# Endometriosis

- Endometriosis is an enigmatic disease of yet-unknown origin and pathogenesis.
- It is sustained by theories from long ago, when Sampson  described it as ectopic implants of menstrual shredding passed to the abdominal cavity through the Fallopian tubes.
- Recently, Brosens and Benagiano  suggested that it starts with neonatal hormonal deprivation bleeding that many newborn girls express in a retrograde fashion. Implants would remain until puberty.

- A celomic theory states that embryonic cells from the Müllerian ducts persist in ectopic locations. At puberty, stimulated by estrogens, they grow to build up endometriotic lesions

- There is no reliable serum maker for this disease, and imaging still leaves much of it undiagnosed.
- Ultrasound (US) has a good sensitivity and specificity for endometriomas (83% and 89%, respectively).
- Unfortunately, in the case of deep infiltrating endometriosis (DIE), uterosacral ligaments, rectovaginal septum, vagina, and bladder, the overall pooled sensitivity and specificity of US transvaginal studies (TVSs) range between 53% and 93%6 .

- High-resolution magnetic resonance imaging (MRI) with bladder, vaginal, and rectal contrast has been a breakthrough in recent times.

- Is there a psychological trait common to women with endometriosis?
- Several publications search for predictors of psychological distress  but few focus on the personality of patients with endometriosis.
- Even fewer identify associations with their psychological aspects.
- On patient health questionnaires, women with endometriosis show a high frequency of positive results for psychiatric disorders significantly associated with pain severity.
- No personal traits allow us to identify subjects prone to develop endometriosis.

- ***Laparoscopy*** is the “gold standard” for the diagnosis of endometriosis.
- Surgical biopsies allow histological confirmation.
- Laparoscopy should be performed preferably by experienced  surgeons.
- Removal of all disease present must be accomplished in the same procedure.

- The recent World Endometriosis Society (WES) Consensus for the Current Management of Endometriosis states that “Individualized care benefits from a multidisciplinary network of experts sufficiently skilled in providing advice on, and treatment of endometriosis and its associated symptoms, based on the best available knowledge, their extensive experience and their transparent record of success rates”.

- Medical management is a centerpiece.
- According to the Consensus, old-time favorites such as danazol or gestrinone should be used only in the absence of side effects when other treatments have proven ineffective.
- Progestagens have proven efficacy, whereas gonadotropin-releasing hormone (GnRh) agonist therapy is not recommended for long-term use.
- Oral progestin-only pills have demonstrated their ability to control the extent of endometriotic lesions on a long-term basis.

- Combined oral contraceptives (OCs) provide initial pain relief, but the long-term efficacy as a treatment for endometriosis lacksclinical evidence.
- Moreover, there are even some data supporting potential adverse effects on the progression of the disease.

- Ulipristal entails rare but severe risks such as endometrial hyperplasia, endometrial carcinoma, and hepatic damage.
- As recently as August 2018, the US Food and Drug Administration (FDA) had not approved the use of this drug for the treatment of myomas (and endometriosis as well).
- In June 2018, the European Medical Agency (EMA) approved its use as a preoperative treatment of fibroids. This short-term use before surgery could be considered for endometriosis.

- Newly introduced oral GnRh antagonist elagolix NR is associated with few minor side effects (hot flashes), excellent reduction of endometriosis-associated pain, and arrest of the progression of the disease when used for an extended period of 12 months at a 200-mg daily dose.
- Some moderate detrimental effects on bone density were reported, suggesting that this drug should be used with a hormonal backup.

- Surgery should be considered, during laparoscopy, in the treatment of the disease.
- All lesions present should preferably be resected.
- The issue of endometriomas, a never-ending dilemma, is discussed with sound evidence from recent literature.

- Infertility treatments for patients with endometriosis need special consideration.
- Surgery and assisted reproduction techniques (ARTs) cross over according to the different stages of the disease and the patient’s age.
- Minimal and mild disease frequently benefit from expert surgery. Advanced moderate and severe stages usually require in vitro fertilization (IVF)

- DIE should be treated only by expert surgeons, preferably by interdisciplinary teams.
- The question of whether it should be operated before infertility treatments remains controversial.
- Quality of surgery and certification of expertise are being revised by the Consensus group of the WES.

# Diagnosis

***A. Anamnesis***

- Listen to the patient. Carry on a detailed anamnesis in a very slow fashion. This simple action gives us the best approach to the disease.
- She has so much to tell, to show with her face and expression. In most cases, the disease can be understood just by listening.
- The omnipresent symptom is pain: cyclic pelvic pain, dysmenorrhea, periovulatory pain, chronic non-cyclic pelvic pain, dyspareunia (positional or permanent), dyschezia, and dysuria.

- There are many other pain presentations that nobody even thinks of until confronted with an endometriosis patient who, incidentally, has exactly “that type of pain”.
- A young girl we operated last year referred to right shoulder pain at menstruation.
- At laparoscopy, a large diaphragmatic series of blue and red lesions was excised. She was relieved after surgery

- Involuntary infertility, even when not the cause for consultation, should also be regarded as one of the frequent symptoms of endometriosis.
- Less frequently, cyclic nasal bleeding, umbilical bleeding, cyclic hemoptysis, cyclic constipation, and urinary urgency are reported by patients with endometriosis.

***B. Pelvic examination***

- Even today, with the advancement of imaging diagnosis, pelvic examination (in expert hands) continues to be praised as an effective clinical tool for the diagnosis of endometriosis.
- It should be done with care, slowly, beginning with abdominal palpation.
- Only after no pain is registered, proceed to pelvic examination.
- This should be done with extreme delicacy and respect.
- Bimanual palpation of the uterine/bladder pouch, the Douglas pouch, and adnexa can reveal exquisitely painful sites typical of endometriosis.

- Fixed uterine retroversion is frequently due to uterosacral ligament compromise or adhesions at the Douglas pouch.
- Painful uterine mobilization is another typical sign of endometriosis.
- Compression of the uterine fundus is frequently painful when adenomyosis is present.
- Dyspareunia frequently corresponds with extremely painful palpation of the uterine-sacral ligaments.

- Always look at your patient’s face during examination.
- Rictus of pain cannot be avoided.
- It will tell you exactly where the pain is more intense, helping to clinically determine the extent of the disease.
- Careful and expert pelvic examination provides a lot of information at a very low cost.

***C. Biomarkers***

- As of today, of the many biomarkers for endometriosis proposed in peripheral blood and endometrium, not one has been validated for endometriosis.
- This could be due to patient selection, sample collection, or analytical procedures.
- There is a current need to develop a non-invasive test for patients with symptomatic endometriosis.

- We still lack a reliable marker for the disease.

- Ca 125, considered a marker for endometriosis, is helpful only in postoperative follow-up.
- It usually decreases after surgery and rises when the disease recurs or progresses.
- Clinical presentations vary. Signs, symptoms, and markers do not correlate well with the extent of disease.

- Many publications describe gene abnormalities in patients with endometriosis.
- It would take a whole chapter to name them but none has yet been validated for the diagnosis of endometriosis.
- These alterations have been reported for the last 15 to 20 years.
- Some are showing ties with the disease.
- The large number of different approaches shows that the road is still unclear.

- There is a clear final recommendation:

“***Laparoscopy remains the gold standard for the diagnosis of endometriosis and using any non-invasive tests should only be undertaken in a research setting.***

- **Imaging**
- Today, some authors state that **TVS “allows a better accurate diagnosis of rectosigmoid endometriosis than MRI”.**
- Nevertheless, they propose it as a first-line imaging technique because of its low cost and feasibility.

- The International Deep Endometriosis Analysis group, confronting the wide variety of terms and descriptions used to identify endometriosis at TVS, proposes some basic steps that should be followed at the time of examination:

- 1. Routine evaluation of uterus and adnexa (search for adenomyosis and presence, or absence, of endometriomas).
- 2. Evaluation of transvaginal sonographic soft markers such as specific tenderness and ovarian mobility.
- 3. Assessment of the Douglas pouch status (sliding sign).
- 4. Assessment for DIE nodules at the anterior and posterior compartments.

- All steps should be performed, though not necessarily in this order, with a small liquid content in the bladder.
- A dynamic examination assessing the real-time mobility of the pelvic organs is mandatory in these cases.

- **Transvaginal US is the first option for the imaging diagnosis of ovarian endometriomas.**
- **TVS is a useful test in the case of ovarian endometrioma.**

**Computerized axial tomography**. “Computed tomography has no role in the routine evaluation of endometriosis except in very few particular scenarios”.

- An inguinal endometriotic nodule and a case of round ligament endometriosis that looked like a hernia were the only references found after a quick search of different databases, including Medline, linking endometriosis and computerized axial tomography (CAT) scans.
- Contrast studies might be of use for the diagnosis of ureteral stops, stenosis, or deviations in the case of lateral pelvic side-wall DIE.

- **Magnetic resonance imaging** .A recent publication shows an interesting algorithm that allows clinicians to predict the probability of bowel resection at the time of laparoscopy for DIE using MRI.

- This suggests that MRI is more useful than TVS for the diagnosis of adenomyosis.

**Laparoscopy**

- Laparoscopy is the “gold standard” for the diagnosis of endometriosis.
- It certifies the presence of the disease and its extension.
- By means of tissue biopsies and its pathological analysis, the aggressiveness of the lesions can be determined.
- It is also the opportunity to perform the initial treatment of endometriosis.

**Classifications**

- The WES consensus on the Classification of Endometriosis was held at the XII World Congress on Endometriosis in São Paulo, Brazil, in 2014.
- Fifty-five representatives of 29 national and international, medical and non-medical organizations from a range of disciplines contributed.

- It produced a statement that says: “until better classification systems are developed, we propose a classification toolbox”.

- This includes the revised American Society for Reproductive Medicine (rASRM) classification, the Enzian classification, and the endometriosis fertility index (EFI).

- The most used staging system is the rASRM classification (1997), which ignores DIE.
- Kecktein in 2003 and Haas in 2013 proposed the Enzian classification for DIE as a complement to rASRM.
- In 2010, Adamson and Pasta introduced the EFI, although it is strictly related to endometriosis-associated infertility

- The Consensus reported that “however, the classification systems in current use continue to attract criticism from women with endometriosis and those providing care for them because of the poor correlation with disease symptoms as well as a lack of predictive prognosis and, to date, unclear pathways of treating pelvic pain and infertility based” on them.

**Management**

- Vercellini and Somigliana et al. summarize current available medical treatments for symptomatic endometriosis in a recent publication. According to them, they all act by inhibiting ovulation, reducing serum estradiol levels, and diminishing uterine blood flow.
- They state that several drugs can be used “with a similar magnitude of effect, in terms of pain relief”.
- They can be categorized by price, as low-cost drugs (OCs and most progestogens) or high-cost drugs (dienogest, GnRH agonists, and the newly introduced elagolix).

- They recommend starting treatment with low-cost drugs and step up to high-cost ones only in case of “inefficacy or intolerance”.

- For them, OCs are useful for superficial peritoneal disease or endometriomas smaller than 5 cm in diameter, and progestogens have a better effect in severe dyspareunia associated with deeper infiltrating lesions.

- Back in the late 1970s, danazol NR was “the” drug.
- It relieved pain after diagnostic laparoscopy or conventional ovarian cystectomy—not much more was accomplished in the operating room (OR) at that time.
- Patients gained weight, grew a beard, and had elevated hepatic enzymes, but pain was gone, and progression probably arrested.

- In 1988, Taymor et al. questioned its clinical efficacy in infertile women.
- This prospective randomized study showed danazol to be ineffective in improving pregnancy rates over doing nothing at all in patients with minimal endometriosis.
- Years later, the World Consensus for the Current Management of Endometriosis recommended it only before IVF in severe endometriosis.

- Danazol is a drug of the past. OCs, progestogens, GnRH agonists, and lately GnRH antagonists (elagolix) and (to some extent) hormonal receptor modulators (such as ulipristal) are current specific medications.
- The role of antiestrogens is not clear, nor is that of natural origin substances (such as resveratrol), antiaromatases, anti-angiogenic molecules, and immunomodulators.

- Pain

- Pain is the most common reason for consultation; moreover, infertile patients often have chronic pelvic pain as well.
- Arrest of pain is always a priority.
- Their QOL improved immediately after a correct laparoscopic surgery in superficial endometriosis of different severities.

- The traditional management of pain includes different approaches and different pathways.
- The group headed by Catherine Allaire states that, other than non-steroidal anti-inflammatory drugs (NSAIDs), “further work is required for nonhormonal therapies such as antiangiogenic and immune-modulating drugs”.
- They list as “traditional hormonal therapies” estrogen-progestin contraceptives, progestins, and GnRH agonists.

**Other hormonal**

- treatment options are androgens and aromatase inhibitors.
- “Research also suggests a possible role for GnRH antagonists and selective progesterone receptor modulators, always discussing with each patient side effects and/or desire for pregnancy to ensure personalized treatment and optimal outcomes”.

- The European Society for Human Reproduction and Embryology (ESHRE) proposes a clear and simple guideline.
- It recommends, as a Good Practice Point, to “counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or Progestagens”.
- It nevertheless states that “it is clearly a paradox that by recommending empirical treatment in symptomatic (young) women” we might induce a delay in diagnosing the disease.

**Hormones**. The guideline recommends prescribing hormonal treatment—combined OCs, progestagens, anti-progestogens, or GnRH agonists—“as one of the options, as it reduces endometriosis-associated pain”.

- It also “recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain”.

- Combined estrogen and progestin OCs are recommended, as they reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain, in a continuous protocol.
- Also, vaginal contraceptive rings or transdermal estrogen/ progestin patches are suggested.

- Recommended progestogens are medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, and noretisterone acetate.
- Anti-progestogens such as gestrinone are considered.
- The different side effect profiles of each one of those drugs, especially thrombosis and androgenism, should be regarded.
- The use of a levonorgestrel-releasing intrauterine device is also an option. Aside from difficult cycle control in some users, dienogest in doses of 2 mg per day results in very effective pain reduction and control of the disease progression.
- It can be used over prolonged periods of time provided that no recurrent bleeding occurs. This is the main cause of discontinuation.

**Anti-hormones**. According to the guideline, evidence regarding dosage or duration of GnRH agonists is limited.

- “Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment” since this will not reduce the effect of the pain treatment.
- The guidelines recommend giving “careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density”.

**Aromatase inhibitors**. These options are considered for those who have pain from rectovaginal endometriosis, refractory to other medical or surgical treatment.

- They should be prescribed in combination with OC pills, progestagens, or GnRH analogs.

**Analgesics**. The guideline asks a simple question: “Are analgesics effective for symptomatic relief of pain associated with endometriosis?” Then it tells us that evidence on the use of NSAIDs for endometriosis is scarce.

- For the guideline, NSAIDs have a “favorable effect on primary dysmenorrhea and are widely used as a first-line treatment of endometriosis-associated pain”60. However, it recommends the use of NSAIDs or other analgesics to reduce endometriosisassociated pain.
- Clinicians should discuss the associated side effects with the patient.

- The off-label use of a COX-2 inhibitor, etoricoxib, available in many countries could replace rofecoxib.
- As was demonstrated long ago, its tolerance and fewer upper gastrointestinal clinical events versus the traditional NSAID diclofenac are notable, although this difference was not reported in relation to the rare and very serious adverse side effects that both drugs can produce.

- The Practice Committee of the ASRM states that “first-line medical treatment for pain due to endometriosis is often a nonsteroidal anti-inflammatory drug”.

- This everyday practice, difficult to change, affects women without a certified diagnosis of endometriosis.

- Opioid derivatives such as codeine and tramadol have rarely been studied for the treatment of endometriosis-associated pain.
- Many doctors prescribe them to these women: “Obstetrician– gynecologists reported prescribing a median of 26 opioid pills across all indications combined”.
- “Opioid-related deaths recently exceeded motor vehicle accidents as the leading cause of injury-related death in the United States”

- “In 2015, 2 million Americans had a prescription opioid use disorder, and more than half of those who reported prescription opioid misuse obtained the drugs through diversion of prescribed medications”.

- The use of this type of analgesics should be limited to very exceptional cases in which other drugs have failed and during the least span of time.

## What's new?

### Elagolix

- The elagolix phase III clinical trial66 introduced a new and promising treatment for endometriosis.
- Oral anti-gonadotrophic agents have a sound future.
- They arrest the progression of the disease and dramatically reduce pain. Relief is fast and significant.
- New clinical trials for similar drugs are ongoing.
- In the publication of reference, elagolix compared with placebo showed a significant decrease from baseline in the mean pain score. This significant effect was seen at months 3 and 6 of treatment.

- One adverse side effect, bone density damage, was  dosedependent.
- Decrease in lumbar spine bone mineral density (BMD) following 6 months of treatment with elagolix compared with placebo was significantly different for each elagolix dose.
- “The proportion of participants with lumbar spine BMD decrease from baseline greater than 3% was also dose-dependent”, as was the case of decreases in BMD of the total hip and femoral neck.

- Current protocols for similar drugs include addback hormonal therapy to minimize the effect on bone density.
- How long can the patient be treated with GnRH antagonists that produce medically induced menopause-like status? This is a question for the near future since trials provide only up to 12 months of treatments.
- With addback therapy, these drugs could probably be used for prolonged periods of time.

- On July 24, 2018, the FDA approved elagolix for the management of moderate to severe pain associated with endometriosis.

- Recent studies address other advantages: dyspareunia and pain reduction across a range of baseline characteristics have been shown to be consistent.
- During the first 12 weeks of treatment with either leuprolide acetate (LA) or elagolix, subjects had lower estradiol (E2) levels compared with women who received placebo.

**Proellex**

- Selective progesterone receptor modulators are a class of drugs with progesterone antagonist activity that may confer therapeutic benefit for reproductive disorders in premenopausal women.
- Endometrial structure, which is dynamically controlled by circulating sex hormones, is likely to be perturbed by progesterone receptor modulators through their progesterone antagonist properties.

- Its performance as a treatment for endometriosis was proven.
- It is a drug with progesterone antagonist activity.
- A major concern was the alteration of the eutopic endometrium.

- The structure of this tissue, dynamically controlled by circulating sex hormones, is altered by progesterone receptor modulators through their progesterone antagonist properties.

- Some presented anomalies, including formation of cystically dilated glands, and secretory changes coexisting with mitoses and apoptotic bodies.
- Increasing daily dose and duration made the cysts predominant and their lining inactive or atrophic.

- Proellex has been questioned by the FDA because of liver enzyme increases shown by patients who received treatment in the endometriosis clinical trial.
- Clinical trials were halted and the company that developed the drug is now redirecting future studies to vaginal administration.
- A partial halt of the studies has not yet been reverted by the drug authority.

**Ulipristal**

- In his doctoral thesis, Simpson, after a 3-month treatment course with ulipristal acetate (Esmya) for endometriosis-associated pain, found a good clinical response in 56% of the studied cohort.
- Post-treatment histological and immunohistochemistry changes were correlated to changes in the macroscopic appearance of the disease and changes in symptom severity.

- In this descriptive observational cohort study, ulipristal acetate appears to offer an effective treatment for endometriosis with histological changes in the eutopic endometrium that should be carefully observed.
- “The safety of this compound remains to be elucidated but the results from this pilot study are encouraging and should prompt further exploration”, wrote Simpson.

- A possible relationship with endometrial malignancies and severe liver damage reported excludes it from currently available endometriosis drugs.
- The FDA recently (August 2018) refused, once again, to authorize Esmya (brand name for ulipristal acetate) for human use.
- The drug had been preliminarily approved by the EMA in 2015.
- In May 2018, the EMA issued a warning about the rare occurrence of liver complications.
- In June 2018, the agency approved its use in the preoperative treatment of fibroids (that is, for a short period of time).
- There could be a possible role for ulipristal acetate in the management of endometriosis.

- a surgical pretreatment. long-time use is not guaranteed to be safe at the present time.
- We must keep in mind that endometriosis is a benign condition and care should be taken when prescribing medications with dangerous side effects, even if rare and infrequent

- In regard to hyperplasia, some authors explain it as a singular endometrial alteration induced by progesterone receptor modulators and not a real hyperplasia.
- This modification of the endometrial structure would regress after drug cessation.

**Resveratrol**

- Resveratrol, a natural drug derived from grape wine, induces apoptosis in endometrial stromal cells via the suppression of survivin expression.
- Ines Baranao and her group at IBYME–CONICET (Buenos Aires, Argentina) are working in animal experimentation with endometriosis surgical implants in rats, where they demonstrate the suppressive effect of resveratrol on the progression of the disease.
- Makabe et al. describe how it enhances apoptosis in endometriotic stromal cells.
- There is a long journey yet to be accomplished but these very preliminary results are promising.

**Alternative treatments**

- The Montpellier Consensus included the following: acupuncture, high-frequency transcutaneous electrical nerve stimulation, Chinese herbal medicine, vitamins B1 and B6 , magnesium, tropical heat, spinal manipulation, and behavioral interventions.
- No sound evidence or high-grade studies support those therapies, but if they cause no damage or delay specific treatment, they can be considered supporting therapies.
- Cannabis has been shown to be only moderately effective for the relief of chronic pain and has potentially serious side effects (and there are no studies specifically addressing endometriosis).

- There are not enough comprehensive publications that address, with high-grade evidence, the variety of uses of psychotherapy.

- For instance, group therapy, support or self-help groups, physical activities, and music or drama as co-therapies may be used to allow patients to socialize and overcome their misfortunes and frustrations.

- exercise “might be effective in reducing dysmenorrhea”.
- Weight reduction or specific dietary interventions have no clearly demonstrated effects except for the fact that diet after surgery, with vitamins, minerals, salts, and lactic ferments, appears to be effective in pain reduction in comparison with hormonal treatment.
- There is a consensus that gluten-free diets improve symptoms in some women who have endometriosis and gastrointestinal complains

## Fertility

- The opportunity, quality, and extension of the first surgery are determinant when fertility is the issue.

## Quality of surgery

- Surgery should be provided by experts on the disease.
- Much of the recurrence (or persistence) of endometriosis is related to poor first surgery quality, incomplete removal of all lesions, or wrong attitude at the time of laparoscopy.

- diagnosis and primary treatment of endometriosis. Certainty can be achieved only by laparoscopic staging and biopsy (for histological confirmation of the disease).
- Histology helps to make a better prognosis, according to the activity of the lesions.
- Laparoscopy gives the opportunity to excise all disease present, including adhesions, peritoneal lesions of all types (blue, red, white, scars, and peritoneal pockets), endometriomas, and deep infiltrating lesions.
- Preoperative workup, including contrast MRI, will allow the surgeon to correctly appraise each case before taking the patient to the OR.

- The treatment of endometriosis requires a delicate and experienced surgeon and, if it is the case, an interdisciplinary team, including gastrointestinal surgeons or urologists (or both), in selected patients.
- Multidisciplinary pelvic surgeons may be available at some institutions, where a reduced number of gynecologists operate a large number of patients.
- In most environments, the number of surgeries per year required to sustain expertise in all areas of surgery might be impossible to achieve.
- Therefore, interdisciplinary surgery proves to be mandatory in most locations.

- A recent online consensus meeting organized by the WES addressed the issue of “centers of excellence or expertise” in endometriosis and of “surgical experts” in DIE.
- In a preliminary presentation, many options and requirements were suggested to distinguish a surgeon as an “expert” in endometriosis.
- There is still a long way to go before a final consensus might be achieved.
- Surgical expertise by itself should not be a determinant: real interest in all aspects of endometriosis is required.