

Early Diagnosis and Management to Reduce Disease Burden and Improve Long-term Health Outcomes for Women:

Hypothyroidism, Polycystic Ovarian Syndrome and Endometriosis

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Disclosure Statement

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- I have no financial interest with manufacturers or any commercial products.
- Unlabeled / unapproved use of drugs or devices will not be discussed during this presentation.
- Medicine is an evolving professional art that tries its best to keep up with scientific discoveries. Always consult updated medical references in your patient care.

Objectives

- Identify the variety of clinical presentations of hypothyroidism, polycystic ovarian syndrome (PCOS), and endometriosis seen in primary care and utilize diagnostic criteria to diagnose in a timely manner
- Discuss first-line management options and patient education to improve long-term outcomes and reduce effects/burden of the disease for the patient and the community
- Explain how to reduce need for early referral and improve continuity of care for female patients

Hypothyroidism

Management in the Primary Care Setting

Hypothyroidism - Prevalence

- The most common endocrine disorder seen in primary care/ family medicine setting
- The Colorado Thyroid Disease Prevalence Study (1995, Canaris, et al) had an n=25,682 and revealed a 9.5% prevalence rate of hypothyroidism

Age Group	Male (%)	Female (%)
18-24	~2	~2
25-34	~3	~3
35-44	~4	~4
45-54	~6	~6
55-64	~10	~10
65-74	~15	~15
>74	~20	~20

Symptoms of Hypothyroidism in Women

Overt vs Subclinical Hypothyroidism

Thyroid function test	Hospital 1*	Hospital 2†	Hospital 3‡
TSH (mIU/L)	0.4–4.0	0.30–3.82	0.3–4.7
Free T4 (pmol/l)	9–25	12.0–22.0	9.5–21.5
Free T3 (pmol/l)	2.8–7.5	3.1–6.8	3.5–6.5

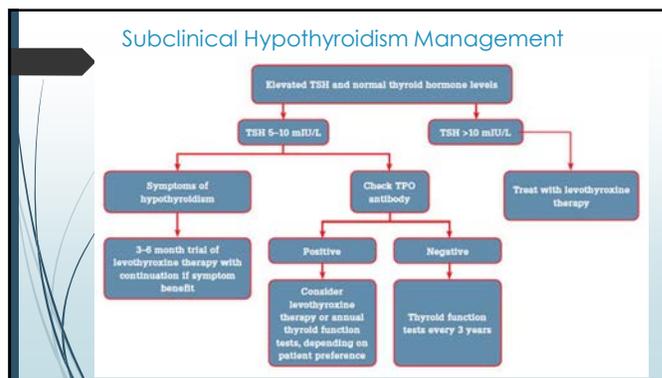
*American Thyroid Association guidelines (2002).
 †Roche assay reference range.
 ‡Siemens assay reference range.
 TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

Overt Hypothyroidism

- Clear hypothyroidism characterized by an increased TSH and a decreased T4 level. All patients with **overt hypothyroidism** are usually treated with **thyroid hormone pills**.

Subclinical Hypothyroidism

- Also called mild thyroid failure, is diagnosed when peripheral thyroid hormone levels (T3 and T4) are within normal reference laboratory range but serum thyroid-stimulating hormone (TSH) levels are mildly elevated.



To treat or not to treat??

TABLE 3
Factors favoring levothyroxine therapy in subclinical hypothyroidism

Thyroid-stimulating hormone (TSH) level > 2 times the upper limit of normal or > 8 mIU/L
 Progressive rise in TSH
 Goiter
 Positive antithyroid antibodies
 Pregnancy or planning pregnancy
 Infertility or ovulatory dysfunction
 Childhood or adolescence
 Dyslipidemia
 Established cardiovascular disease or risk factors for cardiovascular disease
 Depression or bipolar disease
 Therapeutic trial for clinical symptoms of hypothyroidism
 Patient preference

Long-term sequelae

- Hypothyroidism can be the cause of great distress for women throughout adulthood
- The risks and burden associated with unmanaged hypothyroidism include:
 - Depression
 - Infertility
 - Low birth weight delivery and compromised fetal cognitive development
 - GI Issues such as constipation and abdominal pain
 - Obesity
 - High cholesterol/ cardiovascular disease

*** Can you imagine the burdens, such as polypharmacy, related to treating the SYMPTOMS of hypothyroidism instead of diagnosing and treating the root cause?

Treatment Guidelines

- After a review of current literature/studies, the American Thyroid Association (2018) continues to believe levothyroxine should remain the current standard of care.
- Consider TSH, patient age and weight (always start at 12.5-25mcg with > 65 yo and monitor q6-8 weeks until euthyroid)
- The goal is to replace thyroxine to mimic normal, physiologic levels and to eliminate signs, symptoms, and biochemical abnormalities (high TSH)

Table 6. Adjustment of Levothyroxine Dosage Based on Thyroid-Stimulating Hormone Level

Thyroid-stimulating hormone level (mIU per L)	Levothyroxine dosage increase (mcg per day)
5 to < 10	25 to 50
10 to 20	50 to 75
> 20	75 to 100

Information from reference 17.

TABLE 2
TREATMENT THRESHOLDS AND GOALS, BY TSH LEVELS

Thyroid State	Treatment Threshold	Treatment Goal
Primary hypothyroidism	>4.0 mIU/L	1.0 to 4.0 mIU/L
Subclinical hypothyroidism	>10 mIU/L	3.0 to 4.0 mIU/L (ages 60 to 74); 4.0 to 6.0 mIU/L (75 and older)
Symptomatic subclinical hypothyroidism	5.0 to 10.0 mIU/L	3.0 to 4.0 mIU/L (ages 60 to 74); 4.0 to 6.0 mIU/L (75 and older)

Note. TSH = thyroid stimulating hormone. Adapted from Chakravarty, Pearce, and Vaidya (2012); Gharib et al. (2005); and Papapanou and Hayslett (2012).

Education re: Treatment with Levothyroxine

- Take levothyroxine at the same time everyday
- Take it on an empty stomach – at least 30 min before anything else
- Take with 1 glass of water
- Avoid calcium supplements or antacids within 1 hour of taking levothyroxine
- Adverse effects to report to provider immediately: tremors, heart palpitations, diarrhea, sweating (may be too high of a dose or may not be able to tolerate)

Case Study #1

- 29-year old female patient presents with concerns about fatigue and worsening depression, despite being on sertraline. What other questions should you ask for HPI?
- She shares she has increasingly heavier periods also – sometimes passing clots and often requiring double protection. What are next steps for evaluation?
- TSH 14.4 T4 6.5 TPO antibody Positive at 315 – what is your diagnosis and management plan?
- She was treated initially with 50 mcg Levothyroxine and her TSH came down to 5.2. She had minimal relief of symptoms? Increase her dose?
- If treating with levothyroxine, a goal of symptom relief and a TSH < about 4.0 is recommended – you can treat to 1.0 safely if needed for symptom relief
- This patient was titrated up to 88 mcg daily with a resulting TSH of 0.96 and such good symptom relief that, at 1 year she was training for a half marathon, had light periods, and she had weaned herself off sertraline

Case Study #2

- 34 year old female, diagnosed with Hashimoto's Hypothyroidism 2 years ago after her son was born (post partum thyroiditis) presents for a physical and shares she is trying to conceive again. She is currently on levothyroxine 50 mcg daily. First steps?? Any additional HPI questions?
- Her TSH is 3.5 – initial thoughts?
- Consider asking about compliance – if she is not too symptomatic, she may not be compliant in taking her levothyroxine daily – education about hypothyroidism and goal TSH, related to fertility and fetal cognitive development, may be first steps with this type of patient
- If you are trying to conceive, a normal level of TSH for conception should be lower than 2, according to many reproductive endocrinologists.
- This patient returned 2 months after this appt to follow up on her 6 week labs – her TSH after strong compliance was 1.2 and she conceived soon after

Case Study #3

- A 38 year old female presents to you with Chief Complaint: progressively worse constipation over the last 1 year – she has made appropriate dietary adjustments with no improvement. She feels the constipation has caused the 11 lb weight gain she has had and overall feeling of low energy. Any other hallmark questions?
- Irritability and difficulty concentrating are also brought up – are labs indicated? If so, which ones?
- TSH is 4.0 and T4 is normal – Dx?
- SYMPTOMATIC Subclinical hypothyroidism – treatment?
- Absolutely - Levothyroxine 50 mcg daily on an empty stomach
- Follow up in 6-8 weeks – TSH was 1.2 and patient is frustrated that she has not lost weight and is still tired but her constipation has improved
- Reassurance/ Education and Coaching – may consider a 12.5mg increase or even taking 2 tablets one day a week
- Patient returns 8 weeks later for her well woman exam and reports improvement in GI function and decreased bloating/ abdominal pain with 8 tablets a week – she has lost 4 lbs – her TSH at this last visit was 1.1 – when do you recheck?

PCOS

PCOS: The problem

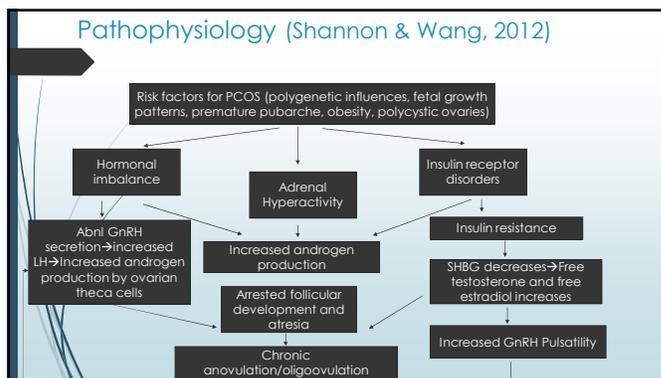
- The most common gynecologic condition in women of reproductive age-bottom line, you WILL see it!
- Affects 5-10% of reproductive age women and 15-20% of women with infertility
- 50-75% of women with PCOS will visit multiple providers prior to a diagnosis- we can catch this earlier!
- Why is early diagnosis important?- prevent or reduce adverse health outcomes, appropriately treat symptoms, educate patients
- PCOS has a "classic" presentation, but not all women with PCOS meet this "classic" phenotype

PCOS SYMPTOMS



Patient Questions about PCOS

- What does this mean?
- Will I be able to get pregnant? Do I even need birth control?
- What are the long-term risks?
- Will I get diabetes?
- Is this why I am overweight?
- How can I manage the affects of hirsutism? Alopecia? Hyperinsulinemia?



Diagnostic Criteria (Goodman, et al. 2015)

Rotterdam 2004	NIH/NICHD	Androgen Excess Society 2006
Includes 2 of the following 3:	Includes all the following:	Includes all of the following:
Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism
Oligo-ovulation or anovulation	Menstrual dysfunction	Ovarian dysfunction and/or polycystic ovaries
Polycystic Ovaries		

*Ovulatory Dysfunction- cycle length >35 days, if cycles 32-25 days with assessment of ovulation with mid-luteal progesterone
 **Signs of hyperandrogenism (Neven et. Al, 2018) - Hirsutism, Alopecia, Acne. If clinical signs are not present, proceed to lab studies and then u/s if necessary.

Diagnosis

So what information do we need to make a firm diagnosis?

- Menses, how frequent?
- Signs of hyperandrogenism! Clinical first, then lab
- Nipple discharge
- Signs of Cushing's- moon faces, buffalo hump

What else should we r/o before making a diagnosis?

- Non-classic Congenital Adrenal Hyperplasia (Goldrat & Delbaere, 2018)
- Thyroid disorders
- Cushing's Syndrome
- Hyperprolactinemia (Mohammad & Seahinsara, 2017)

Labs/ultrasound

- Free and total testosterone, SHBG (can calculate free androgen index= TT/SHBG)
- DHEAS
- TSH
- Prolactin
- 17-hydroxyprogesterone
- Ultrasound if all labs are WNL (Shannon & Wang, 2012)

Long Term Sequelae

Long term screening and quality of life

- PCOS is a major cause of psychological distress and has a negative impact on women's self-reported quality of life- it is important to continue to follow up with these patients and treat symptoms!

So what screening would we recommend for PCOS patients

- Screen for metabolic syndrome- lipid panel, BP, glycemic status with OGTT, fasting glucose or HgbA1c (Goldrate & Delbaere, 2018)
- Screening should occur every 1-3 years based on other risk factors and baseline levels
- High risk women with PCOS- BMI>25 (BMI >23 in Asian women), hx of impaired fasting glucose, GDM, fam hx of DM Type 2, HTN, or high risk ethnicity (Teede et. Al, 2018)
- Screening for anxiety/depression- consider loss of femininity, body image concerns and coping with these can contribute to mental health concerns (Moghadam, Fereidooni, Saffari, & Montazeri 2018)
- Screen for risk factors endometrial hyperplasia if patient is not managed on hormones and has irregular menses
- Reproductive issues
- Obstructive Sleep apnea

Special Considerations- Adolescents

- Anovulation is common in adolescents in the early years post-menarche
- Irregular menses less than 1 year post-menarche is normal pubertal transition
- >1 to <3 years post menarche: irregular menses are considered <21 or >45 days
- >3 years postmenarche: irregular menses considered <21 or >35 days or <8 cycles per year
- More than 1 year post menarche, >90 days between menses is considered irregular
- Pelvic u/s should be avoided <8 years post menarche and in those who have not been sexually active (multi-follicular ovaries are common)
- First r/o other causes of menstrual irregularities, and consider treatment of symptoms and reassessment of PCOS diagnosis if patient cannot be categorized under irregular menstruation due to age/ gynecological age
- Treatment is similar in all ages (Pena, et al. 2020)

Managing Symptoms of PCOS

Lifestyle modifications

- Diet and exercise 150 minutes weekly of moderate intensity or 75 minutes of vigorous intensity (Neven et. Al 2018)
- Benefits: Lowers insulin resistance, improves BMI, improves ovulatory dysfunction

Metformin

- Metformin should be considered in addition to lifestyle modifications in adult women with PCOS and BMI > or =25 kg/m²
- metformin (in conjunction with lifestyle modifications) 500mg-2550 mg (850 mg tid) (Banaszewska, Pawelczyk & Spaczynski, 2019)
- Begin metformin at a low dose and increase by 500 mg increments 1-2x weekly; extended release may minimize side effects
- Metformin- generally safe long term (Teede et. al, 2018)
- Benefits: decreases insulin resistance and improves ovulatory function

Managing Symptoms of PCOS

Combined OCPs

- Best anti-androgenic COC's on the US market include drospirenone- start with 20 mcg ethinyl estradiol- e.g. Yaz, Nikki, Gianvi then stop up to 30 mcg EE if pt needs more estrogen- e.g. Yasmin, Ocella
- Not all women with PCOS respond well to drospirenone, but you can start here
- Benefits: regulates ovulatory dysfunction, reduces clinical signs of hyperandrogenism, prevents endometrial hyperplasia

Spironolactone

- Spironolactone: some suggest this can be added if 6 months on COCs is insufficient (Sannon & Wang, 2012) 25 mg and titrate up; monitor for signs of hypokalemia
- Benefits: Reduction in clinical signs of hyperandrogenism

Case Study

- Sarah is a 22 yo G0 here for annual exam and discussion of birth control options. BP 120/76, HR 82. She is in a monogamous relationship and has been using condoms but now would like to discuss other options. Her BMI is 32 and she reports menses every 35 days- 3 months. They are often heavy with moderate cramping. She reports being relatively healthy, despite being obese. Fam hx significant for hypercholesterolemia (father), hypertension (MGM), and Type 2 DM (MGM)

Case Study, Diagnosis

- After getting a complete history from Sarah, we find out that menarche was age 10, she reports hirsutism on her chin, and you are able to visualize this on her chin as well as her stomach and chest on physical exam
- She has difficulty losing weight, even with regular exercise and a healthy diet
- She has never had her thyroid, lipids or blood sugar checked
- Does she meet criteria?
- Labs: TSH= 2.65 mIU/L, Prolactin=12 ng/mL, 17-hydroxyprogesterone=52
- Does she need testosterone labs?

Let's look at a few other phenotypes (Neven et al., 2018)

- Jane is a 31 yo G1P0010 here for excessive hair growth. She has regular menses q30 days. She has a Mirena IUD for BC. Her BMI is 23.
 - She meets criteria for androgen excess, but has regular menses. We choose to do a pelvic ultrasound and she has increased ovarian volume and 18 resting follicles
 - We do labs to r/o other etiologies and they are all WNL.
 - Now she meets criterial
- Karen is a 28 yo G2P10011 here for annual exam. She has had difficulty losing weight for the past several years. She has irregular cycles q28-45 days. Her BMI is 36. She reports some alopecia and minimal acne but denies hirsutism.
 - She meets criteria for irregular menses but is borderline for androgen excess. We draw testosterone (free and total). Free testosterone=4.2 pg/mL and Total=98 ng/dL
 - Normal TSH, prolactin, and 17-hydroxyprogesterone
 - She now meets criteria with androgen excess and irregular menses
- Shannon is a 33 yo G0 here for irregular menses. She has a period every 3-4 months. Denies hirsutism, acne, alopecia. Her BMI= 20. She uses condoms for BC. She likes not having regular periods but her boyfriend told her she should get checked out.
 - She has no clinical signs of androgen excess, so we draw labs that are all WNL. TSH, prolactin, and 17-OH progesterone are also WNL
 - We do a pelvic ultrasound and she has increased ovarian volume and polycystic ovaries
 - Now she meets criterial

When to refer?

- We can begin to diagnose and treat symptoms of PCOS as well as prevent, monitor and treat long-term health effects in the primary care setting. When is it appropriate to refer?

- Infertility
- Abnormal uterine bleeding
- Primary or secondary amenorrhea
- Unclear diagnosis
- Symptoms not managed with hormones or patient prefers no hormones



Endometriosis

Management in the Primary Care Setting

Endometriosis

- Endometriosis is a condition in which tissue similar to the lining inside the uterus (called "the endometrium"), is found outside the uterus, where it responds to the hormones estrogen and progesterone by thickening and induces a chronic inflammatory reaction that may result in scar tissue and, at minimum cause chronic pain. It is primarily found on the pelvic peritoneum, on the ovaries, in the recto-vaginal septum, on the bladder, and bowel.
- In very rare cases it has been found on the diaphragm and in the lungs [1-2].

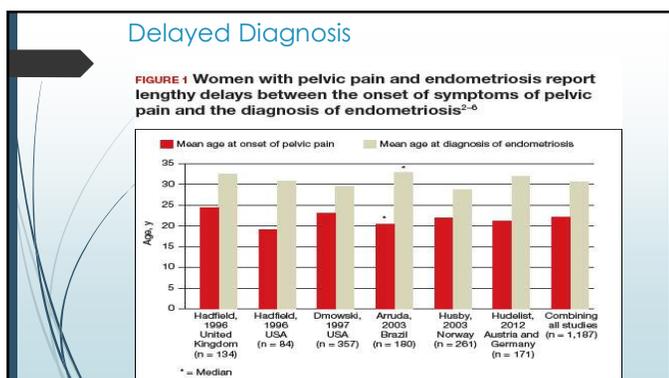
Endometriosis - Prevalence

- 25 to 50% of infertile women have endometriosis
- 45% - 82% of women with chronic pelvic pain have endometriosis

1 in 10 women will be affected by endometriosis

Common Signs and Symptoms of Endometriosis

- Painful periods (dysmenorrhea).** Pelvic pain and cramping may begin before and extend several days into a menstrual period. You may also have lower back and abdominal pain.
- Pain with intercourse.** Pain during or after sex is common with endometriosis.
- Pain with bowel movements or urination.** You're most likely to experience these symptoms during a menstrual period.
- Excessive bleeding.** You may experience occasional heavy menstrual periods or bleeding between periods (intermenstrual bleeding).
- Infertility.** Sometimes, endometriosis is first diagnosed in those seeking treatment for infertility.
- Other signs and symptoms.** You may experience fatigue, diarrhea, constipation, bloating or nausea, especially during menstrual periods.



Burden of Disease vs funding for research

<https://www.herendometriosity.com/endometriosis-management/impact/Effects-on-our-patients>

Annual healthcare costs of endometriosis are estimated at ... **\$70 billion** in the U.S. alone!

Disease	Prevalence	Annual Healthcare Costs	Research Funding
Crohn's Disease	0.4%	\$66,000,000	\$41
Parkinson's	0.2%	\$169,000,000	\$169
Hepatitis B	0.2%	\$49,000,000	\$22
Autism	1.1%	\$245,000,000	\$69
Adult Liver Disease	1%	\$61,000,000	\$170
Diabetes	7%	\$105,000,000	\$58
Adult Mental Illness	9.7%	\$2,570,000,000	\$60
Endometriosis	10%	\$10,000,000	\$0.64

Diagnosis

- Studies have shown that experienced clinicians can predict the presence of endometriosis based on history and physical examination in 80% of cases.
- The gold standard for diagnosis of endometriosis remains laparoscopic visualization, but has more recently been demonstrated to be unreliable
- Confirmatory biopsies of lesions is now a more valuable confirmation of endometriosis

So – in the primary care setting, a history of cyclical pain/ non-cyclical pelvic pain/ IBS type symptoms/ bladder pain should raise suspicion and Endometriosis should be very high on your differential list

Treatment

Flowchart for Endometriosis Treatment:

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    graph TD
        A[Woman presents with pelvic pain and presumed endometriosis] --> B[Treat empirically with a high-dose nonsteroidal anti-inflammatory drug]
        B --> C{No improvement in pain}
        C --> D{Pregnancy desired}
        C --> E{Pregnancy not desired}
        D --> F[A Refer to gynecologist for further evaluation and treatment (e.g., gonadotropin-releasing hormone analogue, danazol, laparoscopy)]
        E --> G[Treat with extended-cycle contraception: Combination estrogen/progestin contraceptive (monophasic combined oral contraceptive, vaginal ring [NuvaRing], transdermal patch [Ortho Evra]) Long-acting progestin-only contraceptive (oral medroxyprogesterone [Provera], depot medroxyprogesterone [Depo-Provera, Depo-subQ Provera], etonogestrel subdermal implant [Implanon], levonorgestrel-releasing intrauterine system [Mirena])]
        G --> H{Pain not controlled}
        H --> I[Go to A]
    
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Treatment Cont'd

Flowchart for Endometriosis Treatment (Cont'd):

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    graph TD
        A[Endometriosis suspected on basis of pain or infertility] --> B{Pain}
        A --> C{Infertility (other causes excluded); concomitant work-up of other infertility factors}
        B --> D[Mild to moderate]
        B --> E[Moderate to severe]
        D --> F[Consider empiric treatment with OCPs or progestins]
        E --> G[Laparoscopic diagnosis]
        G --> H[Surgical excision and ablation of lesions]
        C --> I[Laparoscopic diagnosis]
        I --> J[Surgical excision and ablation of lesions]
        H --> K[Immediate postsurgical therapy with danazol (Dancocrine), OCPs, GnRH agonists or progestins]
        J --> L[In vitro fertilization or superovulation]
        K --> M[Recurrence]
        L --> M
        M --> N[Medical therapy for 6 to 9 months]
        M --> O[Intractable pain and childbearing is not a factor]
        O --> P[Hysterectomy, oophorectomy]
        C --> Q[Expectant management]
    
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Evidence Based Treatment review

Treatment	Evidence
NSAIDs	A 2009 Cochrane review including only one small RCT of naproxen versus placebo showed no conclusive evidence that NSAIDs improve pain; however, because NSAIDs are effective for primary dysmenorrhea, consensus opinion suggests they are reasonable as a first-line treatment for suspected endometriosis ³⁰ .
Combination oral contraceptives	A 2007 Cochrane review including only one study comparing combination oral contraceptives with gonadotropin-releasing hormone analogues showed that both were comparable for pain relief ³¹ ; a Japanese RCT showed that low-dose combined oral contraceptives improved pain compared with placebo ³² .
Medroxyprogesterone	Small RCTs show that oral medroxyprogesterone (Provera) and depot medroxyprogesterone (Depo-Provera, Depo-subQ Provera) are beneficial for pain ^{33,34} .
Levonorgestrel-releasing intrauterine system (Mirena)	Small nonrandomized studies show possible benefit for pain ^{35,36} .
Gonadotropin-releasing hormone analogues	A 2010 Cochrane review showed effectiveness ³⁷ ; however, adverse effects (i.e., menopausal symptoms) limit its use.
Danazol	A 2007 Cochrane review showed effectiveness ³⁷ ; however, androgenic adverse effects limit its use.

NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial. Information from references 30 through 37.

Elagolix – first new tx in over a decade

Suppression of LH and FSH leads to estradiol suppression within ~24 hours^{1,31}

Case Study 1

- 34 yo female presents with complaints of worsening pelvic pain that is present “all the time now!” HPI includes use of combined oral contraceptives in her late teens and 20s to help with her painful and heavy periods, but she has not been on anything for about 6 years since her husband got a vasectomy. Patient has no contraindications to hormones and wonders if she should go back on birth control.

What are your first thoughts?

Case Study 1 cont'd

- Patient returns in 4 months with no relief of pain – she now is stating that she missed several days of work this last few months.
Next steps?

This patient was put on Orilissa 150mg QD and followed up 6 weeks later stating she had a 60% reduction in pain

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