Sheets Pathology

Number: 4

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Cervical Cancer

We previously talked about human papilloma virus (HPV). There are almost 140 serotypes of HPV so far. Certain serotypes (14 of them) cause precursor lesions (high grade lesions). These lesions can progress to carcinoma in situ(CIS) and then invasive cervical carcinoma. **The most common** serotypes that are associated with high grade lesions (which later on cause cervical carcinoma) are **16 and 18**, others include 31, 33, 54, etc. The molecular testing for HPV that is done now (in addition to PAP smear whether done together or separately) is for 16, 18 and non-16,18; i.e. the machine tells you if the sample is 16 positive, 18 positive or non-16,18 positive (the sample can be 16 *and* 18 positive).

Natural history

- 60% of low grade lesions regress and 30% persist. Out of all low grade lesions 10% will probably transform into high grade lesions. However, it is not HPV6 and 11 (that are associated with low grade lesions) that cause high grade lesion; associated high grade serotypes are present in addition to these low grade serotypes. When you look at the Pap smear you will find low grade and high grade serotypes at the same time (in the same sample) and it is marked high grade.
- 30% of high grade lesions regress and 60% persist. Chronic persistent infection with high grade serotypes is what causes high grade CIN and then cervical carcinoma (10% of high grade lesions).

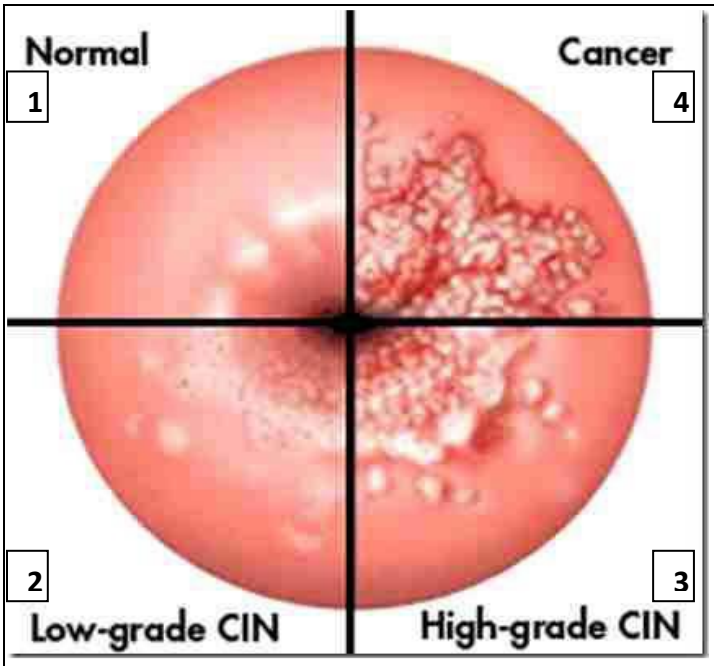
TABLE 19.1 Natural History of Squamous Intraepithelial Lesions (SILs)

Lesion	Regress	Persist	Progress
LSIL (CIN I)	60%	30%	10% (to HSIL)
HSIL (CIN II, III)	30%	60%	10% (to carcinoma)[a]

LSIL, Low-grade SIL; HSIL, high-grade SIL.

Once we detect a high grade lesion in a Pap smear, a colposcopy must be done where a special microscope is used to examine the cervix and vagina (more intensive than pap).

[See picture next page]



1→ this is how a normal cervix looks like; the mucosa is white and shiny with no lesions.

2→ low grade lesions appear whitish and slightly elevated

3→ high grade lesions

4⟶ cancer

HGSIL Detection

An experienced colposcopist knows very well from where the biopsy should be taken. A definitive management is not done until there is a tissue diagnosis. If the biopsy was wrongly taken from normal tissue, lesions will be missed. It is very important to know exactly from where to take the biopsy to have an accurate tissue diagnosis.

The issue here is to detect early cancers. In 40s and 50s, cervical cancer was 2nd cause of cancer death but now it is the 13th or 14th cause of cancer death because of the success of the Pap smear, the best screening test in the history of cancer screening. The inventor of Pap smear, George Papanicolaou, struggled for years to convince people that you can detect cancer cells by looking at morphology of cells (cytology).

To help in taking the biopsy from the right place **Acetic acid test** or **Lugol's solution test** are done. They put a substance on the cervix and take the biopsy from the place that didn't take this substance up. There are other techniques which help the colposcopist to know from where to take the biopsy.

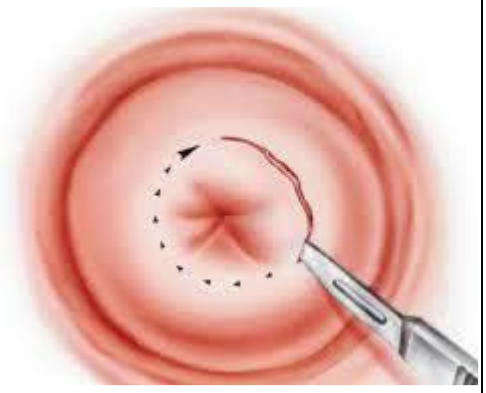
If the Pap smear was termed high grade but the biopsy from colposcopy turned out to be negative we should look at the Pap smear again. If it was confirmed to be high grade (high grade cells where found), we should believe it (not the colposcopy) because it samples/scrapes more area. The colposcopist must have missed the lesions (the biopsy was not done correctly). This could be because the lesion is in the T-zone and the T-zone is somewhat up.

The location of the T-zone differs depending on age, reproductive and sexual history. In a virgin female before menarche T-zone is up. With the menstrual cycle, it becomes somewhat lower. After marriage (with intercourse) it becomes even lower. That's why in colposcopy or vaginal examination you can see the nice red columnar epithelium. But after delivery it becomes up again so in a 55 year old female (postmenopausal) you need to take the sample from higher places to sample T-zone.

There are a lot of technical issues but you need to remember that when the Pap smear is true you believe it.

Treatment of high grade lesions or early invasive cancer

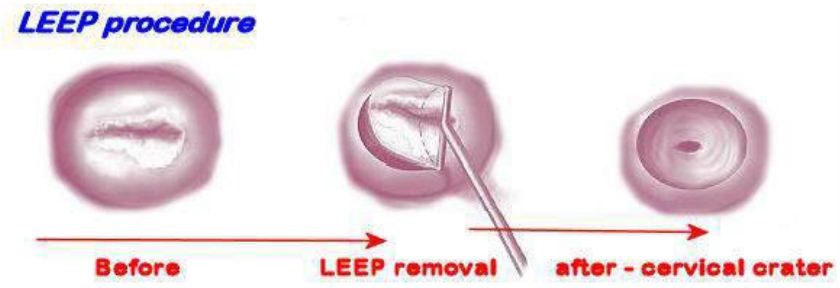
- **Cone excision**: The treatment was previously done using cone excision procedure. In this procedure, a big amount of ecto- and endo-cervix was removed which will include the T-zone. The excision is cone-shaped with a base externally (exocervical margin) and an apex towards inside (endocervical margin). The removed tissue is then examined to make sure we removed the lesion and to see if the endocervical margin is clear or not and inform the doctor with the result.



  This procedure is big and it is associated with morbidity and complications (like cervical incompetence and frequent abortions).

- **LEEP procedure**: Nowadays, we do a simpler procedure which is LEEP excision (**L**oop **E**lectrosurgical **E**xcision **P**rocedure). The concept is the same but here we use a wire or blazer which results in smaller cone with less morbidity and complications.

  Nowadays, Cone excision is only done in rare occasions where there is micro-invasion and a bigger piece is needed out.



Invasive cervical carcinoma

Most of cervical carcinomas are squamous (75%), a small proportion is mixed adeno and squamous which are called adenosquamous carcinomas (20%) and the rest are small cell carcinomas and adenocarcinomas. Almost all of them are HPV-associated even adenocarcinomas.

The incidence of cervical carcinoma has roughly plateaued because we reached the maximum saturation in terms of early detection. However, it is now believed that the incidence of adenocarcinomas of cervix is going up because there are no specific standards for the examination and detection of adenocarcinomas compared with squamous carcinomas.

Small cell carcinoma (neuroendocrine carcinoma) of the cervix is a very bad disease just like SCC of lung. They are very aggressive; they are small cells that can easily reach blood stream and metastasize. At the time of diagnosis you assume the patient has metastasis. Actually, SCCs of any organ (prostate, lung, cervix, etc.) are aggressive and fatal, they are considered as leukemia; i.e. there is no point of resection and they are treated by chemotherapy.

Squamous CC peak at age 45 (10-15 years after the initial exposure to HPV). Initial exposure usually is when females start sexual activity (according to culture).*

Nowadays, invasive cervical carcinoma is often seen **in unscreened women.
We should not see invasive cervical carcinoma because we have successful screening by Pap smear; lesions are detected and treated early. Most of the cases of invasive cervical carcinomas that we see now are in unscreened women (because of Ignorance, sometimes have multiple partners, prostitutes). They present with vaginal bleeding, leukorrhea and dyspareunia.

As we said, biopsy is always needed to confirm diagnosis and examine depth of invasion (above or below 3mm) before planning treatment. Depth of invasion in any epithelial or mucosal cancer (vaginal, vulvar, etc.) dictates staging. Grading and depth of invasion are important predictors of stage and prognosis, that's why we need a proper and deep biopsy. Cancer cells then usually spread to pelvic lymph nodes.

*remember: the development of cervical carcinoma from HPV usually needs years of persistent long-term infection.

In the 80's and during surgery on a patient with invasive cervical carcinoma (while under anesthesia), surgeons would send lymph nodes to pathologists for frozen sections to see whether cancer has spread to lymph nodes or not. If it has not spread (negative) they proceed with radical hysterectomy. If it was positive (cancer has spread) they stop (don't do radical hysterectomy) because we add morbidity without any benefit; they are only treated with radiotherapy and chemotherapy.
Nowadays, in situ and early invasive cancer can be treated with simple hysterectomy. Otherwise, radical surgery is needed. Some are treated either with radiotherapy alone or with radiotherapy followed by radical hysterectomy.

00:00-15:00

Risk factors for invasion: smoking, HIV, alcohol.

HPV vaccines: quadrivalent (HPV 6, 11, 16, 18) and more (divalent and 9-valent); are promising preventive measures. They are not part of our national program but it is available. It is given at the age of 9 and repeated after 1 and 3 months.

Uterine Pathology

Diseases of the endometrium

Endometrial pathology is very common.

1. **Endometritis** whether acute (neutrophilic) or chronic (plasma cells).

   Acute endometritis is not very important because endometrium is a dynamic cyclical functional organ. So, if there is superficial inflammation in the endometrium it will shed and clear up by itself.

   On the other hand, chronic endometritis is very important. It is not an easy diagnosis and it is commonly associated with what we call ***chronic pelvic inflammatory disease*** (usually multiple organisms: N.gonorrhoeae, C. trachomatis, etc.). Chronic endometritis is histologically characterized by the presence of plasma cells in the endometrium (1 or 2 cells are enough for diagnosis, usually there is more).

2. **TB**: The other chronic inflammatory condition of the endometrium is ***granulomatous endometritis*** caused by tuberculosis in endemic countries or immunocompromised patients. Usually you don't see TB endometritis alone; it is usually associated with

tubal TB (TB salpingitis). That's because tubal TB spreads to endometrium and sometimes ovaries.

Remember:

- The primary target of TB is the lungs and lymph nodes. Extra-pulmonary sites include fallopian tubes and endometrium.
- Immunocompromised states leads to reactivation of **latent** TB.

In our region we still see TB and it is sometimes a cause of infertility because of associated nodules and sclerosis of fallopian tubes that lead to abnormal motility. While investigating infertility you sometimes discover tubal TB.

The hallmark of TB infection is necrotizing granulomatous inflammation (granulomas with central necrosis). Wherever you see necrotizing granulomatous inflammation you have to rule out TB especially in endemic areas.

3. Retained POC (products of conception) and IUCD (Intrauterine Contraceptive Device) associated

Retained POC are commonly seen either after delivery or abortion.

Females who use IUCD (or IUD) are at a higher risk to develop chronic endometritis. IUCD is a foreign body and can cause endometritis in some people. Once chronic endometritis has developed on top of IUCD, IUCD has to be removed.

All the previous pathologies are benign. The most common **signs and symptoms** of endometrial pathology include systemic signs of inflammation (like fever), abdominal pain and menstrual abnormalities.

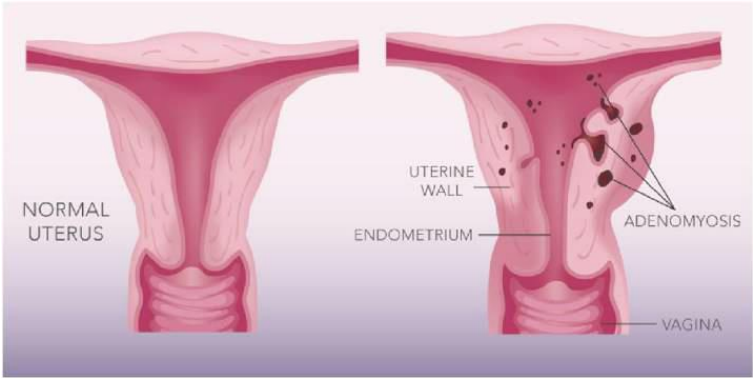
Diagnosis is usually by taking a biopsy. **Treatment** is by antibiotics or removal of IUCD and POC (according to the pathology).

15:00-26:00

Diseases of the myometrium

The 2 common diseases of the myometrium are adenomyosis and leiomyoma (or fibroid). Leiomyomas are discussed in the next lecture.

***Adenomyosis*:** Endometrial tissue *deep in myometrium*.



When we section the uterus (we usually take from anterior and posterior), we must see mucosa, submucosa with endometrial glands, myometrium and finally serosa. If you see **benign** endometrial glands deep in the myometrium this is adenomyosis. These glands are functional most of the time, so they will undergo the same changes that occur in the endometrium during the menstrual cycle (i.e. they have bleeding, shedding…). This leads to abdominal pain.

Patients with adenomyosis have abdominal pain especially with cycles (cyclical pain, before or during menses). It is said that adenomyosis is associated with higher incidence of infertility because of adhesions (the uterus is not functioning well for proper implantation). When extensive it causes menorrhagia, dysmenorrhea and pelvic pain (especially before menses). Sometimes high resolution ultrasound examination of the uterus shows abnormal myometrium. It can co-exist with endometriosis.

When glands are outside the serosa (outside the uterus) it is called **endometriosis**. Adenomyosis and endometriosis are probably the same pathology but they differ in location. In adenomyosis the glands are in the myometrium (inside the uterus) and in endometriosis the glands are outside the uterus.

Endometriosis: Endometrial glands and stroma *outside uterus*. It can be anywhere but **common locations** are ovaries, pouch of Douglas, uterine ligaments, cervix, tubes and rectovaginal septum. However, it has been diagnosed everywhere; in lungs, peritoneum, umbilicus, heart, etc. It could be multifocal.

When a patient presents with chronic abdominal pain a laparoscopy is done to see what's wrong. They might find red spots on the ovary or peritoneum for example. They then take a biopsy to rule out endometriosis. When pathologists examine the biopsy, they see endometrial glands and stroma and sometimes hemosiderin-laden macrophages. This is an evidence of previous functionality of these glands with each cycle. With each cycle, there is bleeding that leads to deposition of iron which is then phagocytosed by macrophages.

The 3 **hallmarks of endometriosis** anywhere are benign endometrial glands, stroma and hemosiderin-laden macrophages.

Theories:

Several theories were proposed to explain the pathogenesis of endometriosis

1) **Regurgitation** (favored): during menstrual cycle, shed tissue should go out through the vagina. Instead, it goes up the tube and into the ovary, uterine ligaments and peritoneal cavity (retrograde). It seeds there and gets its blood supply and becomes functional.
   This is the most accepted theory in the pathogenesis of endometriosis because it explains most cases of endometriosis which are around or near the uterus.

2) **Benign metastases:** endometrial glands and stroma travels through lymphatics or blood to distant organs (brain, lungs, etc.) and lives there.

3) **Metaplasia:** For example, mullerian epithelium of the tube turns into endometrial glands with stroma around them.

26:00-36:00

4) **Extra-uterine stem cell differentiation:** Stem cells are everywhere, they are undifferentiated cells. Abnormal environment around these cells might drive its differentiation toward benign endometrial tissue.

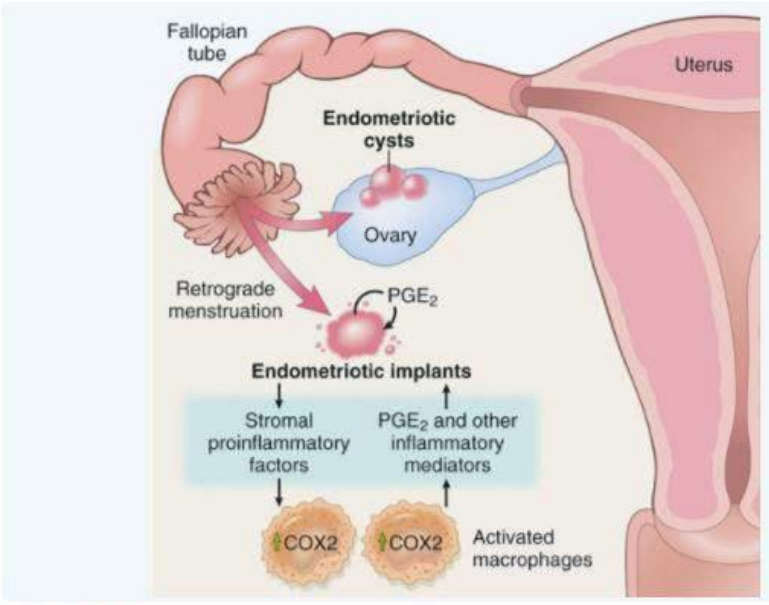


FIG. 19.9 Proposed origins of endometriosis.

This figure illustrates the regurgitation theory of endometriosis.

A lot of research suggests that there are mediators which enhance the presence of endometriosis.

Regurgitation and implantation of glands is not easy; it needs mediators like COX1, COX2, PGE2, etc. to make those endometrial glands that gets implanted outside the uterus survive and form endometriosis.

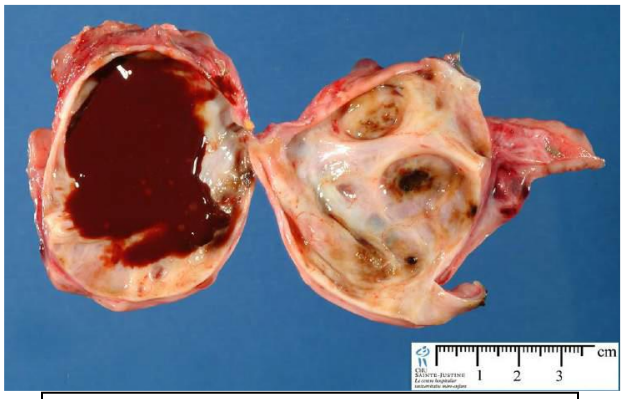
Endometriosis clinically

It appears as red spots in laparoscopy. During laparoscopy, a biopsy is taken to be examined under the microscope and to look for evidence of endometriosis.

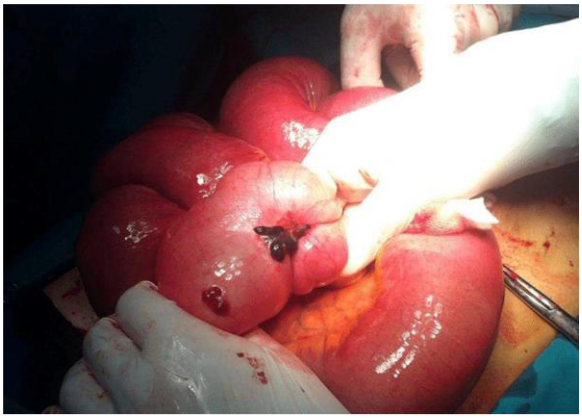
In ovaries, it sometimes results in cysts that fill with blood with each cycle. Old blood is called chocolate blood and the cysts are called ***chocolate cysts*** or ***endometriotic cysts***. When the cysts are opened we see blood, and under the microscope we see endometrial glands and stroma.
Any ovarian cyst might be sent to pathologists as frozen section to rule out malignancy.

Some people say that endometriosis is more common in the high socio-economic class. You can read about the relation between the two.

Gross features



Gross appearance of an opened ovarian chocolate cyst

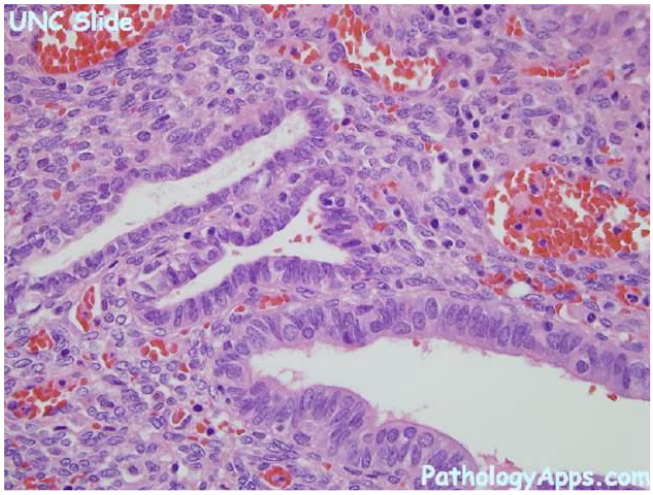


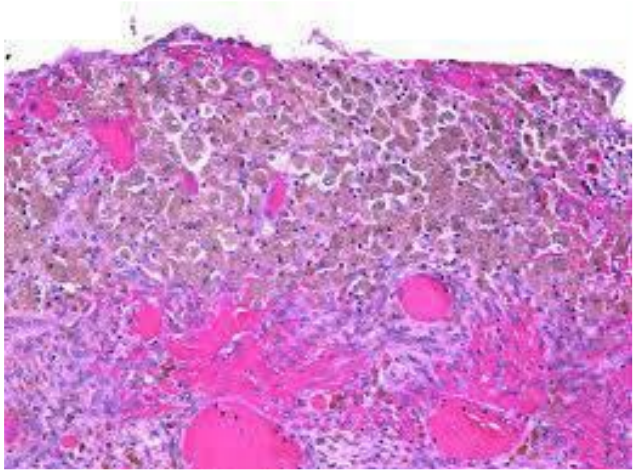
Intraoperative appearance of endometriosis on the surface of the small bowel

A surgeon opens the abdomen of a patient with abdominal pain and finds red spots on the small bowel. A frozen section is ordered to make sure it is not malignancy.

Microscopic features

When examined histologically:





You can see endometrial glands and stroma.

The brown material is hemosiderin-Laden macrophages. Sometimes we don't see epithelium or glands and we only see abundant hemosiderin-Laden macrophages which raises the diagnosis of but does not confirm endometriosis (we are not 100% sure).

Usually when we examine any tissue, we make several cuts at different levels. So, if something didn't appear in the same slide it might appear in the next. So if we look at more levels we might find the glands.

Signs and symptoms depend on distribution, location and quantity.

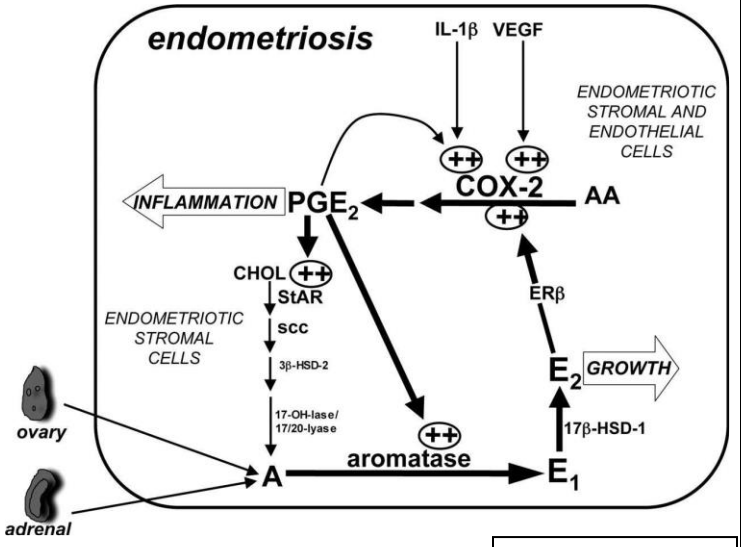
- The most common signs and symptoms are severe dysmenorrhea, pelvic pain bleeding and adhesions. This is because most cases involve organs around the uterus.
- Massive endometriosis on the ovaries and fallopian tubes leads to scarring of tubes and ovaries, cyclical abdominal pain and discomfort and infertility.
- If in lungs, patients might present with bloody plural effusion.
- If it is rectal → painful defecation
- uterine and bladder serosa → dyspareunia and dysuria

It affects 10% of women in reproductive age and 50% of infertile women. Endometriosis is claimed to be responsible for many cases of infertility because of resultant adhesions.

Treatment is not easy; there are many algorithms on how to treat it. It is surgical and/or medical. Some people might need to surgically remove the involved organ.

Because COX2 and PGE2 are involved in the implantation and growth of endometriosis anywhere, anti-COX2 and PGE2 can be used to treat endometriosis.

However, there is no full agreement about the best way to treat endometriosis. Endometriosis is not an easy disease to treat.



36:00-45:00

THE END

GOOD LUCK