Medical management of Endometriosis

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Goal of treatments

- Manage the patient’s pain with medical therapy for as long as possible

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- Limit the number of surgical interventions

- Women whose pain **do not** respond to the medical treatments are offered laparoscopy for diagnosis and treatment.
Treatments

- Medical
- Surgical
Current treatments

Based on suppressing estrogen production and inducing amenorrhea:

- hypo estrogenic environment → inhibits ectopic endometrial growth and prevents disease progression
disadvantages of current medical treatments

1. Suppressive rather than curative therapy
2. High recurrence rate after discontinuation
3. Contraceptive rather than fertility-promoting
4. Not effective for Endometrioma
5. Not effective for existing adhesions
6. Limited medical options for DIE and extrapelvic disease
First line of treatment

- Treat primary dysmenorrhea
- Available, low cost, acceptable side effects
- Commonly combined with contraceptive hormonal therapy

- Women who desire conception → avoid selective COX–2 inhibitors (celecoxib)
Estrogen–Progestin contraceptive

- First line treatment
  - Can be used long-term, inexpensive, well-tolerated
  - Provide contraception
  - Decreased ovarian and endometrial cancer
- Mechanisms:
  - Suppress ovarian function, decidualization & atrophy of endometrial tissue
No formulation is superior
Best regimen: Begin with COCs containing 20mcg ethinyl-estradiol in continuous fashion

Continuous regimen more effective than cyclic one in reducing pain.
Progestin

- First line treatment
- Include:
  - Medroxy progestrone acetate 30mg Daily/DMPA 150 mg every 3 months
  - Dydrogestrone 20–30mg Daily (*Duphaston*)
  - Norethindrone acetate 5mg PO daily
  - Dienogest 2mg PO daily/ Dienogest + estradiol valerate (*Natazia*)
Mechanisms:
- Inhibit endometrial tissue growth by decidualization & atrophy
- Suppression of matrix metalloproteinase
- Inhibition of angiogenesis

Side effects:
Breakthrough bleeding/amenorrhea/weight gain/depression
Levonorgestrel IUD

- Postoperative reduction of dysmenorrhea recurrence
- Reduce pain caused by peritoneal or rectovaginal endometriosis
GnRH agonist analogues

- Second line treatment
- Include:
  - Naferelin 200mcg daily/BD intranasal
  - Leuprolide 3.75mg IM monthly or 11.25 every 3 months
  - Buserelin 300mcg daily intranasal/200mcg daily SC
  - Goserelin 3.6mg SC monthly
  - Triptorelin 3.75mg IM monthly
Mechanisms:

- Long time Receptor binding in pituitary gland → down regulation of pituitary-ovarian axis → hypo-estrogenic state.

Side effects:

Hypo-estrogenic state symptoms & bone loss

Add back therapy to minimize hypoestrogenic side effects:
- Norethindrone acetate 5mg daily
- Estrogen–progestin therapy
Danazol

- Effective but not commonly used because of androgenic side effects
- Recommended dose: 400–800 mg daily for 6 months
- Vaginal Danazole → treatment of rectovaginal endometriosis (danazol ring 1500mg)
- Side effects:
  Weight gain/acne/muscle crump/ edema/ hirsutism/ voice deepening
New medical agents to treat endometriosis related pain

- GnRH antagonists
- Selective progesterone receptor modulator & progesterone receptor antagonists (PRAs & SPRMs)
- Selective estrogen receptor modulator (SERMs)
- Aromatase inhibitors
- Non hormonal
  - Anti-angiogenic drugs
  - Antioxidants drugs
  - Immunomodulators
  - Epigenetic agents
Second line treatment

Include:

- **Injectable**
  - Ganirelix
  - Cetrorelix (in one trial: 3mg SC weekly for 2 months)

- **Oral**
  - Elagolix 150mg Daily or 200mg BD
  - Abarelix
  - Ozarelix
  - Relugolix
Mechanism:
suppress pituitary gonadotropins → hypo-estrogenic state
Do not cause initial flare up (like GnRH agonists)

Side effects:
Hypo-estrogenic state adverse effects (especially hot flushes) & bone loss + headache
Include:
- Mifepristone (5−10 mg daily)
- Ulipristal acetate (UPA) → insufficient data
- Gestrinone
- Asoprisnil → insufficient data

Mechanism:
Anti-proliferative effect on endometrium without hypo-estrogenism side effects
**Gestrinone:**

Androgenic, anti–progestogenic, anti–estrogenic, anti–gonadotropic effects (central & peripheral actions)

- Amenorrhea (50–100% of cases → dose dependent) → menses resumption after 33 days of drug discontinuation
- Long half life → 2.5 mg twice a week

**Side effects:**

nausea, muscle cramps, androgenic effect (weight gain, acne, seborrhea, oily hair–skin)

✓ *Pregnancy contra indicated.*
SERMs

- Mechanism:
  Bind to E receptors as agonist or anagonist selectively
- **Raloxifine** used to treat osteoporosis since 1999

  *Rate of recurrence of symptoms following treatment discontinuation after 6 months was higher in the raloxifene group compared with placebo: **study termination***

- **Bazedoxifene** used to treat osteoporosis
  - effectively antagonizes estrogen–induced uterine endometrial stimulation
  - BZA is able to cause regression of endometriotic lesions (*in vitro & animal studies*) under investigations
Aromatase inhibitors

- Include:
  - Letrozole 2.5 mg PO daily
  - Anastrozole 1 mg PO daily
✓ *Used in women with severe, refractory endometriosis related pain.*

- Side effects:
  Bone loss
  Ovarian follicular cyst development
✓ *To suppress: AI combined with GnRH analogues or COCs or norethindrone acetate 5 mg daily*
  Hot flash, weight gain, spotting, depression..
Efficacy:
- improving endometriosis–related pain symptoms
- intestinal symptoms in patients with colorectal endometriosis
- urinary symptoms in patients with bladder endometriosis
- decreasing the volume of endometriotic rectovaginal nodules

** especially in combination with GnRH Agonist..
Intra vaginal ring releasing ATZ and LNG has been developed and it is under investigation for the treatment of endometriosis.
Non hormonal new agents

1. Immunomodulators: Selective inhibition of $\text{TNF-}\alpha \rightarrow \text{animal}$ trials showed effectiveness on pain control and treatment of endometriosis non fibrotic adhesions (Etanercept)

2. Pentoxifylline $\rightarrow$ anti inflammatory effects, no significant effect on pain reduction, infertility, recurrence of endometriosis.
3. **Anti-angiogenic drugs** → *VEGF* is the most important angiogenic factor in endometriosis.

✓ **bevacizumab**, a recombinant monoclonal antibody against VEGF, inhibited the development of endometriotic lesions.

**In addition..**

✓ dopamine and its receptor-2 have a critical role in the regulation of VEGF mediated growth of implants → In mice, *cabergoline* decreased the size of endometriotic implants by inhibiting angiogenesis.
4. **Antioxidants**
   - *Omega-3 fatty acids* (800 mg/day for 12 months)
   - *N-acetylcysteine* (600 mg three times per day, 3 consecutive days per week)
   - *Statins* (antioxidant, anti-proliferative, anti-angiogenic) → simvastatin/atorvastatin
   - *anti diabetic drugs* → such as pioglitazone
   - *Elocalcitrol & all-trans-retinoic acid*
5. Epigenetic agents act generally on histone deacetylases:
   - trichostatin A
   - Valproic acid
Endometriosis is a benign chronic hormonal disease that requires a long-term therapy:

- Control of pain symptoms
- Prevention of recurrence

The choice is based on:
Age, preference of the patients, reproductive plans, intensity of pain, severity of disease, incidence of adverse effects

Researches are focusing on finding both new active hormonal and non-hormonal drugs for treating patients with endometriosis.
References..

- Berek & Novak Gynecology 2020
- Speroff’s clinical gynecology 2020
- Up to date (Jun 2020)

https://doi.org/10.1080/14656566.2018.1494154
Thank you for your attention