(339) MANAGEMENT OF REFRACTORY ENDOMETRIOSIS

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ENDOMETRIOSIS

Teenager: severe dysmenorrhea often starting at menarche

OCs

20s: chronic pelvic pain (between periods)

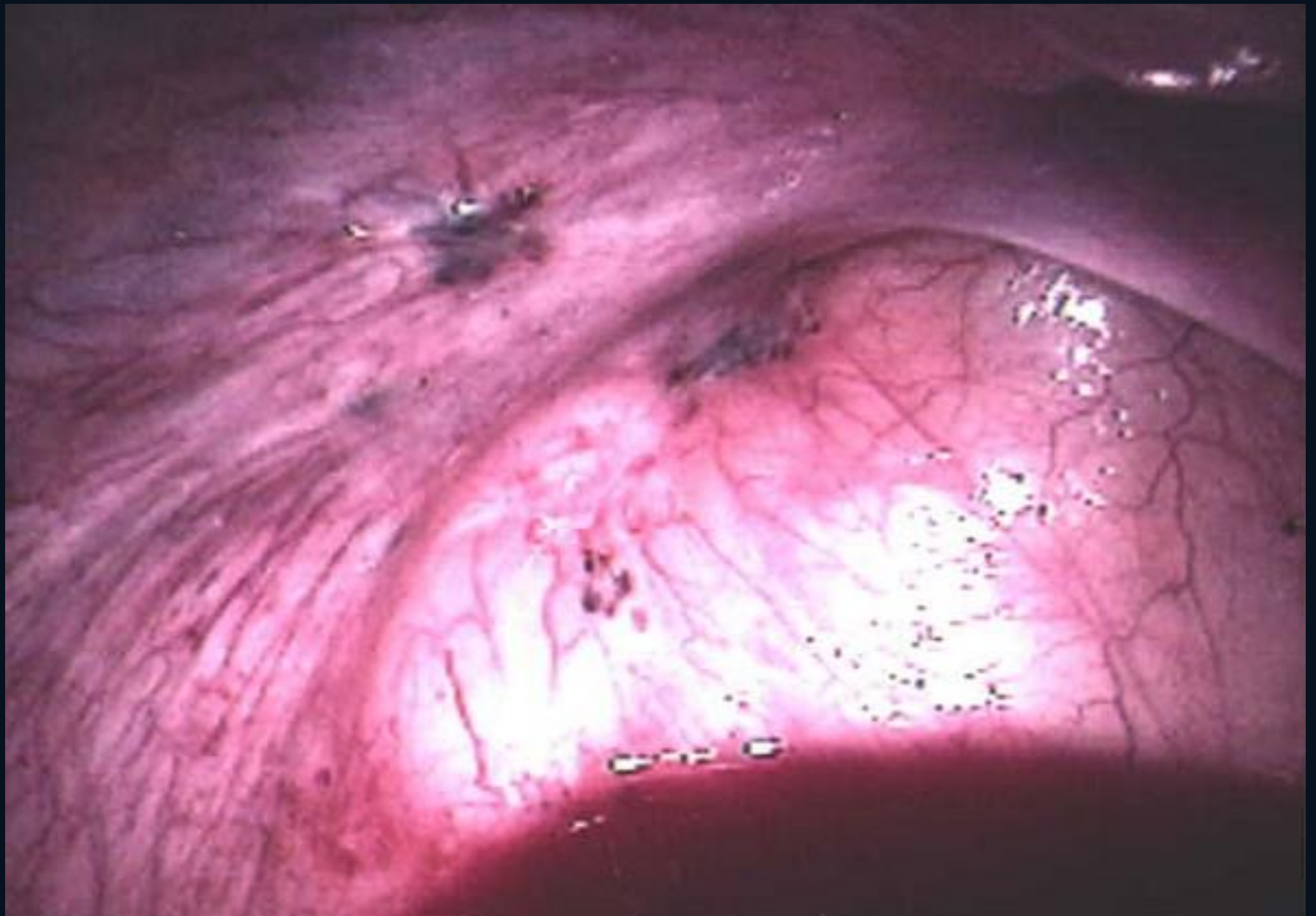
OCs, Depot Progestin, Depot GnRH agonist

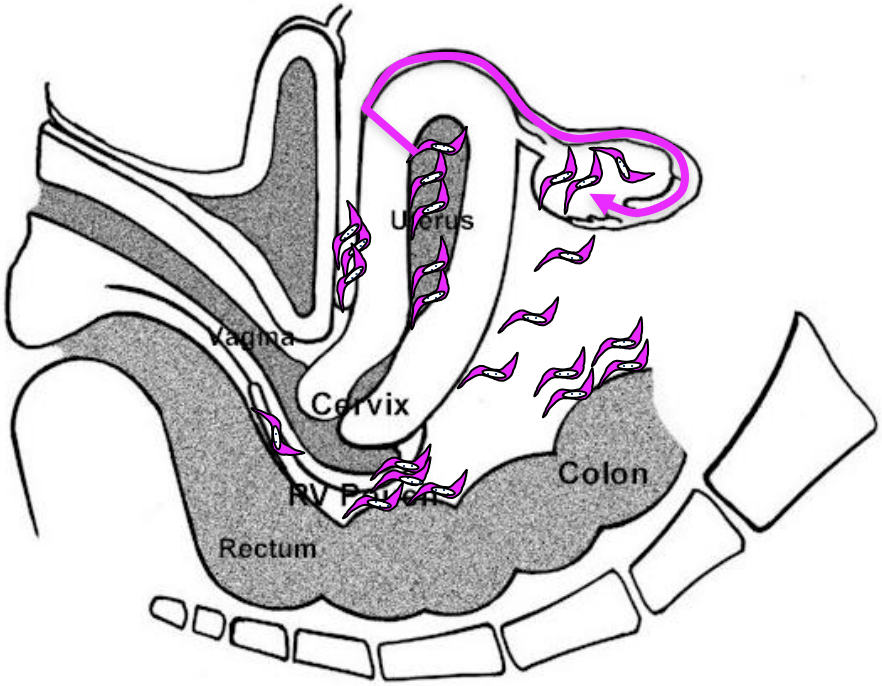
Late 20s, early 30s: first laparoscopy and diagnosis, commonly stage 1-2

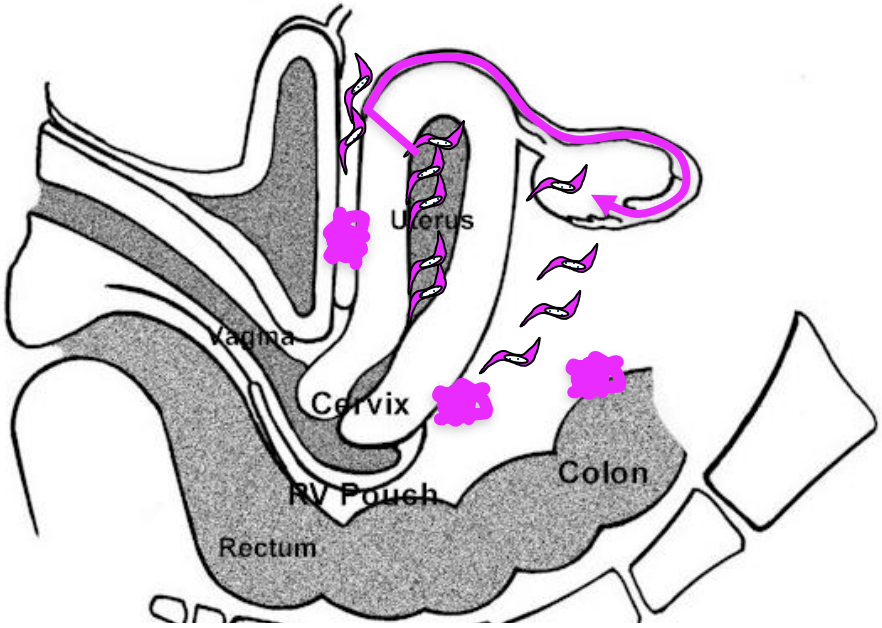
Depot GnRH agonist

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

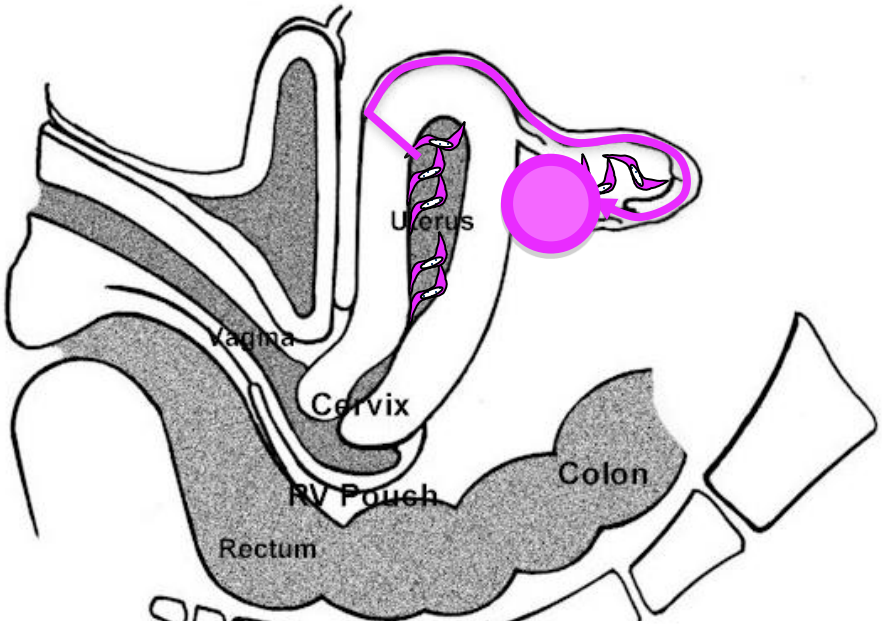
TH-BSO



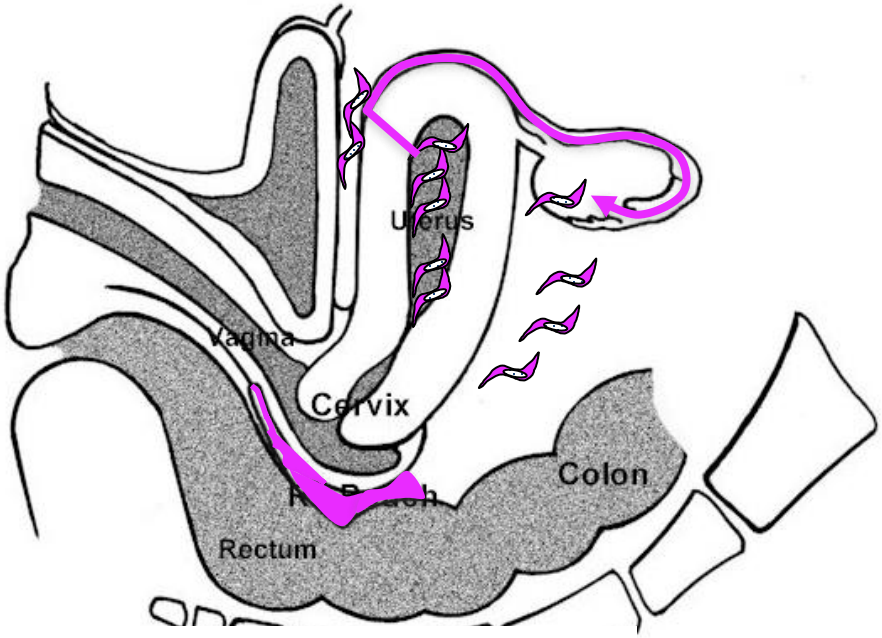




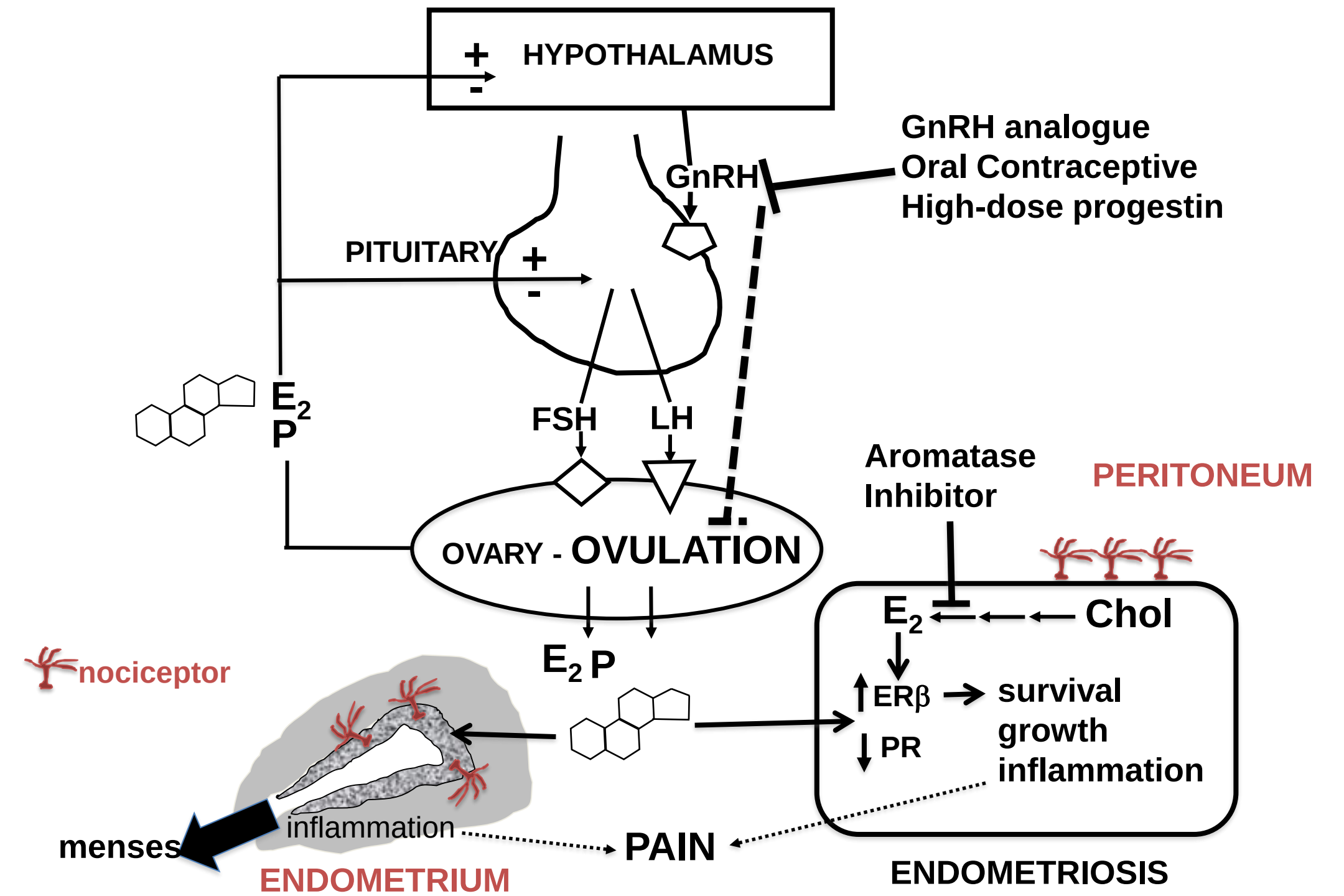
PERITONEAL ENDOMETRIOSIS



OVARIAN ENDOMETRIOMA



RECTOVAGINAL NODULE


+
HYPOTHALAMUS
-
GnRH
GnRH analogue
Oral Contraceptive
High-dose progestin
PITUITARY
+
-
E2
P
FSH
LH
Aromatase
Inhibitor
PERITONEUM
OVARY - OVULATION
E2 P
E2
Chol
nociceptor
ERβ
survival
growth
inflammation
PR
inflammation
menses
PAIN
ENDOMETRIUM
ENDOMETRIOSIS

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 ablation)

Treatment Options for Refractory Pain

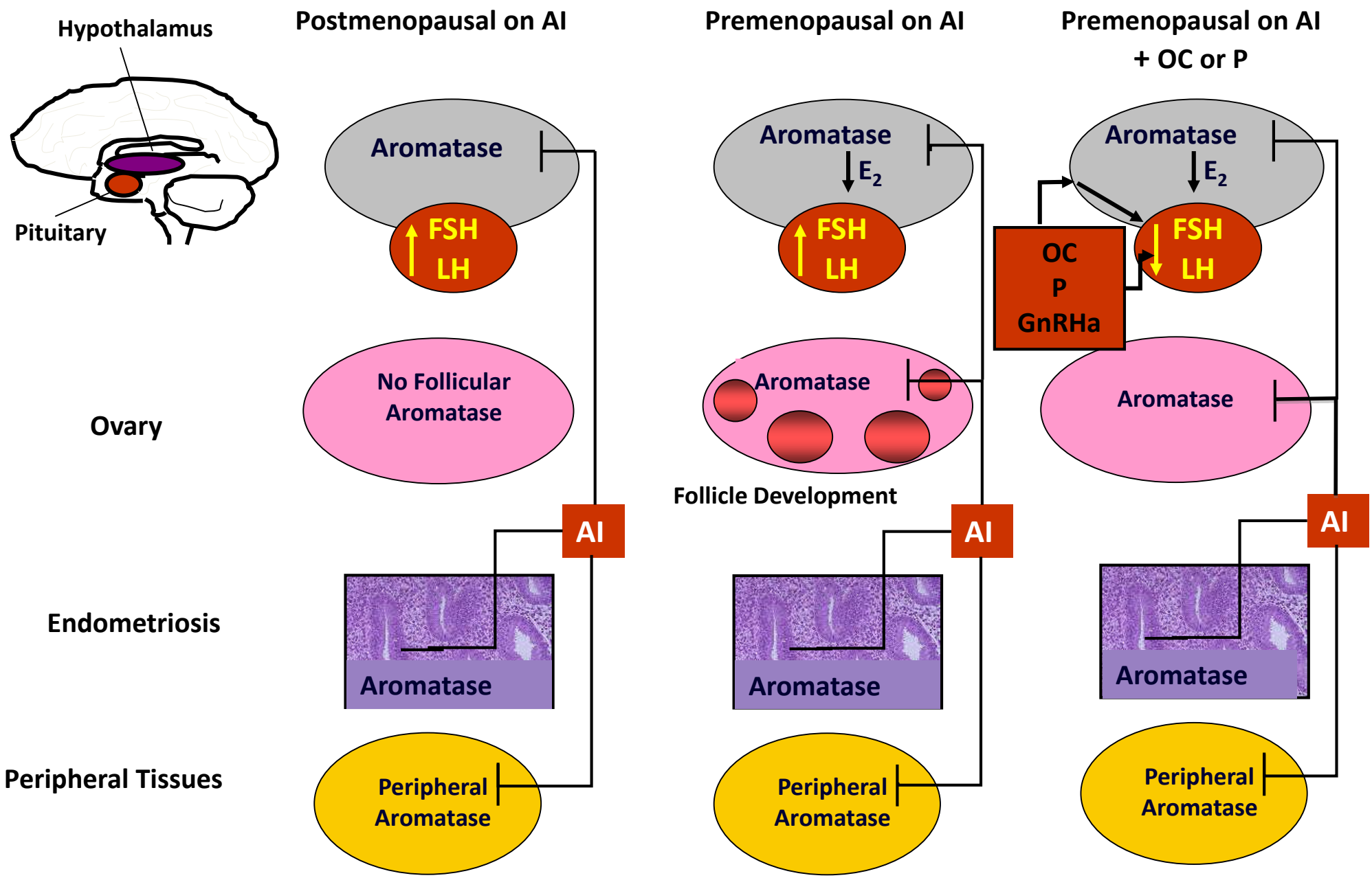
1. Medical Treatment
2. Laparoscopic resection/ablation
3. TH-BSO

Ineffective Treatments for Refractory Endometriosis

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

Experimental Treatments

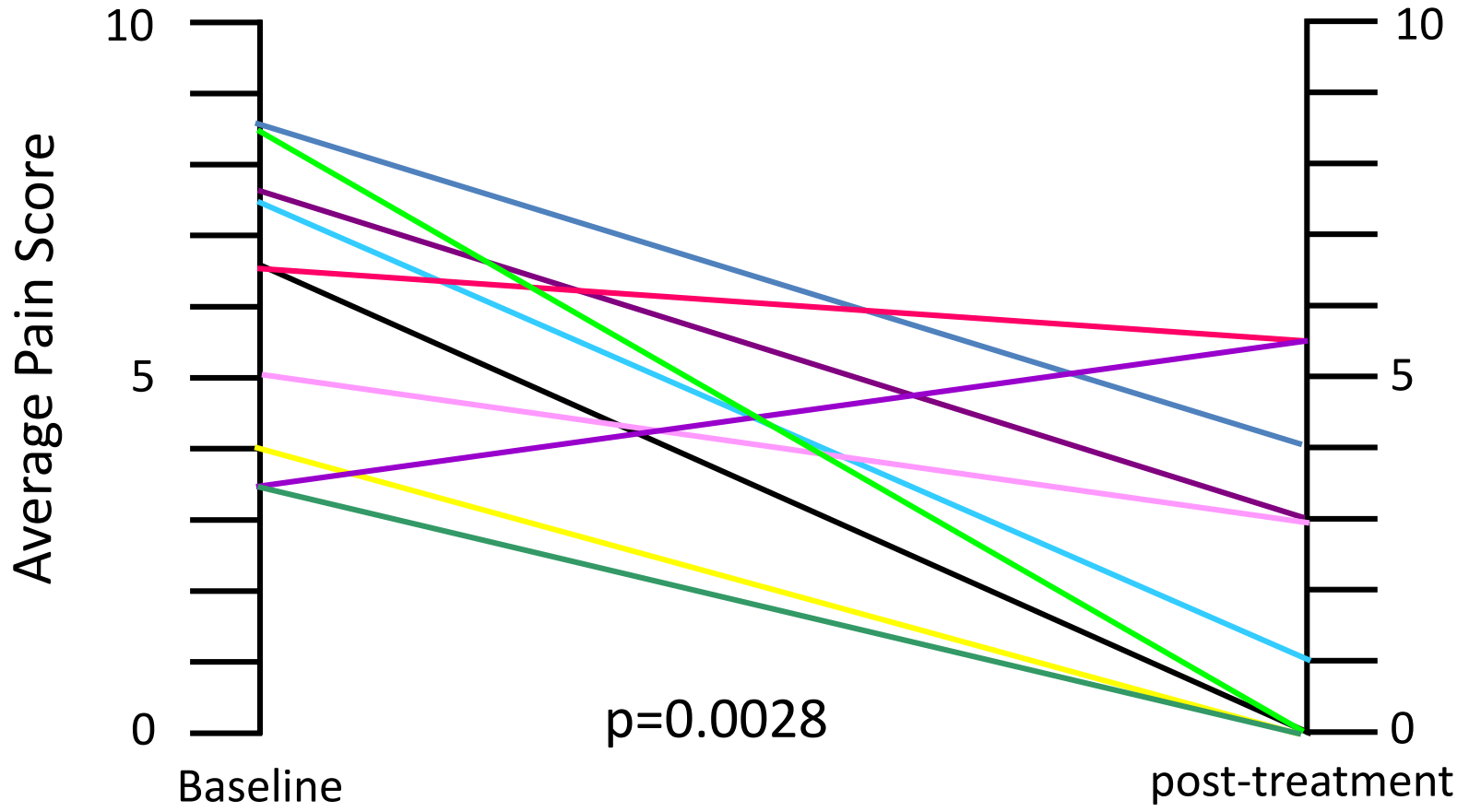
- Aromatase inhibitors (letrozole 2.5mg/d or anastrozole 1mg/d)
- AI only in post menopausal women
- AI + OC or AI + NEA in premenopausal women
- RU486 5mg/d, ulipristal acetate 5 or 10 mg/d
- Other selective progesterone receptor modulators (SPRMs) or antiprogestins
- Oral GnRH antagonists



Takayama et al, Fertil Steril, 1998; Ailawadi et al, Fertil Steril, 2004; Soysal et al, Human Reproduction, 2004; Amsterdam et al, Fertil Steril, 2005; Abushahin et al, Ferti Steril, 2011

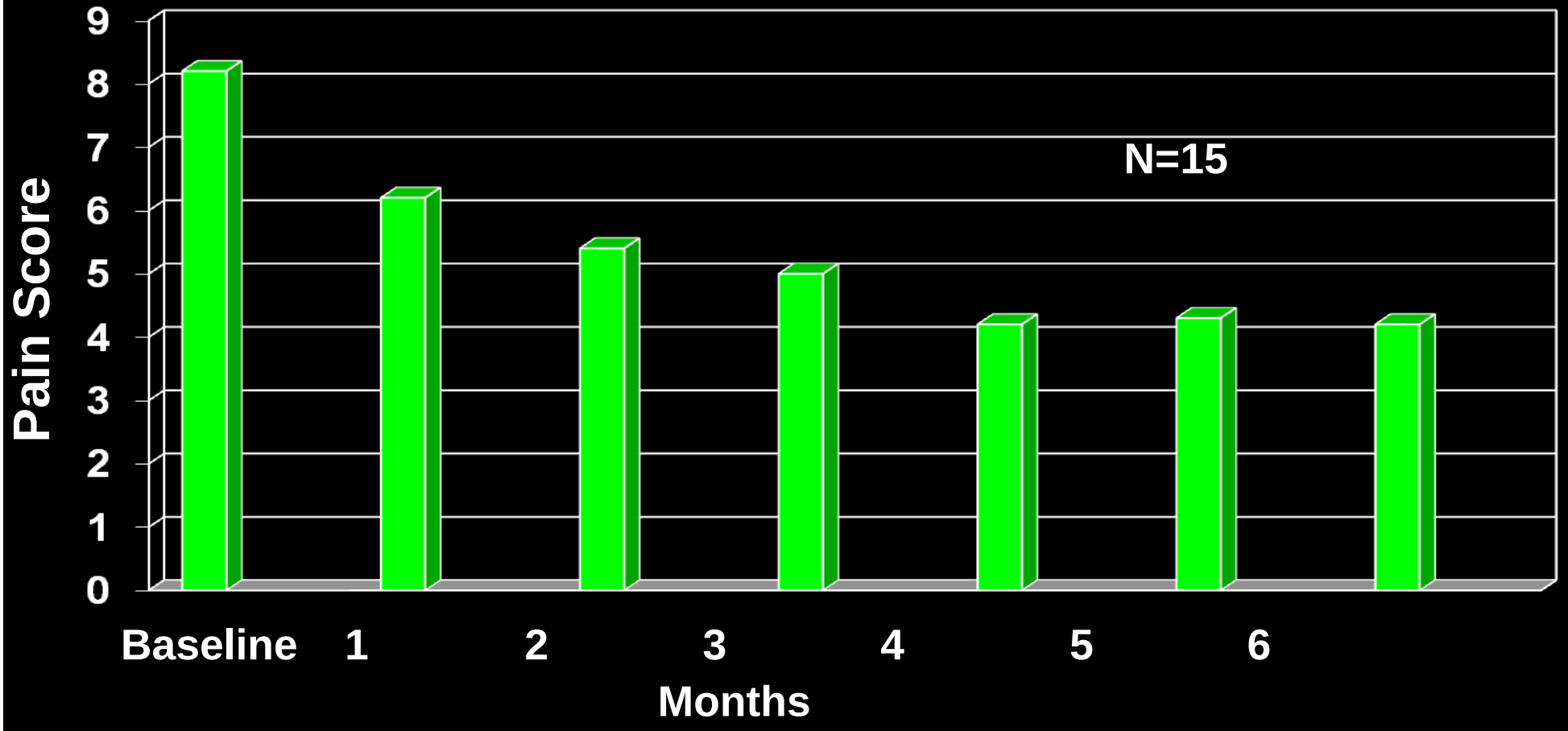
PREMENOPAUSAL WOMEN TREATED WITH LETROZOLE AND NORETHINDRONE ACETATE

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



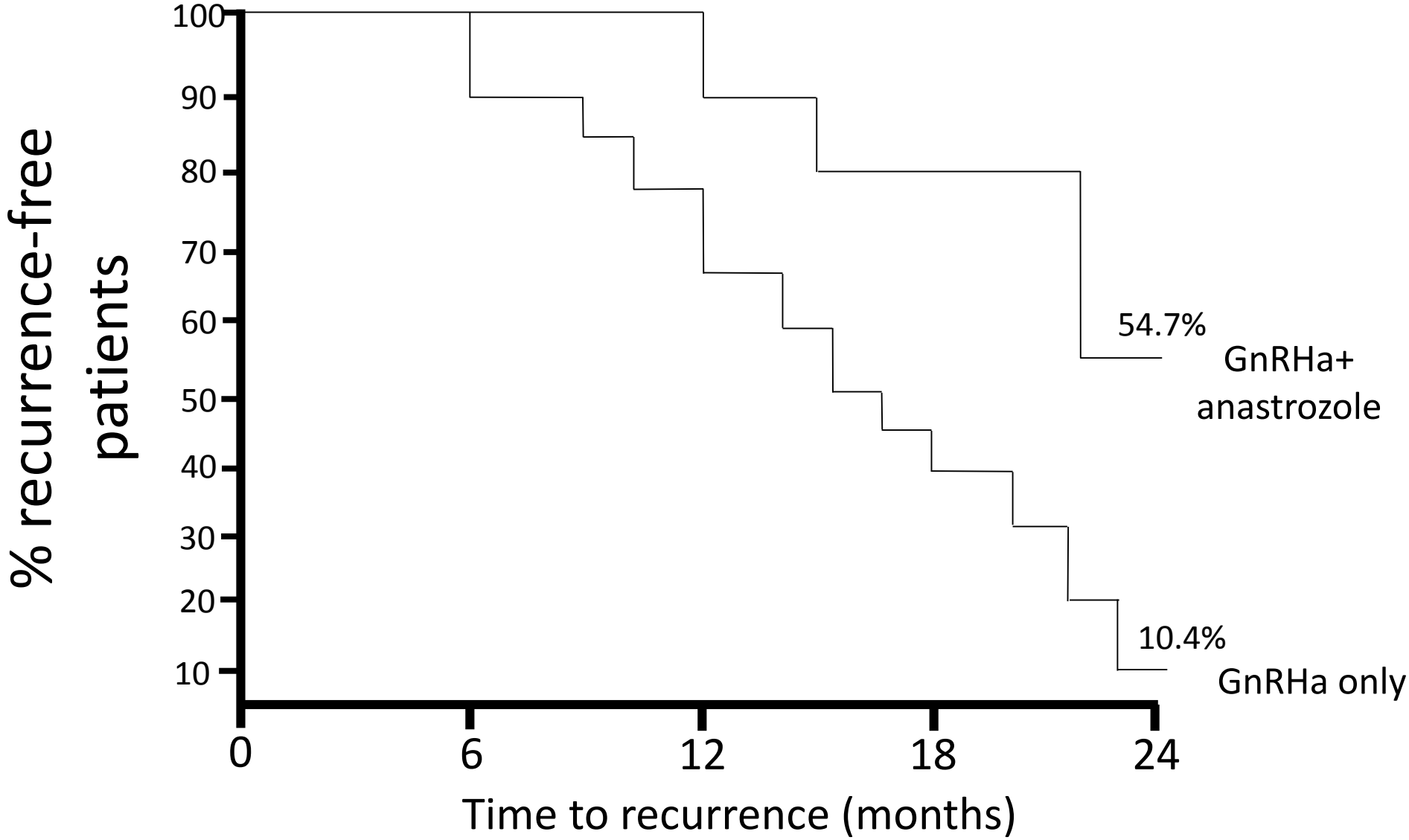
Ailawadi, et al, Fertil Steril, 2004

Anastrozole and Alesse® for Refractory Endometriosis and Chronic Pelvic Pain



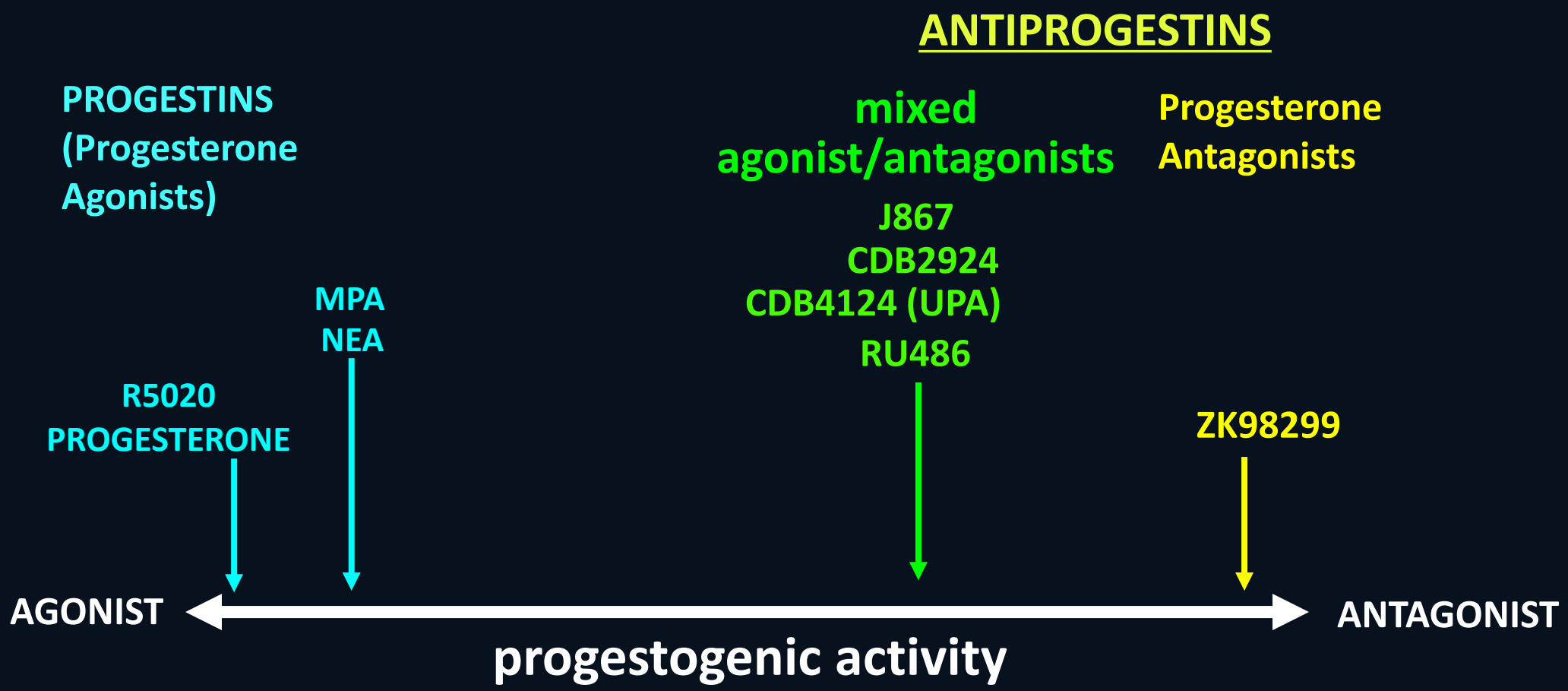
Amsterdam, LA, et. al. Fertil Steril 2005;84:300-4.

randomized trial, n=80



Soysal et al, Human Reprod, 2004

PROGESTERONE RECEPTOR MODULATORS



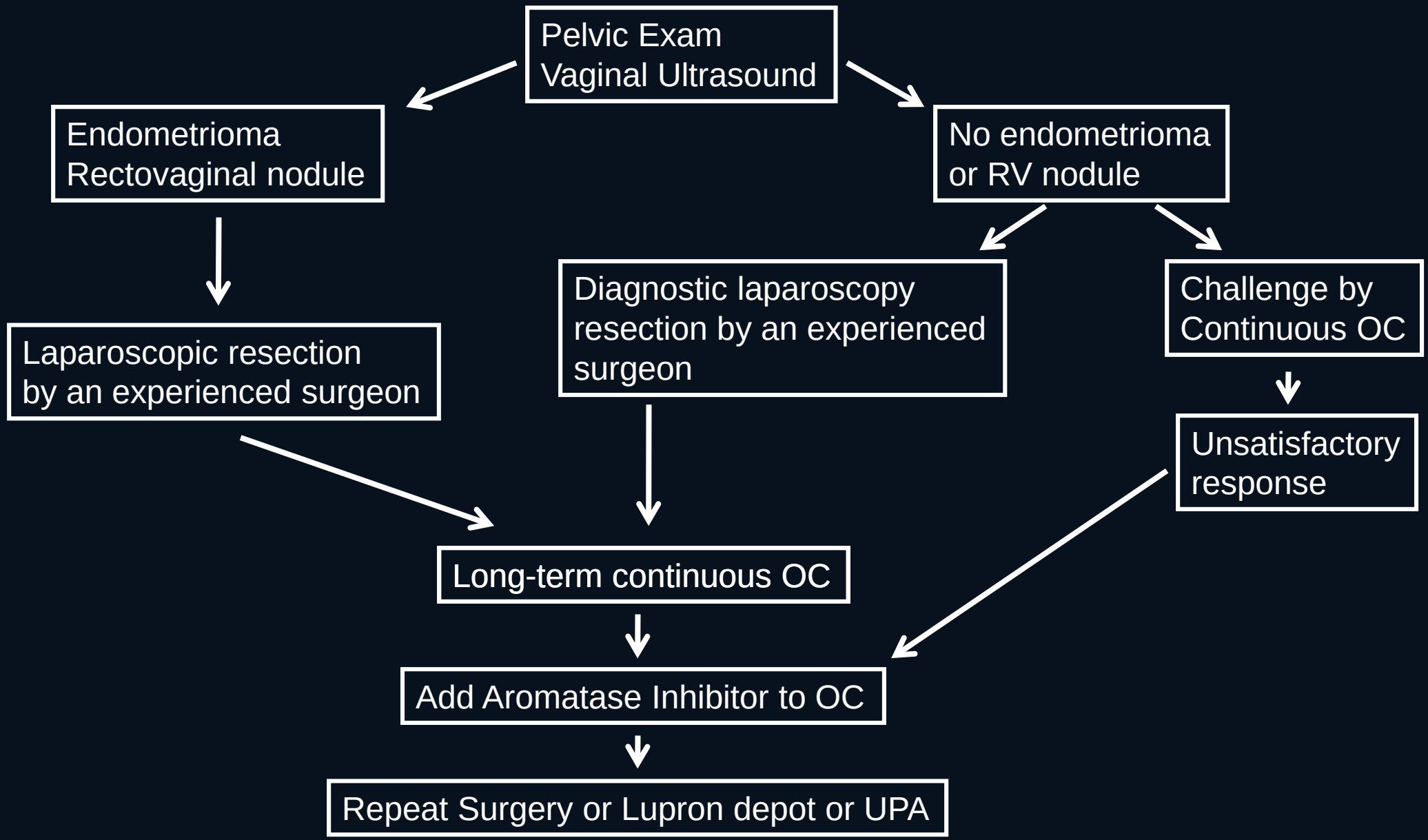
ANTIPROGESTINS

- 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

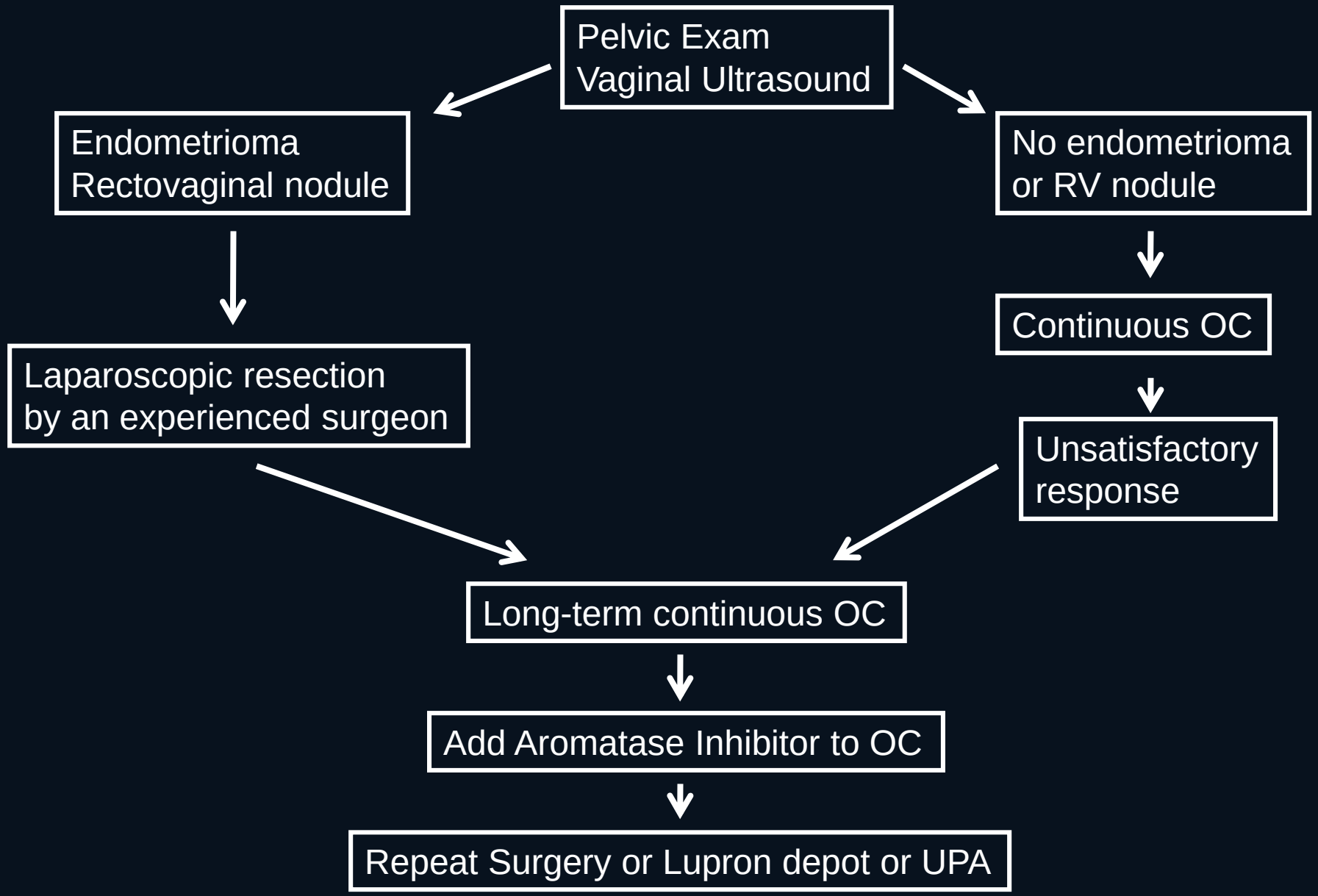
UNDIAGNOSED ENDOMETRIOSIS

(dysmenorrhea, dyspareunia, chronic pain)



ESTABLISHED ENDOMETRIOSIS

(RECURRENT SYMPTOMS)



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.

MORE SPECULATIONS

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.”

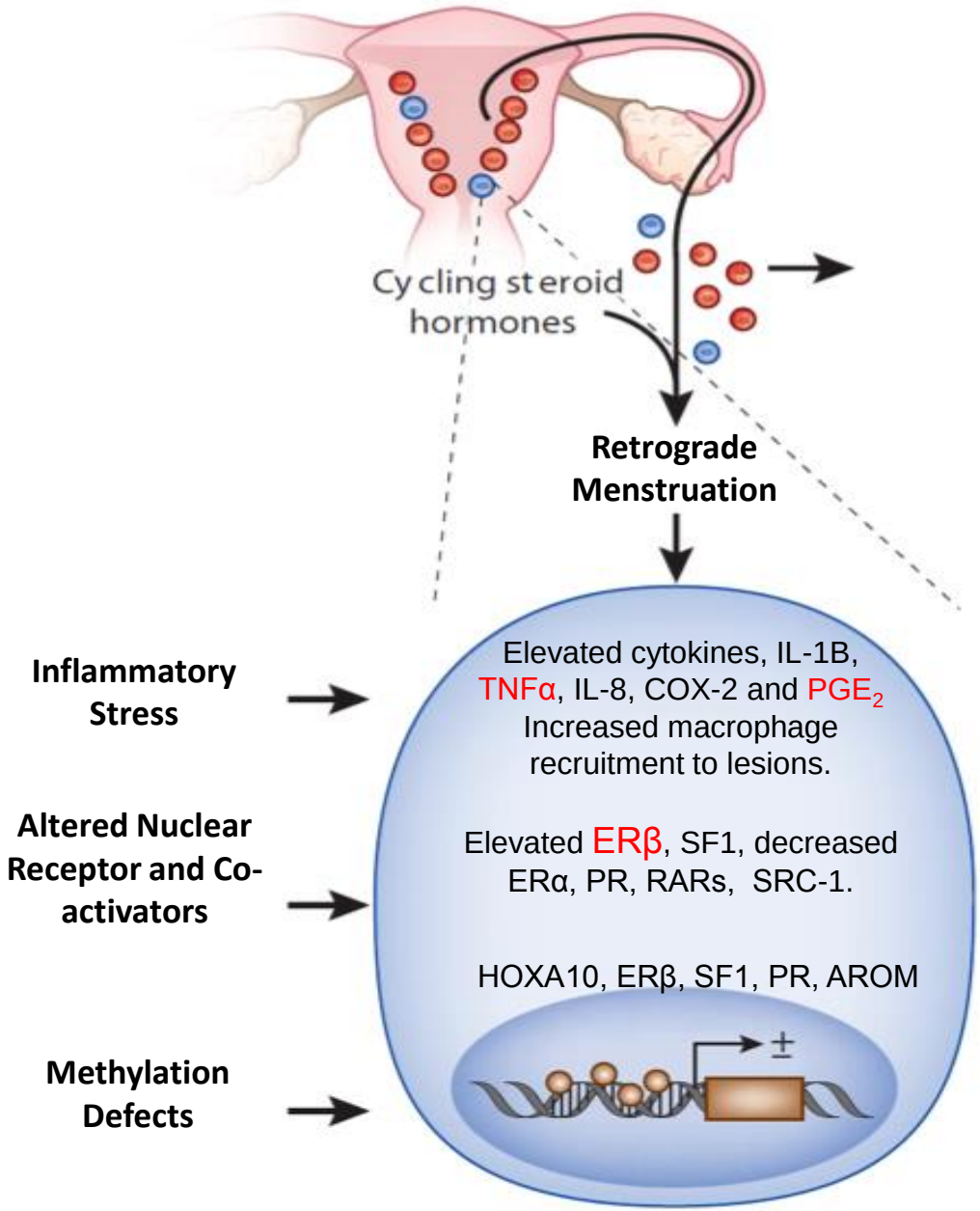
UNMET NEEDS: ENDOMETRIOSIS

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?