Medical treatment of the endometriosis

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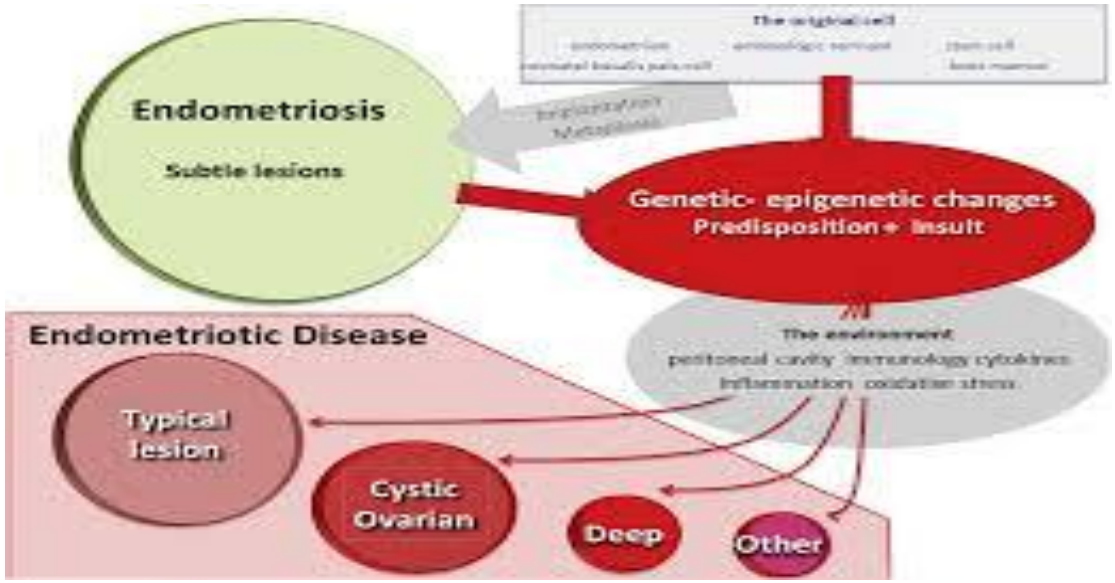
Pathogenesis of endometriosis

- Chronic inflammation
- Cell proliferation
- Invasion

Neoangiogenesis is the key to the

- Estabilization
- Progression
- recurrence



Endomertiosis associated pain

- Central sensitization
- key factor in the addition to the peripheral nociceptive effect of endometriotic lesions

(Hoffman, 2015).

- amplifies pain signaling from the periphery

(Brawn et al , 2014).

- It is associated with
- Myofascial trigger points

(Stratton et al, 2015)

- Psychological comorbidities

(Yosef et al, 2016).

What is the best for endometriosis-associated pain?

- Endometriosis is a chronic condition, and patients require new medical therapies that provide long-term benefit, in terms of prevention of both disease progression and pain recurrence, that is sustained after treatment cessation.

- The **treatment goals** for endometriosis include pain relief, avoiding rupture or torsion, excluding malignancy, and preventing symptomatic or expanding endometriomas

Currently:

- Treatment of endometriosis-associated pain based on:

1. suppressing estrogen production and inducing amenorrhea,

2. hypoestrogenic environment: inhibits ectopic endometrial growth and prevents disease progression

(Barbieri, 1999).

Limitations of current endometriosis treatment

1. Suppressive rather than curative therapy
2. Temporary relief of symptoms during treatment.
3. Discontinuation: recurrence of the symptoms

Limitations of current endometriosis treatment

- After medical treatment or surgical treatment, the recurrence of endometriosis was estimated to be 21.5%at 2 years and 40% to 50%at 5 years .

- (Guo, 2009)

Limitations of current endometriosis treatment

- 1. blocking the hypothalamo pituitary-ovarian axis: suppression of ovulatory function

- 2. endometrial atrophy: hinders embryo implantation.

No improvement in natural conception after a course of ovarian suppression by medical therapy

(Fedele et al, 1992, RCT).

Infertile women with endometriosis

- No benefit in the use of ovulation suppression
- Pain: NSAIDs: the only medical option consistent with the maintenance of fertility
- If pregnancy is desired, NSAIDs that negatively affect ovulation such as COX-2 inhibitors should be avoided

Duffy DM et al 2011

What is the best for endometriosis-associated pain?

- endometriosis requires a life-long personalized management plan with the goal of maximizing medical treatment and **avoiding repeated surgical procedures**.

- The treatment for endometriosis is essentially chosen by each individual woman, depending on **symptoms, age, and fertility**.

- A combination of surgical treatment and either preoperative or postoperative medical therapy has been suggested for endometriosis

What is the best for endometriosis-associated pain ?

- established medical therapies provided a better outcome than placebo.
- All available hormonal therapies appear to have similar efficacy, but their tolerability profiles differ.
- **none** seems to be **better than another**.

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Endometrioma:

- Medical T: not effective
- Surgical T: Hazardous
- The treatment goals for endometriomas:
- pain relief, avoiding rupture or torsion, excluding malignancy, and preventing symptomatic or expanding endometriomas.

- Medical therapy does not resolve endometriomas

(Dunselman et al, 2014).

Endometrioma

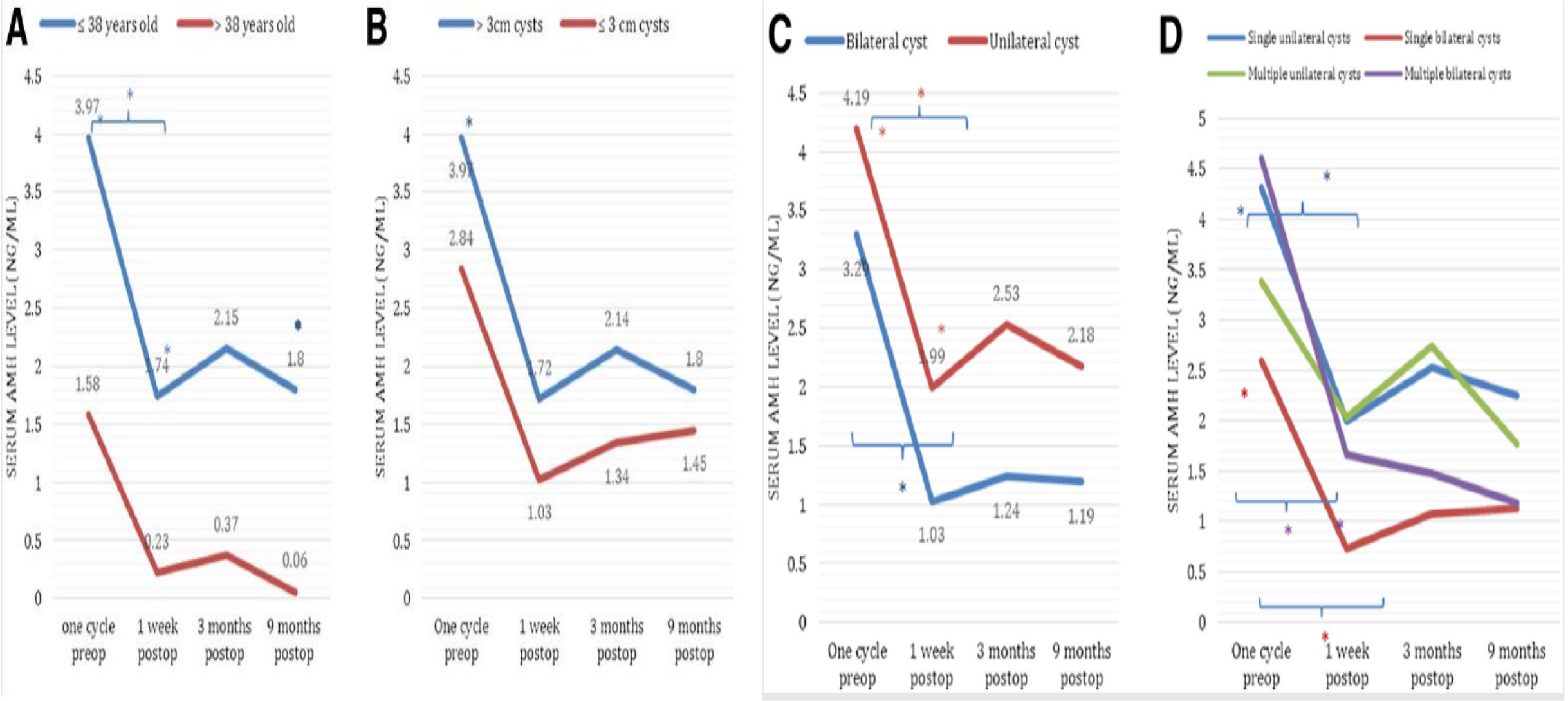
- Surgical removal:
- negatively affects ovarian reserve.
- statistically significant fall of AMH
- with a weighted mean difference of 1.13 ng/mL

(Raffi et al, 2012; 19 SR of 237 patients).

The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas

S Alborzi, P Keramati, M Younesi, A Samsami, N Dadras

Fertility and sterility 2014,101 (2), 427-434



DIE :

DIE: subtype of endometriosis :

1. uterosacral ligaments,
2. rectovaginal septum,
3. bowel, ureters, or bladder.

- Symptomatic urinary endometriosis,
- medical therapy: variable response may also require surgery.

(Fedele et al, 2008)

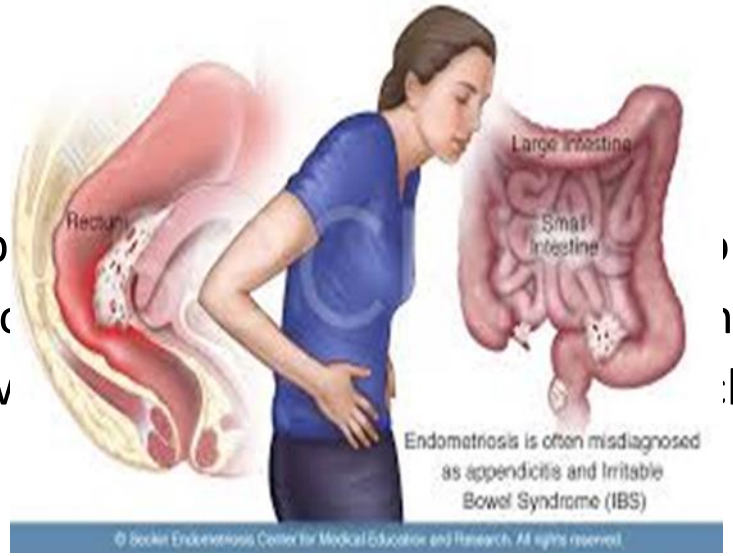
-

DIE :

- Bowel endometriosis
- einstein (São Paulo). 2019;17(2):1-6:
- recto-sigmoid endometriosis. Medical treatment should b …r
- patients with bowel endometriosis. Surgical treatment sh… pain
- symptoms unresponsive to hormonal therapy, lesion grow… clusion
- surgery if:

1. fail medical management or
2. develop obstructive symptoms

(Abrao et al, 2015).

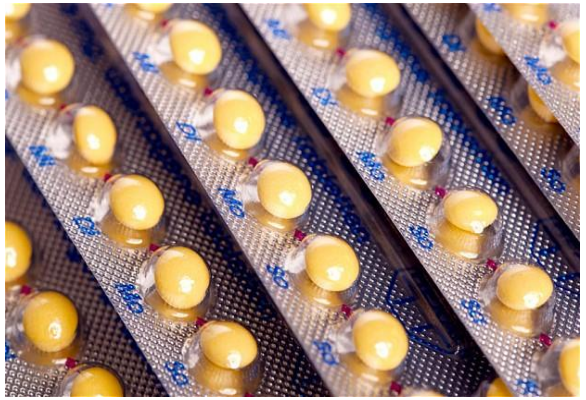


- Failure of medical treatment: frequently encountered with these aggressive disease phenotypes.

Criteria for the ideal medication for endometriosis (Bedaiwy, 2017)

- 1. Curative rather than suppressive
- 2. Treats pain and fertility at the same time
- 3. Acceptable side effect profile
- 4. Long-term use should be safe and affordable
- 5. Noncontraceptive nature
- 6. No interference with spontaneous ovulations and normal implantation
- 7. No teratogenic potential and safe to use periconceptionally
- 8. Inhibits the growth of already existing lesions
- 9. Aborts the development of new lesions
- 10. Effictive for all endometriosis phenotypes superficial disease, endometriomas, DIE, and extrapelvic endometriosis and adenomyosis

Hormonal therapy:



- Oral contraceptives (OC),
- progestogens,
- danazol,
- GnRH-a,
- anti-progestogens
- LNG-IUS

The Practice Committee of the American Society for Reproductive Medicine American Society for Reproductive Medicine, Birmingham, Alabama Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril. 2014;101(4):927-35.

Combined hormonal contraceptives (CHCs), OCP:

first-line hormonal option

1. block endogenous ovarian estradiol
2. create a progesterone dominant hormonal environment that down-regulates the local estrogen-receptor response and prevents the proliferation of endometriotic lesions
3. significantly reduced nerve fiber density in endometriotic lesions
4. inhibition of angiogenesis

OCP:

- Improve pain symptoms,
- sometimes significantly reduce the volume of menstrual flow,
- well tolerated
- not expensive

OCP:

- Ocs :in both a cyclic and a continuous fashion in the treatment of symptoms associated with endometriosis.
- Combined OCs containing the more androgenic progestogens (19-nortestosterone derivatives) traditionally have been used to treat endometriosis symptoms
- Combined OCs containing the new generation progestogen, desogestrel, also have proven effective.

Razzi S, Luisi S, Ferretti C, Calonaci F, Gabbanini M, Mazzini M. et al. Use of a progestogen-only preparation containing desogestrel in the treatment of recurrent pelvic pain after conservative surgery for endometriosis. Eur J Obstet Gynecol Reprod Biol. 2007;135:188-90.

OCP:

- A low-dose combined **OC** administered in a cyclic regimen to women with endometriosis was found as effective as **GnRH-a** treatment for relief of dyspareunia and dysmenorrhea.

- A prospective observational trial demonstrated that **continuous** low-dose combined OCs were **more effective than** cyclic combined OCs in controlling endometriosis symptoms in patients after surgical treatment for endometriosis.

Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, and Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril. 2003;80:560-3.

OCP:

- The most common side effects :

1. headaches,
2. gastrointestinal disturbances (abdominal distension, nausea),
3. weight gain
4. cardiovascular changes,
5. changes in sexual desire and mood.
6. Venous Thromboembolism ethinyl estradiol (20 µg) as compared to high dose (30 µg) have a lower risk

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Progesterone, progestogens/gestagens

- reducing pain &suppressing the extent of endometriotic lesion. through several mechanisms:

1. induce anovulation
2. reduce the expression of aromatase
3. reduce the expression and enzyme activity of 17ß-HSD1 (conversion of estrone to estradiol)
4. alter estrogen receptors,
5. inhibit angiogenesis,
6. decrease expression of matrix metalloproteinases needed for the growth of the endometriotic implant
7. they directly inhibit progesterone-mediated cell proliferation and the production of inflammatory cytokines

Progestogens

- Based on controlled trial data, it appears that oral “mini-pill” treatment should be the first-line therapy

Progestins used in the treatment of endometriosis include:

- medroxyprogesterone acetate (150 mg intramuscularly every three months or oral **10 to 100 mg per day for 3–6 months**)
- norethindrone acetate also known as norethisterone acetate **(2.5 mg per day for 12 months),**
- subdermal implant (etonogestrel) which offers contraceptive benefits for at least three years
- levonorgestrel-releasing intrauterine devices which contain **52 mg levonorgestrel and release 20micrograms of hormone per day over a five-year period** may be used.
- dienogest **(2 mg or 4 mg per day**)
- as well as cyproterone acetate, dydrogesterone, gestrinone, lynesterole, and megesterol acetate

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Progestogens

first choice should be low-dose oral norethisterone acetate, given the extremely favorable cost-effectiveness profile

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Progestogens:

- Treatment with medroxyprogesterone acetate (MPA), dydrogesterone, or norethindrone acetate, pain has been reduced by **70%-100%.**

- A **meta-analysis** of four randomized, controlled trials comparing MPA to danazol alone, danazol and combined OCs, or a GnRH-a concluded that MPA was as effective as the other treatments (odds ratio [OR] 1.1;95% CI 0.4–3.1)

Laschke MW, Menger MD. Anti-angiogenic treatment strategies for the therapy of endometriosis. Hum Reprod Update 2012;18:682-702: 492-6.

Progestogens:

- Randomized studies concluded that dienogest was significantly better than placebo and as effective as the GnRH-a buserelin, LA, or triptorelin in reducing pain symptoms with **diminished side effects** of hot flushes and bone mineral density loss treatment of endometriosis.

McCormack PL. Dienogest. A review of its use in the treatment of endometriosis. Drugs. 2010;70:2073-88.

Dienogest

- 2-mg oral pill taken daily
- When compared with prior use of NETA 2.5 mg, DNG 2 mg produced comparable ameliorations in overall pain relief, psychological status, sexual functioning, or health-related quality of life. However, DNG was better tolerated

Vercellini P et al 2016

Dienogest

- DNG 2 mg/day was superior to placebo in reducing pelvic pain, with equivalent results to GnRH agonists (buserelin , leuprorelin , leuprolide acetate, and triptorelin), in controlling pain symptoms associated with endometriosis
- It was also effective when used for prolonged durations up to 52 weeks with tolerable side effects.

Andres MdeP et al 2015

Dienogest

- BMD at the lumbar spine significantly decreased after the first 6 months of treatment in both COC after GnRH agonist (3.5%) and DNG (2.3%) groups, but the groups did not differ statistically. After 6 months, further decrease in BMD was not observed until 24 months in both groups. In addition, no cases of pain or endometrioma recurrence were found.

- J.-W. Seo et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology 236 (2019) 53–57

Levonorgestrel-Releasing Intrauterine System

- A randomized, controlled trial comparing the LNG-IUS to expectant management after laparoscopic surgical treatment for symptomatic endometriosis found that the LNG-IUS was more effective **than** no treatment in reducing symptoms of dysmenorrhea.
- Other studies have demonstrated improved symptoms associated with rectovaginal endometriosis and a significant decrease in the extent of disease observed at second-look laparoscopy after 6 months of treatment with the LNG-IUS. Relief of endometriosis pain with the LNG-IUS is **similar** to GnRH-a.

BayogluTekin Y, Dilbaz B, Altinbas SK, and Dilbaz S. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril. 2011;95: 492-6.

Lockhat FB, Emembolu JO, and Konje JC. The evaluation of the effectiveness of an intrauterine-administered progestogen (levonorgestrel) in the symptomatic treatment of endometriosis and in the staging of the disease. Hum Reprod. 2004;19:179-84.

Levonorgestrel-Releasing Intrauterine System

- In a randomized trial, immediate postoperative insertion of LNG-IUS was associated with less recurrence of sever dysmenorrhea compared with surgery alone at the end of 1 year of follow-up with greater patient satisfaction.

Vercellini P et al 2003

- These results were further confirmed in a double-blind RCT where the effectiveness of postoperative LNG-IUS was compared with expectant management in patients with moderate to severe endometriosis

Tanmahasamut P et al 2012

Side Effects of progestron

- progestin-only methods are devoid of:
- estrogen-associated side effects of the COCs,
- the androgenic side effects of danazol,
- the bone loss associated with GnRH analogs.
- associated with better lipid profil
- The short-term side effects of progestin treatment include irregular uterine bleeding, spotting, weight gain and mood changes, depression, and irritability

Regidor PA et al 2001

- Long-term use
- DMPA is associated with bone loss
- NETA can lead to a reduction in HDL and significant increases in LDL&triglycerides

GnRH agonists

are **a second-line** therapy, when first-line therapies are ineffective, not tolerated or contraindicated

- buserelin, goserelin, leuprolide, nafarelin or triptorelin
- inhibiting of GnRH pulsatility and consequently the synthesis of gonadotropins
- GnRH agonists affect only the hypothalamopituitary- gonadal axis, **but not extraglandular sites of estrogen biosynthesis.** Therefore, estrogen production occurs in the adipose tissue, the skin and local endometriotic lesions during these treatments.

GnRH agonists

- use of GnRH agonists is generally **restricted to a 6-month** course.
- it is mandatory to **start GnRH agonist with “add-back therapy”**

1. **Norethindrone acetate is the only FDA approved addback therapy**,
2. low dose estrogen
3. a combination of estrogen and progesterone

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GnRH agonists

- The add-back therapy should be started at the same time as the agonist rather than delaying until a period of hypoestrogenism has occurred. This approach has been shown to decrease bone loss and improve vasomotor symptoms and compliance

Barbieri RL. Endometriosis and the estrogen threshold theory: relation to surgical and medical treatment. J Reprod Med. 1998;43:287-92.

GnRH agonists

- In addition, antiresorptive drugs **like Raloxifene (60 mg daily, p.o.)** have been used to preserve the bone tissue during GnRH agonist treatment in premenopausal women with severe endometriosis

- A **Cochrane analysis** found that GnRH-a were more effective than placebo for endometriosis pain relief but were similar to the LNG-IUS and danazol.

Brown J, Pan A, and Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev. 2010;12:CD008475

- A long-term follow-up study of patients treated with a GnRH-a alone for 6 months revealed a 53% recurrence of disease/symptoms 2 years after treatment.

Waller KG and Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril. 1993;59:511-5.

GNRH agonist:

- **long-term safety** data on this treatment regimen (GNRHa+add back) are **limited**

Crosignani P, Olive D, Bergqvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update 2006;12:179–89.

The combination of **GnRH agonists and norethindrone acetate is only approved for 12 months.**

Danazole :

- 400-800 mg /day divided dose

- side effects of danazole are common and include hirsutism, acne, weight gain, and deepening of the voice.

Farquhar C, Prentice A, Singla AA, Selak V. Danazol for pelvic pain associated with endometriosis. The Cochrane Library. 2007.

Danazole :

- Typically this medication is administered orally; however, vaginal administration as well as vaginal and intrauterine delivery systems have been reported.(specially for recto vaginal nodule)
- Danazol provided comparable pain relief to GnRH-a but was not as well tolerated

Ferrero S, Tramalloni D, Venturini PL, and Remorgida V. Vaginal danazol for women with rectovaginal endometriosis and pain sympotms persisting after insertion of a levonorgestrol-releasing intrauterine device. Int J Gynecol Obstet. 2011;113:116-9.

gesterinone:

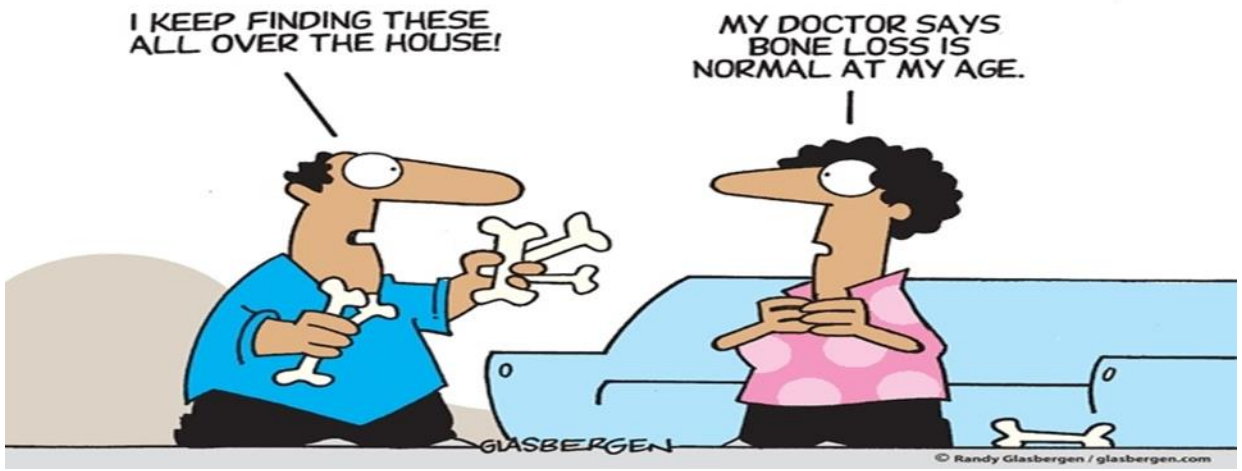
- androgen derivative 19 nortestestron,

- Gestrinone is administered orally daily to weekly with doses ranging from 2.5-10 mg.
- Side effects relate to both androgenic and antiestrogenic effects. **Gestrinone** was shown to be as effective as danazol and GnRH analogues.

Brown J, Kives S, and Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev. 2012;3:CD002122

Other medications:

- GNRH antagonist:(Elagolix, Cetrorelix)
- SPRM:(Mifepristone, Asoprisnil, Ulipristal acetate, Tanaproget)
- SERM:(Raloxifine, Bazedoxifene, Chloroindazole, Oxabicycloheptene)
- Aromatase inhibitors:(Letrozole,anastrozole)
- Nonhormonal Imunomodulaters:(Etanercept, IFN-2b, Loxoribine, Lipoxin, Infliximab, Pentoxifylline)
- Antiantiangiogenics:(Caplostatin, Endostatin, Cabergoline, Bromocriptine ,Quinagolide,…….
- Omega-3 fatty acids,
- Cannabinoid agonists



GNRH antagonist

- Injectables (Ganirelix, Cetrorelix)

(Kupker et al., 2002)

- 3-mg once a week over 8 weeks
- Safe and efficient .
- Oral nonpeptide forms

(Elagolix, Abarelix,Ozarelix, TAK-385).

GNRH antagonist

- is **competitive receptor occupancy**, thus suppressing pituitary gonadotropin in a dose-dependent manner

- The main advantage during GnRH antagonist treatment is preserving basic estrogen production, serum estradiol oscillating around a mean concentration of 50 pg/mL, thus limiting the side effects associated with hypoestrogenism

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GNRH antagonist

- Both oral and injectable forms of GnRH antagonists are effective in reducing endometriosis-associated pain and all patients reported a pain-free period.
- **cetrorelix** : 3 mg once a week over 8 weeks could be a feasible medical treatment for endometriosis associated pain
- **Elagolix** :approved for the management of moderate to severe pain associated with endometriosis. If low Elagolix doses are used, ovulation is not consistently inhibited, and patients should use non-hormonal contraceptive systems.
- If high Elagolix doses are used to control severe pain for long periods of time, add-back therapy should be added, similar to that prescribed when using GnRH agonists

GnRH antagonists

- inhibits the pain symptoms by reducing the estrogen levels
- Superior to agonists
- avoids the lag seen with the GnRHa
- work more effectively and faster in improvement of symptoms.

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Elagolix

- dose dependent(150 mg/day -200mg towice /day)
- approved for the management of moderate to severe pain associated with endometriosis.
- If low Elagolix doses are used, ovulation is not consistently inhibited, and patients should use non-hormonal contraceptive systems.
- If high Elagolix doses are used to control severe pain for long periods of time, add-back therapy should be added, similar to that prescribed when using GnRH agonists

- Short half-life (6 h): rapid elimination of drug from the body if the treatment is interrupted for any reason

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Elagolix

- Efficacy, safety, and tolerability
- demonstrated in phase 1 and 2 trials

(Melis et al, 2016).

- Elagolix Vs SC DMPA

for endometriosis associated pain

- Similar efficacy
- Minimal impact on BMD over a 24-w period

(Carr et al, 2014: RCT)

Selective progesterone receptor modulators (SPRMs).

- SPRMs represent a class of nuclear progesterone receptor ligands which act as agonists, antagonists, or combined agonists / antagonists, depending on the progesterone-sensitive tissue.

- mifepristone, ulipristal acetate, asoprisnil, opanpristone, lonaprisan, telapristone acetate, PRA-910, ZK 136799 and vilaprisan. Can be administered orally, via *IUD* systems or as vaginal rings.

(SPRMs). Mifepristone

- (RU486) is the first and the most studied SPRM.

- antiglucocorticoid, antiprogestogen and weak anti-androgen activity.
- It acts as a competitive receptor antagonist at the progesterone receptor in the presence of progesterone, and as a partial agonist in the absence of progesterone.

(SPRMs) Mifepristone

- induction of medical abortions,
- it has proven effective in the treatment of dysmenorrhea and dyspareunia,
- with side effects of amenorrhea and hot flushes
- inappropriate for long-term application as a result of the antiglucocorticoid properties and hypoadrenal state it generates.
- A minimum dose of 50 mg mifepristone for six months demonstrated a significant regression of endometriotic lesions and a decrease in clinical symptoms.

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Mifepristone

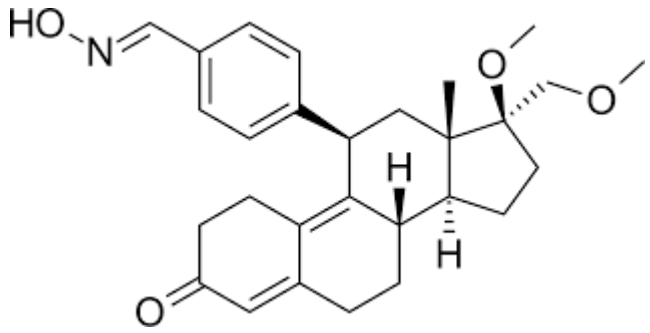
(Zhang YX, 2016)

- Humans
- Reduction of endometrial thickness
- alleviation of symptoms during 6 mo of treatment.

(Mei et al., 2010)

- Rats
- SC implanted capsules an effective means for long-term treatment of chronic endometriosis.
- positive effect on pain symptoms
- induced amenorrhea without causing hypoestrogenism.

Asoprisnil



- (Chawlisz et al., 2005)
- Humans
- 5, 10, 25 mg significantly reduces nonmenstrual pelvic pain/dysmenorrhea scores.
- Phase 3 trials were discontinued due to development of endometrial proliferation and hyperplasia

Ulipristal acetate

- approved as
- 1. an emergency contraceptive
- 2. treatment of fibroids

(Hunaidi et al., 2013)

- Rats
- Decreases COX-2 expression
- The feasibility for the treatment of endometriosis has yet to be determined

Selective estrogen receptor modulators (SERMs)

- bind to nuclear α- or β- estrogen receptors and exert estrogen or antiestrogen actions depending on the tissue type.

- The majority of findings were obtained in animal models and the effectiveness of SERMs in human endometriosis has still to be evaluated

- experimental models SERMs show a direct effect on endometrial blood vessels and suppress endometrial prostaglandin production without the systemic effects of estrogen deprivation.

SERMs

- **Raloxifene,** used for the treatment of postmenopausal osteoporosis, estrogen antagonist effect on the rat uterine tissue, producing implants regression

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SERMs

- Raloxifine
- 2nd generation SERM

used for the treatment of postmenopausal osteoporosis

Stratton et al., 2008

- Humans :Rate of recurrence of symptoms following treatment discontinuation after 6 months was higher in the raloxifene group compared with placebo: study termination

Atlintas et al., 2010

- Rats :Statistically significant reduction of implanted endometrial tissue comparable to anastrozole.

Yao et al., 2005

- Rats: At 10.0 mg/kg caused statistically significant regression of implant (P<.05).

Yavuz et al., 2007

- Rats :Similar to anastrazole in significant reduction of the endometriotic implants

Bazedoxifene

- 3rd generation SERM

Lyu et al., 2015

- Rats
- Statistical significant reduction in volume of implants.

Naqvi et al., 2014

- Mice
- decrease endometriotic lesion compared with control.

Kulak et al., 2011

- Mice
- Statistically significant regression of endometriosis.

Aromatase inhibitors (Ais):

- inhibit local estrogen production in endometriotic implants, ovary, and adipose tissue.,
- studies reported that aromatase is more abundant in endometriotic tissues than in the normal endometrium

- AIs are likely to maintain low estrogen levels in extra-ovarian sites

- AIs decrease the endometriosis-associated pain, reduce the size of extrauterine endometrial lesions, and improve patients' quality of life

Aromatase inhibitors (Ais):

- increase FSH levels through feedback of the hypothalamo-pituitarygonadal axis, sometimes leading to the development of ovarian cysts
- Long-term use of AIs is associated with an increased risk of osteoporosis and bone fractures secondary to hypoestrogenism
- ESHRE guidelines recommend concomitant use of Ais and oral contraceptives, progestins, or GnRH agonists for women of reproductive age with endometriosis.

Aromatase inhibitors (Ais):

- There are two types of aromatase inhibitors**, nonsteroidal and steroidal**.
- **Nonsteroidal inhibitors (anastrozole, letrozole**) inhibit estrogen synthesis **via reversible competition**,
-
- **steroidal inhibitors** which resemble the structure of **androstenedione (exemestane)irreversibly** inhibit the enzyme by binding covalently to the binding site of aromatase

Aromatase inhibitors (Ais):

- . AIs can be administered orally, in various doses,
- **1 mg daily for anastrazole**
- **2.5 mg daily for letrozole**

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Letrozole

Agarwal et al., 2015

- Humans
- With progestin add-back:
- 75% reduction of endometrioma volume
- improved pain symptoms after 3 mo of TT

Almassinokiani et al., 2014

- Humans
- Effect comparable with OCP in endometriosis- related pelvic pain.

Ferrero et al., 2011

- Humans
- reduction in endometriosis related pain.

Anastrazole

Bilotas et al., 2010

- Mice
- reduced VEGF and PGE in peritoneal fluid; with no effect on PGE level.
- Dose: 1 mg daily

central sensitization

- Tricyclics and antiepileptics
- Multidisciplinary approach
- Physiotherapy
- Psychological therapy

(Peters et al, 1992)

Immunnomodulators

Tumor necrosis factor-a

- Proinflammatory cytokine able to initiate inflammatory cascades
- increased in the peritoneal fluid and serum of women with endometriosis
- implicated in the pathogenesis of endometriosis

(Bedaiwy et al, 2002)

- 1.Etanercept

Barrier et al., 2004

Baboons Statistically significant decreases endometriotic lesion surface area

- 2. IFN-2b

Bedawy et al., 2001

Human

cell culture statistically significant suppression of endometrioma.

Ingelmo et al., 2013

Rats

greater reduction in implant size compared with placebo

- 3.Loxoribine

Keenan et al., 1999

Rats

Reduced NK cells and endometriotic lesions.

- 4. Lipoxin

Xu et al., 2012

Mice

- Inhibited endometriotic lesion development,
- suppressed MMP-9, and decreased VEGF.

Kumar et al., 2014

- Mice
- A4 compound decreased PGE2 production, aromatase expression, and estrogen signaling.

Rapamycin

Ren et al., 2016

Mice

- Reduced VEGF serum level and MVD: decreased endometriotic lesions in SCID m Laschke et al., 2006

Hamsters

- Decreased VEGF and MVD: inhibition of endometriotic cell proliferation.

Infliximab

- TNF-a blocker

Koninckx et al., 2008

Humans

- **No effect** in endometriosis-related pain.
- not enough evidence to support the use of anti- TNF-a drugs in the management of women with endometriosis for the relief of pelvic pain (Cochrane SR, Lu et al, 2013).

Pentoxifylline

- competitive nonselective phosphodiesterase inhibitor have properties that could be used for endometriosis- associated pain ory

Kamencic and Thiel, 2008

Humans

- better VAS score after 2 and 3 mo from surgery compared with controls.

Vlahos et al., 2010

Rats

- reduction in VEGF-C, decreased volume and no. of endometriotic implants.
- Lack of evidence to recommend pentoxifylline for pain relief or to improve the chances of spontaneous pregnancies

(Cochrane SR, Lu et al, 2009).

Clarithromycine

- Clarithromycin may be an appropriate treatment in endometriotic patients. However, the non-significant differences between the real and placebo groups necessitate further studies on the therapeutic efficacy of clarithromycin

Alboezi et al 2019

Levamisole

- This study indicates a possible successful role for levamisole in the treatment of experimental endometriosis.
- Further studies to assess the effects of high dose levamisole on endometriosis are recommended

Alborzi et al 2013

Antiangiogenic agents.

- Neoangiogenesis
- Essential for:
- Initiation
- growth,
- invasion
- recurrence
- Antiangiogenic agents
- many
- has been evaluated in vitro
- clinical evidence for the efficacy and safety of most of them: still lacking

(Laschke M, Menger, 2012)

Antiangiogenic agents

- Statin family
- Caplostatin, Endostatin, Angiostatin, Lovastatin, Atorvastatin, Simvastatin
- effective in vitro in reducing angiogenesis and endometriotic implant size
- in mice, rats, and human cells in vitro

(Almassinokiani et al, 2013).

Antiangiogenic agents

- 2. Lodamin

Becker et al., 2011

Mice

- reduction of endothelial progenitor cells: suppression of endometriotic tissue growth.
- 3. Romidepsin

Imesch et al., 2011

Human cell culture

Decreased VEGF secretion

Icon

Krikun et al., 2010

Immunoconjugator &anti angiogenesis

Increase Anti endothelial factor

Mice

- Destroyed endometriotic implants through vascular disruption without toxicity, effect on fertility, or teratogenicity.
- could serve as a nov
  and effective treatm

Dopaminergic agonists

- Cabergoline Novella-Maestre et al., 2009

Mice/human cell culture

- decreased VEGF and VEGFR-2 protein Bromocriptine expression

Hamid et al., 2014 Humans

- better result in reducing endometrioma size compared with triptorelin acetate
- Cabergoline and quinagolide

Delgado-Rosas et al., 2011

Mice: equal effect in reducing endometriotic lesions

- Cabergoline and bromocriptine

Ercan et al., 2015

Rats: comparable to GnRHa in reducing endometriotic lesion

Rosiglitazone

Lebovic et al., 2007

Baboons

- Statistically significant reduction of endometriotic lesion

Chang et al., 2013

Human cell culture

- Inhibited aromatase and COX-2 expression: decreased PGE2 production.
- Increase risk of
- myocardial infarction
- death from cardiovascular causes.
- premature termination of all clinical trials

(Moravek et al, 2009).

Omega 3

- Decrease adhesion formation
- Decrease inflammation and colagen deposition

- Fertility sterility 2014, herington et al

Take home messages:

- endometriosis requires a **life-long personalized management plan** with the **goal** of maximizing medical treatment and avoiding repeated surgical procedures.

- The **treatment choices** for **symptomatic** endometriosis are based on patient preferences, age, fertility, treatment goals, the side-effect profile, and the efficacy, costs, associated comorbidities and availability.