MANAGEMENT OF REFRACTORY ENDOMETRIOSIS

Serdar Bulun, MD
JJ Sciarra Professor and Chair
Department of Ob/Gyn
Northwestern University
ENDOMETRIOSIS

Teenager: severe dysmenorrhea often starting at menarche

OCs

20s: chronic pelvic pain (between periods)

OCs, Depot Progestin, Depot GnRH agonist

Late 20s, early 30s: first laparoscopy and diagnosis, commonly stage 1-2

Depot GnRH agonist

30s-40s: multiple and usually ineffective follow-up laparoscopies, experimental medications

TH-BSO
PERITONEAL ENDOMETRIOSIS

OVARIAN ENDOMETRIOMA

RECTOVAGINAL NODULE
HYPOTHALAMUS

PITUITARY

OVARY

OVULATION

GnRH

FSH

LH

E₂

P

GnRH analogue

Oral Contraceptive

High-dose progestin

E₂

P

PERITONEUM

Aromatase Inhibitor

E₂

Chol

ERβ

survival

growth

inflammation

PAIN

ENDOMETRIUM

ENDOMETRIOSIS

menses

nociceptor

inflammation

menses
Current Surgery: Laparoscopic Resection/Ablation

- Allows assessment of extent of disease
- Should be performed by an experienced surgeon
- Resection is superior to vaporization or fulguration
- En bloc stripping of cul-de-sac peritoneum may reveal microscopic disease
- Rectovaginal dissection should be considered especially for dyspareunia
Current Medical Treatment Options

- Oral contraceptives (OCs); continuous use
- Progestins (Depot-MPA; oral NEA)
- IUD - levonorgestrel
- GnRH agonists (monthly injections) only (up to 3 months)
- GnRH agonist + NEA (2.5 mg or 5 mg daily; >3 months)
- Danazol
Response Rates for Pain Relief

• In the absence of a RV nodule or endometrioma, response rates to laparoscopic surgery and medical treatment in treatment-naïve patients are similar: 90-100%. Pain recurs in ~90% of patients within 2 to 5 year after discontinuation.

• Response rate to surgery or medication decreases in previously treated patient population. Average response rate: ~50%. Pain recurs in most patients within 6 months to 2 years after discontinuation.
Refractory Endometriosis

- Endometriosis previously diagnosed by laparoscopy
- Pain not responding to recent medical and surgical treatment attempts (ovarian suppression by OC, progestin or GnRHa and laparoscopic ablative surgery)
Treatment Options for Refractory Pain

1. Medical Treatment
2. Laparoscopic resection/ablation
3. TH-BSO
Ineffective Treatments for Refractory Endometriosis

- Endometrial ablation
- Hysterectomy without oophorectomy
- LUNA
- Progestin IUDs??
- Presacral neurectomy
Experimental Treatments

- Aromatase inhibitors (letrozole 2.5mg/d or anastrozole 1mg/d)
- AI only in post menopausal women
- AI + OC or AI + NEA in premenopausal women
- RU486 5mg/d, ulipristal acetate 5 or 10 mg/d
- Other selective progesterone receptor modulators (SPRMs) or antiprogestins
- Oral GnRH antagonists
Hypothalamus ➔ Pituitary ➔ FSH, LH ➔ Ovary ➔ No Follicular Aromatase ➔ Endometriosis ➔ Peripheral Tissues ➔ Peripheral Aromatase

Postmenopausal on AI:
- AI
- Aromatase
- FSH, LH

Premenopausal on AI:
- AI
- Aromatase
- FSH, LH

Premenopausal on AI + OC or P:
- AI
- Aromatase
- FSH, LH

PREMENOPAUSAL WOMEN TREATED WITH LETROZOLE AND NORETHINDRONE ACETATE

Pre- and Post-treatment Pain Scores (n=10)

Anastrozole and Alesse® for Refractory Endometriosis and Chronic Pelvic Pain

Pain Score

Baseline    1    2    3    4    5    6

randomized trial, n=80

GnRHa+ anastrozole

54.7%

GnRHa only

10.4%

Soysal et al, Human Reprod, 2004
PROGESTERONE RECEPTOR MODULATORS

PROGESTINS (Progesterone Agonists)
- R5020
- PROGESTERONE
- MPA
- NEA

AGONIST

progestogenic activity

mixed agonist/antagonists
- J867
- CDB2924
- CDB4124 (UPA)
- RU486

ANTIPROGESTINS

Progestosterone Antagonists
- ZK98299

ANTAGONIST
ANTIPROGESTINS

• Amenorrhea in majority of patients (anovulation and direct endometrial effects)

• Pain relief possibly better than progestins

• Cystic glandular dilatation often associated with both admixed estrogen (mitotic) and progestin (secretory) epithelial effects

• Endometrial thickness is related to cystic glandular dilatation

Hawkins-Bressler, et al, JRM, 2018
UNDIAGNOSED ENDOMETRIOSIS
(dysmenorrhea, dyspareunia, chronic pain)

- **Pelvic Exam**
- **Vaginal Ultrasound**

**Endometrioma**
Rectovaginal nodule

- **Laparoscopic resection by an experienced surgeon**

**No endometrioma or RV nodule**

**Diagnostic laparoscopy resection by an experienced surgeon**

- **Challenge by Continuous OC**
  - Unsatisfactory response

**Long-term continuous OC**

- **Add Aromatase Inhibitor to OC**

- **Repeat Surgery or Lupron depot or UPA**
ESTABLISHED ENDOMETRIOSIS
(RECURRENT SYMPTOMS)

Pelvic Exam
Vaginal Ultrasound

Endometrioma
Rectovaginal nodule

Laparoscopic resection
by an experienced surgeon

No endometrioma
or RV nodule

Continuous OC

Unsatisfactory
response

Long-term continuous OC

Add Aromatase Inhibitor to OC

Repeat Surgery or Lupron depot or UPA
SPECULATIONS

The symptomatology of endometriosis represents a spectrum of a broad chronic disease involving a basic pathology in pelvic tissues including the endometrium.

The disease becomes initially manifest with the so-called primary dysmenorrhea in teenage years and advances to laparoscopically visible endometriosis.

Sampson’s hypothesis explains the majority of the cases of peritoneal endometriosis, rectovaginal nodule and ovarian endometrioma.
In epigenetically susceptible women, the risk of development of endometriosis or its symptoms increases in direct proportion with the number of ovulatory menses.

Long-term suppression of menses with OCs in young women with primary dysmenorrhea should decrease the risk of symptomatic endometriosis.

It would be clinically beneficial to view pelvic symptoms associated with endometriosis as a spectrum and broaden its definition to a “systemic disease characterized with estrogen-induced inflammation, pelvic pain responsive to hormonal suppression or surgical resection of endometriotic tissue.”
UNMET NEEDS: ENDOMETRIOSIS

In patients with chronic pelvic pain and endometriosis, a useful diagnostic test geared towards response to a specific treatment is needed. On the other hand, a test that will simply replace laparoscopic visualization will not likely be clinically useful because this phenotype is extremely prevalent and nonspecific.

The key challenge is to treat endometriosis-associated pelvic pain not responding to currently available modalities. At least half of the patients with a diagnosis of endometriosis are not satisfied with the available treatments.

Endometriosis-associated infertility is poorly understood, and there are no specific medical treatments.
Molecular Aberrations in Endometriosis

How do inflammatory signals and nuclear receptor alterations contribute to disease in endometriosis?

- Elevated cytokines, IL-1β, TNFα, IL-8, COX-2 and PGE₂
- Increased macrophage recruitment to lesions.

- Elevated ERβ, SF1, decreased ERα, PR, RARs, SRC-1.

- HOXA10, ERβ, SF1, PR, AROM