Endometriosis

Clinical features and diagnostic evaluations

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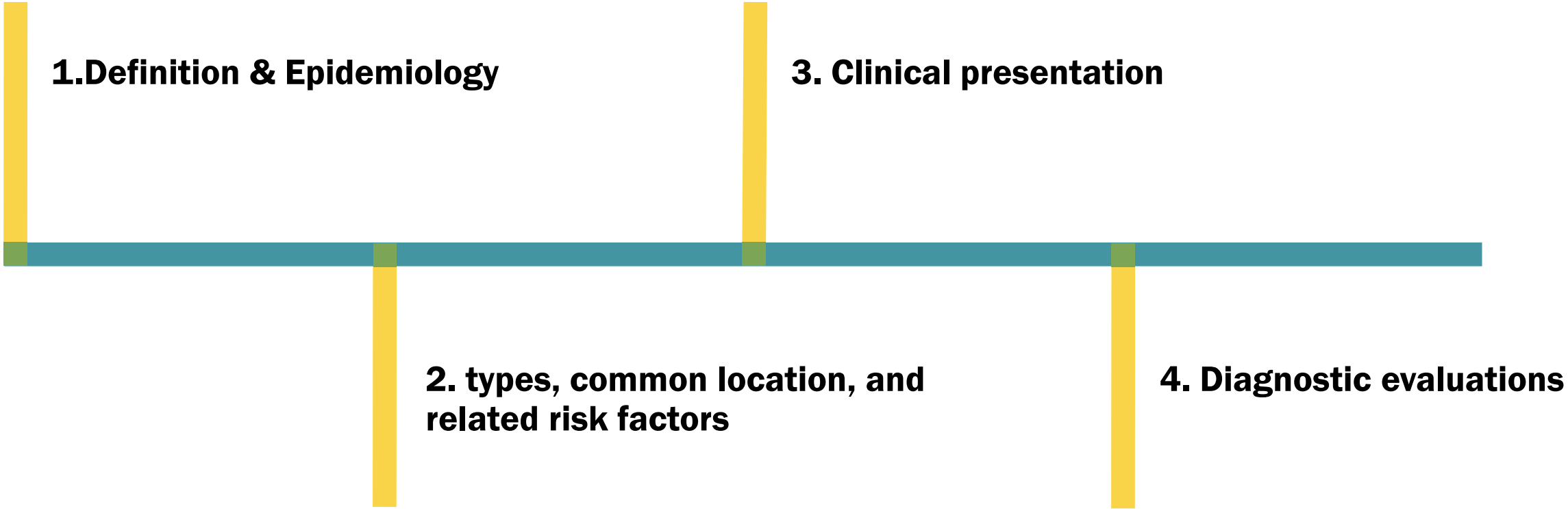
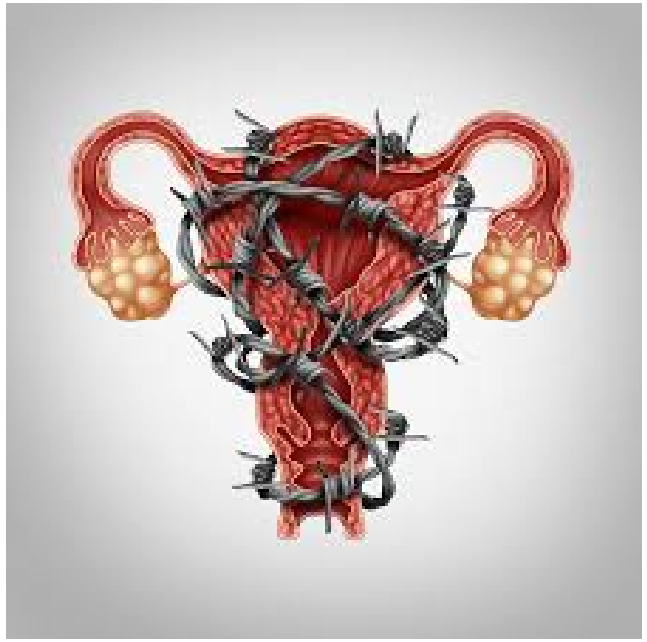
May , 2021


1.Definition & Epidemiology
3. Clinical presentation
2. types, common location, and related risk factors
4. Diagnostic evaluations

Definition

- presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction(Sarria-Santamera et al., 2021).

- The mean age at time of diagnosis ranges between 25 to 35 years old.
- It is 6 to 7 times more prevalent among the first-degree relatives of affected women than in the general population.



Epidemiology

- Based on the study performed by Antonio et al. in 2021, pooled incidence rate of endometriosis was:

    1. 1.36 per 1000 person-years for studies based on hospital discharges
    2. 3.53 per 1000 person-years for cohort studies
    3. 1.89 per 1000 person-years for population-based integrated information systems

- Endometriosis is rare in premenarchal girls but may be identified in 50–70% of adolescents and young women under age 20 with complaints of chronic pelvic pain or dyspareunia(Hirsch, Dhillon-Smith, Cutner, Yap, & Creighton, 2020).

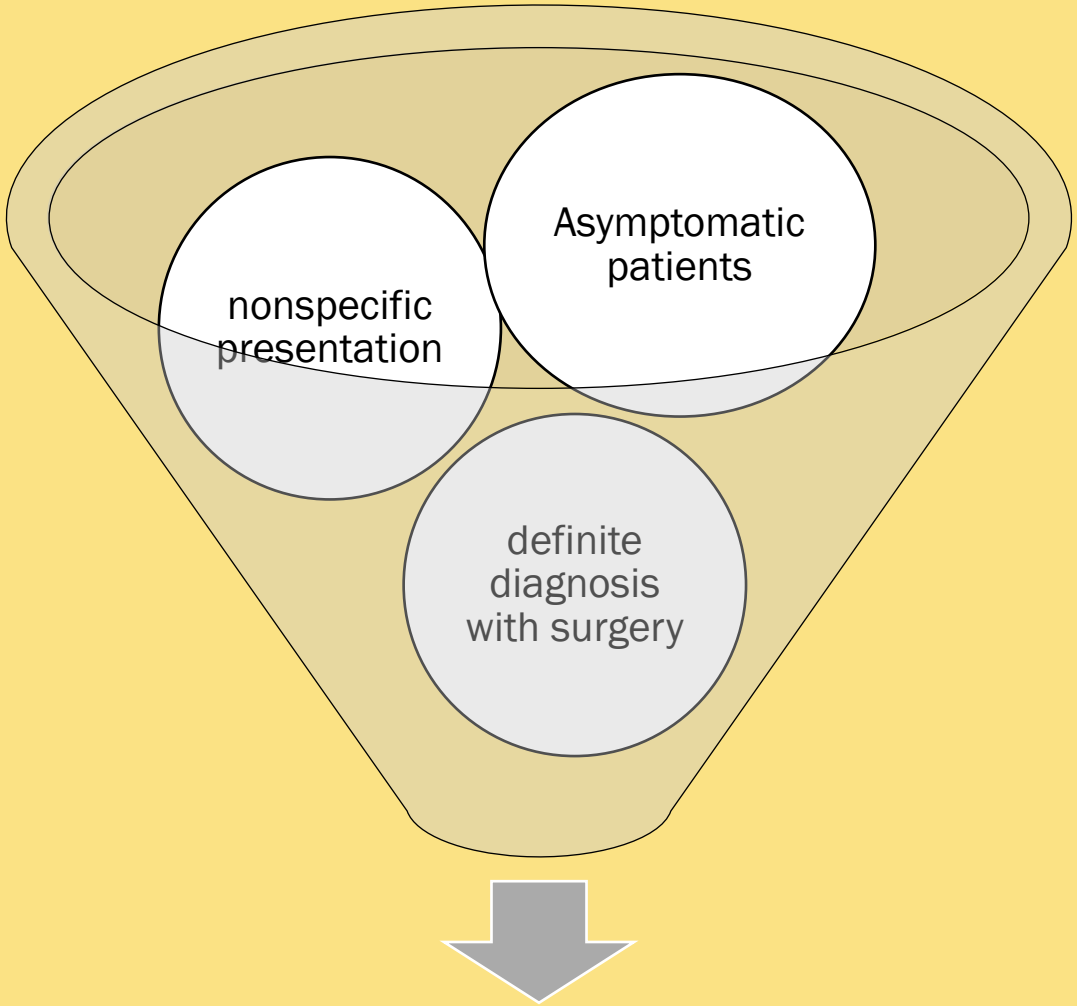
- Most cases in young women under age 17 are associated with Mullerian anomalies that include cervical or vaginal obstruction.

- Fewer than 5% of women who require surgery for endometriosis are postmenopausal, and most have received estrogen therapy.

- The prevalence of asymptomatic endometriosis may be somewhat lower in Blacks and higher in Asians than in White women, although the biologic basis for these differences is not clear.

- Interestingly, the prevalence of endometriosis is inversely related to body mass index.

- In a meta-analysis of 13 case-control studies including nearly 8000 women with epithelial ovarian cancers(EOC), women with a self-reported history of endometriosis had three times the risk of clear cell EOC and double the risk of endometrioid and low-grade serous EOC but no change in risk of high-grade serous or mucinous EOC.



Challenge in Determining the prevalence of endometriosis in the general population

Pathogenesis:

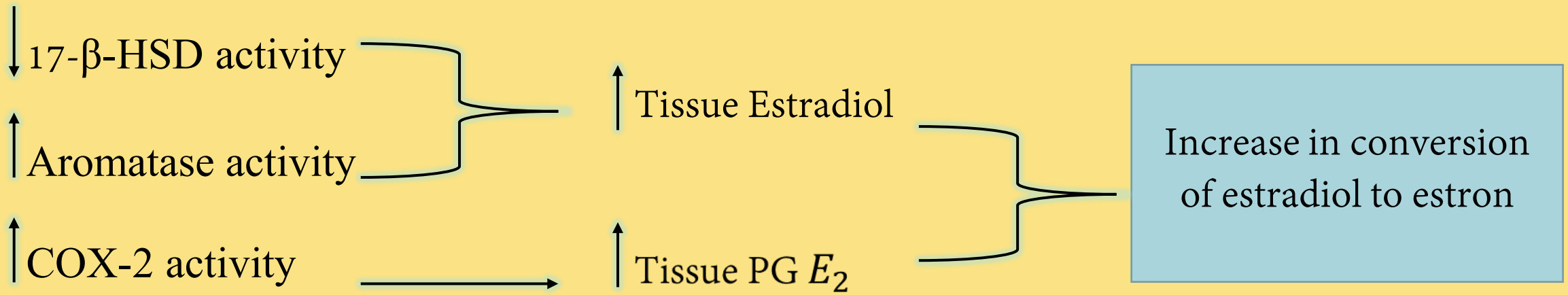
- Multifactorial:

1. Ectopic endometrial tissue
2. Altered immunity
3. Imbalanced cell proliferation and apoptosis: somatic mutation in 79 % of deep endometriosis lesion(Anglesio et al., 2017)
4. Aberrant endocrine signaling
5. Genetic factors: at least, six genomic regions are statistically associated(Rahmioglu et al., 2014)

Main differences between women with endometriosis and healthy ones:

1. Increase in localized estrogen production
2. Increase in localized prostaglandin production
3. Resistance to progesterone and its activity

In women with endometriosis:



Sampson's theory of retrograde menstruation:

- Endometrial cells flow backwards through the fallopian tubes and into the peritoneal cavity during menses.
- Other potential sources of ectopic endometrial cells:
    1. Mesothelium, stem cells, Mullerian rests(Burney & Giudice, 2012)
    2. Bone marrow stem cells(Burney & Giudice, 2012)
    3. Embryonic vestiges(Longo, 1979)
    4. Lymphatic or vascular dissemination(Javert, 1952)
    5. Coelomic metaplasia

Risk of endometriosis

Increase by:

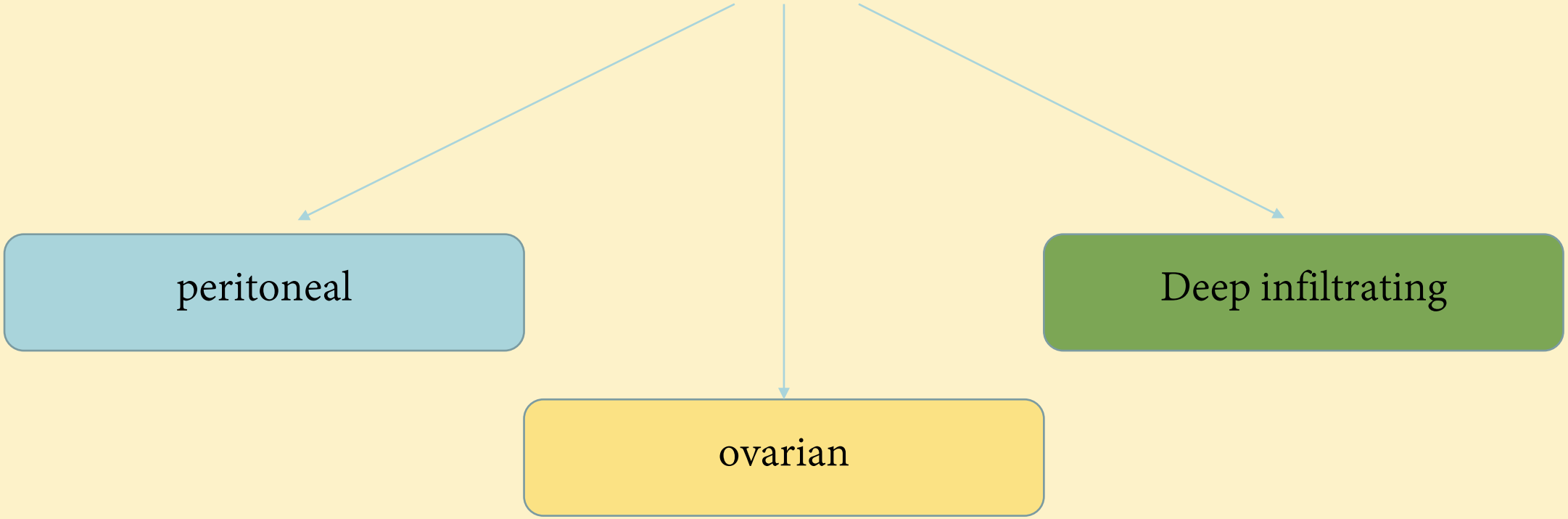
- Nulliparity
- Early menarche
- Late menopause
- Menstrual cycles ≤ 27 days
- Heavy menstrual bleeding
- Obstruction of menstrual outflow
- Prolonged exposure to endogenous estrogen
- Height greater than 68 inches
- Lower body mass index
- Exposure to severe physical or sexual abuse in childhood or adolescence
- High consumption of trans unsaturated fat
- Heavy consumption of alcohol and caffeine
- Exposure to diethylstilbestrol in utero

Risk of endometriosis

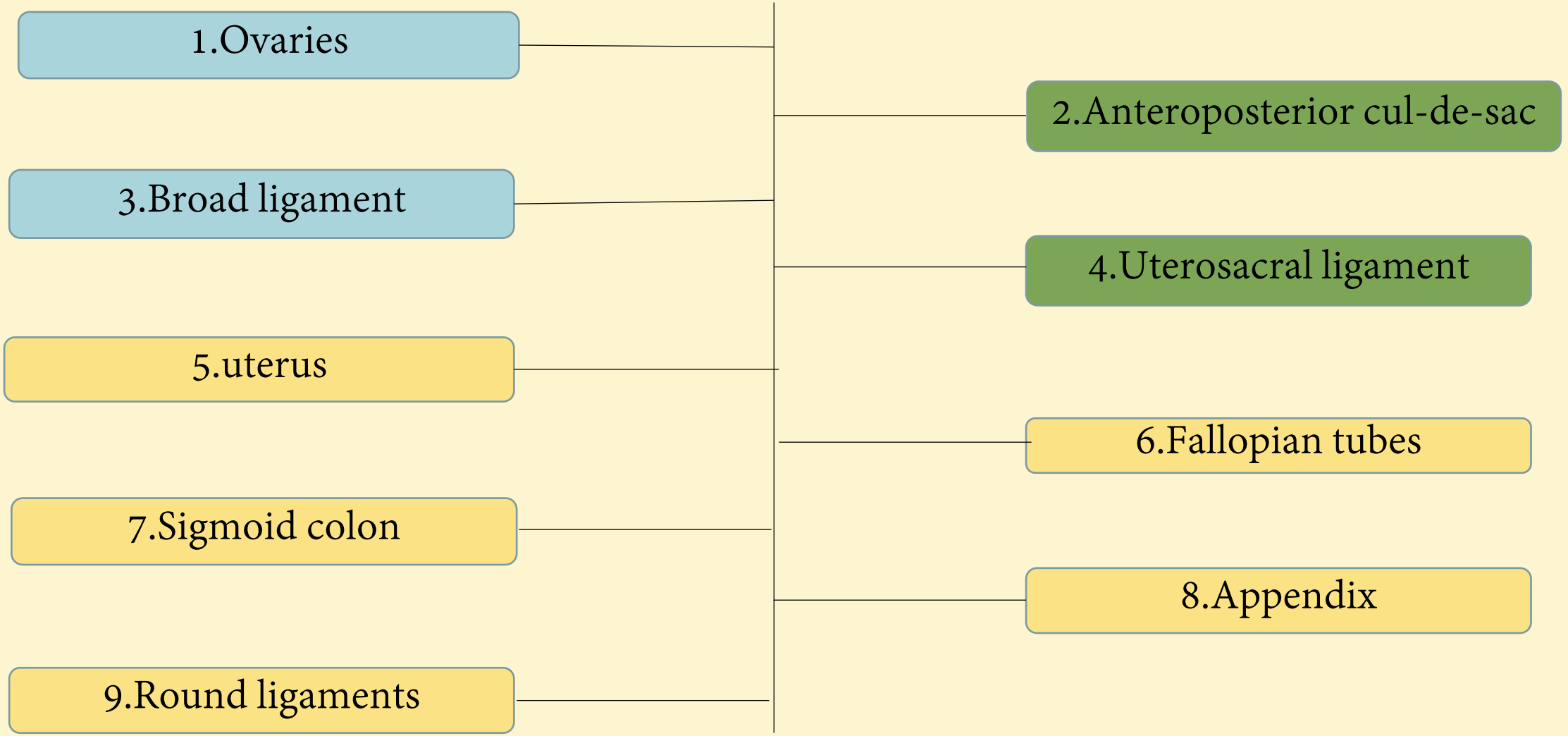
Decrease by:

- Pregnancy
- Multiple births
- Prolonged periods of lactation
- Regular exercise
- Smoking
- Late menarche
- Increased consumption of long-chain omega-3 fatty acid

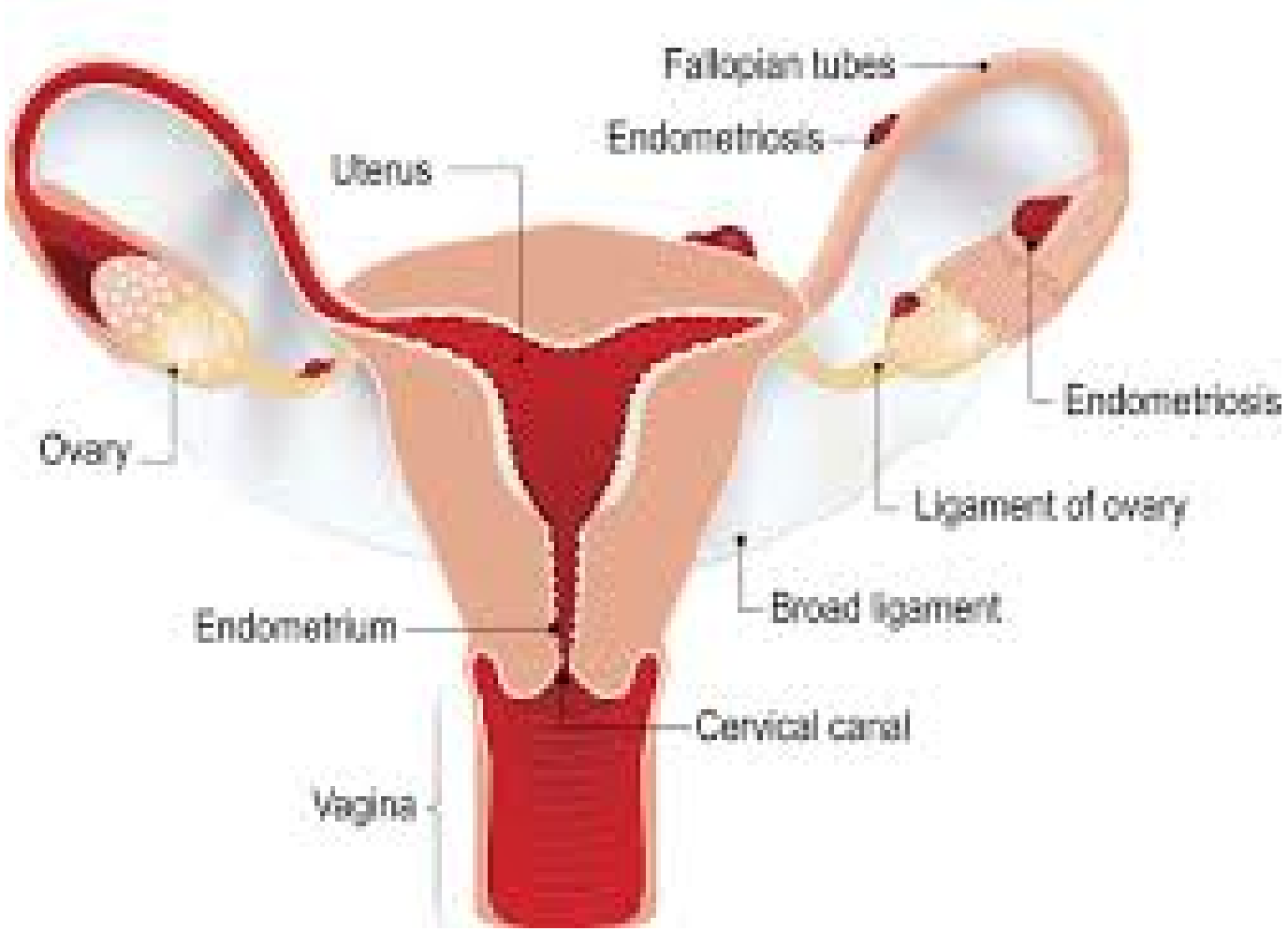
main types of endometriosis



Most common sites of endometriosis (in decreasing order of frequency)



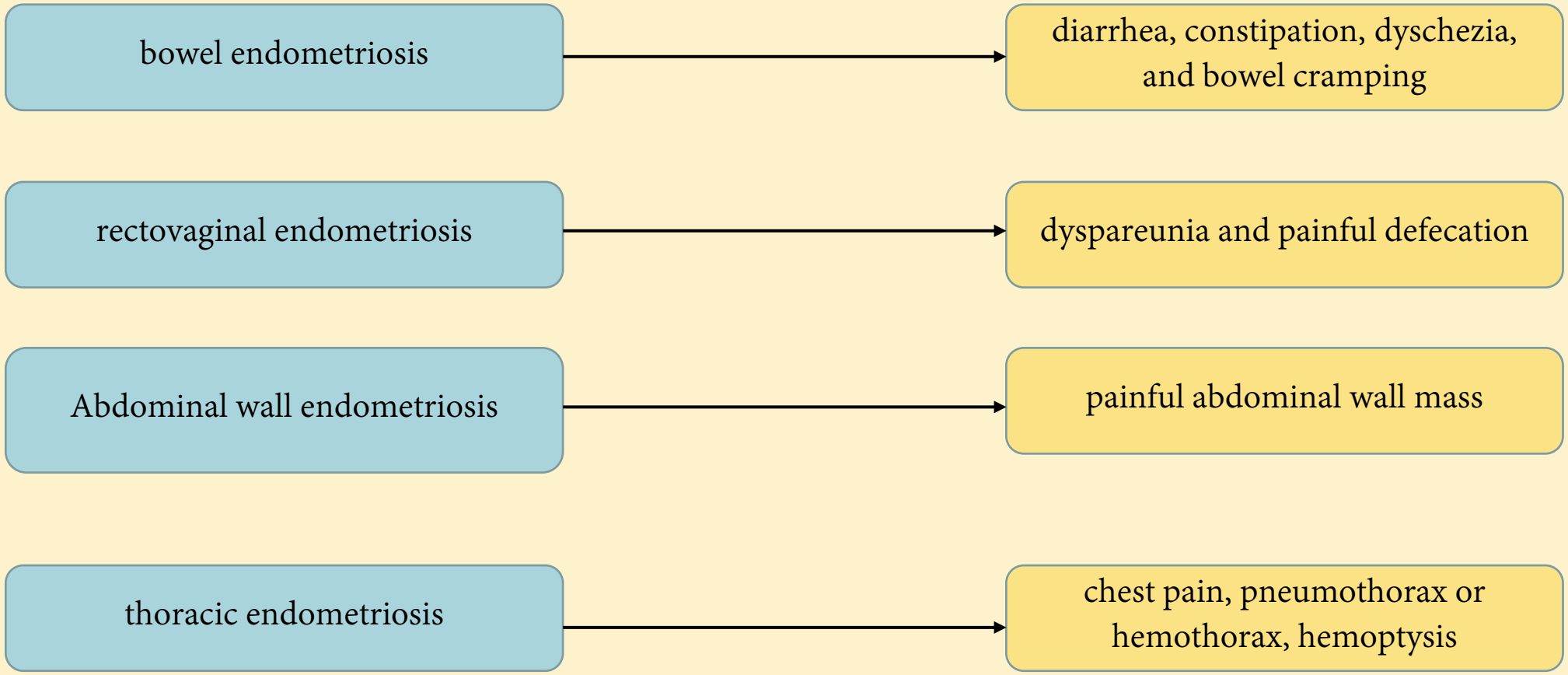
ENDOMETRIOSIS

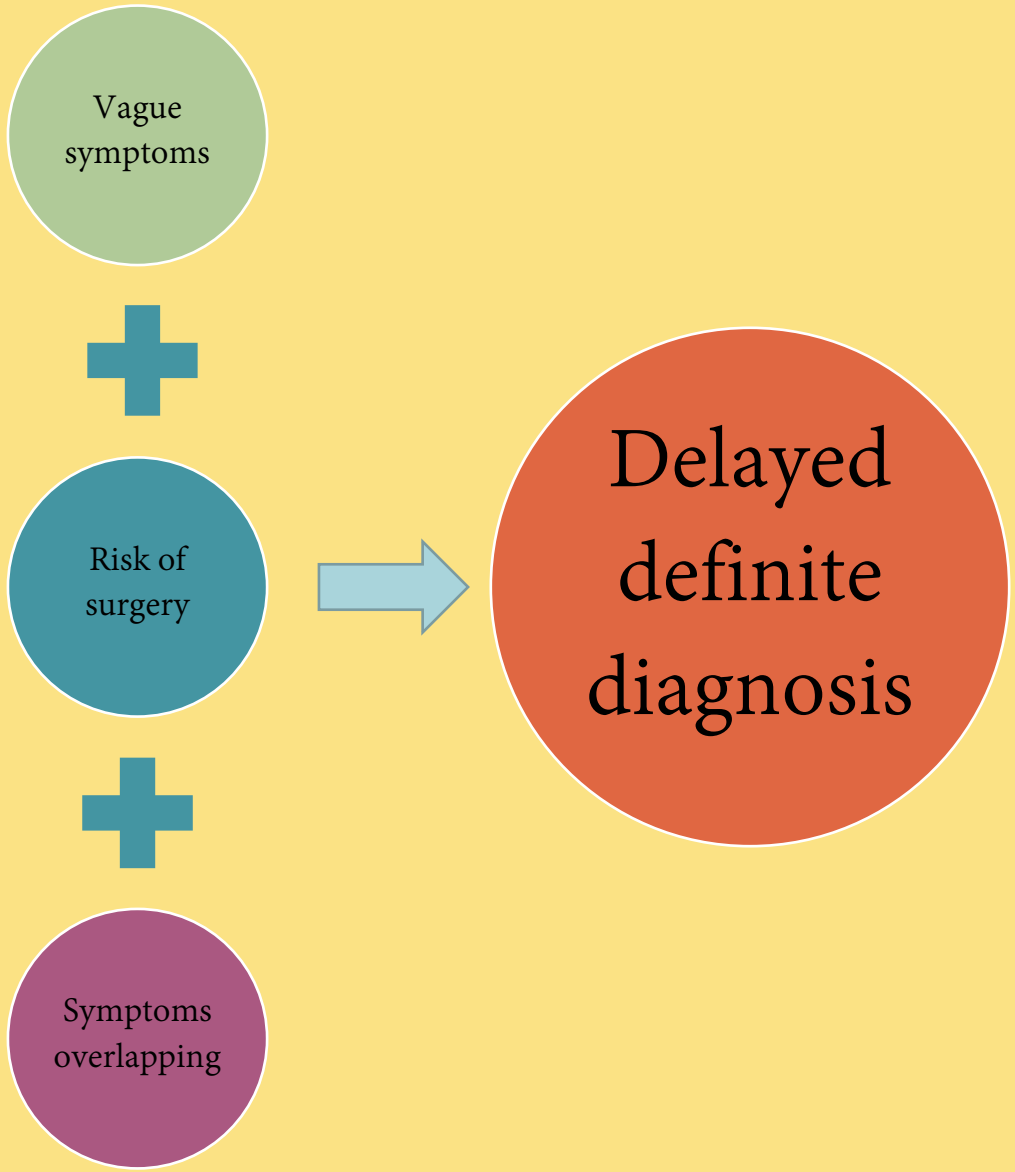


Relationships between the type of endometriosis and patients' symptoms

peritoneal or deeply infiltrating endometriosis	→	dyspareunia
bladder endometriosis	→	nonspecific urinary symptoms of frequency, urgency, and pain at micturition
Ureteral endometriosis	→	colicky flank pain or gross hematuria

Relationships between the type of endometriosis and patients' symptoms





Studies have reported an average diagnostic delay of 7 to 12 years in women with endometriosis

Diagnostic evaluation

Symptoms and physical examination

- Dysmenorrhea
- Chronic pelvic pain
- Infertility
- …

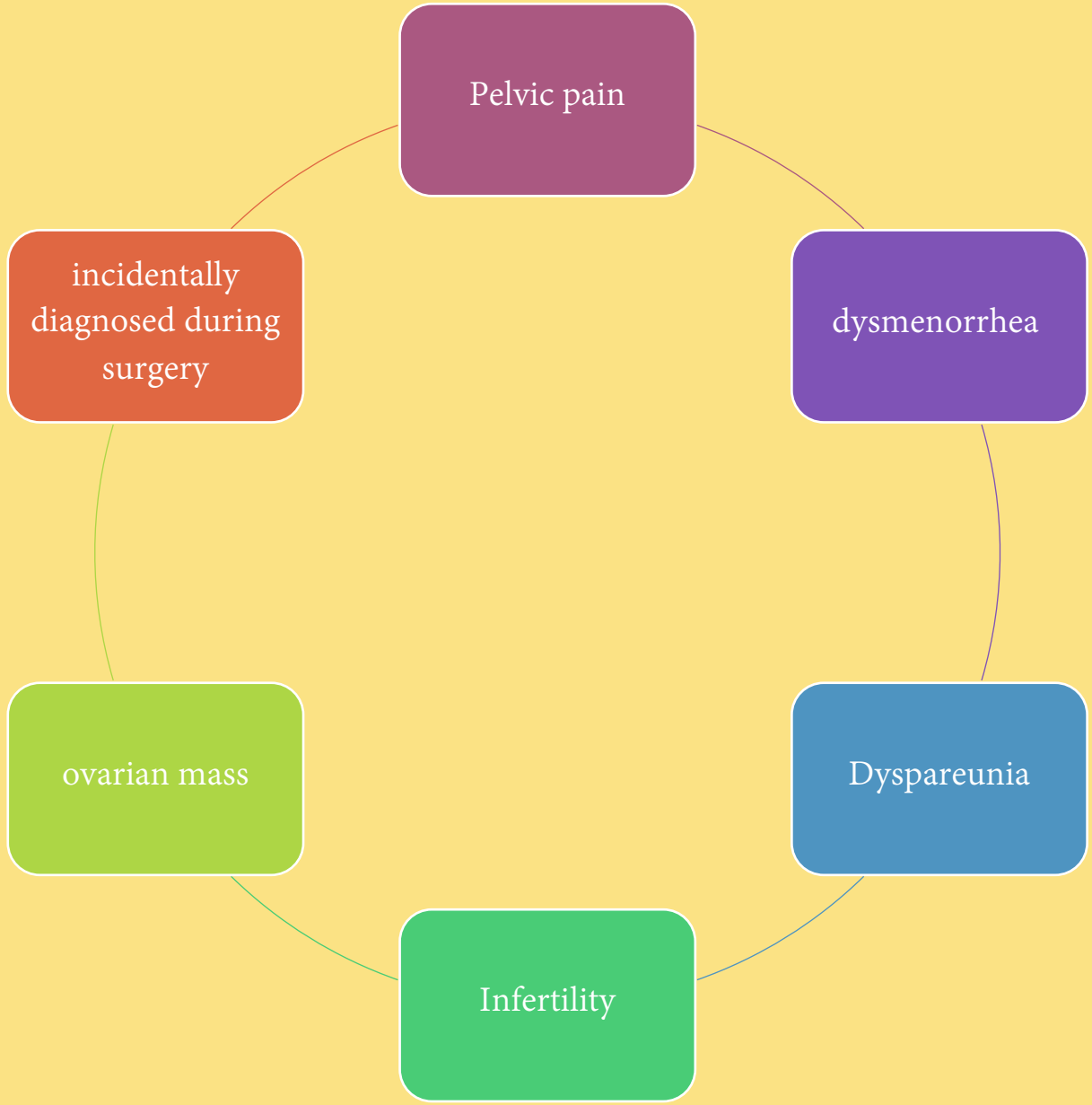
Laboratory and imaging evaluation

- No pathognomic laboratory findings.
- Role of CA-125
- Role of ultrasonography
- Role of MRI

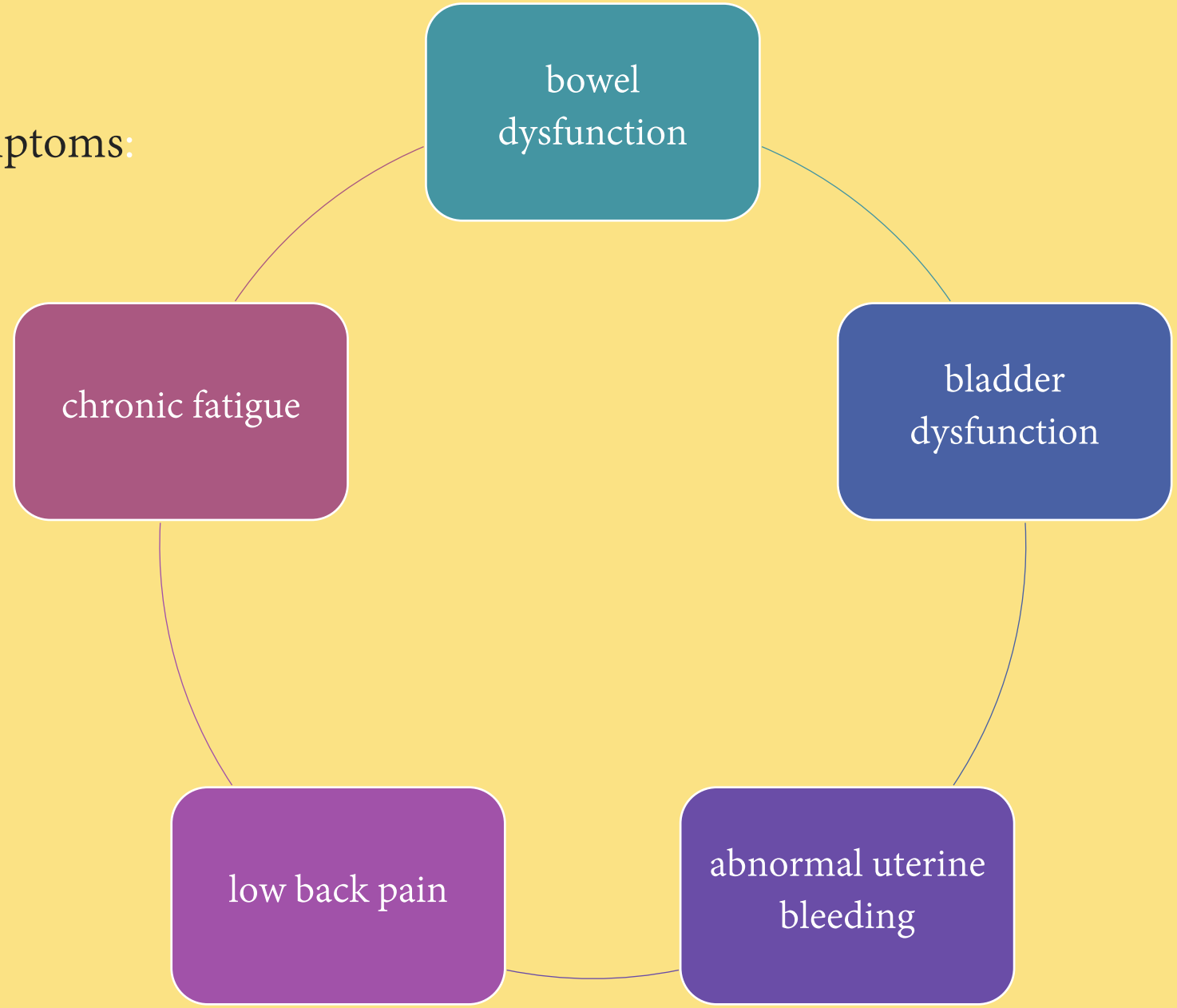
surgery

- Gold standard for diagnosis and treatment
- Classification

Clinical manifestation:



Additional endometriosis symptoms:



Some feature of symptoms:

Pain

- Diffuse, located deep in the pelvis, dull, and aching
- may radiate to the back and thighs or be associated with rectal pressure, nausea, and episodic diarrhea.
- it may be more common, severe, and associated with dyspareunia and painful defecation in women with deep infiltrating disease involving the cul-de-sac and rectovaginal septum.

Dysmenorrhea

- Dysmenorrhea that is new in onset, progressive, or severe strongly suggest endometriosis.
- It often begins before onset of menstrual flow and usually persists throughout menses.

Dyspareunia

- new in onset and most intense with deep penetration
- immediately prior to menstruation.

The pain associated with endometriosis has been attributed to three primary mechanisms:

1. The direct and indirect effects of focal bleeding from endometriotic implants
2. The actions of inflammatory cytokines in the peritoneal cavity
3. Irritation or direct infiltration of nerves in the pelvis

The intensity of pain associated with deep infiltrating endometriosis relates to the depth of penetration and to the proximity or direct invasion of nerves.

In a study of 1000 women with endometriosis, approximately :

- 80 percent presented with pain
- 25 percent with infertility
- 20 percent with an endometrioma (ovarian mass).

- Comparing women with minimal and mild endometriosis to those with more advanced stages of disease, dyspareunia was significantly more common in women with limited disease (51% vs. 39%), whereas infertility (22% vs. 30%) and an ovarian mass (7% vs. 29%) led to a diagnosis more often in those with advanced endometriosis.

Physical examination:

lack of findings does not exclude the disease

depend upon the location and size of the implants

- nodules in the posterior fornix
- tenderness on vaginal examination
- immobility of the cervix or uterus
- adnexal masses
- lateral placement of the cervix or uterus

- The external genitalia are typically normal. Occasionally, speculum examination may reveal characteristic blue-colored implants or red proliferative lesions that bleed on contact.

- Focal tenderness, thickening, induration, and nodularity of the uterosacral ligaments (palpable at the 4 o'clock and 8 o'clock positions at the base of the cervix) are the most common, and frequently the only, physical findings.

- Physical examination has its greatest diagnostic sensitivity when performed during menstruation, but even then, a normal examination does not exclude the diagnosis.

Overall, compared to surgical diagnosis of endometriosis, physical examination has relatively poor sensitivity, specificity, and predictive value and should not be used as a means to rule out endometriosis.

- The pooled sensitivity and specificity of physical examination (P/E) for the diagnosis of deep infiltrating (DIE) were 71% and 69%, respectively(Zhang, He, & Shen, 2020)

- The area under curve (AUC) was 0.76 which indicated that P/E has an intermediate level of diagnostic value(Zhang, He, & Shen, 2020)

- The clinical utility of P/E for DIE was average and Fagan's nomogram indicated that post-test probability (positive, 37%; negative, 10%) differed significantly from pre-test probability (20%)

Role of ultrasonography in evaluation of endometriosis:

Endometriomas appear typically as:

1. cystic structures with diffuse low-level internal echoes surrounded by a crisp echogenic capsule.
2. Some have internal septations or thickened nodular walls.

When the characteristic features are present, transvaginal ultrasonography has 90% or higher sensitivity and almost 100% specificity for detection of endometriomas.

Transvaginal or transrectal ultrasonography can be especially helpful when deep infiltrating disease involving the bladder, the uterosacral ligaments, or the rectovaginal septum is suspected.

Transvaginal ultrasonography can detect ovarian endometriomas, but cannot image pelvic adhesions or superficial peritoneal foci of disease.

- The pooled sensitivity and specificity of TVUS for the DIE were 76% and 94%, respectively(Zhang, He, & Shen, 2020)

- The area under curve (AUC) was 0.92 which indicates the high diagnostic value of TVUS(Zhang, He, & Shen, 2020)

- The clinical utility of TVUS for DIE was good and Fagan's nomogram indicated that post-test probability (positive, 75%; negative, 6%) differed significantly from pre-test probability (20%)

In the study by Zhou et al., the diagnostic accuracy of TVUS in the preoperative detection of uterosacral ligaments (USL) in patients with clinical suspicion of deep infiltrating endometriosis had 65% pooled sensitivity, 92% pooled specifity, 7.80 positive probability ratio, and 0.38 negative probability ratio. So TVUS provides an excellent comprehensive diagnostic performance for DIE of the USL(Zhou et al., 2021).

Transrectal ultrasonography (TRUS):

- The pooled sensitivity and specificity of TRUS for the diagnosis of DIE were 91% and 80%, respectively(Zhang, He, & Shen, 2020)

- The area under curve (AUC) was 0.93 which indicates the high diagnostic value of TRUS(Zhang, He, & Shen, 2020)

- The clinical utility of TRUS for DIE was good and Fagan's nomogram indicated that post-test probability (positive, 53%; negative, 3%) differed significantly from pre-test probability (20%)

In the study by Goncalves et al., TVUS with bowel preparation was compared to diagnostic laparoscopy (DL) for the identification of ovarian and deep site of endometriosis(Goncalves et al., 2021):

1. DL was able to detect retro-cervical, ovarian, and bladder endometriosis with similar sensitivity and specificity as TVUS-BP
2. DL was not able to detect vaginal endometriosis (in comparison to 85.7 % sensitivity and 99.1 % specificity of TVUS-BP)
3. DL was notably poor at detection rectosigmoid endometriosis, with a sensitivity of 3.7-5.6 % in comparison to 96.3 % sensitivity with utilization of a preoperative TVUS ($p<0.001$)
4. Preoperative TVUS-BP was accurate in identifying all sites of ovarian and deep endometriosis that were evaluated. It had significantly higher sensitivity than DL in detecting rectosigmoid endometriosis. These results suggest that TVUS-BP can replace DL for the diagnosis and treatment planning for patients with ovarian and deep endometriosis.

systematic review to determine the optimal imaging modality for the detection of rectosigmoid deep endometriosis by Gerges et al. 2020

- To review the diagnostic accuracy and determine the optimum imaging modality for the detection of rectosigmoid deep endometriosis (DE) in women with a clinical history of endometriosis.
- 30 studies (n = 3,374) were included in the analysis. The overall pooled sensitivity and specificity, from which the likelihood ratio of a positive test (LR+), likelihood ratio of a negative test (LR-) and diagnostic odds ratio (DOR) were calculated, were as follows for transvaginal ultrasound (TVS) 89% , 97% , 28.8 , 0.12, and 248, for magnetic resonance imaging (MRI) 86%, 97% , 21.0 , 0.15 , and 144, for computed tomography (CT) 93% , 95% , 20.3 , 0.07 , and 280 , and for transrectal endoscopic sonography (RES) 92% , 98% , 37.1, 0.08 , and 455 , respectively.
- The sensitivity of transvaginal sonography (TVS) for the detection of DE seems to be slightly better than magnetic resonance imaging (MRI), although RES was superior to both. Specificity of both TVS and MRI were excellent. As TVS is the simpler, faster, and more readily available, we believe it should be the first line diagnostic tool for the women with suspected DE.(Gerges, Li, Leonardi, Mol, & Condous, 2020)

Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery, study by Deslandes et al. 2020

- The primary aim was to determine the accuracy of TVUS for DIE.
- The secondary aim was to determine accuracy specifically when a sonographer performed the TVUS examination.
    - Analysis of the returned articles revealed the TVUS is a valuable diagnostic tool for DIE before surgery. Sensitivities ranged from 78.5% to 85.3%, specificities from 46.1% to 92.5%, and accuracies from 75.7% to 97%.
- Most authors reported site-specific sensitivities and specificities, which varied greatly between locations. Site-specific sensitivities and specifities ranged from (respectively) :
    1. 10% to 88.9% , and from 75% to 99.6% for uterosacral ligaments
    2. 20% to 100% , and from 96.4% to 100% for bladder
    3. 33.3% to 98.1% , and from 86% to 100% for rectosigmoid colon
    4. 31% to 98.7% , and from 90% to 100% for pouch of Douglas(Deslandes, Parange, Childs, Osborne, & Bezak, 2020)

Role of magnetic resonance imaging(MRI) in evaluation of endometriosis:

For detection of peritoneal implants, MRI is superior to transvaginal ultrasonography but still identifies only 30–40% of the lesions observed at surgery.

For detection of disease documented by histopathology, MRI is approximately 70% sensitive and 75% specific.

The principal advantage MRI has over ultrasonography is its ability to distinguish more reliably between acute hemorrhage and degenerated blood products.

Gadolinium contrast offers no additional diagnostic value.

MRI also can be used to aid in the diagnosis of deep infiltrating and rectovaginal disease.

MRI can be helpful in the detection and differentiation of ovarian endometriomas from other cystic ovarian masses, but cannot reliably image small peritoneal lesions.

- The pooled sensitivity and specificity of MRI for the diagnosis of DIE were 82% and 87%, respectively(Zhang, He, & Shen, 2020)

- The area under curve (AUC) was 0.91 which indicates the high diagnostic value of MRI(Zhang, He, & Shen, 2020)

- The clinical utility of MRI for DIE was good and Fagan's nomogram indicated that post-test probability (positive, 60%; negative, 5%) differed significantly from pre-test probability (20%)

Neither ultrasound nor MRI can be used to rule out endometriosis.

Diagnostic performance of computed tomography for bowel endometriosis: A systematic review and meta-analysis by Woo et al. 2019

- Purpose: To perform a systematic review and meta-analysis regarding the performance of CT for diagnosis of bowel endometriosis.

- Twelve studies (1091 patients) were included. Pooled sensitivity and specificity were 0.92 and 0.95 , respectively.

- History of prior surgery for endometriosis was the only significant factor affecting heterogeneity ($p < 0.01$). Specifically, studies that included patients with such history demonstrated significantly greater specificity than studies that did not.

CT shows excellent performance in the diagnosis of bowel endometriosis. Due to small number of included studies and publication bias, further studies may be needed to validate these results(Woo, Suh, & Kim, 2019)

Intraoperative enhanced imaging for detection of endometriosis: A systematic review of the literature, study by Al-Taher et al. 2018

- Enhanced imaging using contrast agents has potential to provide a better identification of peritoneal endometriosis.

- The aim of this systematic review is to provide an overview of the literature on what is known about the intraoperative laparoscopic visual enhancement of peritoneal endometriosis using contrast agents.

- Nine suitable studies were identified. Intraoperative visualization of endometriosis was analyzed with or without histologic confirmation. Four studies evaluated 5-aminolevulinic acid-induced fluorescence (5-ALA), 1 study evaluated indigo carmine, 2 studies evaluated methylene blue (MB), 1 study evaluated indocyanine green (ICG) and 1 study evaluated so-called bloody peritoneal fluid painting. All studies, with a combined total of 171 included patients, showed potential of enhanced visibility of endometriosis using contrast agents. A combined total of 7 complications, all related to the use of 5-ALA, were reported.

They conclude that the use of contrast-based enhanced imaging during laparoscopy is promising and that it can provide a better visualization of peritoneal endometriosis. However, based on the limited data no technique of preference can yet be identified.(Al-Taher et al., 2018)

Role of CA-125 for evaluation of endometriosis

- CA-125 is a cell surface antigen expressed by derivatives of the coelomic epithelium (including the endometrium).
- Levels of CA-125 often are elevated in:
    1. women with advanced endometriosis
    2. during early pregnancy and normal menstruation
    3. In women with acute pelvic inflammatory disease
    4. leiomyomata.

- Serum CA-125 has been inappropriately advocated as a screening test for diagnosis of endometriosis, but a meta-analysis including 22 studies using surgically diagnosed disease as the gold standard concluded that the marker performs rather poorly.
- sustained elevation of serum CA-125 after surgical treatment predicts a relatively poor prognosis.

the serum CA-125 concentration does not have the necessary sensitivity to be an effective screening test for the diagnosis of endometriosis.

Surgical evaluations for endometriosis

- **Laparoscopy with histologic examination of excised lesions has traditionally been the gold standard for the diagnosis of endometriosis.**

- The optimal time during the menstrual cycle to perform laparoscopy is not clear, 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, typically observed on the ovaries and on peritoneal surfaces in the cul-de-sac, uterosacral ligaments, and ovarian fossa.

Surgical evaluations for endometriosis

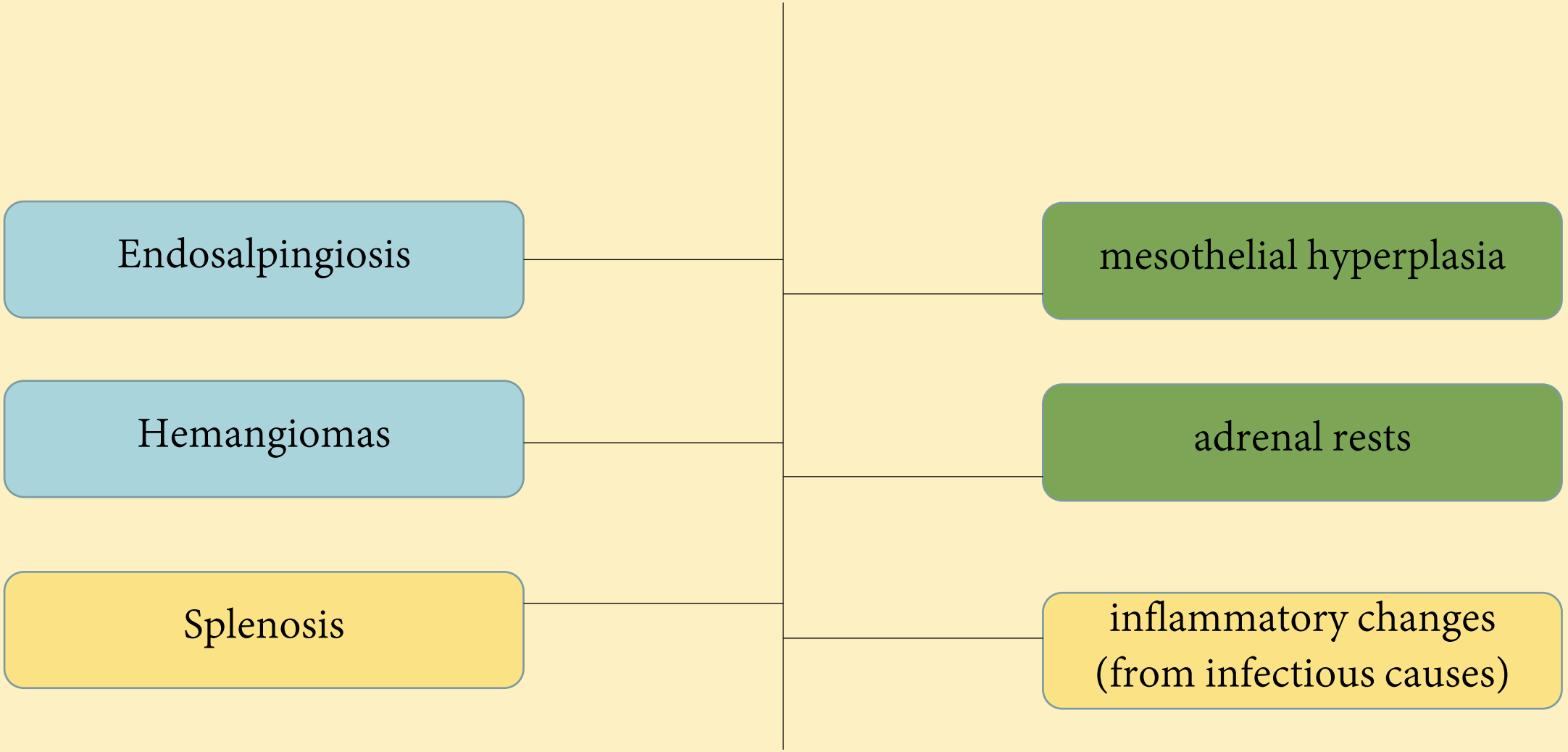
- Strict histologic criteria will confirm the surgical diagnosis of endometriosis in approximately 50–65% of excised lesions.

- When diagnosis is in doubt, biopsy of suspicious areas should be performed to prevent misdiagnosis.

- A negative laparoscopy is relatively reliable for excluding endometriosis, although it cannot rule out microscopic disease.

- Occult disease is not uncommon in women with pelvic pain; based on this, even laparoscopy cannot be considered a true gold standard for the diagnosis of endometriosis.

lesions that can be confused with endometriosis



Surgical exploration:

Indications:

1. diagnosis of persistent pelvic pain that does not respond to medical therapy

2. evaluation of severe symptoms that limit function

3. treatment of anatomic abnormalities, such as bladder lesions.

Surgery, almost always laparoscopy, allows both definitive diagnosis and treatment.

- Women with classic endometriosis lesions at laparoscopy but negative histology are treated for endometriosis because negative biopsies can result from inadequate sampling.

- Laparoscopy that does not demonstrate visual or histologic disease is highly reliable for excluding endometriosis.

- While endometriosis can be present in the absence of an apparent lesion, it is not standard practice to perform random biopsies during laparoscopy.

classification of endometriosis

- The classification of endometriosis used most commonly in clinical practice is descriptive and relatively simple:

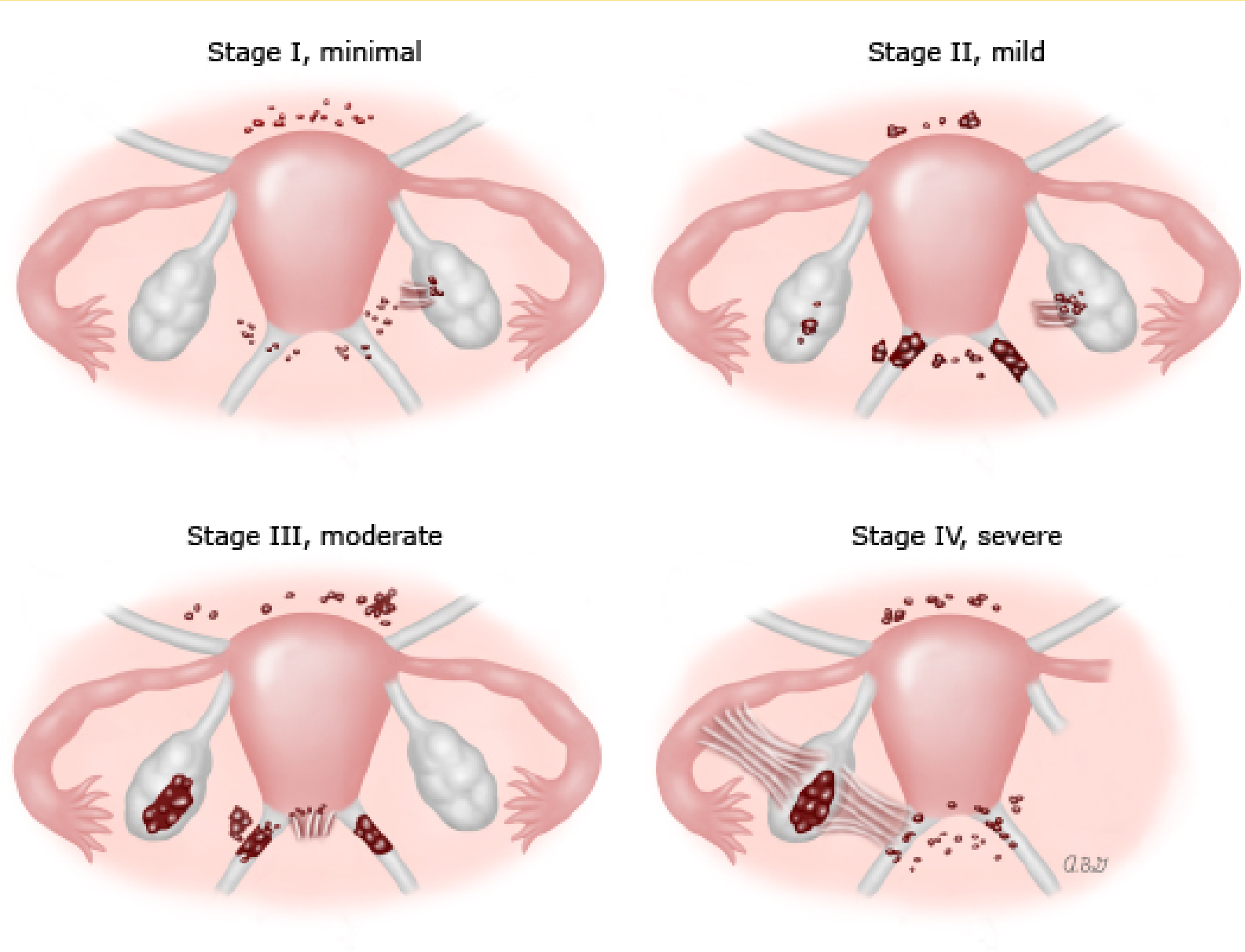
Stage I: Minimal endometriosis—isolated superficial disease on the peritoneal surface with no significant associated adhesions.

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

Examples of the classification of endometriosis



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