Pharmacological treatment of women with Endometriosis

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Disclosure of interest: nothing to declare
“Endometriosis: enigmatic in the pathogenesis and controversial in therapy”

endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures
Approaches to treatment of Endometriosis

- **Expectant management**
  
  A period of observation with no treatment except medications to relieve pain

- **Pharmacological treatment**
  
  Drugs that temporarily suppress/ eliminate Menstruation or drugs targeted against Proliferation of endometriosis lesions

- **Surgery**
  
  Excision, fulguration adhesiolysis
Is there a place for expectant management in Endometriosis?

Primarily for two groups of patients:
- Women with no or minimal symptoms
- Peri menopausal women

**CON**: Endometriosis is a progressive disease.
Most studies suggest that OCP reduce the incidence of endometriosis.

**PRO**: Some studies suggest no effect or a slight increase
Endometriosis is often not curable or preventable
Premature intervention can only harm
Clinical manifestations of endometriosis:
- Pain
- Infertility
- Pelvic mass

Other indications for medical treatment:
- Suppress recurrence after operation
- Previous to IVF

The dependence of endometriosis on cyclic production of menstrual cycle hormones has been the basis for medical therapy.
Note on treatment of Endometriosis

**Medical therapy** has been the subject of several RCTs. Pros and cons are well known, and the impact on symptoms fairly clear.

**Surgery** Only a few RCTs available on the effect of for symptomatic disease, long-term outcomes not clear

Contrary to drug trials, technical skills and experience play an important role in surgery trials.
Why Pharmacological Treatment?

**Pain** - Excellent response with drugs recurrent pain symptoms are 44% with surgical management and 53% with medical management

**Fertility** - In women who wish to preserve their reproductive potential pharmacological treatment is a viable option

**Pelvic mass & recurrence post operation** : Alleviation

**Previous to ART** : Possible benefit (ESHRE guidelines 2013)
Should endometriosis be suppressed prophylactically by continuous OCP to cause regression of asymptomatic disease and enhance subsequent fertility?

The Royal College of Obstetrician Gynecologists: combined OCP the drug of choice for treating symptoms of endometriosis. A safe and economical treatment and as an alternative to surgery.

Should women with endometriomata (cysts of endometriosis in the ovaries) undergo surgical intervention before ART?

Cochrane review: Further trials are required.
# Medical treatment of Endometriosis

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<thead>
<tr>
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<th>Adverse effects</th>
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<td>Oral contraceptives</td>
<td>Inhibition of H-P-O axis. Pseudo Pregnancy.</td>
<td>Headache, nausea, hypertension</td>
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<td>P.O. Medroxyprogesterone (Provera)</td>
<td>Inhibition of H-P-O axis. Pseudo Pregnancy.</td>
<td>Weight gain, depression, irregular menses, headache</td>
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<td>Depo-Provera IUD (Mirena)</td>
<td>Decidualization and atrophy</td>
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<td>Dienogest</td>
<td>Anti-androgenic</td>
<td>Headache, breast discomfort, depression and acne</td>
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<td>Danazol</td>
<td>Androgen like, Inhibits ovarian steroidogenesis</td>
<td>Estrogen deficiency, androgenic side effects, weight gain</td>
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<td>(GnRH) agonists IM (Decapeptyl, Leuprorelin)</td>
<td>Inhibition of H-P-O axis. Pseudo menopause</td>
<td>Osteoporosis, Vaginal dryness, Hot flashes</td>
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Classification of Progestins

Progestogenes

C-19 nortestosterone

Estranes

Dienogest

Norethindrone

Norethisterone acetate

Ethynodiol diacetate

Lynestrenol

Norethynodrel

Gonanes

Norgestrel

Levonorgestrel

Norgestimate

Desogestrel

Gestodene

Pregnanes

Megestrol acetate

Cyproterone acetate

Medroxyprogesterone acetate

Spironolactone

Drospirenone

Progesterone derivatives

Dienogest is a progestin that combines the properties of both 19-nortestosterone derivatives and progesterone derivatives

Main Properties:
- Strong progestational effect on endometrium
- No estrogenic / androgenic / mineralocorticoid effect
- Relatively short plasma half-life of approximately 9-10 hours
- High oral bioavailability >90%
- Anti-androgenic effects
- Anti-proliferative effects
- Relatively moderate inhibition of gonadotropin secretion
- Mainly peripheral mode of action

Visabelle VS. Leuprolide Acetate
Change in Estradiol Levels

Adapted from Strowitzki T et al. Hum Reprod 2010.

Difference statistically significant ($P=0.0003$)
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## Treatment of Endometriosis
### Emerging Drugs

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<td>Aromatase inhibitors (letrozole, anastrozole, BGS-649)</td>
<td>Avoid aromatase dependent increase in PGE levels via increase in the cyclooxygenase-2 (COX-2) expression and aromatization to estrogen</td>
<td>Hypo estrogenism, Osteoporosis Real effect questionable</td>
</tr>
<tr>
<td>GnRH antagonist (P.O Elagolix) TAK-385 (Abarelix-Depot)</td>
<td>Inhibition of H-P-O axis. Pseudo menopause Immediate blocking action on GnRH receptors, No ‘flare-up’ effect</td>
<td>So far Elagolix was safe, well tolerated. To be launched for endometriosis in 2015</td>
</tr>
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<td>Selective ER modulators (SERMs)</td>
<td>Estrogen agonist in bone, preserving BMD, but no stimulation of endometrium or breast tissue</td>
<td>reversible elevation of liver enzyme, Bone loss</td>
</tr>
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<td>Selective ER-α and β agonists</td>
<td>Anti inflammatory role Antagonize the development of lesions Opposes action ER-α</td>
<td>Raloxifene-earlier 2nd surgery compared to placebo studies only in mice</td>
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<td>SPRMs (RU 486)</td>
<td>Selective progesterone receptor modulators</td>
<td>One study terminated d/t increased liver enzymes</td>
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<tr>
<td>Statins</td>
<td>effect on oxidative stress, VEGF and metalloproteinases</td>
<td>Study stopped recruiting patients</td>
</tr>
<tr>
<td>TNF-a blockers</td>
<td>Anti – inflammatory Anti – adhesion and proliferation</td>
<td>Insufficient evidence</td>
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<td>Pentoxifylline</td>
<td>Inflammation modulator : inhibition of TNF-a production by macrophages</td>
<td>Cochrane : Insufficient evidence</td>
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<td>Anti-angiogenics (VEGF)</td>
<td>Inhibition of VEGF dependent growth of endometriosis</td>
<td>Has not been tested in women with endometriosis</td>
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<td>Dopamine receptor 2 agonist (Cabergoline and quinagolide)</td>
<td>Reduce neovascularization by dephosphorylation of VEGFR-2</td>
<td>Only one study in humans in patients with hyperprolactinemia - lesion reduction</td>
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Lipoxin A₄ (LX4)

An anti-inflammatory and lipid mediator that recently characterized as an estrogen receptor agonist.

**In mouse model:** prevents the progression of de novo and established endometriosis.

- Attenuates prostaglandin E₂ production and estrogen signaling
- Reduced endometriotic lesion
- Downregulated the pro-inflammatory cytokines IL-1β and IL-6, as well as the angiogenic factor VEGF.

*PLoS One* **Feb 2014**
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<th>Pharmacologic treatment</th>
<th>Surgery</th>
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| **Advantages**                | Avoid premature interventions | • Delay progression of the disease  
• Improvement in symptoms (80-90%) | • Diagnosis  
• Preventing or delaying disease or symptom progression |
| **Disadvantages**             | Disease progression  | • Side effects  
• Cost  
• Compliance  
• Recurrence (50%) | • Trauma  
• Infectious  
• **Ovarian reserve**  
• Adhesions  
• Recurrence (50%) |
Treatment decisions should be integrated, combined and individualized according:

- The severity of symptoms
- The extent and location of disease
- The desire for pregnancy
- The age of the patient
- The medication side effects
- The surgical complication risks
- The cost
ESHRE Guidelines 2013

Pain

- NSAIDs or other analgesics reduce endometriosis-associated pain
- Clinicians are recommended to prescribe hormonal treatment to reduce endometriosis-associated pain.
- Add back therapy is recommended in long term GnRH analogue treatments
- In women with pain from rectovaginal endometriosis is refractory to other medical or surgical treatment, Aromatase inhibitors in combination with oral contraceptive pills progestagens, or GnRH analogues
In women operated on for endometriosis, clinicians are recommended to prescribe postoperative use of a levonorgestrel-releasing intrauterine system (LNG-IUS) or a combined hormonal contraceptive for at least 18-24 months for the secondary prevention of endometriosis-associated dysmenorrhea.
The effectiveness of surgical excision of deep nodular lesions before treatment with ART in women with endometriosis-associated infertility is not well established with regard to reproductive outcome.

Preservation of fertility should be discussed.
It is recommended that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary.

The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.

Endometriosis surgery should be avoided in women with diminished ovarian reserve who should be offered ART straightaway

(Expert Opin. Emerging Drugs (2012) 17(1):83-104)
In infertile women with endometrioma <3 cm there is no evidence that cystectomy prior to treatment with ART improves pregnancy rates.

- Clinicians can prescribe GnRH agonists for a period of 3 to 6 months prior to treatment with ART to improve clinical pregnancy rates in infertile women with endometriosis.

- Cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI.
In women with endometrioma >3 cm only consider cystectomy prior to ART to improve endometriosis-associated pain or the accessibility of follicles.

- It is recommended that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.
None of the approaches is curative and both have advantages and disadvantages, the two options: drug therapy and surgery co-exist while the debate continues.
Conclusions

- Pharmacological treatment is a viable option for treatment of pain & dysmenorrhea in endometriosis.
- Future non hormonal tissue by directed specific drugs will enable to improve treatment.
- Medical treatment combined with ART are the preferable approach to infertility associated with endometriosis.