Endometriosis

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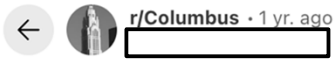
Objectives

- Epidemiology
- Pathogenesis & Pathophysiology
- Diagnosis
- Medical management
- When to refer

Medical Miracle! This Woman Convinced Her Doctor to Google 'Endometriosis'



Do you have an OBGYN who took your endometriosis seriously? Does this exist?

7 year delay in diagnosis!

The Stats

- 2009 annual economic burden of endometriosis estimated $69.4 billion (Simoens 2012)
- High healthcare costs similar to costs for management of Diabetes, Crohn's, Rheumatoid arthritis (Zondervan 2020)

The Stats

- Women with endometriosis lost 10.8 hours of work weekly (Nnoaham 2011)
- 28.5% non-work activity impairment
- Significantly lower HrQoL scores

The Stats

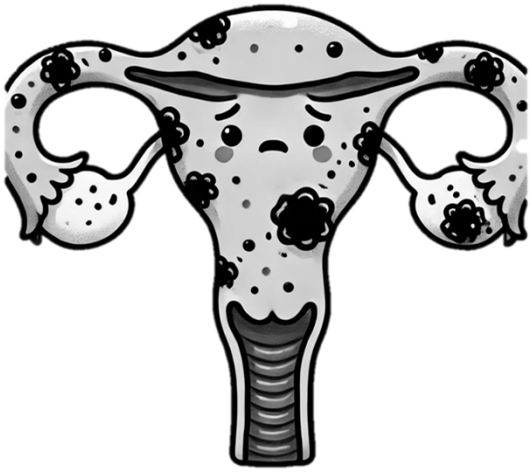
Prevalence:

- **10%** of women
- **35 - 50%** in women w/ infertility (Meuleman 2009)
- **47 - 67%** of symptomatic adolescents (Dessole 2012)
- **Up to 87%** of women with chronic pelvic pain (Alborzi 2006)

What is endometriosis?

What is endometriosis?

Endometriosis is the presence of endometrial-*like* tissue outside the uterus



Why endometrium-*like*?

Endometriosis lesions vs. endometrium have different characteristics:

- Lack 17-B hydroxylase (don't metabolize E2) (Vercillini 2014)
- Make their own aromatase (Zeitoun 1998)
- Increased expression of estrogen receptor B (Bulun 2009)
- Differential methylation → progesterone resistance (Attia 2000)
- Nerve fibers + ns IGF-1 (Zondervan 2021)

Pathogenesis & Pathophysiology

Pathogenesis & Pathophysiology

1. Where does endometriosis come from?
2. What promotes disease progression?
3. Why does it hurt?

Where does endometriosis come from?

?

Where does endometriosis come from?

1. Uterine origin
2. Tissue from outside the uterus

Uterine origin theories

Retrograde menstruation

- 90% of women have menstrual blood in the peritoneal cavity during menses (Halme 1984)

Retrograde menstruation

- Escape from immune clearance
- Attachment & invasion of peritoneal epithelium
- Development of local neurovascularity
- Continued tissue growth

Extra-uterine origin theories

Coelomic metaplasia

- Transformation of normal peritoneal tissue to ectopic endometrial tissue
- What stimulates this transformation?
- Endocrine disrupting chemicals?

Extra-uterine origin theories

Induction theory

- An endogenous stimulus promotes differentiation of peritoneal cells to endometrial cells
- Hormones? Immunologic factors?

Extra-uterine origin theories

Bone marrow

- Progenitor cells from bone marrow may differentiate into endometriotic tissue
- Histologically confirmed endometriosis in patients without menstrual endometrium or men with prostate cancer

Extra-uterine origin theories

Benign metastasis theory

- Lymphatic or hematogenous dissemination of endometrial cells
- May explain endometriosis in the brain, lung, bone, and lymph nodes

Pathogenesis

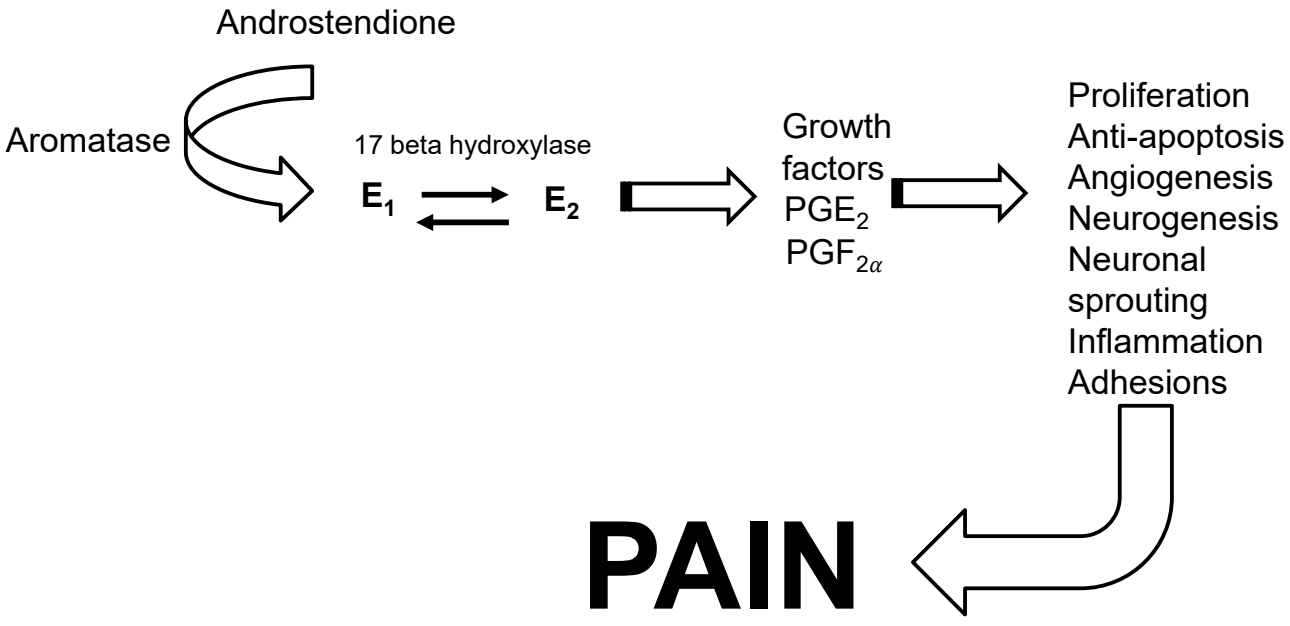
1. Where does endometriosis come from?
2. What promotes disease progression?
3. Why does it hurt?

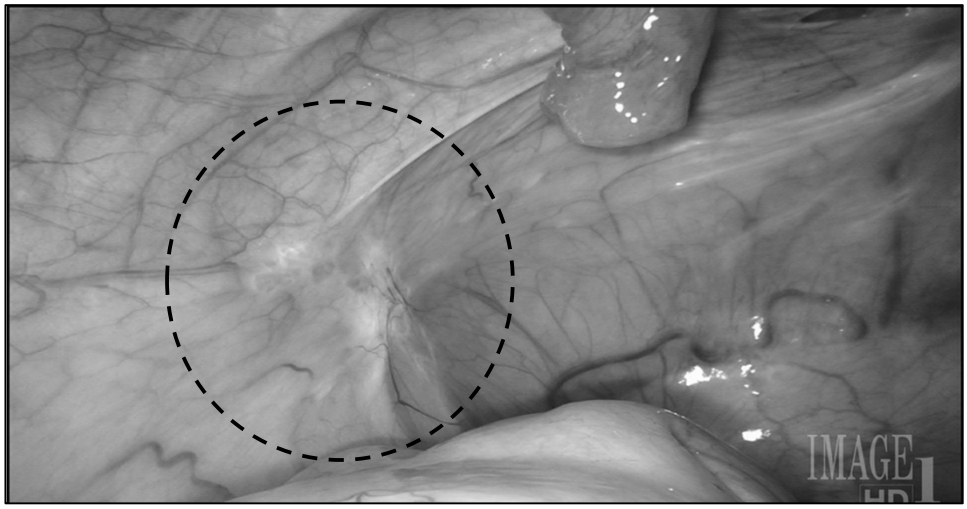
Pathogenesis

- Estrogen-dependent disorder
- Endometriotic tissue is different → marked increase in local bioavailable estradiol

Pathogenesis

1. Where does endometriosis come from?
2. What promotes disease progression?
3. Why does it hurt?

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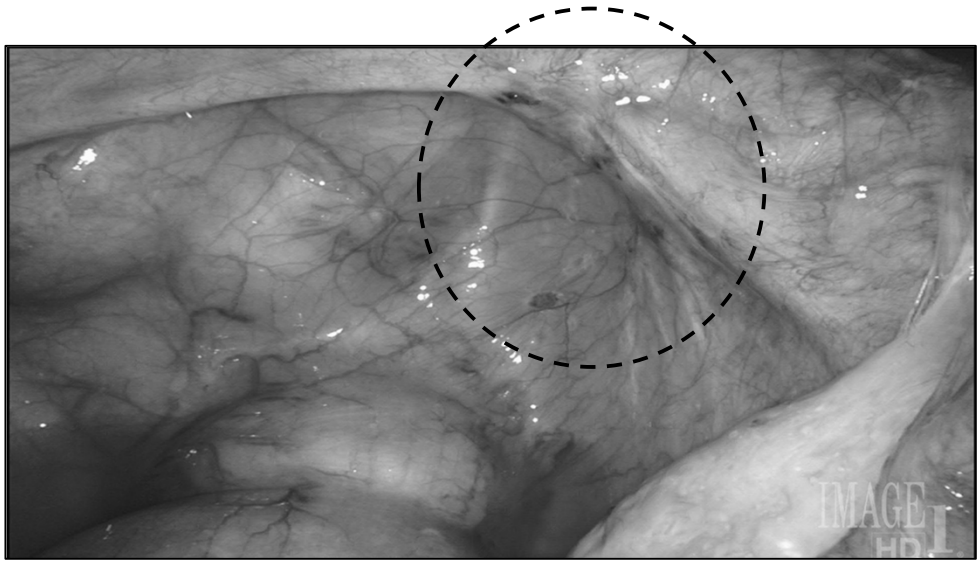
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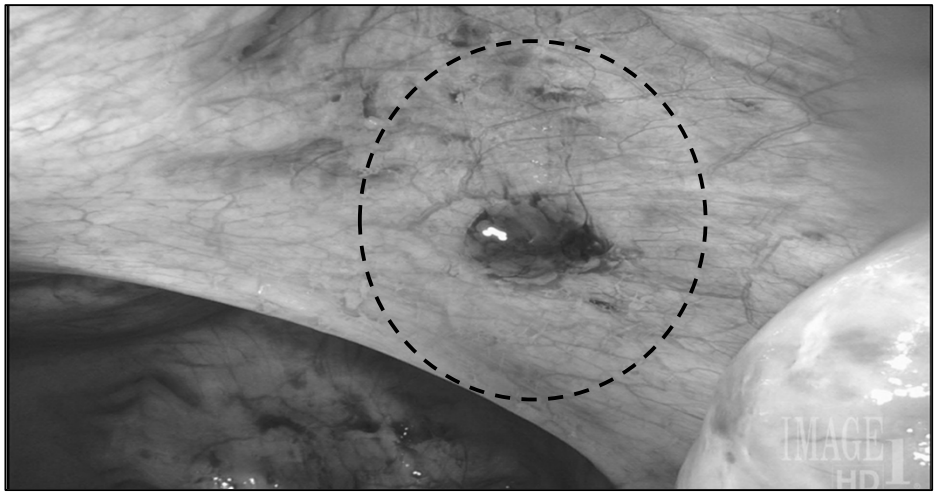
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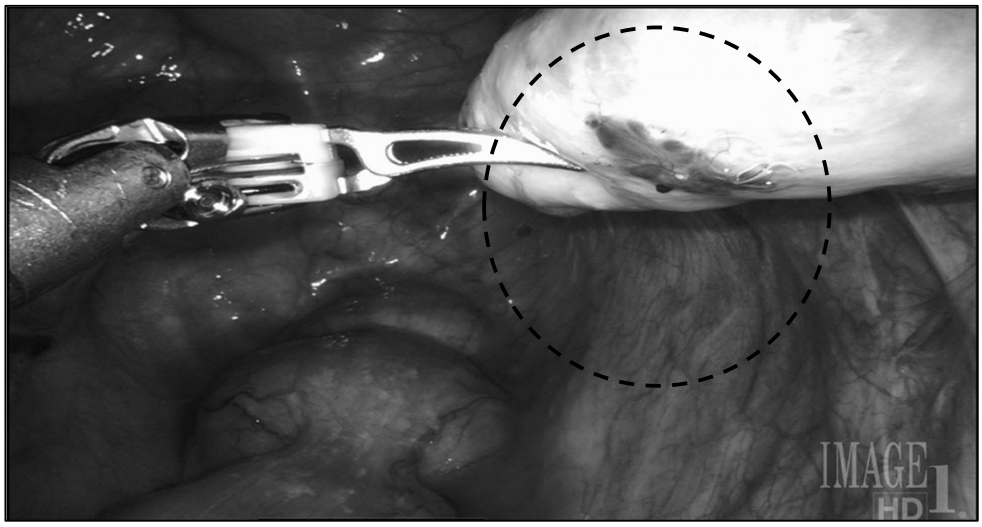
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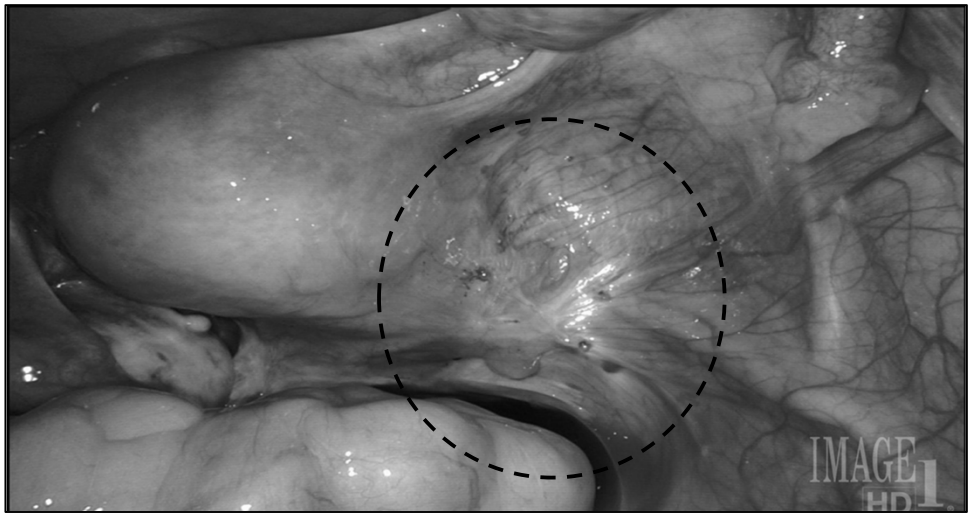
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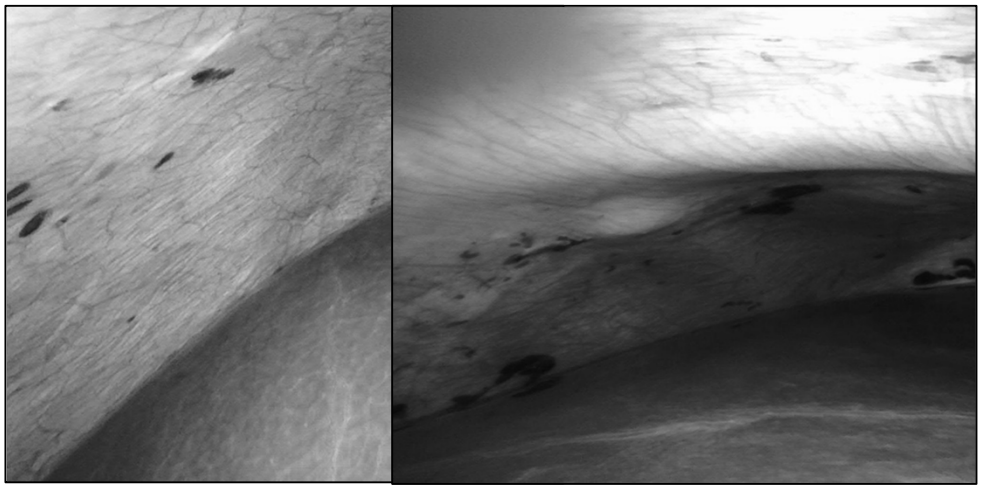

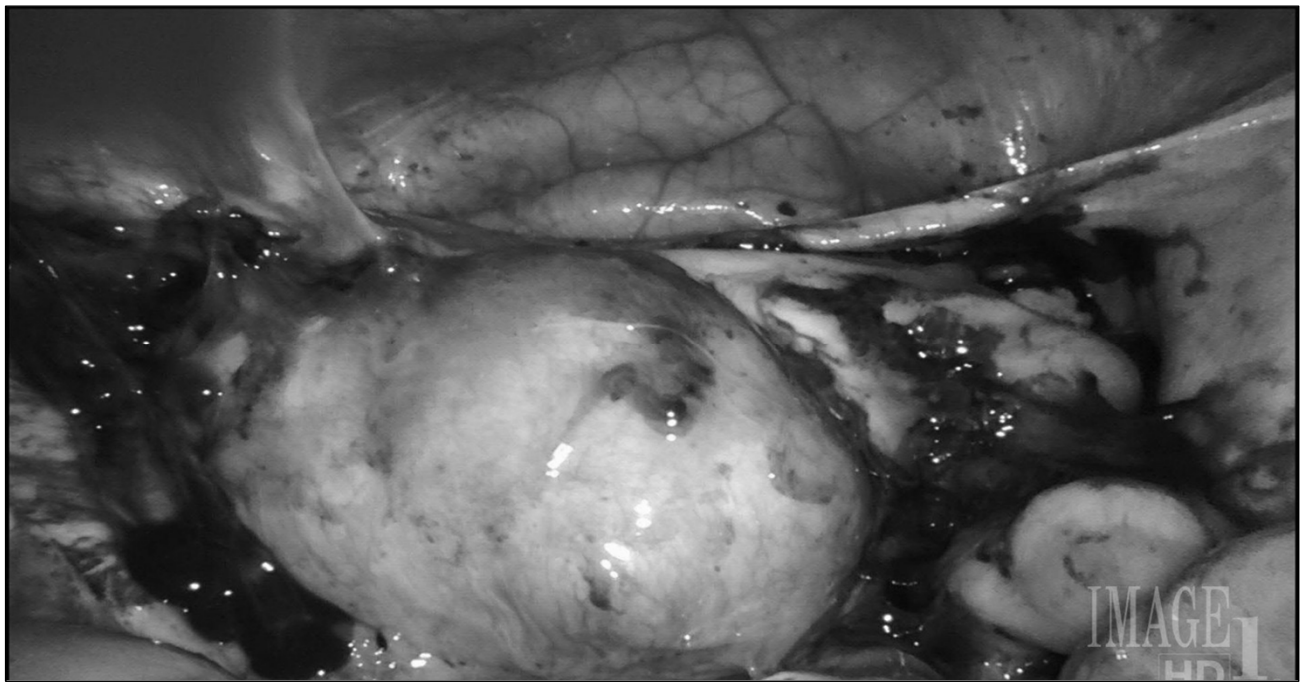
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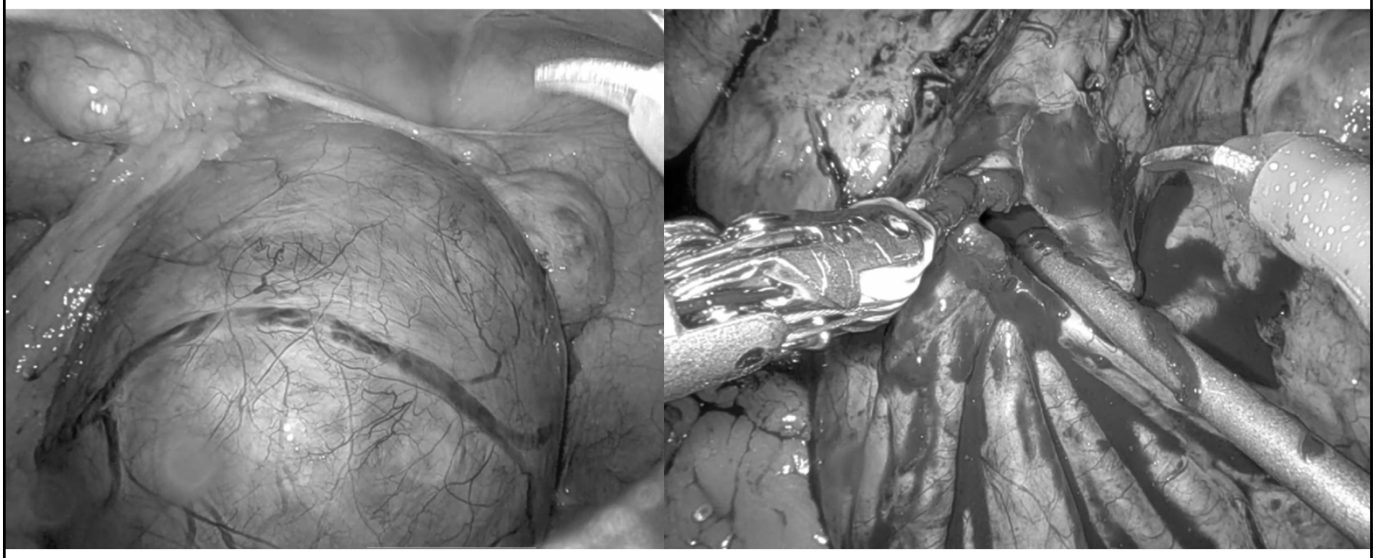


Diagnosis

Diagnosis

Requires surgery

laparoscopic lesion visualization / excision with histologic confirmation of endometrial glands or stroma, and/or hemosiderin-laden macrophages

Classic Symptoms

- **D**ysmenorrhea
- **D**yspareunia
- **D**yschezia
- **D**ysuria
- Non-menstrual pelvic pain

Additional / Associated Symptoms

- Bowel symptoms (diarrhea, cramping, constipation)
- Rectal bleeding
- Heavy menstrual bleeding
- Ovary pain
- Recurrent “UTI”
- Back pain
- Cyclic shoulder pain

Empiric diagnosis

- Likelihood of endometriosis increases with the number of symptoms present (Ballard 2008)
  - 1 symptom (OR 5.0)
  - 7 symptoms (OR 84.7)

Empiric diagnosis

- Progressively worsening dysmenorrhea
- Unresponsive to NSAIDs or hormonal therapy
- Physical exam findings
  - Uterine tenderness
  - Uterosacral nodularity

Imaging

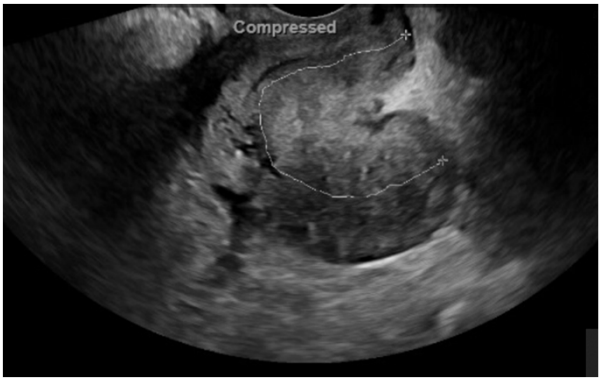
- Cannot be used to rule out endometriosis!

Imaging

- Cochrane review & ACOG committee opinion:
- TVUS first line investigation
- Not a replacement for surgery

Imaging

- Ultrasound is sensitive for detecting ovarian endometriomas and deep endometriosis – but is operator dependent
- 70% of women with symptoms and a normal ultrasound will have superficial endometriosis findings at surgery



Imaging

- MRI protocolled for deep endometriosis / endometrioma
- Sensitivity: 94%; specificity 77% (Bazot 2017)
- Cochrane review: “approached diagnostic criteria for a replacement test for deep invasive endometriosis”
- May be most helpful for diagnosis of rectosigmoid endometriosis

Biomarkers

- No minimally invasive biomarker has been established
- Currently being studied:
  - Endometrial biopsy
    - BCL2
    - IL6
  - Serum
    - CA-125 with IL-8 and TNF-α
    - VEGF, CA-125, Annexin V, and glycodelin
    - Anti-endometrial antibodies

Predicting endometriosis

- Nnoaham et al validated a model which combines symptoms, history, and ultrasound to predict endometriosis
- Not very good at predicting “any-stage” endometriosis
- *Menstrual dyschezia is strongly associated with deep endometriosis*

Treatment

Medical Management

- U.S. FDA approved options for endometriosis-associated pain:
- Progestins
  - Depot medroxyprogesterone acetate
  - Norethindrone acetate
  - Danazol
- Gonadotropin-releasing hormone (GnRH) agonists
  - Leuprolide acetate
  - Goserelin acetate
  - Nafarelin acetate
- GnRH receptor antagonists
  - Elagolix
  - Relugolix

Medical Management - COC

- First line treatment: NSAIDS + combined oral contraceptive
- Goal: suppression of follicular development and ovulation
- Standard vs. continuous use for menstrual suppression
- Side effects:
  - Increased risk of VTE, nausea, fluid retention, depression, weight gain, breast tenderness, headache, breakthrough bleeding

Medical Management - Progestins

Progestins

- Suppress follicular development and ovulation
- Decidualize eutopic and ectopic endometrial tissue
- Anti-inflammatory and anti-angiogenesis effects
- Inhibit matrix metalloproteinases

Medical Management - Progestins

- Norethindrone acetate (NETA)
  - 2.5 mg to 15 mg
- Medroxyprogesterone acetate
  - Administer every 10 – 12 weeks
- Danazol
  - Rarely used because of androgenic side effects
- Side effects similar to OCP

Medical Management – 2nd Line

- 1/3 of patients don't respond to OCP or progestins due to progesterone resistance
- Gonadotropin-releasing hormone agonist/antagonist

Medical Management – GnRH agonist

- GnRH agonists (leuprolide) → hypoestrogenic state by suppression of the hypothalamic-pituitary-ovarian (HPO) axis
- Symptoms may worsen at first
- Initially leuprolide causes stimulation of pituitary gonadotropins → increased estrogen
- With continuous administration, LH and FSH production is inhibited (negative feedback)

GnRH agonist – adverse effects

- Significant short and long-term hypoestrogenic side effects
  - Hot flashes
  - Vaginal dryness
  - Reduction in bone mineral density (up to 10%!)
  - Unfavorable lipid profile changes

GnRH agonist – adverse effects

- Can mitigate side effects with “add-back” therapy
- The only FDA approved agent for add-back therapy is norethindrone acetate (NETA)
  - NETA is partly converted to ethinyl estradiol
  - Helps estrogen deficiency effects
  - Maintains endometrial decidualization

GnRH agonist – comparison

- GnRH agonists have not been shown to be superior to other hormonal treatments for endometriosis pain
- Double-blind RCT: GnRH agonist with add-back vs. continuous combined OC found
  - Both strategies significantly reduced nonmenstrual pain and dyspareunia
  - *No significant difference between groups*

GnRH agonist – how to prescribe

How to prescribe:

- 1, 3, 6 mo injection
- Medication usually clinic administered
- Plan for 6 mo – 1 year
- Decide add-back plan
- DEXA scan at 1 year mark

Medical Management – GnRH antagonist

- Elagolix (Orilissa) is an oral, nonpeptide GnRH antagonist that suppresses ovarian function in a dose-dependent manner
- Binds GnRH receptors in the anterior pituitary without inducing activation
- Half life is 6 hours
- Does not provoke initial gonadotropin release – no flare

GnRH antagonists – the data

- Elaris Endometriosis I and II trials
- Multicenter, double-blind, randomized, placebo-controlled, phase 3 trials
- Participants: Premenopausal women 18 - 49 years w/ a surgical diagnosis of endometriosis & moderate/severe pain
- 6-month treatment
- Two dosing regimens (150mg daily and 200mg twice daily)
- 150 sites in the US and Canada
- Outcomes: dysmenorrhea, non-menstrual pelvic pain

GnRH antagonists – the data

	EM-I (clinical response %)			EM-II (clinical response %)		
	150mg dose	400mg dose	Placebo	150mg dose	400mg dose	Placebo
Dysmenorrhea	46.4%	75.8%	19.6%	43.4%	72.4%	22.7%
Nonmenstrual pelvic pain	50.4%	54.5%	36.5%	49.8%	57.8%	36.5%

GnRH antagonists – expectations

- Continued menses
- Amenorrhea
  - Low dose 14 – 28%
  - High dose 47 – 66%
- Does not suppress ovulation
- Should use contraception!

GnRH antagonists – adverse effects

- Most common: hot flushes, headaches, nausea
- Short and long-term hypoestrogenic side effects
- Bone mineral density changes (with add-back)
- Elaris EM-I 6 month BMD decrease > 5% at lumbar spine:
  - Low dose 3.8%
  - High dose 20.9%
- BMD recovery at 12 months – “most” (53.3%–59.1%) partially or fully recovered (Simon 2024)

GnRH antagonists – adverse effects

- Lipid changes in first 1-2 months and remain stable
- Total cholesterol, LDL, HDL, and triglycerides increase
- Return to baseline lipid profile within 1 month after treatment discontinued

GnRH antagonists – contraindications

- Pregnancy
- Known osteoporosis
- Severe hepatic impairment or limited treatment with moderate hepatic impairment
- No concomitant use of organic anion-transporting polypeptide 1B1 inhibitors (*e.g.*, cyclosporine and gemfibrozil)
- Concomitant use with rifampin
- Clinical monitoring recommended when coadministered with digoxin

GnRH antagonists – comparisons

- Elagolix noninferior to DPMA for reduction in dysmenorrhea and non-menstrual pelvic pain (Carr 2014)

GnRH antagonists – summary

- No proven benefit compared to other hormonal management
- Suboptimal safety/efficacy/tolerability/cost profile
- Discontinuation rate 25%
- Pain relief comes at the price of hypoestrogenic symptoms and BMD reduction
- Expensive ($850/mo)

GnRH antagonists – why prescribe?

- If patient not improved/satisfied with CHC or other hormonal treatment
- Wants to avoid surgical intervention

GnRH antagonists – how to prescribe

- Counseling: add back therapy
- Add-back options
  - *Estradiol 1mg + norethindrone 0.5mg daily*
  - Estradiol 0.5 mg + norethindrone acetate 0.1 mg daily
  - Estradiol 1 mg + cyclic progestogen 200 mg
- A phase 3 clinical trial assessing efficacy/safety of elagolix with COC is currently ongoing
- Consider a LNG-IUS

GnRH antagonists – monitor

- Anticipate decrease in pain within 4 weeks
- Follow up within 3 months
- Continue up to 24 months (150 mg once daily dose)
- Continue up to 6 months (200 mg twice daily dose)
- Can consider step-down from elagolix 200 mg twice daily to elagolix 150 mg once daily (no data)

Other GnRH antagonists

- Relugolix + 1 mg estradiol and 0.5 mg of norethindrone (Myfembree)

Surgical management

Surgical management

- 2020 Cochrane review
- *"Compared to diagnostic laparoscopy, it is uncertain whether laparoscopic treatment reduces overall pain associated with minimal to severe endometriosis."*

Surgical management

- Surgery may not improve symptoms
- May lead to adhesive disease
- May contribute to central sensitization
- Risks may outweigh benefits regarding excision surgery

Surgical management

Approach to surgical intervention throughout reproductive lifespan

- #1 surgery for diagnosis and initial treatment
- #2 if necessary in sub/infertility scenario
- #3 if recurrent endometrioma
- #4 if hysterectomy is desired

Myths

Myth: Pregnancy helps

- Beecham (1949) declared pregnancy as a prophylactic and curative measure
- Interruption of the menstrual cycles could be mechanism for beneficial effect of pregnancy?
- Recommendation for pregnancy even in 2016

Myth: Pregnancy helps

- Leener et al 2018 Literature review:
- *"There is **no evidence** that pregnancy can be expected to generally reduce the size and number of endometriotic lesions"*

Myth: Hysterectomy = cure

- Hysterectomy **may be** a reasonable option for the treatment of chronic pelvic pain.
- "It can not be determined whether [improvement in pain] is due to intermingling of patients with and without cyclic pain" (Martin 2006)

Clinical Paradigm

Clinical paradigm

- Approach endometriosis as a chronic, inflammatory, systemic disease
- Plan for hormonal suppression until pregnancy desired
- Refer to OBGYN if minimal improvement
- Multidisciplinary management
- Minimize number of surgeries in lifetime

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