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ENDOMETRIOSIS

INTRODUCTION

- Endometriosis is defined as endometrial glands and stroma that occur outside the uterine cavity
- The lesions are typically located in the pelvis but can occur at multiple sites including the bowel, diaphragm, and pleural cavity

SITES OF INVOLVMENT

- Superficial Peritoneal lesions
- Ovarian lesion
- Deeply infiltrating endometriosis
- Multiple sites including the bowel, diaphragm, and pleural cavity

CLINICAL MANIFESTATIONS

- **Patient presentation:**
- Women with endometriosis classically present during their reproductive years with pelvic pain (including dysmenorrhea and dyspareunia), infertility, or an ovarian mass
- Women can also present with endometriosis that was incidentally diagnosed during surgery or imaging for other indications
- While the peak prevalence of endometriosis occurs in women 25 to 35 years of age , the disease has been reported in premenarcheal girls and in 2 to 5 percent of postmenopausal women
- In a study of 1000 women with endometriosis, approximately 80 percent presented with pain, 25 percent with infertility, and 20 percent with an endometrioma (ovarian mass)

- Endometriosis should be suspected in women with infertility, dysmenorrhea, dyspareunia, or chronic pelvic pain, although these symptoms can be associated with other diseases
- Endometriosis can be associated with significant gastrointestinal symptoms (pain, nausea, vomiting, early satiety, bloating and distention, altered bowel habits). A characteristic motility change (ampulla of Vater–duodenal spasm, a seizure equivalent of the enteric nervous system, along with bacterial overgrowth) is documented in most women with the disease

Pain

- In adult women, dysmenorrhea may be especially suggestive of endometriosis if it begins after years of pain-free menses. Dysmenorrhea often starts before the onset of menstrual bleeding and continues throughout the menstrual period. In adolescents, the pain may be present after menarche without an interval of pain-free menses.
- Dysmenorrhea associated with endometriosis is dull or crampy pelvic pain that typically begins one to two days before menses, persists throughout menses, and can continue for several days afterward. Pelvic pain is typically chronic and described as dull, throbbing, sharp, and/or burning . Pelvic pain or pressure are also the most common symptoms associated with an adnexal mass
- The distribution of pain is variable but most often is bilateral. Local symptoms can arise from rectal, ureteral, and bladder involvement, and lower back pain can occur. Some women with extensive disease have no pain, whereas others with only minimal to mild disease may experience severe pelvic pain

- Possible mechanisms causing pain in patients with endometriosis include local peritoneal inflammation, deep infiltration with tissue damage, adhesion formation, fibrotic thickening, and collection of shed menstrual blood in endometriotic implants, resulting in painful traction with the physiologic movement of tissues
- The character of pelvic pain is related to the anatomic location of deep endometriotic lesions . Severe pelvic pain and dyspareunia may be associated with deep endometriosis . In rectovaginal endometriotic nodules, a close histologic relationship was observed between nerves and endometriotic foci and between nerves and the fibrotic component of the nodule. Increasing evidence suggests a close relationship between the density of innervation of endometriotic lesions and pain symptoms

Infertility

- Trend toward a reduced MFR in infertile women with minimal to mild endometriosis when compared to women with unexplained infertility. Endometriotic ovarian cysts that negatively affect the rate of spontaneous ovulation
- Dose–effect relationship: A negative correlation between the r-AFS stage of endometriosis and the MFR and cumulative pregnancy rate
- Reduced MFR and cumulative pregnancy rate after donor sperm insemination in women with minimal to mild endometriosis when compared to those with a normal pelvis
- Reduced implantation rate per embryo after in vitro fertilization (IVF) in women with endometriosis when compared to women with tubal factor infertility
- Increased MFR and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis

- When endometriosis is moderate or severe, involving the ovaries and causing adhesions that block tubo-ovarian motility and ovum pickup, it is associated with infertility
- Numerous mechanisms (ovulatory dysfunction, luteal insufficiency, luteinized unruptured follicle syndrome, recurrent abortion, altered immunity, and intraperitoneal inflammation) are proposed as explanations, but an association between fertility and minimal or mild endometriosis remains controversial

Endocrinologic Abnormalities

- Endometriosis is associated with anovulation, abnormal follicular development with impaired follicle growth, reduced circulating E2 levels during the preovulatory phase, disturbed luteinizing hormone (LH) surge patterns, premenstrual spotting, luteinized unruptured follicle syndrome, and galactorrhea, and hyperprolactinemia

Extrapelvic Endometriosis

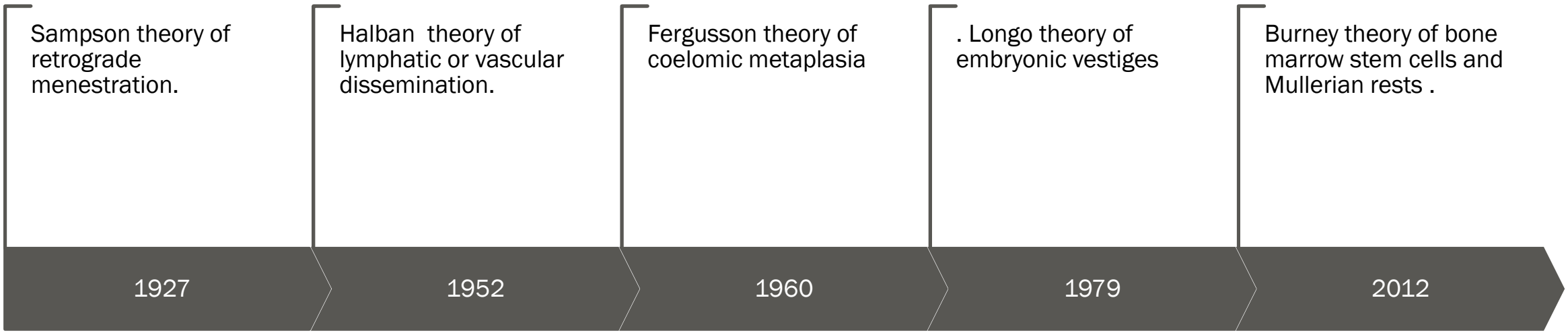
- Extrapelvic Endometriosis Extrapelvic endometriosis, although often asymptomatic, should be suspected when symptoms of pain or a palpable mass occur outside the pelvis in a cyclic pattern, Endometriosis involving the intestinal tract (especially colon) is the most common site of extrapelvic disease and may cause abdominal and back pain, abdominal distention, cyclic rectal bleeding, constipation, and obstruction.
- Ureteral involvement can lead to obstruction and result in cyclic pain, dysuria, and hematuria.
- Endometriosis lesions on the diaphragm often result in cyclic shoulder pain. Pulmonary endometriosis can manifest as pneumothorax, hemothorax, or hemoptysis during menses.
- Umbilical endometriosis should be suspected when a patient has a palpable mass and cyclic pain in the umbilical area

EPIDEMIOLOGY AND RISK FACTORS

- Determining the prevalence of endometriosis in the general population is challenging because some women are asymptomatic, those with symptoms can have varied and nonspecific presentations, and definitive diagnosis typically requires surgery
- While the prevalence varies with the population being studied, approximately 10 percent of reproductive-age women globally have endometriosis

- Factors associated with an increased risk of endometriosis include nulliparity , prolonged exposure to endogenous estrogen (eg, early menarche [before age 11 to 13 years] or late menopause), shorter menstrual cycles (defined as ≤27 days) , heavy menstrual bleeding , obstruction of menstrual outflow (eg, müllerian anomalies), exposure to diethylstilbestrol in utero , height greater than 68 inches , lower body mass index , exposure to severe physical and/or sexual abuse in childhood or adolescence , and a high consumption of trans unsaturated fat
- Factors associated with a decreased risk of endometriosis include multiple births , extended intervals of lactation , and late menarche (after age 14 years) . Increased consumption of long-chain omega-3 fatty acids has been associated with a reduced risk of endometriosis in one prospective study . Race may also be a risk factor, as the prevalence of endometriosis has been reported as being higher in White and Asian women compared with Black and Hispanic women , smoking and OCPs

PATHOGENESIS



- Immunobiology
- Genetics
- Molecular mechanisms : Estrogen production, prostaglandin production, progesterone resistance
- Epigenetics changes

- The type of endometriosis is suggested by the constellation of symptoms. Examples include:
- Women with peritoneal or deeply infiltrating endometriosis often present with dyspareunia. Deeply infiltrating endometriosis lesions can occur on the uterosacral and cardinal ligaments, pouch of Douglas, posterior vaginal fornix, and anterior rectal wall . Introital, or superficial, dyspareunia can result from lesions of the cervix , hymen, perineum , and episiotomy scars
- Women with bladder endometriosis typically present with nonspecific urinary symptoms of frequency, urgency, and pain at micturition . Symptoms can be worsened with menses. Ureteral endometriosis can be asymptomatic or associated with colicky flank pain or gross hematuria
- Women with bowel endometriosis can present with diarrhea, constipation, dyschezia, and bowel cramping. Women with deeply infiltrating endometriosis implants of the posterior cul-de-sac and rectovaginal septum typically present with dyspareunia and painful defecation. Rectal bleeding may occur but is rare

- Women with thoracic endometriosis can present with chest pain ,pneumothorax or hemothorax ,hemoptysis, or scapular or cervical (neck) pain.
- A cohort study including over 600 women with endometriosis identified a visceral syndrome of seven symptoms associated with endometriosis that included abdominal pain with no relation to menstruation, pain during urination, pain during defecation, constipation or diarrhea, irregular bleeding, nausea or vomiting, and feeling tired or lacking energy
- The severity of endometriosis does not correlate with the number and severity of symptoms; women with advanced disease may have few or no symptoms and those with minimal or mild disease may have incapacitating pain. **However, in women with deep infiltrating endometriosis, the severity of pain generally correlates with the depth and volume of disease**

- **Physical examination** :
- Physical examination findings in women with endometriosis are variable and depend upon the location and size of the implants.
- Physical examination has its greatest diagnostic sensitivity when performed during menstruation , but even then a normal examination does not exclude the diagnosis.
- Findings suggestive of endometriosis include tenderness on vaginal examination, nodules in the posterior fornix, adnexal masses, and immobility or lateral placement of the cervix or uterus
- Occasionally, speculum examination may reveal characteristic blue-colored implants or red proliferative lesions that bleed on contact, both usually in the posterior fornix
- While physical examination findings are helpful, the examination can also be normal; lack of findings does not exclude the disease.

- **Laboratory**:
- There are no pathognomonic laboratory findings for endometriosis. While several urinary and endometrial biomarkers have been studied for the noninvasive diagnosis of disease, none are clinically useful.
- CA-125 is a cell surface antigen expressed by derivatives of the coelomic epithelium (including the endometrium) and is well established as a useful marker for the monitoring of women with epithelial ovarian cancer.
- Serum cancer antigen (CA) 125 concentration can be elevated in women with endometriosis (ie, greater than 35 units/mL)
- Although the role of serum CA 125 in primary diagnosis is undefined . However, serum CA 125 concentrations are not routinely ordered in women being evaluated or treated for endometriosis because other diseases, notably ovarian carcinoma, also elevate the serum CA 125 concentration , also during early pregnancy and normal menstruation, and in women with acute pelvic inflammatory disease or leiomyomata. Serum CA-125 concentrations vary somewhat across the menstrual cycle; in general, levels are highest during the menstrual phase and lowest during the midfollicular and periovulatory phases of the cycle

- Overall, the serum CA-125 concentration does not have the necessary sensitivity to be an effective screening test for the diagnosis of endometriosis. Whereas the serum CA-125 generally is not a reliable predictor of the effectiveness of medical therapy, a sustained elevation of serum CA-125 after surgical treatment predicts a relatively poor prognosis.
- Circulating microRNAs: Thousands of miRNAs circulate in the bloodstream and hence offer the possibility to serve as precise biomarkers of disease
- While the mechanism by which miRNA levels are altered is not fully understood, their serum/plasma levels correlate with levels in cancer tissues, suggesting that miRNAs are shed from tissue and released into the circulation. Microarray expression profiling has also demonstrated altered systemic serum miRNA concentrations in women with endometriosis
- Measurement of these miRNAs may represent a novel, noninvasive diagnostic test for early detection and intervention of endometriosis, and is currently under development

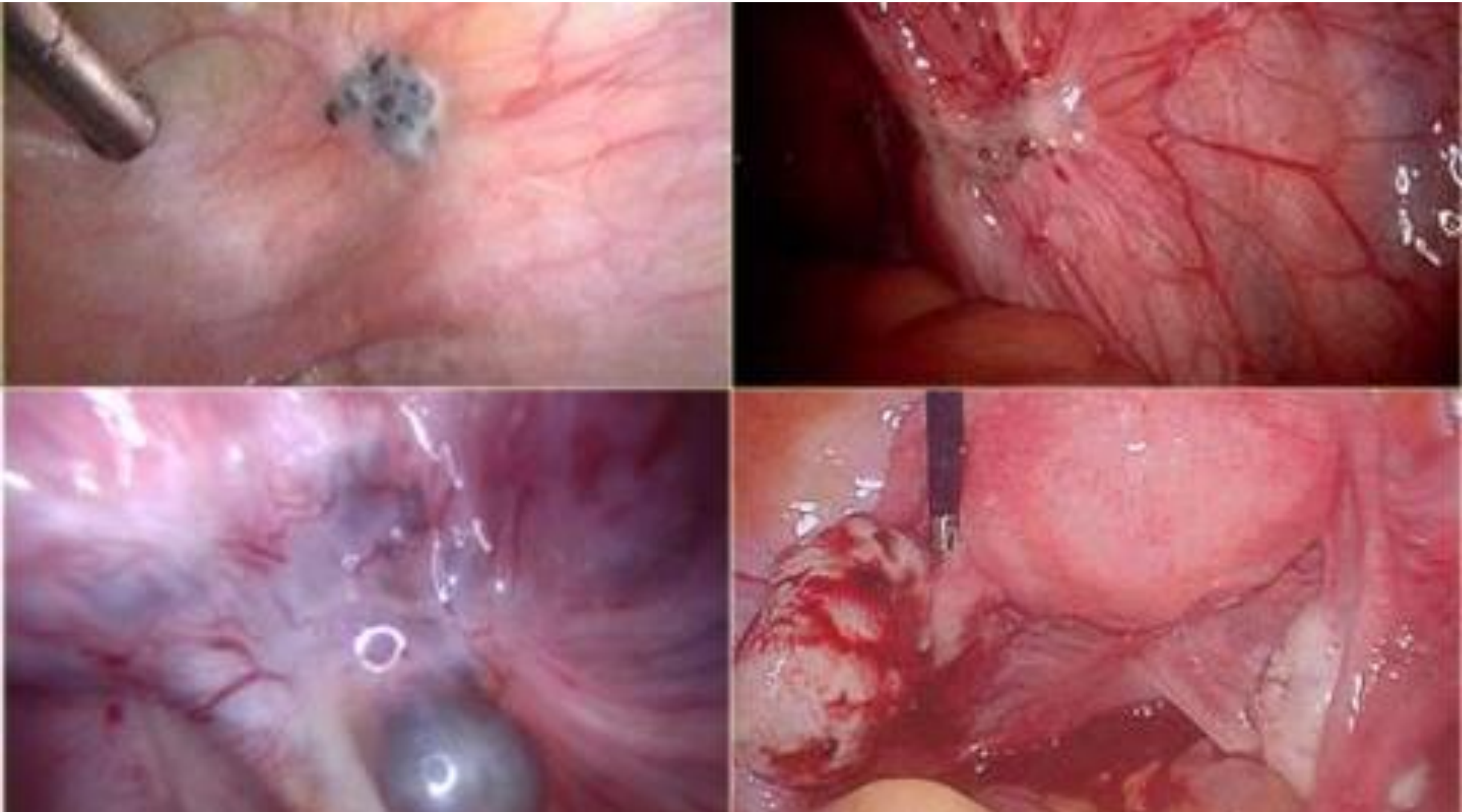
DIAGNOSIS

Definitive diagnosis — Endometriosis is definitively diagnosed by histologic evaluation of a lesion biopsied during surgery (typically laparoscopy)

- While visual confirmation of endometriosis without biopsy is considered diagnostic by some experts, visual confirmation alone is of limited value because the accuracy is impacted by the surgeon's expertise
- Definitive diagnosis of endometriosis is often delayed because the symptoms of endometriosis are vague, the symptoms overlap with a number of gynecologic and gastrointestinal processes, and a surgical diagnosis entails risk. Studies have reported an average diagnostic delay of 7 to 12 years in women with endometriosis.

- The optimal time during the menstrual cycle to perform laparoscopy is not clear, although some may recommend that surgery generally should not be performed during or within 3 months after hormonal medical treatment

- The classic peritoneal implant is a blue-black “powder- burn” lesion (containing hemosiderin deposits from entrapped blood) with varying amounts of surrounding fibrosis, typically observed on the ovaries and on peritoneal surfaces in the cul-de-sac, uterosacral ligaments, and ovarian fossa. However, the majority of implants are “atypical, ” appearing white and opaque, red and flame-like, or vesicular.



- Stage I: Minimal endometriosis—isolated superficial disease on the peritoneal surface with no significant associated adhesions
- Stage II: Mild endometriosis—scattered superficial disease on the peritoneal surface and ovaries, totaling less than 5 cm in aggregate, with no significant associated adhesions
- Stage III: Moderate endometriosis—multifocal disease, both superficial and invasive (including endometriomas >1 cm), that may be associated with adhesions involving the fallopian tubes and/or the ovaries
- Stage IV: Severe endometriosis—multifocal disease, both superficial and invasive, including large ovarian endometriomas, usually associated with adhesions, both filmy and dense, involving the fallopian tubes, ovaries, and cul-de-sac

Role of presumptive diagnosis:

- While definitive diagnosis requires tissue biopsy and histologic confirmation, the combination of symptoms, signs, and imaging findings can be used to make a presumptive, nonsurgical diagnosis of endometriosis
- . A clinical diagnosis can be sufficient to initiate therapy that is low risk and easily tolerated (eg, estrogen-progestin contraceptives in women who are not trying to conceive). However, the presence or absence of a response to empiric treatment cannot be construed as definitive confirmation or exclusion of the diagnosis

Nonsurgical diagnosis — Possible options for non-surgical diagnosis include clinical diagnosis based upon examination and imaging findings or serum diagnosis using microRNA markers.

- A nonsurgical diagnosis of endometriosis includes: (1) ultrasonographic finding of ovarian endometrioma, (2) visual inspection of the posterior vaginal fornix and biopsy of rectovaginal lesions, (3) cystoscopic evaluation and biopsy of detrusor lesions, and (4) physical examination findings of rectovaginal endometriosis that are confirmed with imaging . Although this approach does not require laparoscopy, tissue biopsy can still provide a definitive diagnosis while imaging findings make the diagnosis highly likely. Of note, this approach is useful only for clinicians with significant skill in the examination, sonography, and cystoscopy of women with endometriosis.