Medical Treatments in Endometriosis

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Medical therapy goal

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REVIEW

ENDOMETRIOSIS: CURRENT KNOWLEDGE FROM LAB TO CLINIC

Role of medical treatment of endometriosis

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- All medical solutions for management of endometriosis should be considered symptomatic rather than curative and pain management should be individualized.
- Choice for adequate drug therapy should be led by multiple factors including patient age, patient preference, willing for pregnancy, severity of pain , cost, duration, side effect profiles, risks and accessibility.
- Main purpose of medical treatment should be symptom improvement, reducing or eliminating need for surgery or prolonging time between surgeries, being aware that discontinuation of therapy often leads to recurrence.

Treatment of endometriosis-associated pain

Analgesics

- Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain.
- NSAIDs might inhibit ovulation if taken continuously during the cycle (making conception less likely)
- Evidence for use of NSAIDs for management of pain symptoms related to endometriosis is scarce and limited to a small RCT.

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Analgesics

- NSAIDs have minimal effectiveness when used alone
- Patients using in long-term NSAIDs must be aware that their use can lead to unintended adverse effects (such as GI ulcers, cardiovascular events, HTN, and ARF).

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Hormonal therapies

- ✓Hormonal therapy is based on evidence that endometriosis is a 'steroid dependent' condition.

- ✓Magnitude of this treatment effect is similar for all treatments, suggesting that there is little difference between them in their capacity to reduce pain.

- ✓It is recommended to offer women hormonal treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of options to reduce endometriosis-associated pain.

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Continued:

- There is no evidence that hormonal treatments have a negative effect on disease progression and they generally have limited side effects, prescribing hormonal treatment is recommended.

- Hormonal treatments, such as the contraceptive pill, may be indicated for contraception anyway.

- As there is no evidence of superiority of one hormonal treatment compared to others, GDG recommends a shared decision-making approach.

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Combined oral contraceptives

- OCP treatment results in clinically important and statistically significant reductions in endometriosis-related pain.

- Continuous use of the OCP and the associated achievement of amenorrhea, rather than standard cyclic use, has been suggested as an effective treatment for endometriosis-associated dysmenorrhea and a trend toward lower cyst recurrence rates .

- Nonsignificant differences between continuous and cyclic OCP use were reported for chronic pelvic pain and dyspareunia.

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Continued:

- OCP is cost-effective (cheap), considered safe and often required for contraception, GDG formulated a strong recommendation for use of OCP.

Progestogens

- Both continuous progestogens and continuous gestrinone are effective therapies for the treatment of painful symptoms associated with endometriosis.

- There was no overall evidence of a benefit of one oral progestogen over another. However, this conclusion must be treated with caution due to the paucity of data and lack of placebo-controlled studies.

- Only 1 more recent review was found evaluating the efficacy of progestogens (dienogest).

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Continued:

- It is recommended to prescribe women a mirena or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain.

Combined oral contraceptives and progestins

- COCs and progestins are largely considered as first-line therapies.

- Continuous administration has proven to reduce dysmenorrhea but has no effect on chronic pelvic pain or dyspareunia.

- Some authors have recently suggested that progestin monotherapy such as norethindrone acetate and dienogest may be superior to COCs and should be considered as first-line approach. It is particularly true in women with rectovaginal and extra-pelvic endometriosis.

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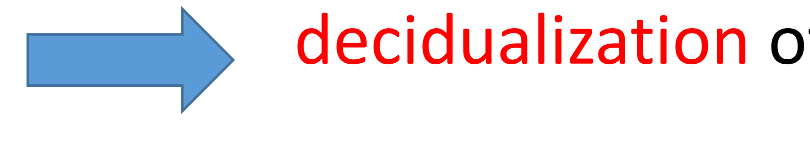
Progestins → ↓ serum level of ovarian steroids  decidualization of endometriotic implants

→ inhibiting inflammatory pathways and response causing apoptosis of endometriotic cells

→ anovulation

→ suppression of metalloproteinase-mediated growth and implantation of ectopic endometrium, inhibition of angiogenesis and also immunomodulation.

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Although LNG-IUD has not been FDA-approved for endometriosis, it has shown to be effective.

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Dienogest is a fourth-generation progestin, which has been increasingly used for endometriosis treatment.

- ✓ Anti-androgenetic activity → it improves skin-related side effects.
- ✓ It acts well on endometriotic lesions but has a minimal metabolic impact since it shows little androgenic, estrogenic, glucocorticoid or mineralocorticoid activity.
- ✓ Inhibits secretion of cytokines and seems to have both anovulatory and antiproliferative effect → Indeed, it acts through modulation of prostaglandins production and metabolism in a way that results anti-inflammatory.

Recommended optimal dosage is 2 mg daily. It has proven to reduce dyspareunia, pelvic pain, dysmenorrhea and premenstrual pain.

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Danazol

- Regarding use of danazol for treatment of endometriosis-associated pain, GDG strongly believes that danazol should not be used unless no other medical therapy is available.

GnRH agonists

- It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.

- GDG recommends that GnRH agonists are prescribed as second line (for example if combined oral contraceptives or a progestogen 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.

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Continued:

- ❖Considering possible impact on BMD, GDG recommends that in young women and adolescents, GnRH agonist should be used after careful consideration and as second line therapy.

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GnRH agonists

- GnRH-a cause initial stimulation of hypothalamic-pituitary-gonadal axis, they may cause an initial worsening of symptoms (flare-up effect) → can be avoided or prevented by treatment with aromatase inhibitors during first 7-10 days of therapy or alternatively giving initial injection in luteal phase of cycle.

- Suitable for women with DIE and extra-pelvic endometriosis and are especially useful for reducing dyspareunia.

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GnRH antagonists

- GnRH antagonists have been added to this update of medical treatment options for endometriosis.

- Data on efficacy can be deduced from a report on the two similar multicentre, RCT of six-month treatment with oral elagolix at 2 doses in women with moderate or severe endometriosis.

- Clinical response (46.4% in the lower dose group, 75.8% in the higher dose group).

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Continued:

- It is recommended to prescribe women GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.

- Similar as for GnRH agonists, GDG recommends that in young women and adolescents, GnRH antagonist should be used after careful consideration.

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GnRH antagonist

- Differently from GnRH-agonist, they maintain sufficient circulating estradiol (E2) levels and have less side effect related to hypoestrogenic state.

- Also, they have an immediate onset of action, without flare-up effect.

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Aromatase inhibitors

- Aromatase inhibitors (AIs) decrease local enzymatic conversion of androgen into estrogen and induce hypoestrogenism reducing endometrioc implants growth and invasion.

- Due to the severe side effects (vaginal dryness, hot flushes, diminished bone mineral density), aromatase inhibitors should only be prescribed to women after all other options for medical or surgical treatment are exhausted.

- Evidence on long-term effects of aromatase inhibitors is lacking.

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Other Medical Treatments

- Selective estrogen receptor modulators (SERMs)
- Selective progesterone receptor modulators (SPRMs)
- Anti-angiogenetic drugs
- Antioxidants drug
- Immunomodulators
- Epigenetic drugs

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Medical therapies adjunct to surgery

Preoperative medical treatment

❖ Surgeons prescribe preoperative medical treatment with GnRH agonists as this can facilitate surgery due to reduced inflammation, vascularisation of endometriosis lesions and adhesions. However, there are no controlled studies supporting this.

❖ From a patient perspective, medical treatment should be offered before surgery to women with painful symptoms in the waiting period before the surgery can be performed.

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Postoperative medical treatment

- GDG recommends that clinicians clearly distinguish adjunctive short-term (< 6 months) hormonal treatment after surgery from long-term (> 6 months) hormonal treatment; the latter is aimed at secondary prevention.

- Women may be offered postoperative hormonal treatment to improve immediate outcome of surgery for pain in women with endometriosis.

- With no proven harm, postoperative hormonal therapy may be prescribed for other indications, such as contraception or secondary prevention

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Medical treatment in endometriosis-associated infertility

Medical Treatment of endometriosis-associated infertility

- Based on results of Cochrane review, suppression of ovarian function (by means of danazol, GnRH agonists, progestogens, OCP) to improve fertility in women with endometriosis is not effective and should not be offered for this indication alone.

- Women seeking pregnancy should not be prescribed postoperative hormonal suppression with sole purpose to enhance future pregnancy rates.

- Those women who cannot attempt to or decide not to conceive immediately after surgery should be offered hormonal therapy as it does not negatively impact their fertility and improves the immediate outcome of surgery for pain.

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Arch Gynecol Obstet (2011) 284:105–110
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GENERAL GYNECOLOGY

A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis

Saeed Alborzi · Bahareh Hamedi · Azizeh Omidvar · Sedigheh Dehbashi · Soroosh Alborzi · Mehrnoosh Alborzi

Authors concluded that there was no benefit of administration of letrozole to improve pregnancy rates

Endometriosis recurrence

- Recently, recurrence was defined as lesion recurrence on reoperation or imaging after previous complete excision of disease
- Endometriosis recurrence rates vary widely in literature, ranging from 0% to 89.6% (different definitions)
- Risk factors for recurrence include surgery-associated variables (presence and extent of adhesions, radicality of surgery) and patient-related factors (positive family history, lower age at surgery)

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Treatment of recurrent endometriosis

- GDG recommends that any hormonal treatment or surgery could be offered to treat recurring pain symptoms.

- Even if treatment options are available, other causes for pain symptoms should be investigated, particularly if recurrence of symptoms occurs soon after adequate surgery.

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REVIEW

ENDOMETRIOSIS: CURRENT KNOWLEDGE FROM LAB TO CLINIC

Deep endometriosis: medical or surgical treatment?

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- Surgery and medical treatment are important tools in the management of DE

- Most societies have stated that one should prioritize medical treatment as first option for non-complicated DE patients, not seeking conception and indicate surgery for those who do not tolerate nor improve with medical treatment, as well as those cases complicated by visceral impairment.

Continued:

- Literature evidence shows that 2/3 of patients with DE will be satisfied with hormonal treatment, and surgery will be effective in relieving pain symptoms and improving QoL in most patients with DE.

When conducting young patients, an effort should be made in avoiding repetitive surgery.
Considering age under 33 is a recurrence risk factor, and pregnancy after surgery is a protective factor perhaps postponing surgery to, moment conception is desired, when possible, would be a wise strategy.
Finally, results of surgery come from specialized centers and may not be generalized to any gynecologist, whereas hormonal treatment is accessible, and results are more reproductible.

Summary

- ✓ Hormonal medical treatment is first line option in endometriosis-associated pain.
- ✓ Magnitude of this treatment effect is similar for all treatments, suggesting that there is little difference between them in their capacity to reduce pain.
- ✓ COCs and progestins are largely considered as first-line therapies.

Thanks for Your
Attention