PAIN RELIEF IN ENDOMETRIOSIS

PHARMACOLOGICAL AND NON-PHARMACOLOGICAL APPROACHES

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PAIN

- **Endometriosis** is a chronic and progressive benign disease characterized by the presence of endometrial tissue outside the uterine cavity.

- Pain is the cardinal symptom of endometriosis.

- A correlation has been demonstrated between lesion site and pain type (i.e. deep dyspareunia) while no correlation exists between the extent of endometriosis and the degree of pain symptoms.
PHARMACOLOGICAL APPROACHES
IDEAL DRUG TO TREAT ENDOMETRIOSIS

MOLECULAR ACTIVITY
- to down-regulate proliferation
- to enhance apoptosis
- to normalize the invasive mechanisms
- to normalize neuroangiogenesis processes

CLINICAL ACTIVITY
- to improve pain symptoms
- to improve infertility
- to prevent establishment of endometriosis
- to prevent progression of endometriosis
- to prevent recurrence of endometriosis after surgery
- to have low-incidence of adverse effects
PAIN RELIEF IN ENDOMETRIOSIS

PHARMACOLOGICAL AND NON-PHARMACOLOGICAL APPROACHES

HORMONAL THERAPIES IMPROVE PAIN BUT THEY DO NOT IMPROVE INFERTILITY
AVAILABLE DRUGS TO TREAT ENDOMETRIOSIS

- Non-steroidal anti-inflammatory drugs
- Progestogens
  - medroxyprogesterone acetate
  - cyproterone acetate
  - desogestrel
  - dydrogesterone
  - norethindrone acetate
  - levonorgestrel-releasing intrauterine system
- Gestrinone
- Combined hormonal contraceptives
  - oral contraceptives
  - vaginal ring
  - transdermal patches
- Gonadotropin-releasing hormone agonists
  - goserelin
  - leuprolide acetate
  - nafarelin
  - buserelin
  - triptorelin
- Danazol
- Gonadotropin-releasing hormone antagonists
- Aromatase inhibitors
- Alternative therapies
  - chinese herbal medicine
  - acupuncture
PROGESTOGENS

MECHANISM OF ACTION

- to cause a stable hypo-estrogenic environment due to the inhibition of the ovarian function
- to induce decidualization and atrophy of the endometriotic lesions through a direct activity on progesterone receptors
- to decrease peritoneal inflammation

EFFICACY

A Cochrane review (13 RCTs, 4935 women) showed that

- medroxyprogesterone acetate (100 mg daily) is effective at reducing all symptoms up to 12 months of follow-up compared with placebo
- there is no evidence of a difference in objective efficacy between dydrogesterone and placebo
- there is no evidence of a benefit with depot administration of progestagens versus other treatments (low dose oral contraceptive or leuprolide acetate) for reduced symptoms
- there is no overall evidence of a benefit of oral progestagens over other medical treatment at 6 months of follow-up for self-reported efficacy

COMBINED HORMONAL CONTRACEPTIVES

MECHANISM OF ACTION
- to decrease of menstrual bleeding
- anti-gonadotropic activity that suppresses ovulation
- to induce decidualization and atrophy of endometriotic implants

EFFICACY

A Cochrane review (1 RCT, 57 women) investigated the effects of the OCP in comparison to other treatments for pain

- The OCP decrease the intensity of dysmenorrhoea
- No evidence of a significant difference between between GnRHa and OCP was observed in terms of dysmenorrhoea at 6 months follow up after stopping treatment

Despite limited evidence of effectiveness, OCP are widely used as treatment for pain in women with endometriosis, which could be due to some practical advantages, including contraceptive protection, long-term safety and control of menstrual cycle.

Dysmenorrhea-associated withdrawal bleeding can be avoided with the use of extended-cycle pills.

GONADOTROPIN-RELEASING HORMONE AGONISTS

MECHANISM OF ACTION
- to suppress gonadotropin secretion by the pituitary gland resulting in a hypoestrogenic state that inhibits endometriosis
- secondary amenorrhea prevents new peritoneal seedlings
- direct local action of GnRH-a in the endometriotic tissue (inhibition of endometriotic cells proliferation)

EFFICACY
- GnRH-a are highly effective in reducing the pain syndromes associated with endometriosis but they are not superior to other methods (such as combined OCs)
- Recurrence of symptoms is common after the medication is discontinued
- A Cochrane review (41 RCTs, 4935 women) showed that
  - GnRH-a are more efficacious in relieving pain symptoms than no treatment/placebo
  - there is no statistically significant difference in pain improvement between GnRH-a and danazol
  - there is no statistically significant difference in pain improvement between GnRH-a and levonorgestrel
  - evidence is limited on optimal dosage or duration of treatment for GnRH-a
  - no route of administration appears superior to another

ADVERSE EFFECTS

- bone loss
- hot flushes (19.6%-90%)
- headache (8.5%-68%)
- stiff shoulder (12.8%)
- vaginal dryness (28%-37%)
- libido decrease (19%-24%)
- fatigue (58%)
- irritability (47%)
- depression (32%)
- sleep disturbances (11%)
- acne (26%)

A treatment longer than 6 months with GnRH agonists should be combined with add-back therapy.

Add-back treatment does not diminish the efficacy of pain relief observed during 3 months or 6 months of GnRH agonist therapy.

In women with pain from rectovaginal endometriosis, refractory to other medical or surgical treatment, clinicians can consider prescribing AIs in combination with oral OCP, progestagens or GnRHa, as they reduce endometriosis-associated pain.

A Cochrane review (1 RCTs, 24 women) showed that:

- comparing NSAIDs (naproxen) to placebo, there is no evidence of a positive effect on pain relief in women with endometriosis
- there is inconclusive evidence to indicate whether women taking NSAIDs (naproxen) were less likely to require additional analgesia or to experience side effects when compared to placebo
- there is inconclusive evidence to show whether or not NSAIDs (naproxen) are effective in managing pain caused by endometriosis
- there is no evidence on whether any individual NSAID is more effective than another

When prescribing NSAIDs, clinicians should discuss the side effects associated with frequent use, including inhibition of ovulation, risk of gastric ulceration and cardiovascular disease, with the patient.

A Cochrane review (2 RCTs, 158 women) investigated the effectiveness and safety of CHM in alleviating endometriosis-related pain.

- The 2 trials described adequate methodology; neither trial compared CHM with placebo treatment.
- There was no evidence of a significant difference in rates of symptomatic relief between CHM and gestrinone administered subsequent to laparoscopic surgery.
- CHM administered orally and then in conjunction with a herbal enema resulted in a greater proportion of women obtaining symptomatic relief than with danazol. Overall, 100% of women in all the groups showed some improvement in their symptoms. Oral plus enema administration of CHM showed a greater reduction in average dysmenorrhea pain scores than did danazol.
- Combined oral and enema administration of CHM also showed a greater improvement measured as the disappearance or shrinkage of adnexal masses than with danazol. For lumbosacral pain, rectal discomfort, or vaginal nodules tenderness, there was no significant difference between CHM and danazol.
- More rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.

A Cochrane review (1 RCTs, 67 women) investigated the effectiveness and safety of acupuncture for pain in endometriosis.

- dysmenorrhea scores were lower in the acupuncture group

- the total effective rate (‘cured’, ‘significantly effective’ or ‘effective’) for auricular acupuncture and CHM was 91.9% and 60%, respectively (p = 0.0004)

- the improvement rate did not differ significantly between auricular acupuncture and CHM for cases of mild to moderate dysmenorrhea, whereas auricular acupuncture did significantly reduce pain in cases of severe dysmenorrhea

- the evidence to support the effectiveness of acupuncture for pain in endometriosis is limited, based on the results of only a single study

- it is necessary to develop well-designed, double-blinded, randomised controlled trials that assess various types of acupuncture in comparison to conventional therapies
Hormonal treatments aim at relief of pain and preventing disease progression/recurrence in the period between conservative surgery and conception seeking.

Patients should be informed that, despite the improvement in pain symptoms, hormonal therapies are not curative and recurrence of symptoms usually occurs when the treatment is interrupted.

Disease progression may occur despite the use of hormonal therapies; therefore, during the endocrine treatment patients should be monitored by ultrasonography to prevent complications caused by disease progression (e.g., hydronephrosis secondary to ureteral obstruction or bowel stenosis).

SURGERY
Laparotomy and laparoscopy are equally effective in the treatment of endometriosis-associated pain, but laparoscopic surgery is usually associated with less pain, shorter hospital stay and quicker recovery as well as better cosmetic outcome, hence it is usually preferred to open surgery.

A Cochrane review (5 studies) assessed the efficacy of laparoscopic surgery in the treatment of pelvic pain associated with endometriosis

- the meta-analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only (OR of 5.72 95%CI 3.09 to 10.60 ; 171 participants, 3 trials)

- a single study reported pain scores 12 months after the procedure; the analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only (OR of 7.72 95%CI 2.97 to 20.06 ; 33 participants, 1 trial).

- There were few women diagnosed with severe endometriosis included in the meta-analysis and therefore any conclusions from this meta-analysis regarding treatment of severe endometriosis should be made with caution.

- It is not possible to draw conclusions from the meta-analysis which specific laparoscopic surgical intervention is most effective.

Surgical removal of deep endometriosis reduces endometriosis-associated pain and improves quality of life.

Surgical removal of deep endometriosis is associated with significant complication rates, particularly when bowel surgery is required.

- intraoperative complication rate: 2.1%
- total post-operative complication rate: 13.9% (9.5% minor, 4.6% major)

There is an ongoing debate about the indication for shaving nodules as opposed to segmental resection.

CONCLUSIONS (1)

- Progestogens and OCP should be considered the first-line therapy for endometriosis-related pain in women who do not desire to conceive.

- Women should be informed that
  - the hormonal therapy is not curative and pain usually recur after the discontinuation of treatment.
  - endometriosis may progress during the long-term use of hormonal therapies.
CONCLUSIONS (2)

- Surgical excision of endometriosis significantly improves endometriosis-related pain
- Surgery for endometriosis is associated with a high rate of complications
- Surgery should be performed in patients
  - with persisting pain despite the use of hormonal therapies
  - in patients with severe pain symptoms who refuse hormonal therapies because they desire to conceive
  - in case of bowel stenosis causing subocclusive symptoms, ureteral strictures