LET'S TALK PCOS AND ENDOMETRIOSIS

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PCOS

HISTORY

- Originally described in 1935 by Stein and Leventhal
- Hippocrates discussed this in 5th century BCE
- Addition of ultrasound criteria in the '80s/'90s
- 2003: Rotterdam Consensus Conference
- 2018: International Evidence-based Guidelines for the Assessment and Management of Polycystic Ovarian Syndrome
- The 2023 International Evidence-based Guidelines for the Assessment and Management of PCOS supports the use of the Rotterdam criteria

PREVALENCE

- One of the most common endocrine/metabolic disorders of females
- Prevalence
  - NIH 6%
  - Rotterdam criteria 10%
  - AE-PCOS 10%

PATHOGENESIS

- Genetics
  - Observation that the same genes influence PCOS risk in a number of different ethnic groups
  - Most genes are related to the control of hormone production and action, insulin resistance, and organ growth
- Heritability ~ 70%
- Complex genetic trait
- Development likely influenced at least in part by environmental factors but more significantly by a number of genetic variants

OBESITY AND PCOS

It is still unclear whether obesity is causative

Current data suggests that obesity is not as frequent in PCOS as previously thought

Newer data suggests that while females with PCOS may appear to be more obese than their peers, much of this increased prevalence may be the result of referral bias

Possible that PCOS is associated with a greater propensity for weight gain (vs being causative)

- Genes relating to weight and energy regulation being studied

Despite wide variation in the prevalence of obesity and type of diet, the prevalence of PCOS appears to be relatively uniform across the globe

CLINICAL MANIFESTATIONS: REPRODUCTION

- **Menstrual dysfunction**
  - Oligo- or amenorrhea caused by infrequent or absent ovulation
  - Endometrial cancer risk (~1.3 per 10,000 women per year <50 yrs old)
    - Associated with low progesterone in conjunction with anovulation, hyperinsulinemia, increased serum IGF-1, hyperandrogenemia, and obesity
- **Ovarian abnormalities**
  - String of pearls
  - Multiple small follicles (abnormal follicle development and function)
    - >12 in each ovary measuring 2-9mm in diameter and/or increased volume (>10 mL consistent with PCOS)
  - Serum AMH
- **Anovulatory infertility**
- **Pregnancy complications**
  - Spont ab rate 20-40% higher than general OB population
    - Mechanism poorly understood
  - Higher risk of GDM, HTN, preeclampsia, premature delivery and C section
  - Possible role of inflammation – elevated CRP

CLINICAL MANIFESTATIONS:
HYPERANDROGENISM

Clinical

Hirsutism

Acne

Biochemical

Total testosterone

DHEAS

CLINICAL MANIFESTATIONS:
METABOLIC ISSUES

Obesity and insulin resistance

~50% of those with PCOS have obesity (40-85%)

Most are also hyperinsulinemic and insulin resistant (in both lean (30%) and obese (70%) women, independent of obesity

Increased prevalence of metabolic syndrome (roughly twofold higher)

DM2

Both due to impairment in insulin secretion as well as insulin resistance

Sleep apnea

Dyslipidemia

Generally low HDL and high triglycerides

CLINICAL MANIFESTATIONS:
CORONARY HEART DISEASE

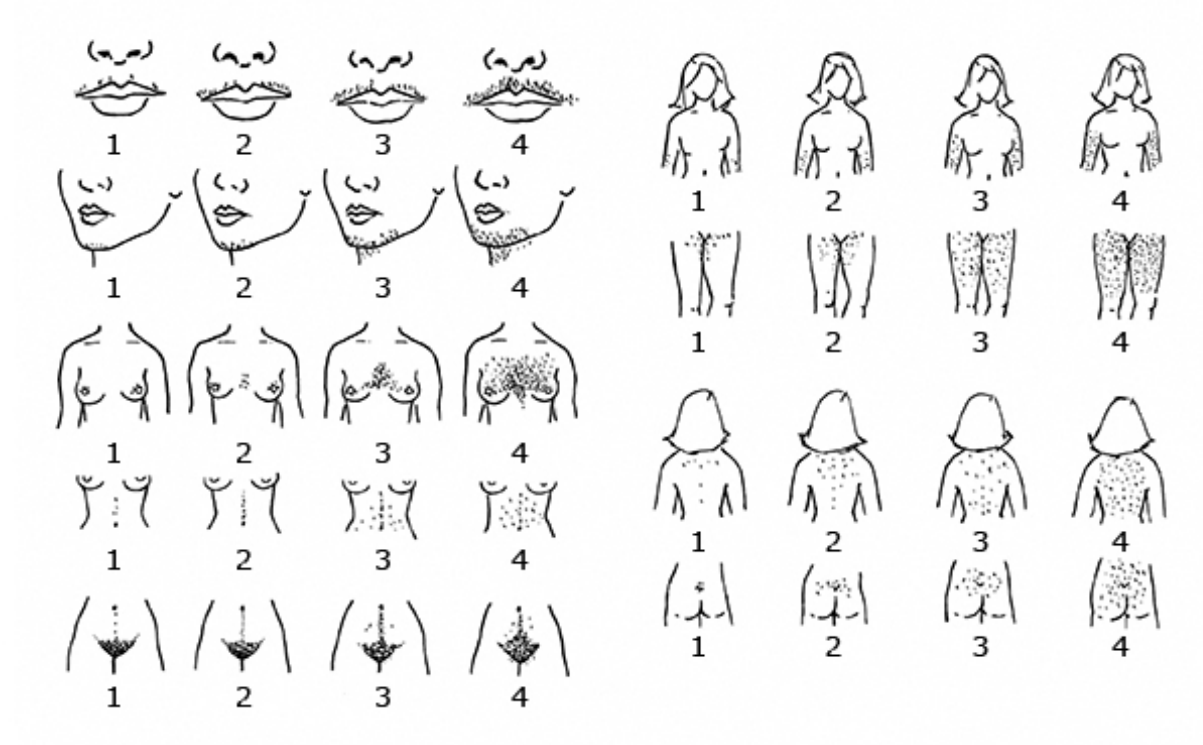
Concerns that those with PCOS are at increased risk for CHD, but risks are not well established

Recommend that all CV risk factors be considered for eval and tx

DIAGNOSIS

- Most women describe a poor diagnosis experience, nearly 50% saw >=3 HCPs prior to dx, and for 1/3 it took >2 yrs to receive a dx.
  - Long delays
  - Inadequate health information (16% satisfaction with educational information given)
  - Body shaming
- Suspect in anyone presenting with irregular menses and/or hyperandrogenism
- Those with PCOS on u/s and no other clinical features of PCOS do not have PCOS and do not require further evaluation

Grading of severity of hirsutism in patients



Ferriman-Gallwey hirsutism scoring system. Each of the 9 body areas that is most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. "Focal" hirsutism (score 1 to 7) is a common normal variant, whereas generalized hirsutism (score of 8 or more) is abnormal in the general United States population. The normal score is lower in East Asian and American Asian populations and higher in Mediterranean populations.

LABS

- **Oligomenorrhea**
  - Hcg
  - PRL
  - TSH
  - FSH (elevated LH:FSH is not a criterion for dx)
- **Hyperandrogenism**
  - Total testosterone (free T not suggested – currently unreliable assays)
  - DHEAS if severe
  - DHEAS
    - Not routinely suggested
  - Serum 17-hydroxyprogesterone
    - Suggested in all those with possible PCOS to r/o NCCAH
    - Early follicular phase if cycling
  - AMH
    - Generally upper range nml or markedly elevated

CLINICAL MANIFESTATIONS: **PSYCHOSOCIAL ISSUES**

Recommendation to screen for dep/anx at time of PCOS dx

Also at risk for:

Disordered eating	**Sleep disorders** • Hypersomnia • OSA	**Sexual dysfunction** • Lower sexual satisfaction • But no difference in Total Female Sexual Function Index

TRANSVAGINAL ULTRASOUND (TVUS)

Not always necessary

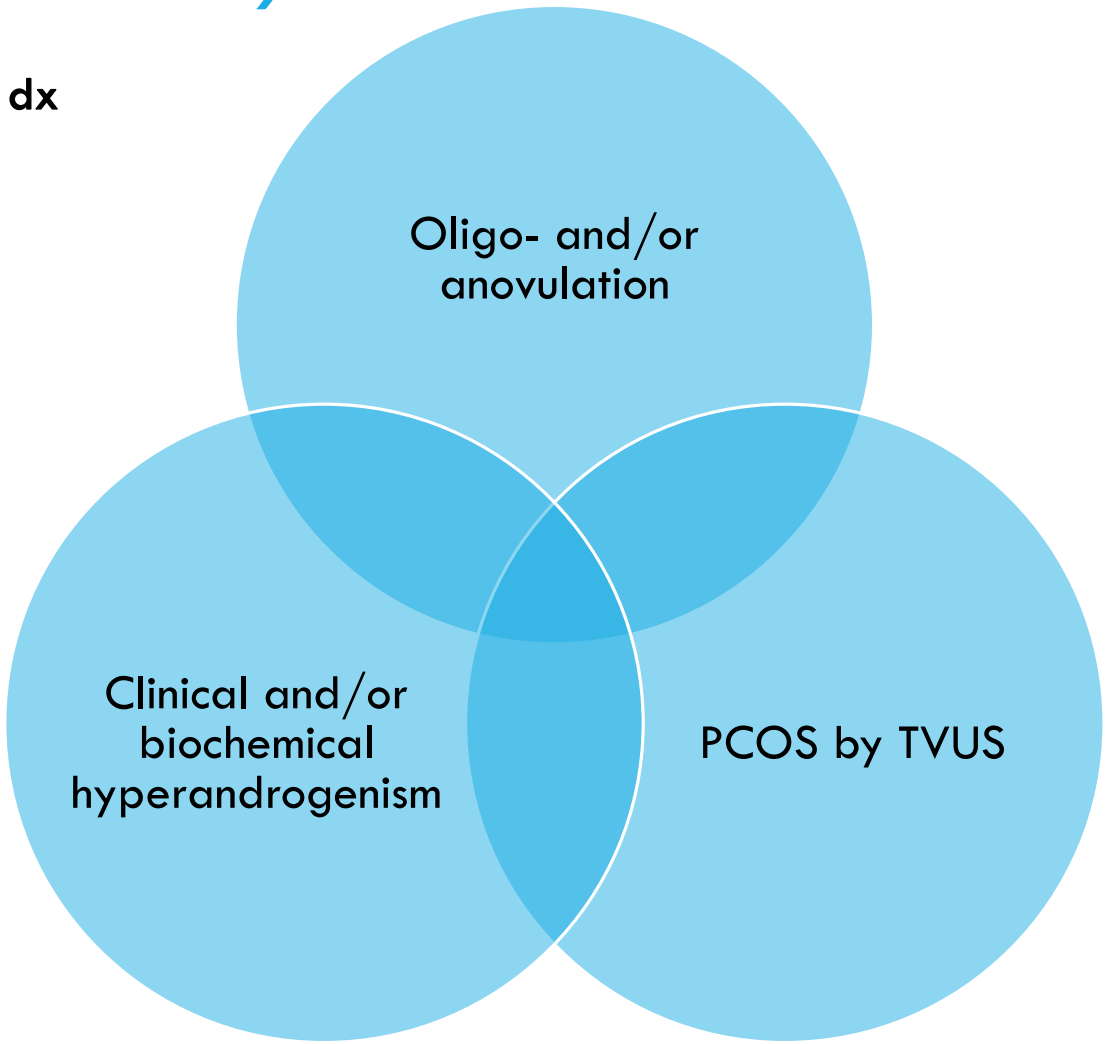
Not recommended for adolescents

Criteria evolving

- Follicle number and size are important
- Ovarian cysts are not relevant!
- 2003 Rotterdam ultrasound criteria
  - >=12 follicles in either ovary measuring 2-9mm in diameter and/or increased ovarian volume (>10mL)
- A 2014 systematic review proposed higher threshold (<=25 follicles per ovary)
  - Technology is not easily accessible to all clinicians (transducer frequency >=8MHz)
- 2018, an international evidence-based medicine group recommended a threshold of >20 follicles/ovary
- Age based criteria have also been proposed

ROTTERDAM CRITERIA (PREFERRED)

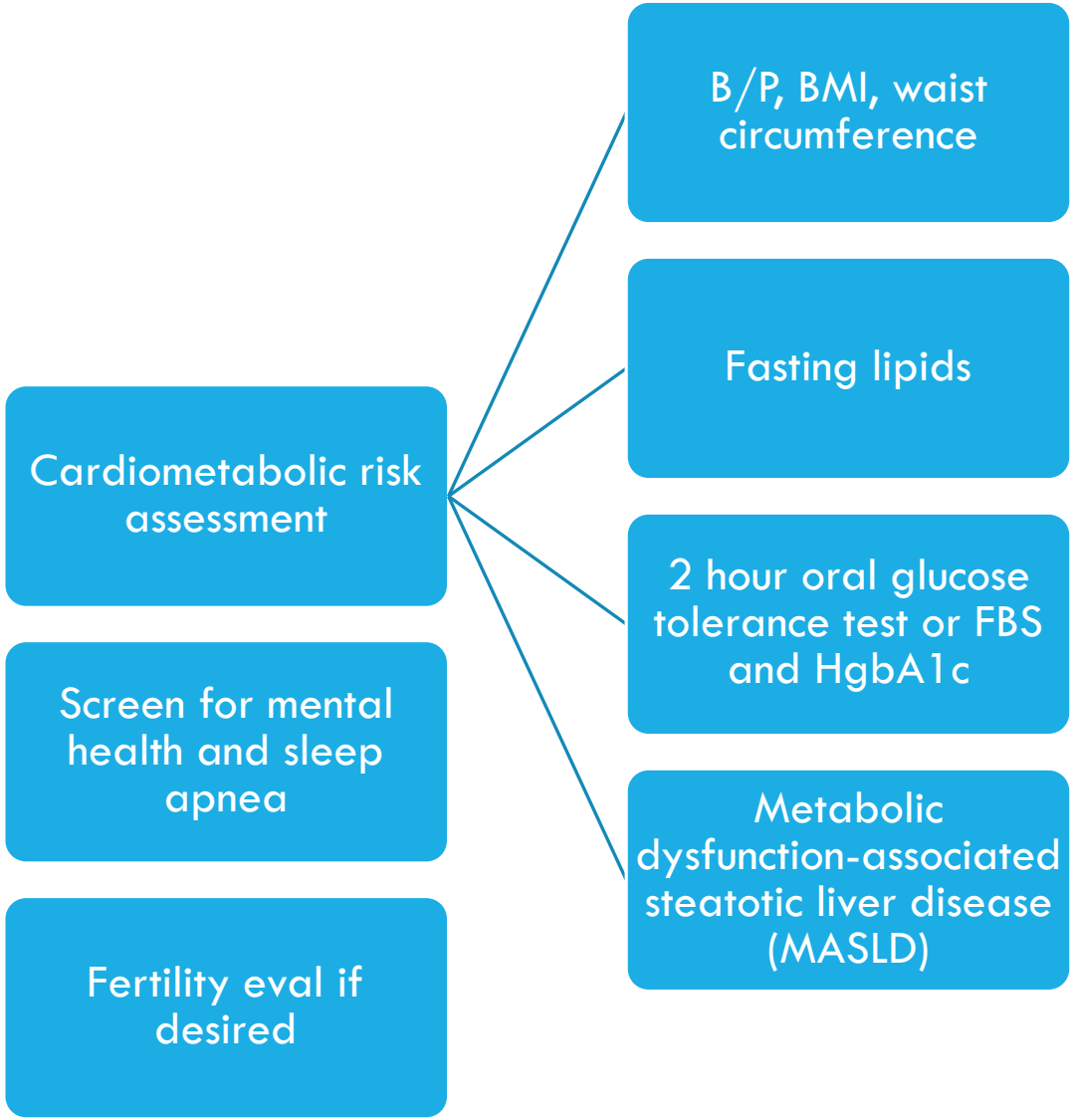
- **Any 2:3 required for dx**



Phenotype A (classic PCOS)	**Rotterdam criteria, 2003[1]**	**AES criteria, 2006[2]**	**NIH criteria, 1992[3]**	**Classic PCOS[4]**
Clinical and/or biochemical evidence of hyperandrogenism				
Evidence of oligo-anovulation				
Ultrasonographic evidence of a polycystic ovary				
Phenotype B (hyperandrogenic anovulation)				
Clinical and/or biochemical evidence of hyperandrogenism				
Evidence of oligo-anovulation				
Phenotype C (ovulatory PCOS)				
Clinical and/or biochemical evidence of hyperandrogenism				
Ultrasonographic evidence of a polycystic ovary				
Phenotype D (nonhyperandrogenic PCOS)				

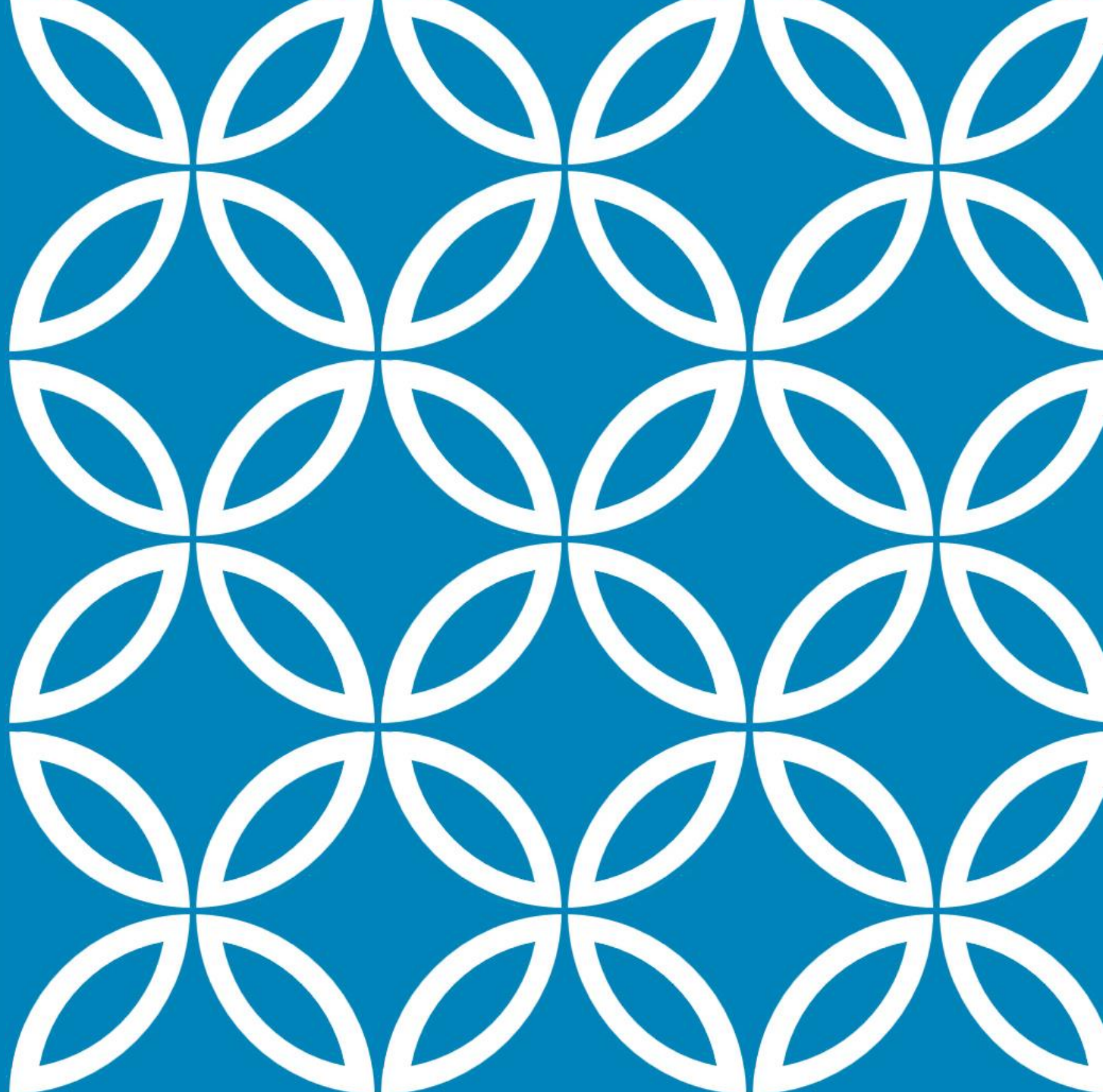
Source: UpToDate

AFTER DIAGNOSIS



PCOS TREATMENT

- 1st assess patient goals
  - Hyperandrogenic symptoms
  - Metabolic abnormalities and risks
  - Prevention of endometrial hyperplasia and carcinoma
  - Conception or contraception



PCOS TREATMENT

- Lifestyle changes *vs* weight loss
- UTD: "Even modest weight loss (5 to 10 percent reduction in body weight) in women with PCOS may result in restoration of normal ovulatory cycles [14-16] and improved pregnancy rates [17] in short-term studies. However, the response to weight loss is variable; not all individuals have restoration of ovulation or menses despite similar weight reduction [11,12,18]. In addition, there are no randomized trials and no long-term data on reproductive or metabolic outcomes with weight loss."

PCOS TREATMENT:
ENDOMETRIAL PROTECTION

- **Endometrial protection with chronic anovulation**
  - 1st line tx: COCs
    - Consider 20mcg EE and norethindrone
  - Intermittent or continuous progestogen tx
    - MPA 5-10mg qd x 10-14 days every 1-2 months
    - Micronized progesterone (MP) 200mg in the same schedule – less well studied
    - Norethindrone 0.35mg qd
  - LNG IUD
  - Metformin restores ovulatory menses in 30-50% of those with PCOS, but endometrial protection is less well established

PCOS TREATMENT: ANDROGEN EXCESS

- **Hirsutism**
  - 1st line is COC
  - Add antiandrogen after 6 months (preferred after at least 1 month) if response is suboptimal
  - May start simultaneously pending severity
  - May use spironolactone alone if no need for contraception
    - if CIs to COCs, need an alternative form of contraception
    - Can be associated with menstrual irregularities
    - 50-100mg BID (titrate dose)
  - Finasteride or dutasteride
    - Inhibits 5-alpha-reductase types 1and/or 2
    - Need contraception if pregnancy risk
  - Endocrine Society Clinical Practice Guidelines advise against use of Metformin to treat hirsutism
    - Minimal to no benefit and less effective than COCs and/or antiandrogens
  - Direct hair removal methods
  - Eflornithine hydrochloride crm 13.9%

PCOS TREATMENT: FERTILITY

- **Letrozole**
  - 1st line. Not FDA approved for ovulation induction
- **Clomiphene citrate**
  - FDA approved, but less effective for live birth rates than letrozole
- **Metformin**
  - Role for fertility is limited. Could be used in combo with letrozole or clomiphene. Current guidelines recommend against routine use in obese women with PCOS except in women with glucose intolerance who have failed lifestyle interventions
- **Gonadotropin therapy**
  - High risk for OHSS
- **Acupuncture**
  - Evidence shows it does not improve live birth rates or IVF outcomes

PCOS TREATMENT: FERTILITY

- **Laparoscopic wedge resection**
  - No longer performed
- **Laparoscopic ovarian drilling/diathermy/electrocoagulation**
  - 2nd line
  - Similar efficacy to gonadotropin therapy, but lower risk of high order multiple gestations or OHSS
- **IVF**
  - Metformin may reduce risk of OHSS, but does not improve clinical pregnancy rates or live birth rates
- **Inositol** appears ineffective for metabolic and endocrine outcomes in PCOS (update as of June 2024)
  - (Fitz V, Graca S, Mahalingaiah S, Liu J, Lai L, Butt A, Armour M, Rao V, Naidoo D, Maunder A, Yang G, Vaddiparthi V, Witchel SF, Pena A, Spritzer PM, Li R, Tay C, Mousa A, Teede H, Ee C. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-based PCOS Guidelines. J Clin Endocrinol Metab. 2024 May 17;109(6):1630-1655. doi: 10.1210/clinem/dgad762. Erratum in: J Clin Endocrinol Metab. 2024 Nov 18;109(12):e2365. doi: 10.1210/clinem/dgae588. PMID: 38163998; PMCID: PMC11099481.)

ENDOMETRIOSIS

- An estrogen-dependent, benign, inflammatory disease that affects females during premenarchal, reproductive, and postmenopausal stages.

RESEARCH FUNDING (PER 2022 NIH DATA)

Endometriosis

Prevalence: 10% (AFAB)

Funding: $2/pt

(0.038% of NIH budget)

Crohn's disease

Prevalence: 0.2% (both sexes)

Funding: $130/pt

EPIDEMIOLOGY

~10% of reproductive age females

Risk factors:

Family history	Nulliparity	Prolonged exposure to endogenous estrogen	Shorter menstrual cycles (<=27 days)	HMB	Obstruction of menstrual outflow	Exposure to DES in utero	Taller height	Lower BMI

PATHOGENESIS

Endo results when ectopic endometrial cells implant, grow, and elicit an inflammatory response

Pathogenesis is multifactorial and not well understood

- Retrograde menstruation is evident in up to 90% of menstruating people, yet most do not develop endo

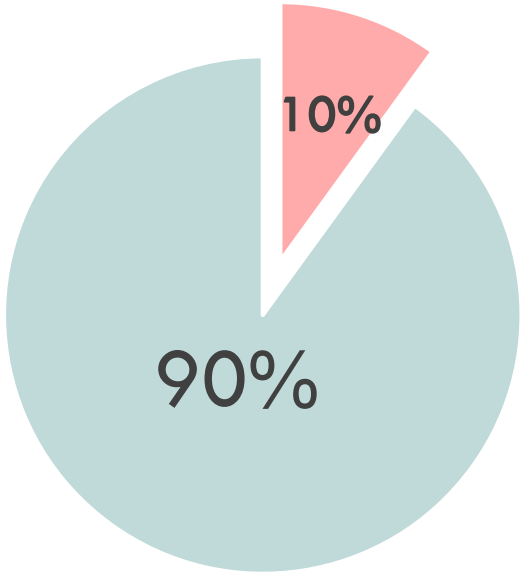
Pain due to inflammatory changes, increased production of inflammatory and pain mediators and neurologic dysfunction related to the endometrial implants

Subfertility appears to be due to anatomic distortion from pelvic adhesions and endometriomas and/or production of substances hostile to normal ovarian function/ovulation, sperm mobility, fertilization and implantation

WOMEN'S HEALTH COLLECTIVE

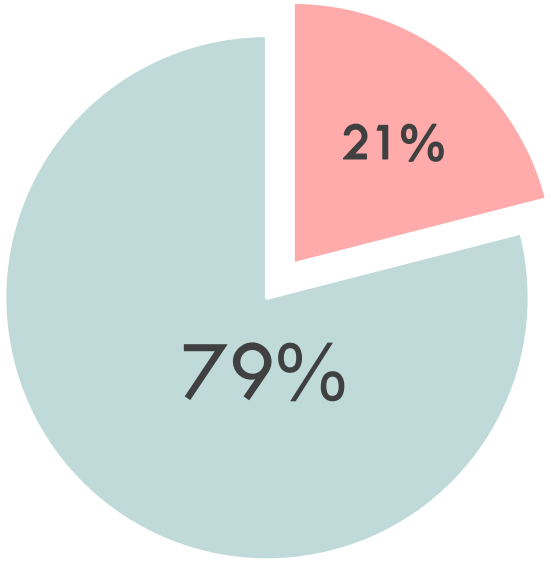
PREVALENCE

Endometriosis rates in women of **reproductive age**



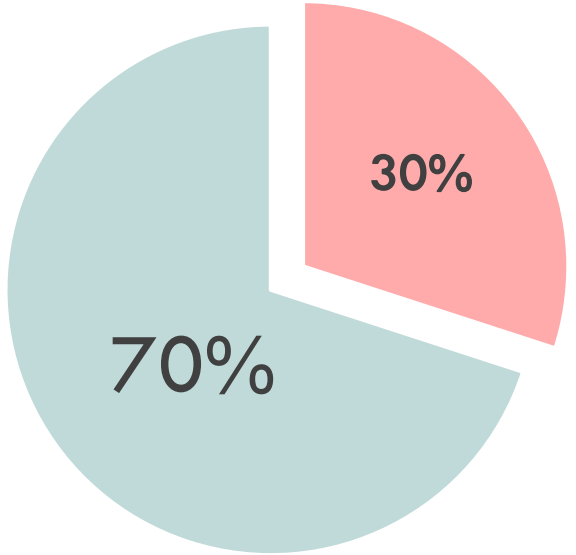
Shafrir AL.*Best Pract Res Clin Obstet Gynaecol*. 2018 Aug;51:1-15

Endometriosis rates in women presenting with **chronic pelvic pain**



Mowers EL. *Obstet Gynecol*. 2016 Jun;127(6):1045-1053

Endometriosis rates in women who present with **infertility**



Prescott J. *Hum Reprod*. 2016 Jul;31(7):1475-82

WOMEN'S HEALTH COLLECTIVE

IMPACT ON QUALITY OF LIFE

Time	Healthcare Costs	Fertility	Sexual Health
• ↓ Average of 6.3 work hours/week • ↓$10,177.54/year	• Annual economic burden (direct/indirect cost) in 2009 was estimated at $69.4 billion	• Patients with endometriosis have > 2 fold higher risk of infertility	• 47% of patients with endometriosis had dyspareunia
Soliman AM, et al. *J Psychosom Obstet Gynaecol.* 2017;38(4):238-248.	Simoens S, et al. *Hum Reprod.* 2012;27(5):1292-1299.	Prescott J, et al. *Hum Reprod.* 2016 Jul;31(7):1475-82.	De Graaff AA, et al. *Hum Reprod.* 2013;28(10):2677-2685.

WOMEN'S HEALTH COLLECTIVE

LESION PHENOTYPES

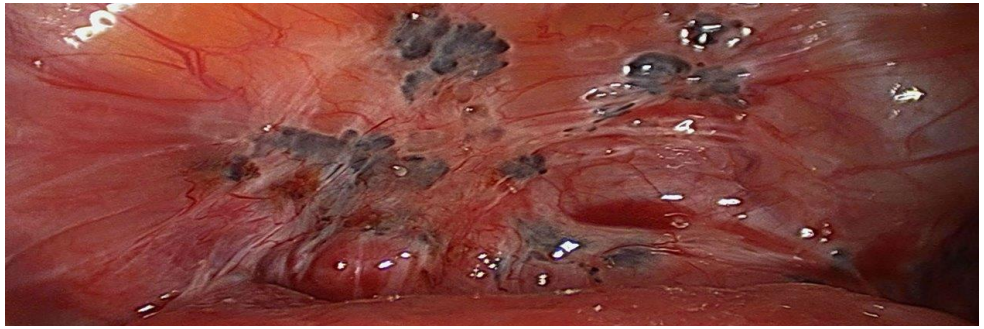
Superficial peritoneal

Ovarian

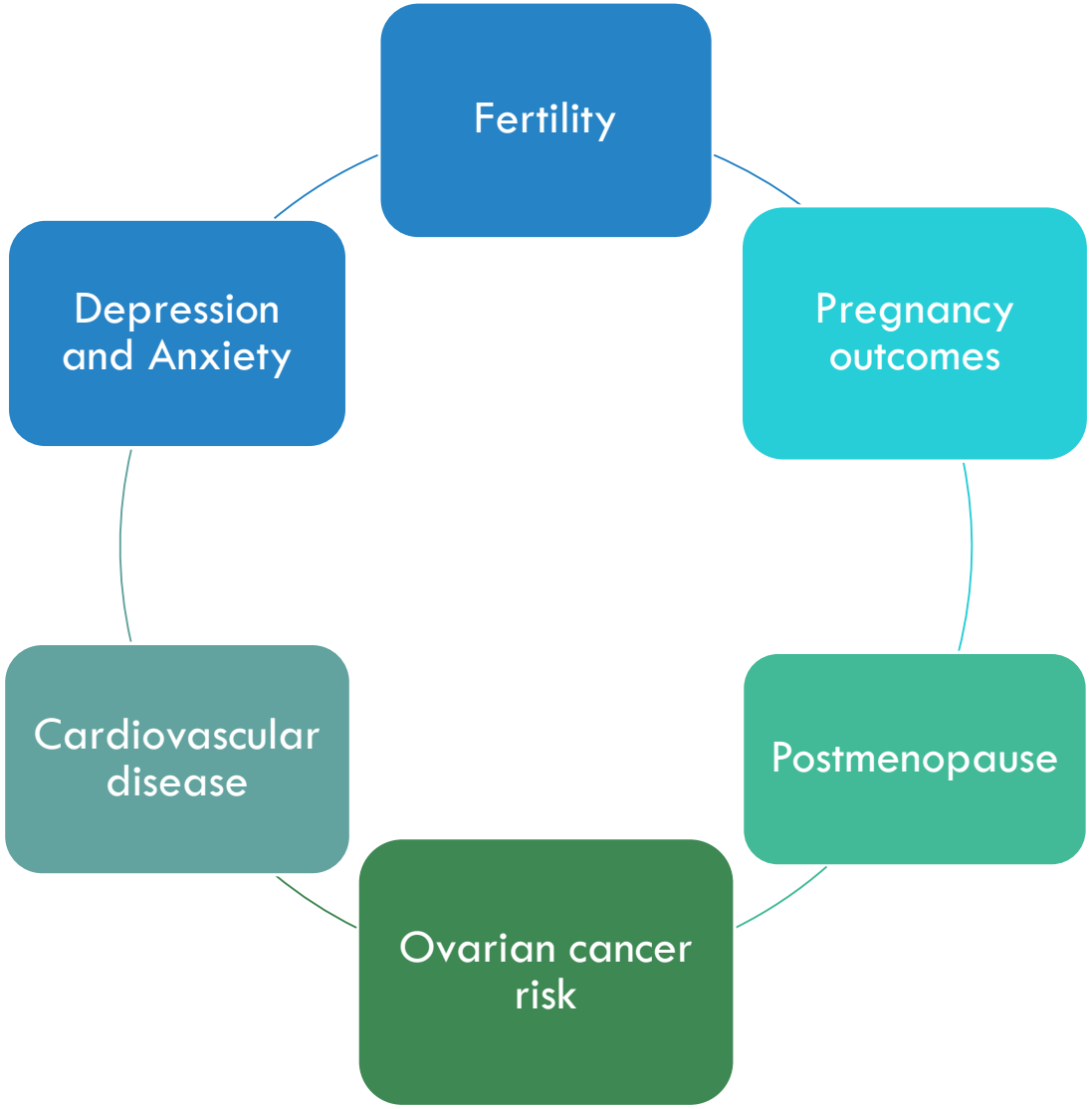
- Ovarian endometrioma forms when endometrium-like tissue forms an ovarian cyst

Deep

- Endometrium-like tissue in the abdomen that extends under the peritoneum
- Generally found in the rectovaginal septum, rectum, rectosigmoid colon, bladder, ureter, uterine ligaments and vagina



WOMEN'S HEALTH COLLECTIVE



CLINICAL IMPACT

PRESENTATION

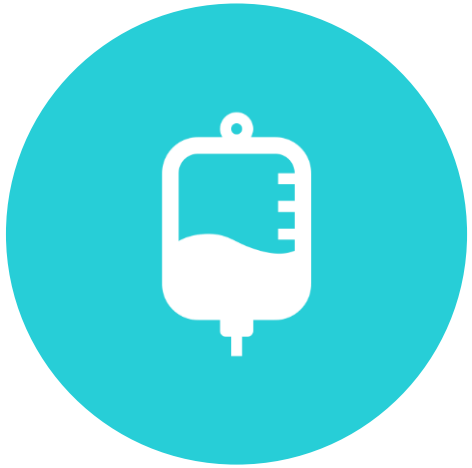
Chronic abdominal/pelvic pain/pressure	Severe dysmenorrhea	Dyspareunia	HMB
Infertility	Bowel/bladder dysfunction (pain, urgency, frequency)	Low back pain	Chronic fatigue

PHYSICAL EXAM

- Focal tenderness on vaginal exam
- Nodules in posterior fornix
- Adnexal masses
- Immobility or lateral placement of cervix or uterus
- Endo lesion visualized on cervix or vaginal mucosa (rare)
- Normal exam

LABS

NONE!



CA 125 CAN BE ELEVATED,
BUT NOT SPECIFIC TO ENDO

IMAGING

***BOTH CAN IDENTIFY ENDO**

***NOT SUPERIOR TO LAP**

***NEGATIVE STUDIES CANNOT EXCLUDE ENDO**

Transvaginal ultrasound

MRI

WOMEN'S HEALTH COLLECTIVE

TO LAP OR NOT TO LAP?

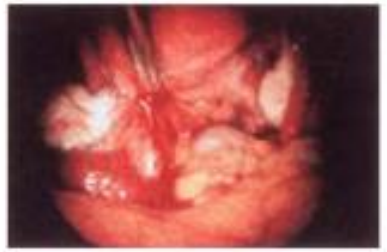
US Guidelines

- Diagnostic laparoscopy is the only definitive method to confirm diagnosis of endometriosis

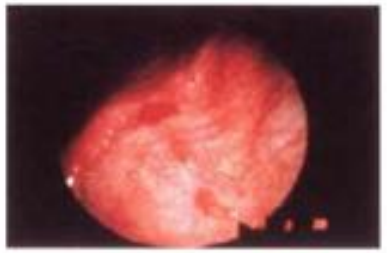
ESHRE

- Laparoscopy is no longer the diagnostic gold standard and is now only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate

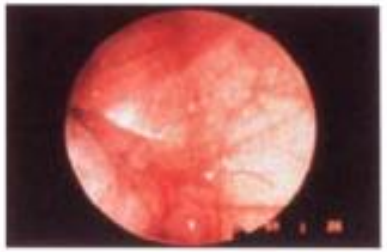
The top, middle, and bottom series are representative of red, white, and black implants, respectively



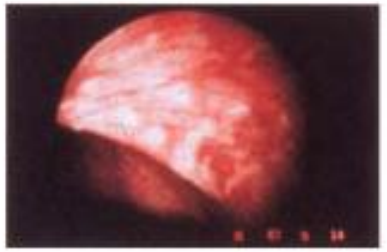
Red



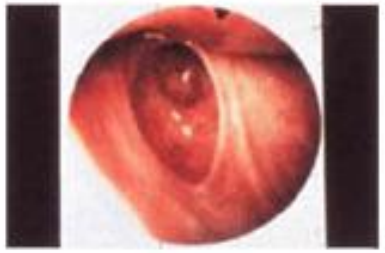
Red-pink



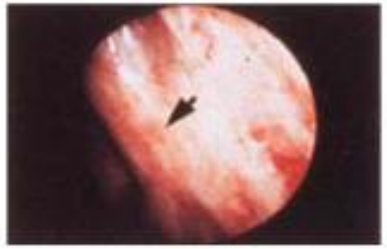
Clear



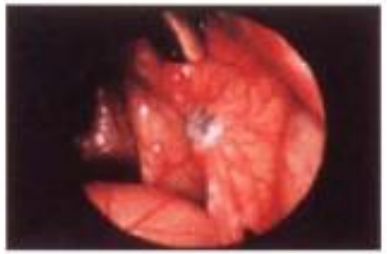
White



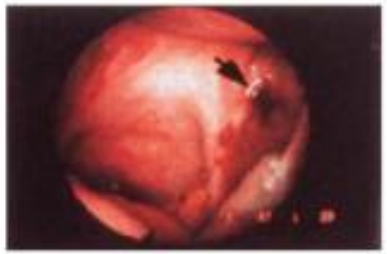
Peritoneal defect



Yellow-brown



Black



Blue

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UpToDate®

TREATMENT

Medication

Surgical

PFPT!!!

Muscle spasm as 1 contributory factor

Acupuncture

In 1 trial (n=67), auricular acupuncture was significantly more effective than Chinese herbal medicine for treating dysmenorrhea associated with endometriosis

Dietary

One study reported a lower risk of developing endo was associated with a high intake of green vegetables and fruit and an increased risk with intake of beef or other red meat or ham

TREATMENT

No data to support one treatment choice over another

Shared decision making

Medical treatments include:

- NSAIDs
- Hormonal contraceptives
- GnRH analogs
- AIs

MEDICATION

NSAIDs

- 1st line tx for pelvic pain, including endo pain
- NO good data proving efficacy in treating endo pain
- Have not been shown to have higher efficacy than other agents or than placebo

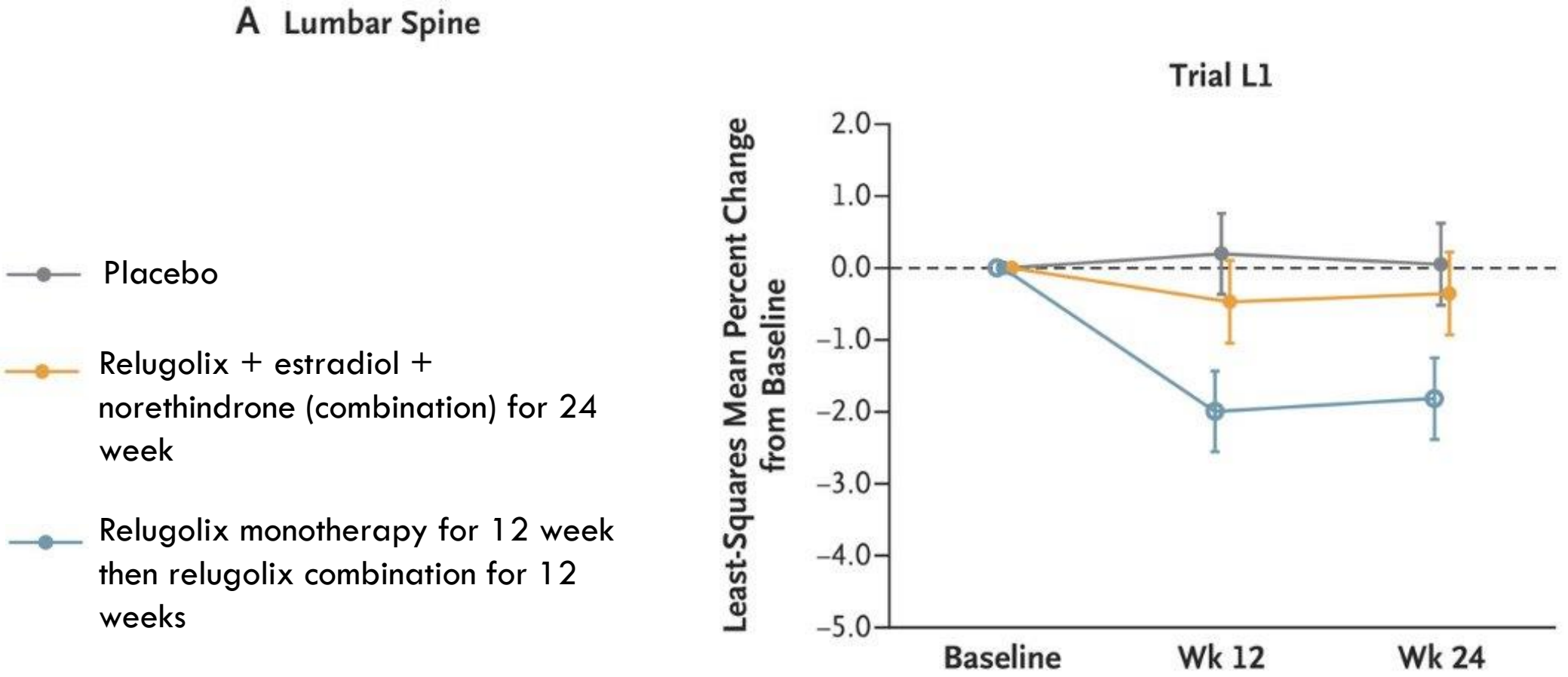
Hormonal contraception

- All have shown pain reduction
- Tx choice based on pt preference/shared decision making
- No formulation has shown superiority
- General recommendation for COCs contains 20mcg EE given continually
  - 2 systematic reviews have shown that continuous dosing is more effective at reducing pain symptoms than cyclic dosing
- MOA may be due to progestin induced atrophy of endometrial tissue and may slow progression of disease

MEDICATION: GNRH ANALOGS

	Agonists	Antagonist
Side effects	○ ↓ bone mineral density (BMD) ○ symptoms of hypogonadism	○ ↓ bone mineral density ○ symptoms of hypogonadism
Approved for endometriosis	○ Nafarelin ○ Goserelin ○ Leuprolide ○ Triptorelin	○ Elagolix ○ Relugolix combination
Method of administration	○ Nasal spray ○ IM (daily, monthly, 3-monthly)	○ Oral
Activity	○ Several weeks to respond ○ Initial flare of symptoms common	○ Effective immediately
Limitation of usage	○ <=6 months ○ With some exceptions up to 1 year	○ <=24 months ○ Dependent on dose and hepatic function

CHANGE IN BMD



Al-Hendy A. *New Eng J Med*. 2021 Feb 18;384(7):630-42.

QUESTIONS???

WOMEN'S HEALTH COLLECTIVE