Treatment of endometriosis-associated pain

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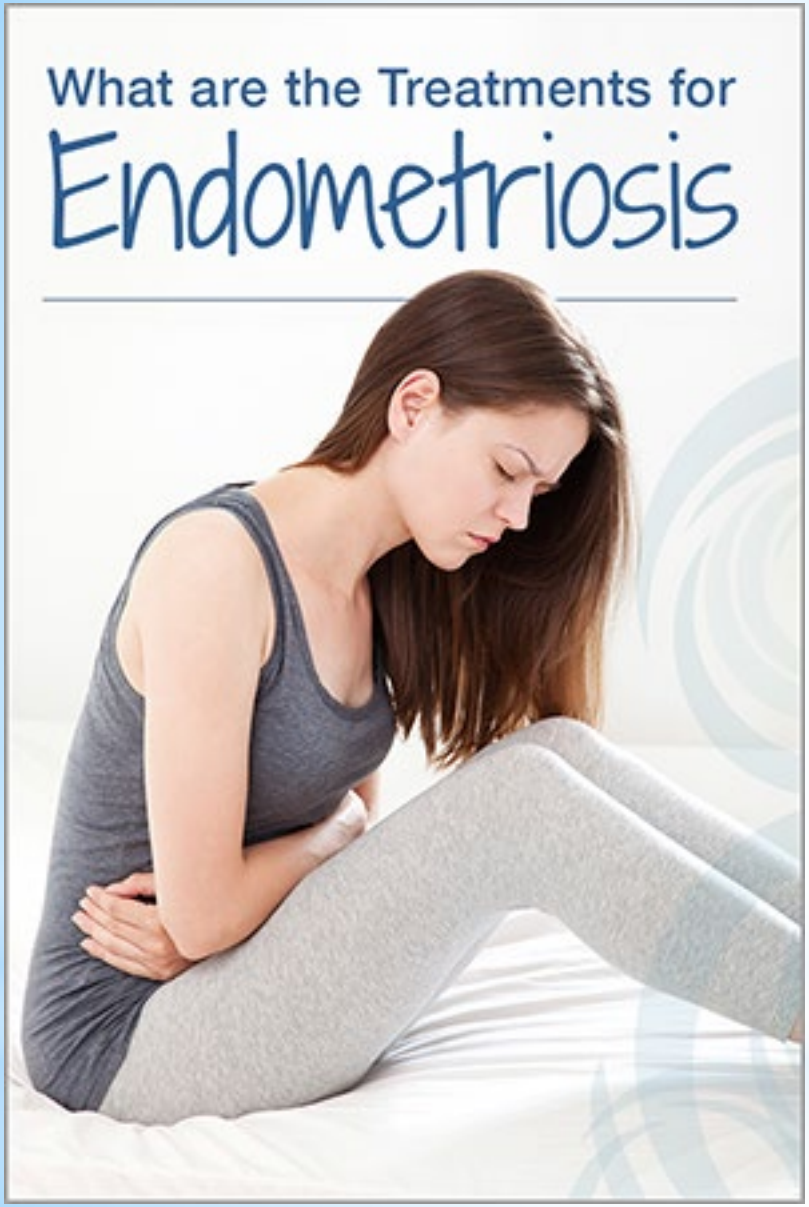


treatment of pain symptoms that are suggestive of endometriosis in the absence of a definitive diagnosis, empirical treatment is appropriate and includes counseling, analgesia, progestins, or combined oral contraceptives

Non steroidal Anti-inflammatory Drugs

- the first-line therapy
- endometriosis is a chronic inflammatory disease
- local antinociceptive effect and reduced central sensitization
- side effects:gastric ulceration, possible inhibition of ovulation

PGs are involved in the follicle rupture mechanism at ovulation,

Hormonal Treatment

estrogen stimulate growth of endometriosis, hormonal therapy is designed to suppress estrogen synthesis, atrophy of ectopic endometrial implants ,interrupting the cycle of stimulation and bleeding.

OCP,*danazol*, *gestrinone*, *Medroxyprogesterone acetate*, GnRH agonists are all equally effective but their side effects and cost profiles differ

Pain relief may be of short duration presumably because endometriosis and endometriosis-associated pain recur after the cessation of medical treatment.

Oral Contraceptives

- inducing a decidualized endometrium, the estrogenic component may stimulate endometrial growth, increase pelvic pain in the first few weeks
- cyclic oral contraceptives may provide prophylaxis against the development or recurrence of endometriosis.
- continuous administration, with out a 7-day break, may be more beneficial in terms of pain relief.
  induce pseudopregnancy caused by the resultant amenorrhea and decidualization of endometrial tissue

Any low-dose *OC* containing 30 to 35*M* g of *ethinyl estradiol* used continuously can be used for the management of endometriosis. **The objective of the treatment is the induction of amenorrhea, which should be continued for 6 to 12 months .**

As compared to cyclic administration, continuous therapy with COC has been shown to have better pain control

the limiting factors include long-term administration, risk of thromboembolism, high rates of recurrence after discontinuation and impaired fertility due to contraceptive action. Combinations containing lower dose of ethinyl estradiol (20 micrograms) as compared to high dose (30 micrograms) have a lower risk of venous thromboembolism and are currently recommended

Continuous vs cyclic use

Continuous use suggested as an effective treatment for endometriosis-associated dysmenorrhea

Nonsignificant differences between continuous and cyclic OCP use were reported for chronic pelvic pain and dyspareunia, and a trend toward lower cyst recurrence rates for a continuous OCP

PROGESTINS

causing initial decidualization of endometrial tissue followed by atrophy.

Medroxyprogesterone Acetate

starting at a dose of 30 mg per day, increasing the dose based on the clinical response

Evidence suggests a possible role for depot MPA in the treatment of endometriosis. In a randomized controlled study, depot MPA (150 mg every 3 months) was more effective in the relief of dysmenorrhea than treatment with a cyclic 21-day OC (ethinyl estradiol 20 µg plus desogestrel 0.15 mg) combined with very low-dose danazol (50 mg per day)

the effect of treatment was evaluated after 3 to 6 months of therapy

Although depot MPA treatment is effective for the treatment of pain associated with endometriosis, it is not indicated in infertile women because it induces profound amenorrhea and anovulation, and a varying length of time is required for ovulation to resume after discontinuation of therapy.

Dienogest

In two randomized trials, treatment during 6 months with *dienogest* 2 mg per day orally demonstrated equivalent efficacy to depot *leuprolide acetate* (3.75 mg,depot intramuscular injection, every 4 weeks) or intranasal *buserelin acetate* (900 μg
per day, intranasally) in relieving the pain associated with endometriosis, offering a different safety and tolerability profile (less bone loss, fewer hot flushes, more irregular
genital bleeding)

Side effects of progestins :

- Nausea
- weight gain
- fluid retention
- breakthrough bleeding caused by hypoestrogenemia. Corrected by short-term (7-day) administration of estrogen.
- Depression and other mood disorders

Table 17.1 Medical Treatment of Endometriosis-Associated Pain: Effective Regimens (Usual Duration: 6 Months)

	Administration	Dose	Frequency
Progestogens			
Medroxyprogesterone acetate	PO	30 mg	Daily
Dienogest	PO	2 mg	Daily
Megestrol acetate	PO	40 mg	Daily
Lynestrenol	PO	10 mg	Daily
Dydrogesterone	PO	20–30 mg	Daily
Antiprogestins			
Gestrinone	PO	1.25 or 2.5 mg	Twice weekly
Danazol	PO	400 mg	Daily
Gonadotropin-Releasing Hormone			
Leuprolide	SC	500 mg	Daily
	IM	3.75 mg	Monthly
Goserelin	SC	3.6 mg	Monthly
Buserelin	IN	300 μg	Daily
	SC	200 μg	Daily
Nafarelin	IN	200 μg	Daily
Triptorelin	IM	3.75 mg	Monthly

PO, oral; SC, subcutaneous; IM, intramuscular; IN, intranasal.

INTERUTERINE PROGESTIN-RELEASING SYSTEM

- The *levonorgestrel* intrauterine system releasing 20*M*.g per day
- high local concentrations of progestin in the pelvis and less progestin secreted into the systemic circulation, the risk of systemic side effects is reduced

- an effective therapy for rectovaginal endometriosis, lessening dysmenorrhea and non-menstrual pelvic pain as well as significantly reducing deep dyspareunia and dyschezia

ovulation is not inhibited, except for the first few months after insertion. This constitutes an important disadvantage, because it has been demonstrated that ovarian endometriomas originates from haemorrhagic corpora lutea

the post-operative endometrioma recurrence rate is about 10% per year for the first quinquennium of follow-up if ovulation is not suppressed

The authors concluded that long-term maintenance therapy using a LNG-IUD is not effective for preventing endometrioma recurrence. Therefore, the best candidate for the use of the LNG-IUD seems to be a parous woman with no further pregnancy desire and with dysmenorrhoea as her main or only pain symptom

Progesterone Antagonists and Selective Progesterone Receptor Modulators

PRAs and selective progesterone receptor modulators (SPRMs) may suppress endometriosis based on their antiproliferative effects on the endometrium, without the risk for hypoestrogenism or bone loss that occurs with GnRH treatment.

Four PRA/SPRMs have been approved by the FDA: mifepristone, ulipristal acetate (UPA) gestrinone, and asoprisnil

The authors conclude that there are insufficient data about the safety and effectiveness of UPA and asoprisnil.

Mifepristone

a potent antiprogestagen with a direct inhibitory effect on human endometrial cells and in high doses, antiglucocorticoid action,

2.5-mg dose may be less effective than 5 mg or 10 mg for treating dysmenorrhea or dyspareunia

mifepristone side effects: amenorrhea
hot flushes

Gestrinone

- a 19-nortestosterone derivative with androgenic, antiprogestagenic, antiestrogenic, antigonadotropic. Amenorrhea occurs in 50% to 100% of women and is dose dependent. Resumption of menses generally occurs 33 days after discontinuing the medication. An advantage of *gestrinone* is its long half-life (28 hours) when given orally

- standard dose is 2.5 mg twice a week.

- clinical side: nausea, muscle cramps, androgenic effects such as weight gain, acne, seborrhea, oily hair and skin.

Pregnancy is contraindicated while taking *gestrinone* because of the risk for masculinization of the fetus.

DANAZOL

- suppression of GnRH , direct inhibition of steroidogenesis, increased metabolic clearance of estradiol and progesterone, direct antagonistic and agonistic interaction with endometrial androgen and progesterone receptors, and immunologic attenuation of potentially adverse reproductive effects

- produce a high-androgen, low-estrogen environment and amenorrhea

- start treatment with 400 mg daily (200 mg twice a day) and increase the dose, to achieve amenorrhea and relieve symptoms

include weight gain, fluid retention, acne, oily skin, hirsutism, hot flashes, atrophic vaginitis, reduced breast size, reduced libido, fatigue, nausea, muscle cramps, and emotional instability. Deepening of the voice is nonreversible ,increased cholesterol and low-density lipoprotein levels and decreased high-density lipoproteins levels

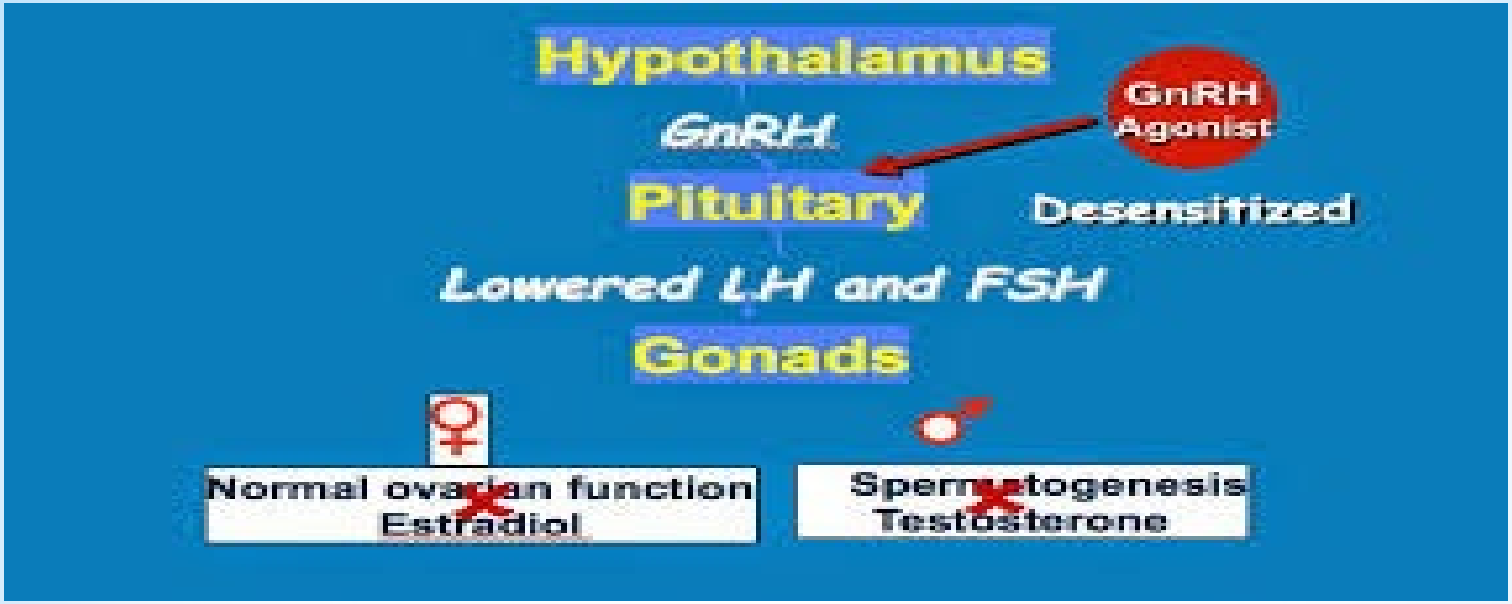
contraindicated in:

- liver disease because it is largely metabolized in the liver and may cause hepatocellular damage.
- hypertension, congestive heart failure, or impaired renal function because it can cause fluid retention.
- pregnancy because of its androgenic effects on the fetus.

vaginal *danazol* ring(1,500 mg) was effective for pain relief in deeply infiltrative endometriosis. This treatment did not cause the classic *danazol* side effects or detectable serum *danazo/* levels, and it allowed ovulation and conception to occur

the GDG strongly believes that danazol should not be used unless no other medical therapy is available, due to its severe side effects

GnRH AGONISTS



- bind to pituitary GnRH receptors and stimulate LH and FSH synthesis and release.

- side effects are caused by hypoestrogenism and include hot flashes, vaginal dryness, reduced libido, and osteoporosis (6% to 8% loss in trabecular bone density after 6 months of therapy).Reversibility of bone loss is equivocal

Gonadotropin-Releasing Hormone			
Leuprolide	SC	500 mg	Daily
	IM	3.75 mg	Monthly
Goserelin	SC	3.6 mg	Monthly
Buserelin	IN	300 µg	Daily
	SC	200 µg	Daily
Nafarelin	IN	200 µg	Daily
Triptorelin	IM	3.75 mg	Monthly

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.

Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.

GnRH agonist may be used for a few months before starting progestogens, or intermittently during progestogen treatment in case of phases of pain relapse or prolonged bleeding and, combined with add-back therapy, in patients not responding to progestogens and unwilling to undergo surgery or in those at very high surgical risk.

Long-term GnRHa use is problematic due to deleterious effects on bone mineral density (BMD). Adults lost 5%–8% of spine BMD after only 3–6 months of GnRHa therapy. BMD may not return to baseline after cessation of treatment

Side effects of GnRH agonists, such as vasomotor symptoms and accelerated bone loss, limit treatment duration to six months. However, treatment can be extended beyond six months if add-back therapy is combined with the GnRH agonist.

Based on the evidence to date, no specific GnRH agonist can be recommended over another in relieving endometriosis-associated pain.
addition of add-back therapy when prescribing GnRH agonist treatment prevents bone loss, while it does not affect the efficacy of the GnRH agonist treatment. As such, add-back treatment is recommended (strong recommendation).

Add-back therapy achieved by:

- progestins only, including *norethisterone*, 1.2 mg, and *norethindrone acetate*, 5 mg, but bone loss is not prevented by *medrogestone*, 10 mg per day

- *tibolone*, 2.5 mg per day

- estrogen-progestin combination (*conjugated estrogens*,0.625 mg, combined with *medroxyprogesterone acetate*, 2.5 mg, or with *norethindrone acetate*, 5 mg; *estradiol*, 2 mg, combined with *norethisterone acetate*, 1 mg)

GnRH agonists should not be prescribed to girls who have not yet attained their maximal bone density, as some concern remains about the long-term effects of GnRH analogs on bone loss.

GNRH agonist can be used in the postoperative period in prevention of endometriosis recurrence.

GnRH antagonists avoid the flare-up phase, typical of GnRH agonists. However, injecting depot GnRH agonists during the mid-luteal phase prevents this potential drawback.
Alternatively, using an oral progestogen for the first 7-10 days after the first GnRH agonist injection may avoid the initial gonadotropin surge

AROMATASE INHIBITORS

Aromatase enzyme helps in the conversion of the steroid precursors into estrogen Unlike GnRH agonists, aromatase inhibitors block estrogen synthesis both in the periphery and the ovaries

helpful in postmenopausal women with endometriosis where peripheral fat is the predominant source of estrogen

anastrozole or *letrozole* stimulate ovulation and continuous administration can result in functional ovarian cysts.
can be prevented by combining aromatase inhibitors with ovarian suppressing drugs such as OCs or *progestins* in premenopausal women

GONADOTROPIN RELEASING HORMONE ANTAGONISTS (GnRH ANTAGONISTS)

administration of GnRH antagonist Cetrorelix provided symptomatic relief and regression of the endometriotic implants as visualized on laparoscopy. With a lower degree of hypoestrogenemia and better tolerance than the GnRH agonists

Gonadotropin-releasing hormone antagonists are available as injectables (ganirelix,cetrorelix) and increasingly as oral nonpeptide forms (elagolix, abarelix, ozarelix).

oral GnRH antagonists can produce a dose-dependent suppression of pituitary function and production of ovarian hormones

Hot flushes were the most frequent side effect.
Elagolix did not completely suppress ovulation at either of the doses. In one of the two trials, the unplanned pregnancy rate in women using elagolix was over 1%

It is interesting to note that the effect of cheap DMPA was similar to that of the novel experimental drug.

stepped-care approach is indicated in women who are not seeking pregnancy, who prefer medical rather than surgical treatment, and who do not have absolute surgical indications, such as sub-occlusive bowel stenosis, obstructive uropathy, endometriomas over 5 cm in diameter, and adnexal masses of doubtful ultrasonographic characteristics. According to this model, low-dose OCs should be used cyclically in women with peritoneal and ovarian endometriosis, stepping up to continuous use with tailored cycling only in those women with persistent dysmenorrhoea despite cyclic OC use. In case of inefficacy on pain during OC use, patients should step up to a low-cost progestogen such as NETA. Independently of pain relief, women should step up to progestogens also in case of intolerance to OC (e.g., migraine). Starting directly with a low cost progestogen should be considered in patients with deep lesions or with deep dyspareunia as their main complaint, as well as in those with contraindications to OCs. Stepping up from a low-cost to a high-cost progestogen (i.e., DNG) should be advised only in case of intolerance to NETA, as it has been demonstrated the DNG, being devoid of androgenic activity, is better tolerated than NETA

In case of inefficacy of or intolerance to progestogens, patients may step up to GnRH agonists or antagonists,

Pentoxifylline

no significant effect on reduction in pain ,improvement of fertility or recurrence of endometriosis

Chinese Herbal Medicine

Recommendation

The GDG does not recommend the use of nutritional supplements, complementary or alternative medicine in the treatment of endometriosis-associated pain, because the potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may feel benefit from this.	GPP

Clinical Tips

- In endometriosis treatment, all options should be administered for a minimum of 3 months, with evaluation of efficacy at the end of the trial.

- CHCs are not appropriate for addback therapy.