Medical Therapies in the Treatment of Endometriosis

Dr sarah Bahramzadeh

Hormonal targets of currently used drugs for endometriosis

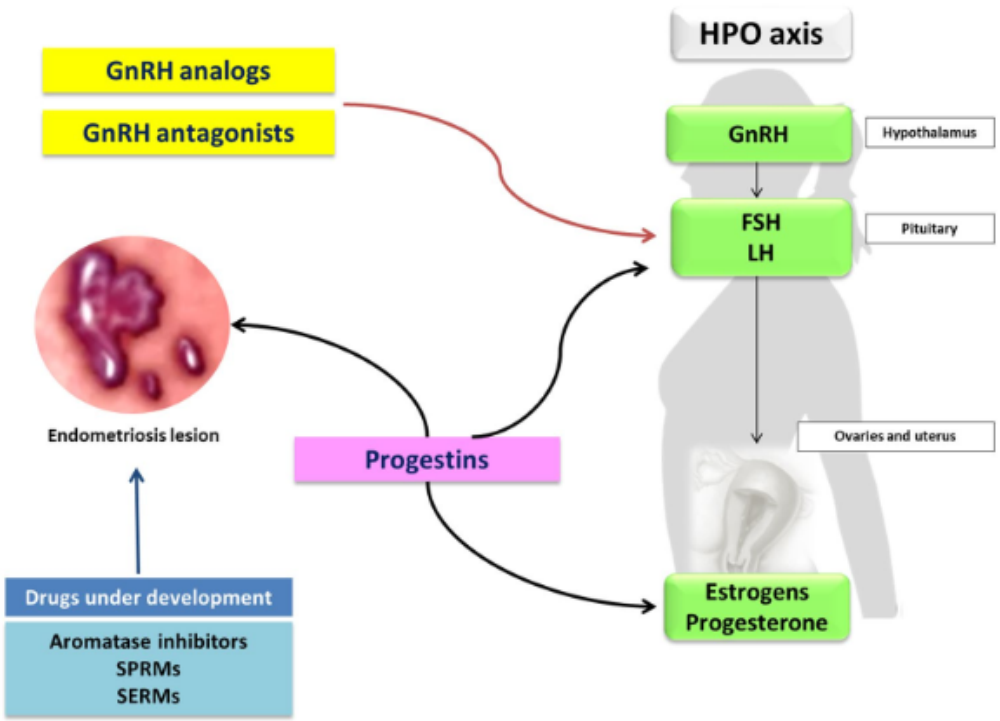


Fig. 4 Hormonal targets of currently used drugs for endometriosis

Endometriosis

Guideline of European Society of Human Reproduction and Embryology

2022

ESHRE Endometriosis Guideline Development Group

Recommendations (11-12)

It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of the options to reduce endometriosis-associated pain.	⊕⊕⊕◯
The GDG recommends that clinicians take a shared decision-making approach and take individual preferences, side effects, individual efficacy, costs, and availability into consideration when choosing hormone treatments for endometriosis-associated pain.	GPP

GnRH Agonist

- GnRH-analogue (goserelin, leuprolide, nafarelin, buserelin, and triptorelin) since the 90s
- Side effect : vaginal dryness, hot flushes, headaches, weight gain , acne , ↓ BMD
- RCT by Tang 2017, ↓ BMD in 50 patients (3.75mg and 1.88 mg leuprorelin) at 20 weeks after treatment, but the degree of loss of BMD was significantly higher in the full dose group (5.6% vs 1.2%)
- 1996,28 patients,↓ BMD after 6 months of GnRH-a treatment.

  reduction was still evident 6 months after GnRH-a interruption

  24 months after withdrawal, BMD reduction disappeared

GnRH Agonist

- Mitwally, 2002,15 endometriosis and 5 PMS, GnRh agonist + add-back:

Bone mineral density was stable after initiation of HRT for the entire F/U(31 m endometriosis ,37 m PMS)

- Mohmed A, 2006, Canada, 5 patients,10 years GnRh agonist + add- back: The BMD in the lumbar spine, the femoral neck, and the total hip region remained relatively stable

- Add-back therapy : low-dose COCs, estrogen or progestins alone, bisphosphonates, tibolone or raloxifene

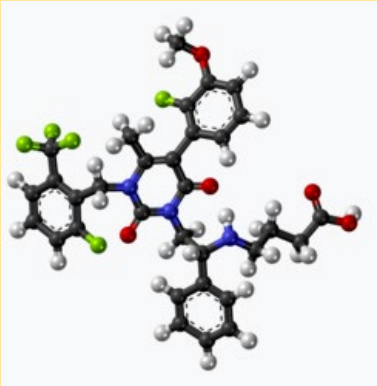
GnRH Agonist

- Consensus from Asian expert Group, 2022: GnRH Agonists May Be Considered for First-Line Therapy Only in Some Specific Situations or as Short-Term Therapy before Dienogest

Recommendations (18-20)

It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.	⊕⊕◯◯
The GDG recommends that GnRH agonists are prescribed as second line (for example if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile.	GPP
Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.	⊕⊕⊕◯

GnRH Antagonist



- Elagolix: short-acting, avoiding severe hypoestrogenism
- 2017,multicenter, double-blind, randomized trials compare:

elagolix 150 mg once daily with 200 mg twice daily with placebo

In both trials, during the 6 months treatment

elagolix ↓ dysmenorrhea , ↓ non-menstrual pelvic discomfort.

Elagolix side effect: hot lash, ↓ BMD , ↑serum lipid

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

Authors: Hugh S. Taylor, M.D., Linda C. Giudice, M.D., Ph.D., Bruce A. Lessey, M.D., Ph.D., Mauricio S. Abrao, M.D., Jan Kotarski, M.D., Ph.D., David F. Archer, M.D., Michael P. Diamond, M.D., +14, and Kristof Chwalisz, M.D., Ph.D. Author Info & Affiliations

GnRH Antagonist

Recommendation (21-22)

It can be considered to prescribe women GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.	⊕⊕⊕◯
The GDG recommends that GnRH antagonists are prescribed as second line (for example if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile.	GPP

Progestins

Progestins:

↓ FSH and LH

relatively hypoestrogenic state

anovulation

Amenorrhen

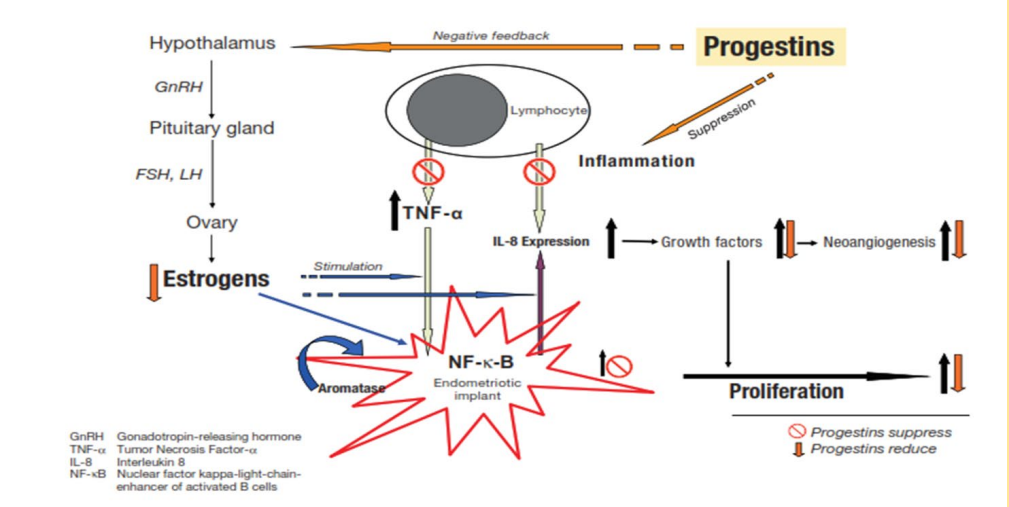
inhibit inflammatory response

provoke apoptosis of endometriotic cells

reduce oxidative stress

inhibit angiogenesis

suppress expression of matrix metallo- proteinases



Dienogest


Dienogest effect on Ovarian Reserve, Cyst Diameter and Pain in Endometriomas

Medical treatment of ovarian endometriomas: a prospective evaluation of the effect of dienogest on ovarian reserve, cyst diameter, and associated pain

Ludovico Muzii, Giulia Galati, Chiara Di Tucci, Mara Di Feliciantonio, Giorgia Perniola, Violante Di Donato, ...show all

Pages 81-83 | Received 10 Mar 2019, Accepted 02 Jul 2019, Published online: 14 Jul 2019

19-nortestosterone derivative

- 2019,32 patients , unilateral endometrioma with pelvic pain, 6-month medical treatment with dienogest

  Diameter of cyst: 40% patients↓

  Volume of cyst : 79% patients↓
- Visual analog scale score and AFC : improve
- AMH did not change significantly from baseline

Dinogest

- Momoeda,2009,135 patients , 2mg of dienogest orally /52 weeks

- most common adverse drug reactions: metrorrhagia (71.9%), headaches (18.5%), and constipation (10.4%)
- bone mineral density:

  −1.6 ± 2.4% at 24 weeks

  −1.7 ± 2.2% at 52 weeks
- Marked or moderate improvement:

  72.5% (95/131 cases) at 24 weeks

  90.6% (106/117 cases) at 52 weeks.

Dienogest

- prospective cohort study , 30 women with a sonographic diagnosis of DIE (intestinal and posterior fornix) treated with DNG for 12 months, ↓ pain related to DIE (dysmenorrhea, dyspareunia, dischezia), improving QoL, even without reducing the volume of DIE nodules

Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission

Joao Paulo Leonardo-Pinto • Cristina Laguna Benetti-Pinto • Kleber Cursino • Daniela Angerame Yela

Dienogest

Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice

General Gynecology | Published: 03 August 2018
Volume 298, pages 747–753, (2018) Cite this article

- retrospective, 37 women , dienogest 2 mg orally at least 60 months: ↓ pelvic pain and avoided pain recurrence post-surgery

Dienogest therapy during the early stages of recurrence of endometrioma might be an alternative therapeutic option to avoid repeat surgeries

Akemi Koshiba, Taisuke Mori, Hiroyuki Okimura, Kanoko Akiyama, Hisashi Kataoka, Osamu Takaoka,

- In case of recurrent OMA after surgery, DNG therapy early after recurrence ↓ the risk of repeated surgery
- 24 months DNG complete resolution of recurrent OMA was achieved in 57.1%

Dienogest

- Consensus from Asian expert Group :

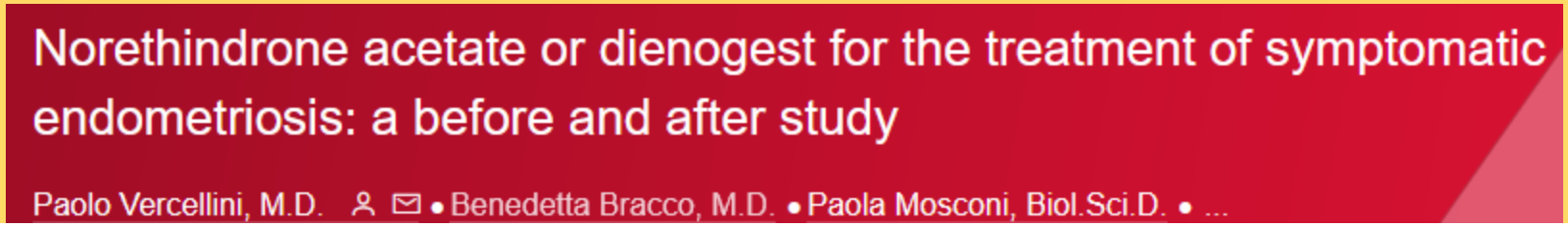
  Dienogest Can Be Used Long-Term If Needed

- Consensus: A Large Evidence Base Exists Supporting the Use of Dienogest Compared with GnRH agonists as First-Line Medical Therapy for Endometriosis

Norethindrone acetate (NETA)

- 19-nortestosterone derivative
- strong progestogenic and androgenic activity, side effects :weight gain, acne, seborrhea
- Low-dose NETA 2.5 mg/day ,effective, tolerable and inexpensive first choice for symptomatic rectovaginal endometriosis, ↓ VAS scores for dysmenorrhea and dyspareunia
- The comparison low dose NETA and DNG :tolerated 58% NETA

  80% of DNG



Medroxyprogesterone acetate (MPA)

- 17-OH progesterone derivative, oral or depot formulation ,IM and SC every 3 m
- MPA as effective as danazol and GnRH-agonists in ↓ pain
- continuous use of depot MPA , ↓ BMD ↑ risk of fracture
- FDA should be administrated only if other methods are unsuitable or unacceptable, and have limited its maximum use to 2 years

OBSTETRICS & GYNECOLOGY

Committee Opinion No. 602

Depot Medroxyprogesterone Acetate and Bone Effects

Author Information

Obstetrics & Gynecology 123(6):p 1398-1402, June 2014. | *DOI:* 10.1097/01.AOG.0000450758.95422.c8

Other progestins

- Desogestrel (DSG) (75 mg/day) effective, safe , low cost

  At 12-month F/U, the rate of satisfied patients:

  ↑ DSG ≥↓ estro-progestin pill

- Gestrinone: limited due to side effects.

- Etonogestrel-releasing subdermal implant (ENG-implanting):

↓ dyspareunia, ↓ dysmenorrhea , ↓ non menstrual pelvic pain

Levonorgestrel intrauterine device (LNG-IUS)

- After the first year of use, ↓ 70–90% in menstrual blood loss
- ↓ pelvic pain caused by peritoneal and rectovaginal endometriosis
- ↓ risk of recurrence of dysmenorrhea after conservative surgery

Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study

Yi-Jen Chen, MD, PhD • Teh-Fu Hsu, MD • Ben-Shian Huang, MD • Hsiao-Wen Tsai, MD •

- 2017,RCT,LNG-IUS was able to control pain symptoms but it was not effective for preventing OMA recurrence

LNG-IUS

BJOG An International Journal of Obstetrics and Gynaecology
Royal College of Obstetricians & Gynaecologists

Systematic Review | Open Access

Postoperative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: a systematic review and network meta-analysis

R Wattanayingcharoenchai, S Rattanasiri, C Charakorn, J Attia, A Thakkinstian

- 6 RCTs and 16 cohorts, 2020
- LNG-IUS ranked highest, followed by DNG and GnRH a + LNG-IUS.
- Long-term use of hormonal treatment either OC or progestin had a significantly lower risk of endometrioma recurrence than expectant treatment

Progestins

Recommendations (15-17)

It is recommended to prescribe women progestogens to reduce endometriosis-associated pain.	⊕⊕◯◯
The GDG recommends that clinicians take the different side effect profiles of progestogens into account when prescribing them.	GPP
It is recommended to prescribe women a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain.	⊕⊕⊕◯

Combined oral contraceptives (COCs)

- Clinical trial,2021,70 women with pelvic pain, dysmenorrhoea or both dienogest (Visanne) 2 mg/day or Yasmin (0.03 mg ethinyl estradiol and 3 mg drospirenone) for 24 weeks
- Both treatments improved the mean VAS score for endometriosis-associated pelvic pain significantly, the difference between them was not significant
- dienogest was associated with fewer side-effects

Randomized Controlled Trial > Eur J Obstet Gynecol Reprod Biol. 2021 Dec:267:205-212.
doi: 10.1016/j.ejogrb.2021.10.029. Epub 2021 Oct 30.

Efficacy of dienogest vs combined oral contraceptive on pain associated with endometriosis: Randomized clinical trial

Lina El Taha [1], Antoine Abu Musa [2], Dalia Khalifeh [1], Ali Khalil [3], Sehrish Abbasi [4], Joseph Nassif [5]

Affiliations + expand

COCs

Randomized Controlled Trial > BMJ. 2024 May 15:385:e079006. doi: 10.1136/bmj-2023-079006.

Long acting progestogens versus combined oral contraceptive pill for preventing recurrence of endometriosis related pain: the PRE–EMPT pragmatic, parallel group, open label, randomised controlled trial

Kevin G Cooper [1], Siladitya Bhattacharya [2], Jane P Daniels [3], Andrew W Horne [4], T Justin Clark [5], Ertan Saridogan [6], Versha Cheed [7], Danielle Pirie [1], Melyda Melyda [8], Mark Monahan [8], Tracy E Roberts [8], Emma Cox [9], Clive Stubbs [7], Lee J Middleton [7]; PRE-EMPT Collaborative Group

- Randomised controlled trial,2024, 405 women, long acting progestogen (DMPA or LNG-IUD) or COCs
- At 3 years, there was no difference in pain scores between the groups
- both groups showing around a 40% improvement compared with preoperative levels

COCs

- systematic review and meta-analysis by Muzii compared continuous versus cyclic OCP:

continuous regimen more efficacious with regards to dysmenorrhea

- Consensus: Oral Progestin-Based Therapies Are Generally a Better Option Compared with COCs Because of Their Safety Profile

Recommendations (13-14)

It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain.	⊕⊕◯◯
Women suffering from endometriosis-associated dysmenorrhea can be offered the continuous use of a combined hormonal contraceptive pill.	⊕⊕◯◯

Danazol

- a derivative of 17α-ethynyl testosterone , since 1971 is FDA approved
- mechanisms : ↓ FSH and LH, ↓ estrogen, ↓prolifration

Adverse effects: seborrhea, hypertrichosis, weight gain,↓HDL,↑ LDL

- Danazol is typically given orally (400 to 800 mg/day).
- Good efficacy and better tolerability :danazol-loaded intrauterine device and off-label vaginal administration (200 mg/day)
- Low-dose vaginal danazol (200 mg per day for 6 months) is effective for the treatment of pain in recurrent endometriosis after surgery

Selective progesterone receptor modulators

- Ulipristal acetate, telapristone acetate, vilaprisan, tanaproget, Mifepristone, asoprisnil
- Common adverse effects: headache, abdominal pain, nausea, dizziness, and heavy menstrual bleeding
- Vilaprisan is a highly potent ,treatment uterin fibroids, endometriosis.
- vilaprisan used in patients with mild or moderate renal or hepatic impairment without dose adjustment
- Vilaprisan , inducing amenorrhea in patients with uterine fibroids

Selective estrogen receptor modulators

Review > Reprod Toxicol. 1998 May-Jun;12(3):217-21. doi: 10.1016/s0890-6238(98)00003-3.

The selective estrogen receptor modulator, raloxifene: an overview of nonclinical pharmacology and reproductive and developmental testing

J Buelke-Sam [1], H U Bryant, P C Francis

- Raloxifene (RLX)
- prevents the loss of bone, ↓ cholesterol, ↓ LH, ↓ mammary gland development.
- Raloxifene treatment results in regression of endometriosis, uterine leiomyomas in rat

Recommendation (23)

In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, GnRH agonists or GnRH antagonists.	⊕⊕◯◯

Aromatase inhibitors

- most common aromatase inhibitors: letrozole and anastrozole
- side effects:vaginal dryness, hot flushes, ↓ BMD


Thank you!