symptomatic women and in 20–40% hysterectomy specimens (depending upon the histological criteria and degree of sectioning).

ETIOPATHOGENESIS

1. The most widely accepted theory for the development of adenomyosis suggests the downward invagination of the endometrial basalis layer into the myometrium as submucosa is absent at endometrial-myometrial interface. Although superficial invasion can be a normal finding, it is the deeper invasion in myometrium which causes adenomyosis.
2. History of previous pregnancy and uterine surgery may predispose to the invasion of endometrium deep into myometrium.
3. Estrogens and progesterone also play a role in the development and maintenance of adenomyosis as it develops during reproductive age groups and regresses after menopause.
4. **Parity:** Unlike endometriosis (seen in low or nulliparous women), adenomyosis is seen in parous women (90% cases).
5. **Age:** Unlike endometriosis (seen in early reproductive age), adenomyosis is seen in forties and fifties (50–80% women).
6. **Hormonal causes:** Adenomyosis is observed in association with increased aromatization and high estrogen levels. Hence, adenomyosis is often coexistent with other conditions associated with high estrogen levels like leiomyoma, endometriosis and endometrial hyperplasia.
7. Use of selective estrogen receptor modulators (SERMs) like tamoxifen is also associated with increased incidence of adenomyosis.
8. Local prostaglandin production causes dysmenorrhea and heavy menstrual bleeding in adenomyosis.

PATHOLOGY

Adenomyosis is usually of two type.

1. **Diffuse adenomyosis:** It is more common. There is involvement of anterior and posterior walls with uniform enlargement.

Gross examination: Uterus is globally enlarged to medium size and usually does not exceed 12 weeks pregnancy size. The surface contour is usually smooth, regular, reddish and soft (Fig. 25.9 A).

On cut section: The uterine surface appears spongy and trabeculated with focal areas of hemorrhage and thickened myometrium (Fig. 25.9 B).

Microscopic (histopathological) examination: The ectopic foci of endometrial glands and stroma are seen in the myometrium (Fig. 25.9 C). These endometrial

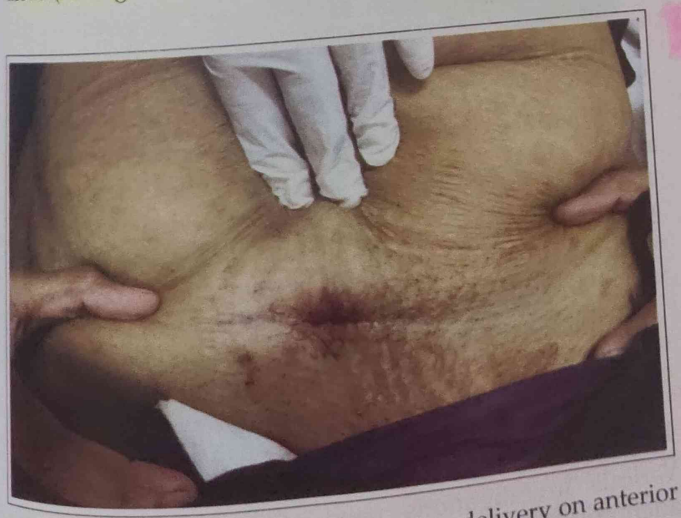


Fig. 25.8 Scar endometriosis after cesarean delivery on anterior abdominal wall

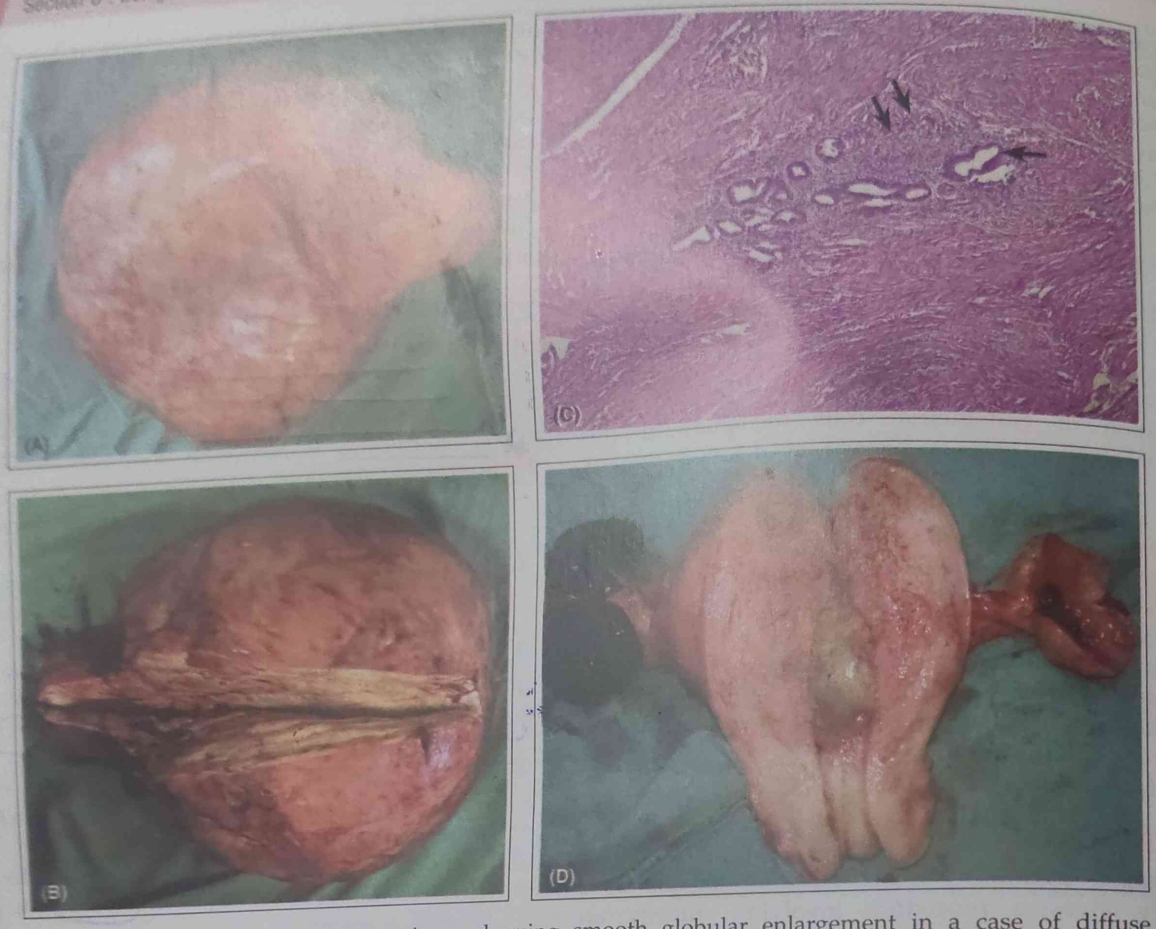


Fig. 25.9 (A) Gross hysterectomy specimen showing smooth globular enlargement in a case of diffuse adenomyosis; (B) Cut section of uterus with adenomyosis showing diffuse thickening of myometrium and hemorrhagic areas of adenomyosis; (C) Histopathological photomicrograph of adenomyosis showing endometrial glands (arrow) and stroma (double arrow) within myometrium (*Kind courtesy:* Prof. Sandeep Mathur, AIIMS, New Delhi); (D) Cut section of a hysterectomy specimen showing focal adenomyoma. Note the absence of capsule or distinct plane of dissection

foci may show proliferative, hyperplastic or secretory changes. There may be areas of hemorrhage due to cyclic changes in them (less common).

2. **Focal localized adenomyosis or adenomyoma:** It is less common and forms a localized nodular swelling in the uterus resembling leiomyoma. However, there is no capsule or distinct plane of dissection in it (unlike leiomyoma with capsule and proper plane of dissection) (Fig. 25.9 D).

   It can sometimes be submucous adenomyoma and may protrude out of cervix as adenomyomatous polyp.

CLINICAL FEATURES

Symptoms

1. Heavy menstrual bleeding (HMB) is seen in 30–35% cases of adenomyosis. It is due to increased prostaglandins production and inadequate myometrial contractility due to enlarged uterus.
2. Dysmenorrhea is seen in 30–35% cases of adenomyosis due to the same reason as HMB. It is usually congestive type of dysmenorrhea increasing with duration of disease and degree of infiltration of myometrium by adenomyosis.
3. Dyspareunia is seen in 10% cases especially around menstruation when uterine tenderness is maximum.

Signs

On bimanual examination uterus is uniformly enlarged and is smooth, soft and globular. The size is usually upto 12 weeks size and is tender on palpation especially around menstruation. Localized adenomyoma is localized swelling in one area of uterus and resembles fibroid but is tender (fibroid is non-tender).

It may sometimes be associated with leiomyoma, endometriosis and endometrial hyperplasia and carcinoma.

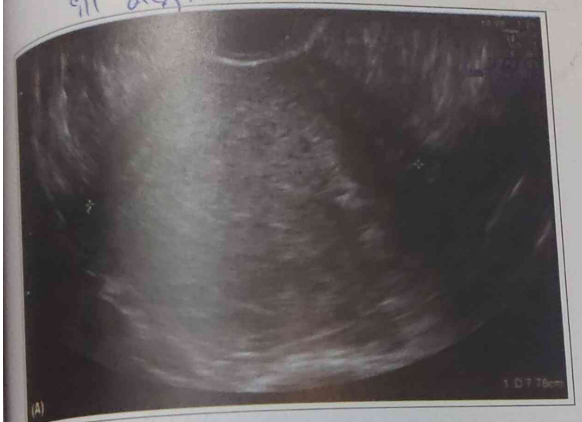
INVESTIGATIONS

Various investigations need to be done to diagnose adenomyosis in clinically suspected cases (dysmenorrhea

and heavy menstrual bleeding in 4th or 5th decades).

Ultrasound: Transabdominal ultrasound does not detect subtle myometrial changes of adenomyosis. Transvaginal ultrasound (TVS) is preferred. Findings on TVS are as follows (Fig. 25.10 A).

(*i*) Globally (uniformly) enlarged uterus
(*ii*) The anterior or posterior myometrial wall containing adenomyosis appears thick.
(*iii*) Heterogeneity of myometrial texture
(*iv*) Small hypoechoic cysts in myometrium (due to cystic glands of ectopic endometrial foci)
(*v*) Striated projections from endometrium to myometrium
(*vi*) Ill-defined endometrial echo. Use of color or power Doppler shows diffuse vascularity in the affected myometrium.



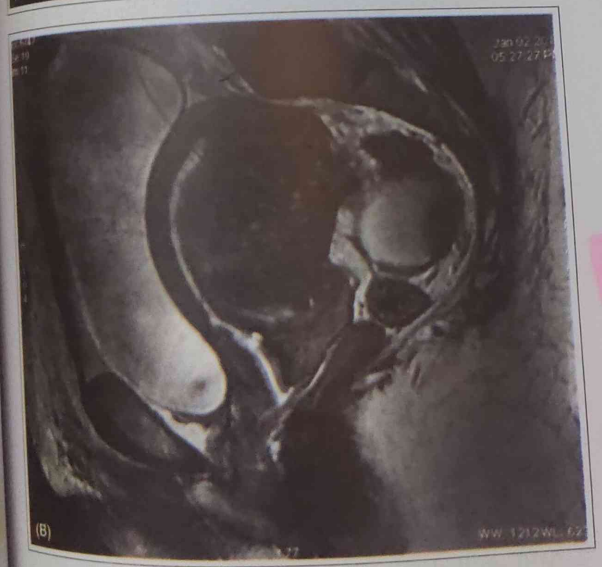


Fig. 25.10 **(A)** Transvaginal ultrasound showing ground glass appearance of Adenomyoma of uterus (*Kind courtesy:* Dr. Ashok Khurana, New Delhi); **(B)** MRI pelvis T2 weighted image showing uterus with diffuse adenomyosis with ill defined, homogenous, low signal intensity areas with sparse high intensity spots.

The revised FIGO (2018) system talks of refined sonographic **MUSA** (Morphologic Uterus Sonographic Assessment) based diagnostic criteria. Identification and evaluation of the junctional zone is best with three-dimensional ultrasonography. The presence of two or more of these criteria are highly associated with a diagnosis of adenomyosis. The eight criteria suggested are as follows (Fig. 25.11):

(*i*) Asymmetrical myometrial thickening
(*ii*) Myometrial cysts
(*iii*) Hyperechoic islands
(*iv*) Fan shaped shadowing
(*v*) Echogenic subendometrial lines and buds
(*vi*) Translesional vascularity where present
(*vii*) Irregular junctional zone
(*viii*) Interrupted junctional zone

2. **Magnetic resonance imaging (MRI):** It is the best modality to diagnose adenomyosis and to differentiate it from leiomyoma. A T2 weighted image usually shows ill-defined, relatively homogeneous low signal intensity (hypoechoic) areas embedded with scattered high intensity spots in the uterine wall. There is thickening of junctional zone in adenomyosis of more than 12 mm. Localized adenomyoma can be confused with leiomyoma even on MRI. However, adenomyoma is usually in the posterior wall of uterus and lacks distinct borders. MRI has higher sensitivity and specificity to detect adenomyosis as compared to TVS.
3. Hysterosalpingography with water-based medium can sometimes demonstrate multiple spiculations or tuft defects extending from endometrium to myometrium in adenomyosis but is not very reliable in the diagnosis of adenomyosis.
4. Hysteroscopic myometrial biopsy of the posterior uterine wall with use of 5 mm loop electrode can diagnose adenomyosis on histological examination, but is rarely performed.
5. Hormone receptor studies have demonstrated estrogen (all cases) and progesterone (60% cases) receptors in adenomyosis.

MANAGEMENT

The main goal of treatment is relief from main symptoms of pain and heavy menstrual bleeding. The medical treatment resembles endometriosis but is less effective.

Medical Treatment

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs):** The drugs like mefenamic acid or ibuprofen can be given to young women with dysmenorrhea and heavy menstrual bleeding but the results are unsatisfactory. These drugs are used as a temporary measure before definitive surgery.
2. **Combined oral contraceptive pills:** They induce endometrial atrophy and decrease prostaglandin production to improve dysmenorrhea and heavy menstrual bleeding but are less effective.

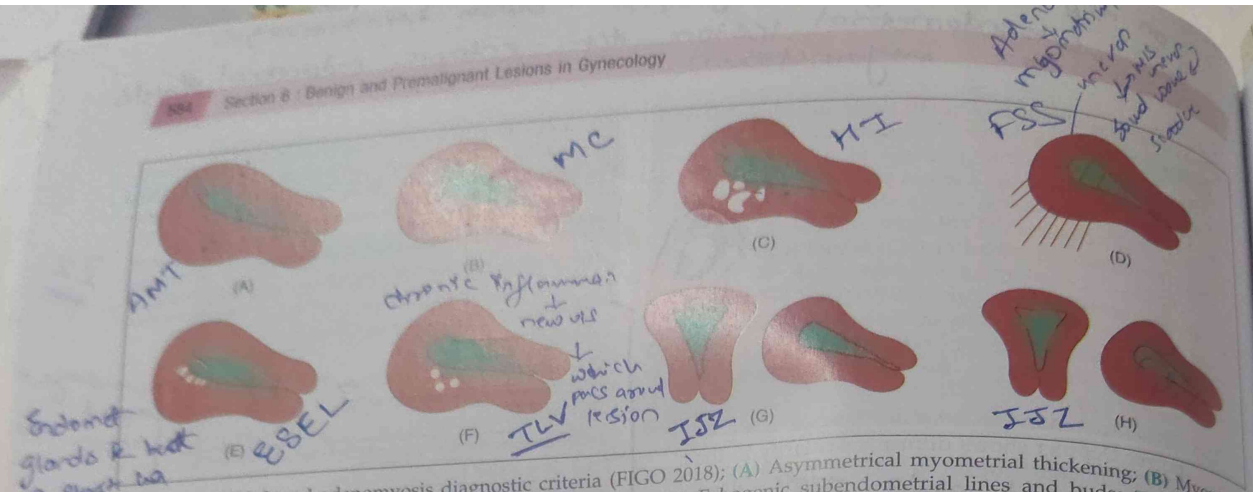


Fig. 25.11: MUSA based adenomyosis diagnostic criteria (FIGO 2018); **(A)** Asymmetrical myometrial thickening; **(B)** Myometrial cysts; **(C)** Hyperechoic islands; **(D)** Fan shaped shadowing; **(E)** Echogenic subendometrial lines and buds; **(F)** Translesional vascularity; **(G)** Irregular junctional zone; **(H)** Interrupted junctional zone

3. **Progestogens:** All progestogens mentioned in the treatment of endometriosis can be tried to induce endometrial atrophy and to decrease PGs but are less effective. Dienogest in double dose of 2 mg twice daily (once daily in endometriosis) for 4–6 months has been found to be somewhat effective for adenomyosis but is much less effective than for endometriosis.
4. **GnRH agonists:** Goserelin or leuprolide depot are used once a month for 3–6 months in women with adenomyosis with infertility, before surgery for pain relief and to decrease size of adenomyoma and vascularity. However, symptoms recur after stopping GnRH agonists. Long-term use can have side effects (see earlier in endometriosis).
5. Aromatase inhibitors like anastrozole have been used after conservative surgery but are not very effective.
6. LNG-IUS (levonorgestrel intrauterine system, Mirena) has been found to be useful in the management of adenomyosis by causing decidualization and atrophy of adenomyosis foci. There is reduction in menstrual blood flow, dysmenorrhea and decrease in size of adenomyotic foci and of uterus. There is reduction in PGs production also.
7. Danazol is less desirable due to androgenic side effects.
8. Danazol loaded intrauterine device has been developed and causes reduction in pain and menstrual bleeding but is still in experimental stage.

SURGICAL TREATMENT

Surgical treatment is usually required for most patients of adenomyosis.

1. **Hysterectomy:** It is the definitive treatment and is the most commonly used effective modality especially in women in their 40s and 50s with completed family. It is also performed after failure of medical treatment. Another indication is adenomyosis associated with other pathologies like leiomyoma, endometriosis endometrial hyperplasia where fertility is not desired. Hysterectomy can be done by laparotomy, laparoscopically or vaginally. Ovaries may be conserved if they are normal and there is no associated endometriosis.
2. **Conservative surgery:** It is performed in younger women who want to preserve their uterus.
   (*i*) Endometrial ablation or resection can be performed hysteroscopically for cases of heavy menstrual bleeding associated with adenomyosis. However, the failure rate is high. Moreover, it can cause adenomyosis as the endometrium can easily invade myometrium after resection.
   (*ii*) **Adenomyomectomy:** If there is localized adenomyoma, it can be resected laparoscopically or on laparotomy. However, it is difficult to perform as there is no capsule which presents difficulty in finding plane of dissection.
   (*iii*) **Myometrial reduction or resection:** It can be tried laparoscopically or on laparotomy by partial resection of uterine walls containing adenomyotic foci. It reduces volume of uterus and disease helping in reducing heavy menstrual bleeding and dysmenorrhea.

INTERVENTIONAL TECHNIQUES

1. Uterine artery embolization (UAE) has been used in patients of adenomyosis to relieve symptoms. On a follow-up of 5 years, 65% women have improved.
2. MRI guided focussed ultrasound surgery (MRgFUS) has been found to be effective in small studies in symptomatic relief of adenomyosis. It destroys the focal adenomyosis. However, it is still not an established treatment.