به نام مهربانترین

In the name of the most compassionate

Endometriosis-related Pelvic Pain

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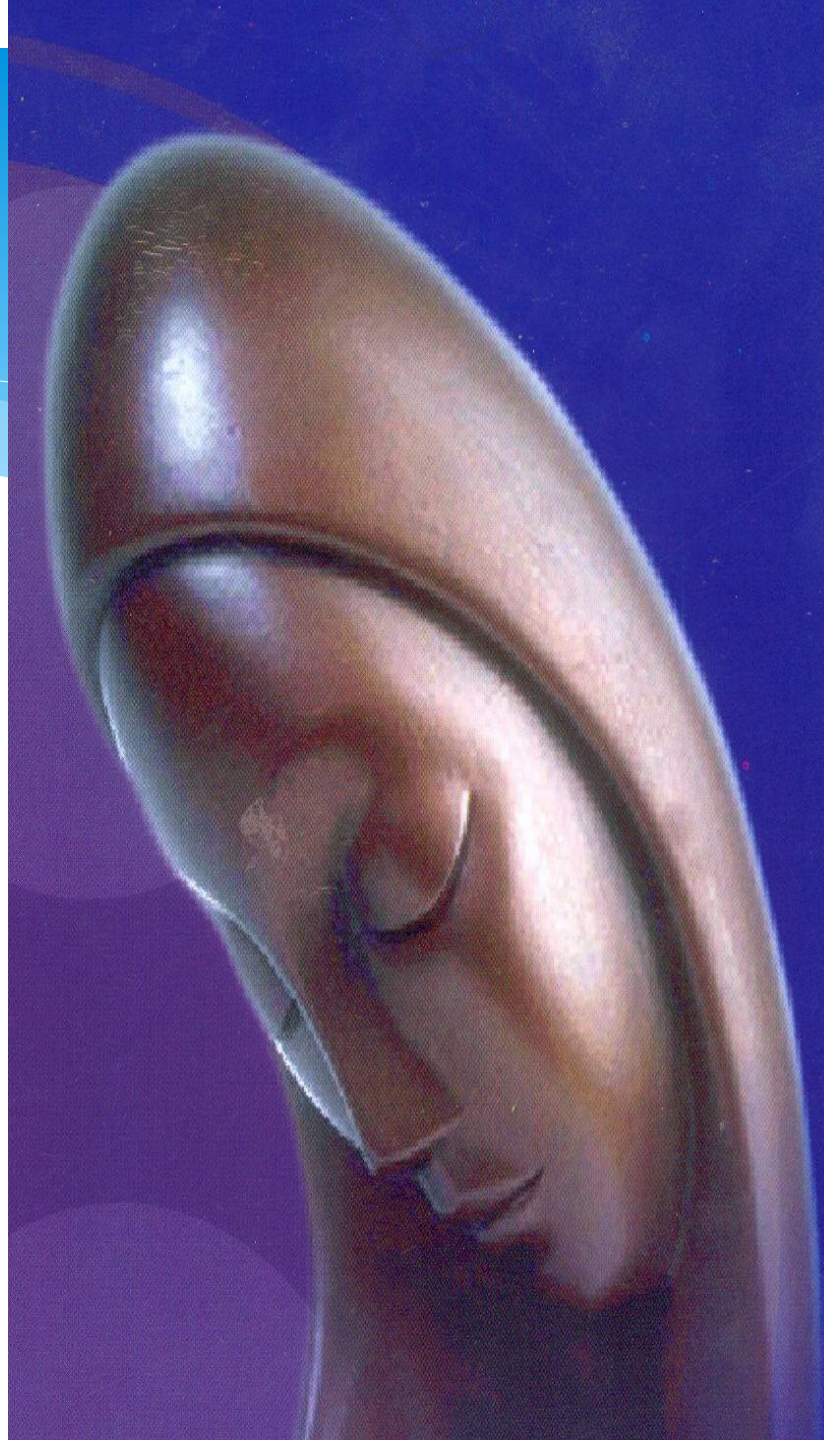
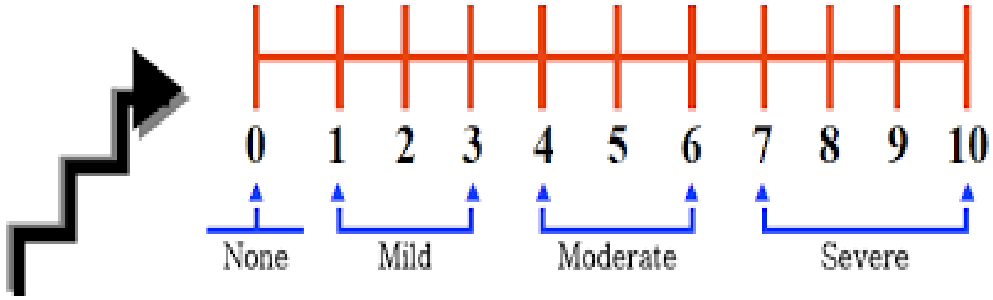
Pain

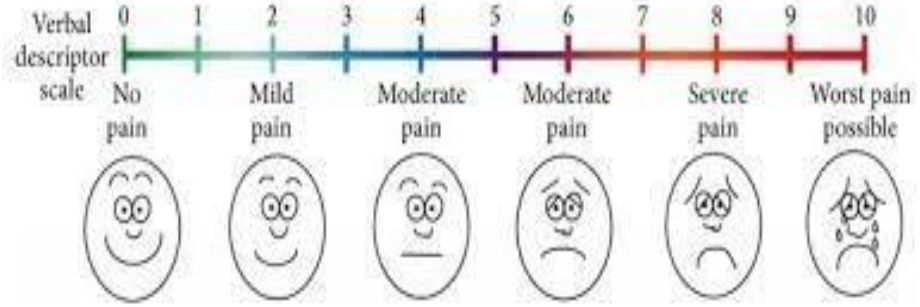
* No cure for endometriosis yet exists; primary treatment is directed toward relief of ***pain***



Pain scale



* visual analogue scale (VAS) and numerical rating scale (NRS) seems the best adapted for endometriosis pain measurement.
* The use of **VAS** or **NRS** for each type of typical pain related to endometriosis:
* Dysmenorrhea,
* Deep dyspareunia
* Non-menstrual chronic pelvic pain
* Other scale:
* Biberoglu and Behrman scale
* CGI and a quality-of-life scale



Treatment Options

- **Medical Therapy**
  - Nonsteroidal analgesics (NSAIDs)
  - hormonal contraceptives (COCs)
  - Progestogens
  - Anti progestins
  - GnRH agonists and antagonists
    - Aromatase inhibitors
    - Other: Antioxidants, Fish oil …….
- **Surgical Treatment**
  - Conservative Surgery
  - Definitive Surgery

Medical treatment for pelvic pain in endometriosis

Advantages
Avoids risk of damaging pelvic organs during surgery
Avoids risk of postoperative adhesion formation
Treats implants not visualized during surgery
Disadvantages
Side effects of medications
High recurrence rates after discontinuation
No effect on existing adhesions
No effect on endometriomas
Treatments involving suppression of ovulation also prevent pregnancy during the treatment period
No effect on infertility

Graphic 69477 Version 3.0

Medical Treatment Options

* As there are no data supporting one treatment or treatment combination over another, the treatment choice is based upon
* **Symptom severity**
* **Patient preferences**
* **Medication side effects**
* **Treatment efficacy**
* **Contraceptive needs**
* **Costs**

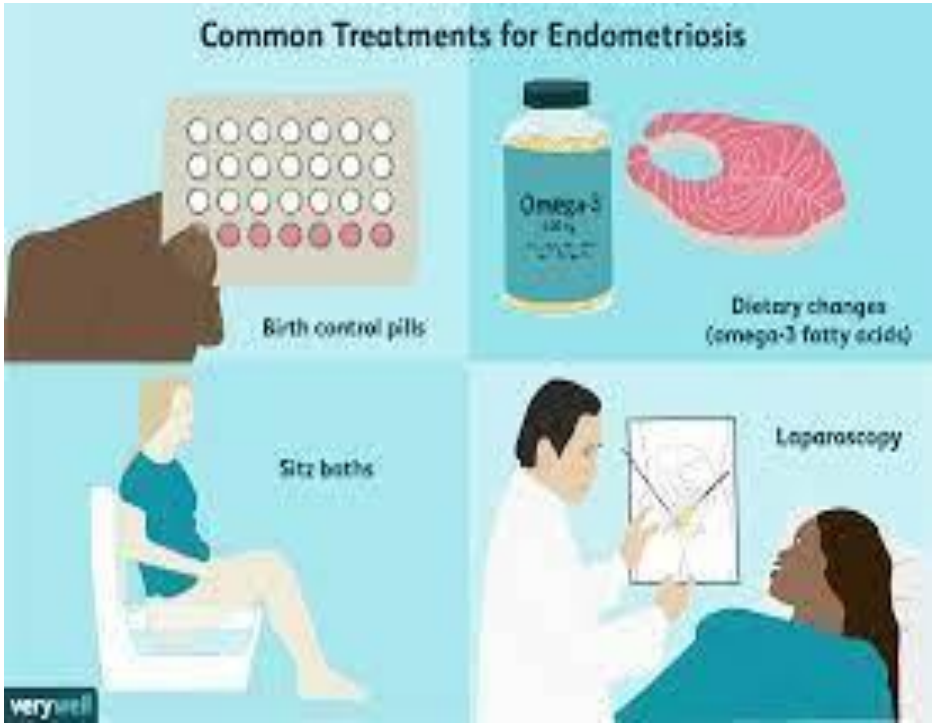
* Medical interventions do not improve fertility diminish endometriomas
* or treat complications of deep endometriosis such as ureteral obstruction .

* We agree with the ***American Society for Reproductive Medicine Practice Committee*** statement that :

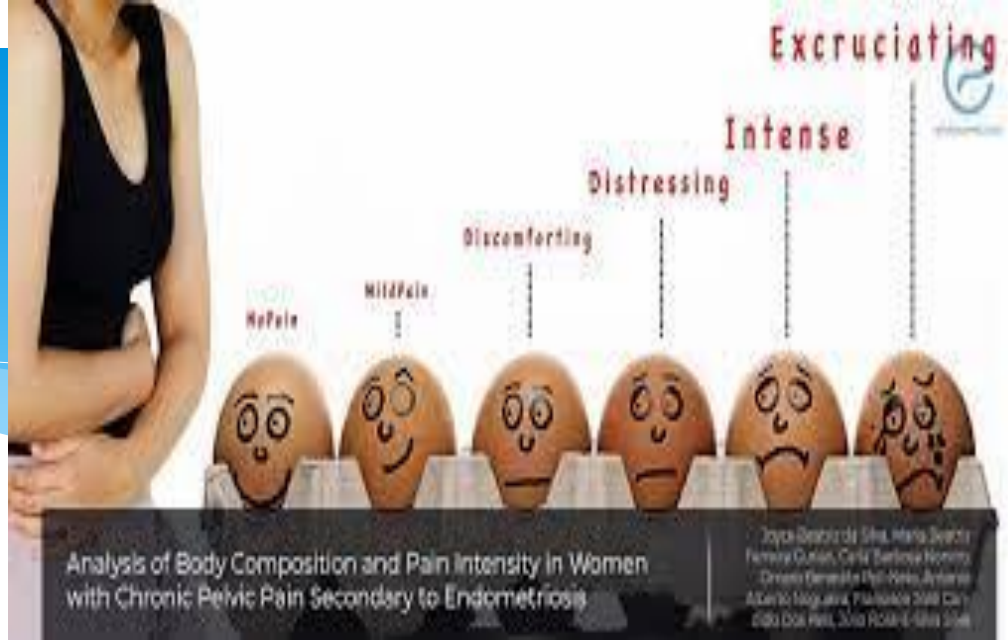
* "endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures“

Treatment decisions

* clinical presentation (eg, pain, infertility, mass),
* symptom severity
* disease extent and location
* reproductive desires
* patient age
* medication side effects
* surgical complication rates
* and cost.



* Prior to treatment, all women should have a thorough history and examination.



* Treatment plan is based on the severity of the patient's endometriosis-related pain.
* As noted above, other causes of pelvic pain are excluded.
* We aim to manage the patient's pain with medical therapy for as long as possible and thus **limit** the number of surgical interventions.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

* NSAIDs are be considered the first-line treatment for dysmenorrhea and endometriosis-related pain.
* There are no high-quality data reporting NSAID efficacy in treating pain due to endometriosis, nor have NSAIDs been shown to be superior to other agents or to placebo .
* Use of NSAIDs is based on their :
* Ready availability
* Low cost
* Acceptable side-effect profile
* Effective reduction of primary dysmenorrhea.
* *While NSAIDs are commonly combined with a contraceptive hormonal therapy, women who desire conception can use* ***NSAIDs alone.***
* ـ

* women with **Mild to Moderate** pain
* (pain symptoms that do not cause regular absence from school or work) and no ultrasound evidence of an **endometrioma,**
* Nonsteroidal anti-inflammatory drugs (NSAIDs) and
* Continuous hormonal contraceptives as the First line of treatment these therapies are **low-risk**
* Have few side effects
* Provide relief of symptoms for many patients

* Women who desire pregnancy can use NSAIDs:
* avoid selective COX-2 inhibitors (celecoxib, rofecoxib, and valdecoxib) as some studies indicate these drugs can prevent or delay ovulation.

If response to NSAIDs is inadequate and future pregnancy is not desired, medical therapy with oral contraceptives or etonogestrel–ethinyl estradiol vaginal ring is appropriate (additional first line therapies).

* second line therapy with combined continuous oral contraceptives or progestogens is recommended.

* While this approach is supported by recommendations from major societies there are no data supporting superiority of one NSAID or hormonal contraceptive over another.
* Selection is based on patient preference, availability, and cost.

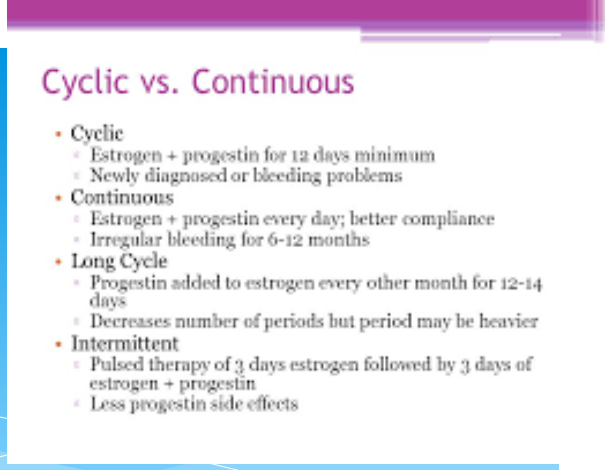
Estrogen-progestin contraceptives

* Combined contraceptives are the first-line treatment for most women with endometriosis-related pain because they can be used
* Long-term
* Well-tolerated
* Relatively inexpensive
* Easy to use
* Provide contraception
* Decreasing the risk of ovarian and endometrial cancers .

* Estrogen-progestin contraceptives are thought to suppress ovarian function and thereby reduce endometriosis disease activity and pain.
* The purported therapeutic mechanism is decidualization and subsequent atrophy of endometrial tissue .
* In addition, estrogen-progestin contraceptives may slow progression of disease, although evidence is conflicting.

* While data from randomly assigned trials support estrogen-progestin therapy to reduce pain ,one meta-analysis of two trials of combined oral contraceptive pills concluded that the evidence was insufficient to make a judgment .
* Study challenges include differing combinations
* Doses of medications
* Duration of follow-up
* Study size and design
* Varying tools used to assess pain.
* Combined estrogen-progestin treatments include **combined oral** contraceptive pills (COCs), transdermal patches, and vaginal rings.

* There are no data supporting superiority of one therapy over another. ***Again,*** drug selection is based on patient preference, **availability**, and cost.
* While we believe this approach of hormonal suppression and NSAID therapy is the preferred first-line treatment for women with **Mild to Moderate** symptoms, it is important to note that initial treatment with a gonadotropin-releasing hormone (GnRH) analog is a reasonable alternative used by some experts.

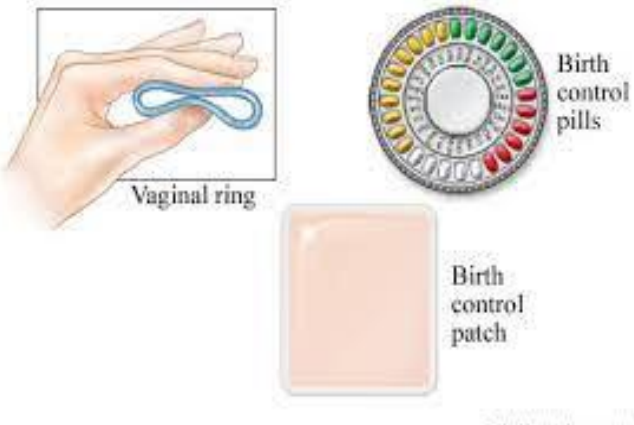


* As no formulation has demonstrated superiority, It typically begin with a COC containing 20 mcg of Ethinyl Estradiol given in a **continuous** dose fashion.

* While both cyclic and continuous-dose hormonal regimens appear to be effective at reducing endometriosis-related pain, two systematic reviews (one with meta-analysis) reported that continuous COC regimens were more effective at reducing pain symptoms than cyclic COC regimens.

* Additionally, one trial reported that the efficacy of COC treatment was **equivalent** to GnRH treatment (goserelin) at **reducing pelvic pain**, but the trial was limited by small sample size (57 women) and relatively short duration (12 months)

- In women without medical contraindications:
- combined estrogen-progestin contraceptives
- (pill, patch, or vaginal ring) combined with an NSAID.
- ●For women who cannot or choose not to use estrogen therapy, Progestin-only contraceptive pills (ie, Norethindrone 0.35 mg taken once daily) with an NSAID.



After 3 to 4 months reassess of ***combined treatment***

Women with adequate symptom improvement are continued on the hormonal therapy/NSAID regimen until pregnancy is desired or the average age of menopause is reached.

Women who unable to take or prefer to avoid combined estrogen-progestin contraceptives or whose symptoms do not improve continue **NSAID** treatment, progestin-only therapy is another treatment option:

1- ***DMPA*** 150 mg/ intramuscular injection every 3 months

2-**Dienogest** can be prescribed as a 2 mg oral pill taken daily

3- oral **Norethindrone** acetate 5 mg taken once daily. but the dose can be increased to 2.5 to 15 mg daily depending on side effects including breakthrough bleeding .

The progestins most commonly used for the treatment of endometriosis-related pain

DMPA 150 mg/ IM every 3 months

oral norethindrone acetate 5 mg taken once daily

Norethindrone

Dienogest

* The choice of progestin depends upon the contraceptive needs of the patient, side-effect profile of the various drugs, and patient preference.

Progestins

* In systematic reviews of progestin therapy for pain associated with endometriosis:
* **MPA** and Dienogest were superior to placebo .

* Guidline:
* we reserve Dienogest for women who do not tolerate Norethindrone acetate because the treatment outcomes appear to be similar , but norethindrone acetate is less expensive

Advantages

* avoids the estrogen-related thromboembolic risk
* Compared with the **GnRH analogs**:
* high-dose oral progestin treatment is not associated with **bon loss** and is less expensive.
* Compared with **Danazol**:
* better tolerated, have no androgenic side effects, and have a less detrimental impact on lipids.

Side effects of progestin

* Irregular uterine bleeding/spotting
* Amenorrhea
* Weight gain
* Mood changes (eg, depression)
* Bone loss (specific to long-term use of depot MPA).
* long-term use of Norethindrone acetate can lead to a significant
* ↓ HDL cholesterol
* ↑ LDL cholesterol
* ↑ Triglycerides
* lipid levels are monitored in patients on long-term therapy.

Alternate progestin treatment options

* Alternate progestin treatment options for the treatment of endometriosis related pain include:
* Etonogestrel Implant
*

* Levonorgestrel intrauterine device
* Because data regarding these agents for the treatment of endometriosis-related **pain** are limited, we prefer progestin therapies reviewed above.

Women with ***severe*** symptoms

* -Regularly missing school or work because of pain
* symptoms that do not respond to the above therapies or
* recurrent symptoms
* are offered a trial of GnRH analog with add-back hormonal therapy or laparoscopy for diagnosis and treatment (if they have not already done so).
* Add-back hormonal therapy limits hypoestrogenic **side effects :**
* (eg, hot flashes, vaginal dryness) and preserves **bone density**.
* *GnRH analog* with *add-back therapy* can be used long-term.
* This strategy limits bone loss, improves vasomotor symptoms, and improves compliance without reducing efficacy .

* We reserve treatment with *Aromatase Inhibitors* for women who continue to have refractory symptoms despite GnRH analog treatment because there are fewer data on long-term use of these agents for endometriosis treatment.

Gonadotropin-releasing hormone agonists/antagonists

* **GnRH agonists** include:
* Nafarelin
* Leuprolide
* Buserelin
* Goserelin
* Triptorelin
* A meta-analysis of **41** trials including nearly 5000 women reported that GnRH analogs were more effective than placebo and as effective as other medical therapies (Danazol, Levonorgestrel , COC) for relieving pain .
* The meta-analysis concluded that the evidence was limited regarding optimal dose and treatment duration and no route of administration appeared **superior** to others.

* In a trial comparing *GnRH agonists* treatment, **laparoscopy,** and combined medical/surgical treatment, all three groups reported an overall cure rate of ≥50 percent
* Commonly used drug regimens:

* Leuprolide acetate 3.75 mg IM injection given monthly
* Leuprolide acetate 11.25 mg IM injection given every 3 months
* Intranasal Nafarelin acetate 200 mcg given twice daily

* Medication selection is driven by *availability* and *cost.*
* To minimize the hypoestrogenic side effects treatment, add-back therapy with oral **norethindrone** acetate 5 mg daily was recommended.

* Endometriosis-related pain is likely treated by the induction of **amenorrhea** and progressive endometrial **atrophy.**
* The hypo estrogenic *adverse effects*:

* hot flushes, vaginal dryness, decreased libido, mood swings, headache, and decreased bone density .
* Negative effects can be reduced by add-back therapy, typically with oral norethindrone acetate or a combination of estrogen and progestin (ie, COC pill)
* When GnRH agonists are used with add-back therapy, side effects are often better tolerated compared with a progestin-only or danazol treatment.

GnRH antagonists

* GnRH antagonists provide a treatment option for women who do not respond to NSAIDs, estrogen-progestin contraceptives, or progestins, and they are easier to dose than GnRH analogs (oral versus intramuscular).

* *GnRH antagonists* suppress pituitary gonadotropin hormone production and create a hypo estrogenic state .
* Unlike GnRH agonists, these agents are effective immediately
* Do not cause an initial surge in LH and FSH,
* Do not require 7 to 14 days for GnRH suppression.
* .

GnRH antagonists

* They are available in both oral and injectable forms
* Cetrotide (Cetrorelix)
* Antagon (Ganirelix)
* Orillissa (Elagolix)
* Firmagon (Degarelix)

* **Symptom relief and adverse events such as :**

* vasomotor phenomena
* vaginal atrophy
* bone loss are also dose-dependent.

* In the United States, elagolix is an oral tablet approved for Moderate-to-Severe Pain .
* Similar to GnRH agonists, it can cause hot flushes or night sweats.
* 150 mg (once daily for up to 24 months)
* 200 mg (twice daily for up to 6 months).
* While the lowest dose that controls symptoms is preferred, the higher dose may be required for women with dyspareunia as part of their symptomatology.
* The medication is started within seven days of menses.

Contraindications: pregnancy and hepatic dysfunction.

* In two phase-3 trials comparing two different doses of the oral GnRH antagonist elagolix
* 150 mg once daily or 200 mg twice daily with placebo on endometriosis-related pain.
* both elagolix groups reported significantly reduced symptoms and improved quality of life at three months of treatment .
* .

* In both trials, at 3 months, reductions in dysmenorrhea pain :
* 44 percent of the low-dose elagolix group,
* 74 percent of the high-dose elagolix group
* 21 percent of the placebo group.
* Non menstrual pelvic pain was decreased in 50, 56, and 36 percent respectively.
* At six months, these responses persisted.
* The improvement in dysmenorrhea in the low-dose elagolix group is modest compared with the approved GnRH agonist.

* Hot flushes
* Headache
* Insomnia
* higher serum lipids levels (total cholesterol, LDL, HDL, and triglycerides) compared placebo.
* A follow-up study that extended both treatment groups for an additional six months (12 months total treatment) reported sustained improvements in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia at both doses .
* Hot flushes were the most common adverse event

New medication

* **Elagolix**, a GNRH antagonist, was approved by the FDA in July 2018 for moderate to severe endometriosis pain.

Aromatase inhibitors

* While danazol is effective at treating endometriosis-related pain,
* not commonly used because of androgenic side effects.
* one systematic review reported symptom relief with vaginal danazol, particularly for women with rectovaginal endometriosis.
* Typical treatments :
* oral anastrozole 1 mg once daily
* oral letrozole 2.5 mg once daily
* These agents appear to regulate local estrogen formation within the endometriotic lesions themselves, in addition to inhibiting estrogen production in the ovary, brain, and periphery.

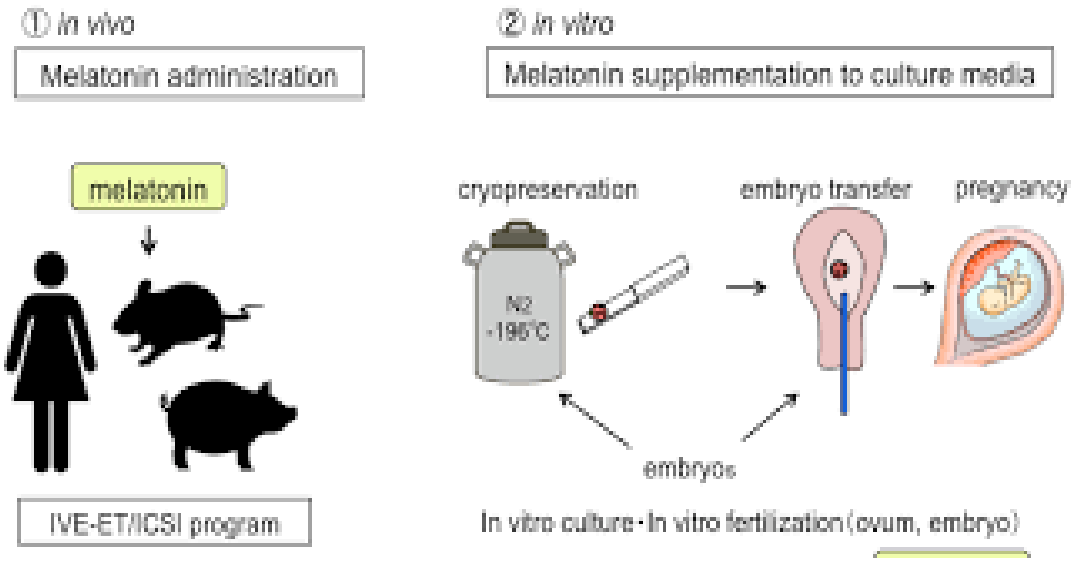
Danazol

* systematic review of five trials:
* six months of danazol treatment was more effective on pain .
* In one of the included studies, the improvement in pain scores persisted at six months after discontinuation of therapy .
* side effects:
* acne, muscle cramps, edema, weight gain (5 percent of body weight), spotting, hirsutism, and voice deepening were common and limited the use of danazol .
* When prescribed, danazol is typically given orally in divided doses ranging from 400 to 800 mg daily, generally for six months. Additionally, one systematic review reported symptom relief with vaginal danazol, particularly for women with rectovaginal endometriosis .

Melatonin

* The antioxidant, and anti-inflammatory effects of ***melatonin*** have been tested in animal and human studies:
* Endometriosis was surgically induced in 25 rats; then a subgroup was treated with melatonin administered intraperitoneally, while another subgroup did not receive any treatment.
* Four weeks later, regression and atrophy of endometriotic lesions were noted in the melatonin-treated group only .

Melatonin



* Melatonin Application in Assisted Reproductive Technology: A Systematic Review and Meta-Analysis of Randomized Trials
  * 27 March 2020

* Following studies in pinealectomized mice have shown an increase of endometriotic lesions in the animals not treated with melatonin compared to those.
* Furthermore, a higher concentration of molecules associated with oxidative stress such as malondialdehyde (MDA) and a statistically significant reduction of antioxidant activity were observed in pinealectomized mice

Diet

* There are no dietary recommendations for prevention or treatment of endometriosis.
* One study reported that a lower risk of developing endometriosis was associated with a high intake of **green vegetables** and fruit and an increased risk with intake of beef or other red meat or ham .
* Risk of endometriosis was not associated with alcohol, coffee, fish, and milk.
* Several studies have addressed the correlation of diet and dysmenorrhea, but not exclusively in patients with endometriosis.

Melatonin

* A small RCT demonstrated improvement in sleep quality, daily pain, dysmenorrhea, dyspareunia, dyschezia and dysuria with the use of melatonin (68).
* A Cochrane review demonstrated improvement in dysmenorrhea, reduction in associated symptoms and reduced use of additional medications with the use of traditional Chinese medicine compared to placebo (27).
*

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Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

ABSTRACT

Other Therapies

* Vitamins B1, E, and D, Omega 3 fatty acids, magnesium and ginger with modest or no effect .

* A recent Cochrane review demonstrated limited effectiveness for fenugreek, fish oil, fish oil plus vitamin B1, ginger, valerian, Vitamin B1, and zinc sulfate .

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ORIGINAL ARTICLE

The effect of vitamin D supplementation on clinical symptoms and metabolic profiles in patients with endometriosis

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ABSTRACT

Background: To our knowledge, data on the effects of vitamin D supplementation on clinical symptoms and metabolic profiles in patients with endometriosis are limited. This study was conducted to determine the effects of vitamin D supplementation on clinical symptoms and metabolic profiles in patients with endometriosis.

Methods: The current randomized, double-blind, placebo-controlled trial was conducted among 60 patients (aged 18–40 years old) with endometriosis. Participants were randomly allocated into two groups (30 participants each group) to receive either 50,000 IU vitamin D or placebo each 2 weeks for 12 weeks.

Results: Vitamin D supplementation significantly decreased pelvic pain (β – 1.12; 95% CI, −2.1, −0.09; p=.03) and total-/HDL-cholesterol ratio (β – 0.29; 95% CI, −0.57, −0.008; p=.04) compared with the placebo. Moreover, vitamin D intake led to a significant reduction in high-sensitivity C-reactive protein (hs-CRP) (β – 0.64 mg/L; 95% CI, −0.97, −0.30; p<.001) and a significant increase in total antioxidant capacity (TAC) (β 47.54 mmol/L; 95% CI, 19.98, 75.11; p=.001) compared with the placebo

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Effects of Vitamin D on Endometriosis-Related Pain: A Double-Blind Clinical Trial

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Full length article

Effectiveness of an antioxidant preparation with *N*-acetyl cysteine, alpha lipoic acid and bromelain in the treatment of endometriosis-associated pelvic pain: LEAP study

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Antioxidant Supplementation Reduces Endometriosis Related Pelvic Pain in Humans

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Evaluation of the Effect of Vitamin E on Pelvic Pain Reduction in Women Suffering From Primary Dysmenorrhea

Maryam Kashanian, M.D., Maziar Moradi Lakeh, M.D., Afsane Ghasemi, M.D., and Shahla Noori, M.D.


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