WOMEN'S HEALTH 2020:
Beyond the Annual Visit

Individualizing Treatment Strategies for Endometriosis

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omnia EDUCATION

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Learning Objectives

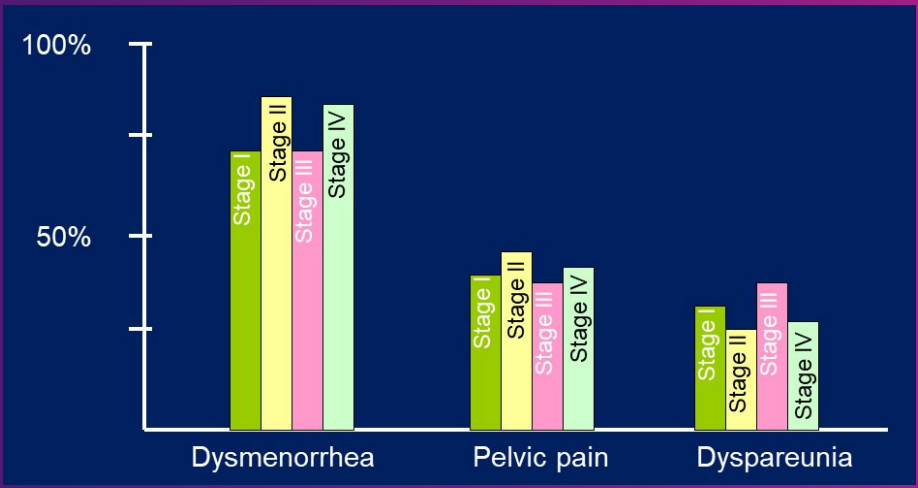
- Identify factors that delay an accurate and patient-centered diagnosis of endometriosis
- Describe validated, guideline-recommended symptom assessment tools that can be used in clinical practice to initiate early intervention
- Employ approaches and tools for endometriosis care that invite patient preferences, goals, and values into clinical decision-making
- Implement a personalized treatment plan for endometriosis-associated pain that considers individual clinical, biologic, and health-related quality of life measures as important outcomes
- Differentiate benefits and disadvantages of various therapies for managing endometriosis when developing a personalized care plan

Prevalence and Presentations of Endometriosis

- Prevalence: 10% of reproductive-age women[1]
- Higher in some subgroups and up to:
  - 50% of women with infertility
  - 21% of women hospitalized for pelvic pain
- Most Common Pain:
  - Dysmenorrhea – 73%
  - Non menstrual pelvic pain (NMPP) – 57%
  - Dyspareunia – 43%

1. Zondervan KT, et al. *N Engl J Med*. 2020;382(13):1244-1256.

Lack of Correlation Between Symptoms and Stage of Endometriosis



Fedele L, et al. *Fertil Steril.*1990;53(1):155-158.

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Classic Image of Endometriosis

- Defined as a pelvic condition
  - Endometrial glands and stroma implanted outside the uterus
- Caused primarily by retrograde menstruation
- Diagnosis made surgically

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New Developments in Endometriosis

- New appreciation that this is a chronic, progressive, inflammatory process that has systemic health impacts
  - Genetic, hormonal, immunologic causes
- New understanding that adolescent and young women are frequently affected
- Recognition that a delay of 7+ years persists in diagnosis
- More reliance on clinical diagnosis
- New medical therapies to treat and suppress its condition

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Challenges in Making the Diagnosis

- Patient hesitancy to discuss problems due to past disappointments and/or stigma
  - Diagnosis missed, treatment incomplete
- Varied physical manifestations
- Nonspecific symptoms
- Past reliance on surgical diagnosis
- Lack of public (and professional) awareness of the problem

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Current Approaches to Endometriosis Diagnosis and Treatments

- Complete history and pelvic exam, including rectal exam, needed
- Surgery reserved for cases that do not respond to medical therapy, have pelvic masses, or are acute presentations (ruptured endometrioma)
  - Other individualized indications
- Design therapies that address woman's current complaint and also bridge to long-term suppression to reduce risk of recurrence

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Imaging Studies & Lab Testing

- Transvaginal ultrasound
  - May identify endometrioma and measure dimensions
  - Addition of color flow Doppler studies may improve its otherwise limited value
- Transrectal ultrasound
  - Enables visualization of rectal regions, bowel wall infiltrates
- CA-125 usually elevated, but non-specified and unhelpful

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Classical Medical Approaches to Treatment

- Pain suppression: NSAIDs including COX2 inhibitors
- Create pseudopregnancy state:
  - Progestin-only contraceptives: LNG-IUS, DMPA, POP, Implant
  - Combination hormonal contraceptives
- Create pseudo-menopausal state:
  - GnRH agonist +/- estrogen/progesterone add-back
  - GnRH antagonists
- Androgen derivatives
- ***Important point***: these are treatments, not cures

Progestin-Only LARC Methods

- Appropriate for women who do not desire pregnancy in the near future
- DMPA-SQ is an FDA-approved treatment for pain with endometriosis
  - Was as effective as GnRH agonists in reducing pain symptoms
- Dienogest as effective as GnRH agonists[1]
  - Progestin with antiangiogenic features
- LNG-IUS reduces recurrence of dysmenorrhea following surgical therapy[2]
- ENG implant equally effective as LNG-IUS in reducing CPP with endometriosis[3]

1. Andres MP, et al. *Arch Gynecol Obstet*. 2015;292(3):523-529.
2. Abou-Setta AM, et al. *Cochrane Database Syst Rev*. 2013;(1):CD005072. Pub3.
3. Carvalho N, et al. *Fertil Steril*. 2018;110(6):1129-1136.

Combined Hormonal Contraceptives

- 2/3 of women have relief from pain and have improvements in QOL[1]
  - Supporting data is low quality[2]
- Overall, CHC treatments provide effective relief of endometriosis-related dysmenorrhea, pelvic pain, and dyspareunia
- Oral contraceptives: any progestin (more potent? LNG, dienogest) or low estrogen (NETA)
  - Shorten or eliminate placebo days
- Vaginal ring: continuous use, provides low estrogen levels with good cycle control

1. Vercellini P, et al. *Fertil Steril*. 2016;106(7):1552-1571.e2.
2. Jensen JT, et al. *Fertil Steril*. 2018;110(1):137-152.e1.

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GnRH Agonists

- Creates pseudo-menopause state – decreases estrogen production
- Frequency of moderate to severe symptoms reduced
  - 82% to 11%[1]
- Duration of therapy limited to 6 months unless hormonal add-back therapy is used
  - Long-term studies demonstrate safety and efficacy[2]

1. Olive DL. *N Engl J Med*. 2008;359(11):1136-1142.
2. Bedaiwy MA, et al. *Fertil Steril*. 2017;107(3):537-548.

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Other Agents

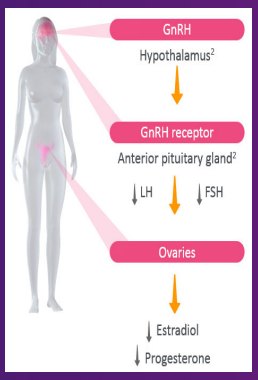
- Danazol: infrequently used due to androgen side effects
  - But effective and FDA-approved
- Aromatase inhibitors: off-label use for women with symptoms resistant to hormone therapy[1]
- GnRH antagonists[2]
  - Elagolix
  - Linzagolix (not FDA-approved)
  - Relugolix (not FDA-approved)

1. Ferrero S, et al. *Reprod Biol Endocrinol*. 2011;9:89.
2. Zondervan KT, et al. *N Engl J Med*. 2020;382(13):1244-1256.

Treatment of Endometriosis-Associated Pain: Elagolix

- In July 2018, the FDA approved elagolix as the first oral GnRH antagonist specifically developed for the treatment of moderate to severe pain associated with endometriosis.

Antagonist Effect: Elagolix Binds Competitively to the GnRH Receptor[1,2]



FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Antagonist Effect[1,2]

- Competes with endogenous GnRH for GnRH receptor occupancy in the anterior pituitary and blocks receptors upon binding, so fewer receptors are activated[1]
- Suppresses LH and FSH in a dose-dependent manner[1]
  - LH and FSH suppression begins within hours of administration and is reversible upon discontinuation[1]
- Leads to decreased serum levels of the ovarian sex hormones estradiol and progesterone[1]

1. Ng J, et al. *J Clin Endocrinol Metab*. 2017;102(5):1683-1691.
2. Bulun SE. *N Engl J Med*. 2009;360(3):268-279.

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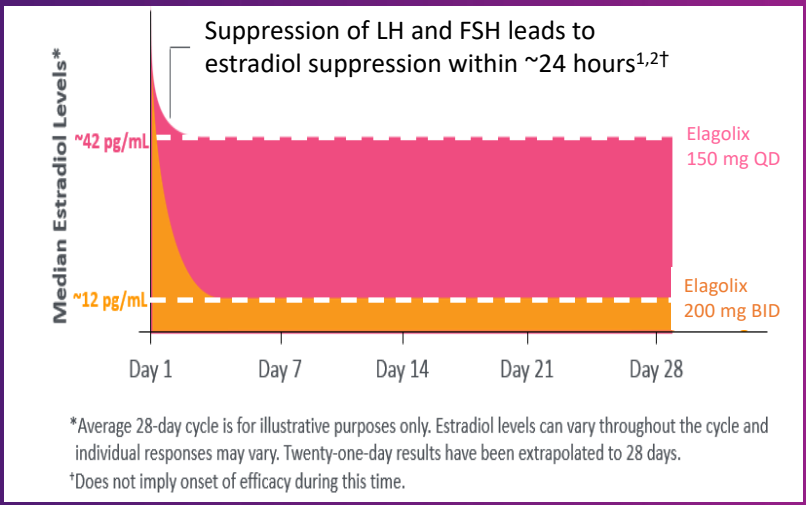
How Elagolix Works: Dose-Dependent LH and FSH Suppression[1,2]



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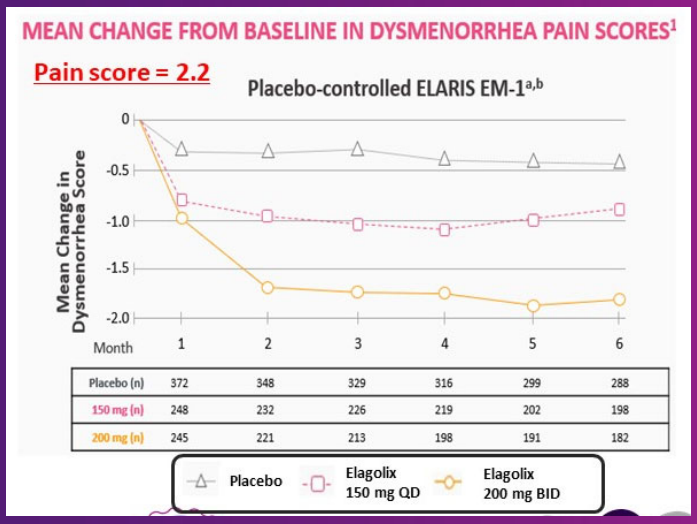
Dysmenorrhea Pain Scores



(Pain = 2.2)

Adapted from: Taylor HS, et al. *N Engl J Med*. 2017;377(1):28-40.

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Medical Therapies Under Investigation

- Aromatase inhibitors *(need for add-back given vasomotor symptoms/bone loss; concern for thrombosis with currently available agents)*
- Selective progesterone receptor modulators
- Immunomodulators
- Angiogenesis inhibitors
- Metalloproteinase inhibitors
- Estrogen receptor inhibitors
- Additional unapproved GnRH antagonists:
  (*OBE2019; Relugolix; ASP1707*)

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How Can We Work Together with Our Endometriosis Patients?

Optimizing Care for Women with Endometriosis: Patient-Centered Care and Shared Decision-Making

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Shared Decision-Making (SDM)

- Shared decision-making (SDM) is an approach in which clinicians and patients communicate using the best available evidence when making decisions
- Steps:
  - Introducing choice
  - Describing options, often by integrating the use of patient decision aids or support
  - Helping patients explore preferences and make collaborative decisions
- Components:
  - Understanding the risks associated with the condition
  - Understanding the options, including the benefits, risks, alternatives, and uncertainties
  - Weighing personal values regarding potential benefits and harms and respecting "what matters most" to patients as individuals
  - Participating in decision-making at the desired level

Stacey D, et al. Ann Pharmacother. 2004;38:566-68.
Elwyn G, et al. J Gen Intern Med. 2012 Oct; 27(10): 1361–1367.

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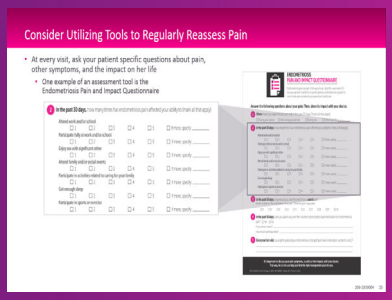
Strategies for Endometriosis Care

- General
  - Listen to your patient attentively: goals, fears, experiences
  - Develop relationship of trust and teamwork
  - Use decision aids when appropriate
- Treatment risk and benefits
  - Explain goals of therapy
  - Personalize treatment selection
    - Management plans should consider
      - Symptom severity
      - Potential for recurrence
      - Desire for fertility
      - Other considerations: cost, side effects, and route of administration
  - Describe risks that are common, including feared risks
  - Monitor for tolerance, compliance, persistence, and effectiveness



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Challenges in Shared Decision-Making

- Physicians typically spend less than 1 minute out of a 20-minute office visit discussing treatment and plans[1]
- Average time of an office visit is 7½ minutes[2]
- Informed decision-making occurs in only 9% of office visits[2]
- Physicians ask patients if they have questions in less than half of office visits[2]
- Patients recall only a fraction of the information presented[3,4]

1. Waitzkin H. *JAMA*. 1984;252(17):2441-2446.
2. AbbVie Endometriosis Dialogue Survey. 1/2017.
3. Braddock CH III, et al. *JAMA*. 1999;282(24):2313-2320.
4. Lloyd AJ, et al. *Lancet*. 1999;353(9153):645.

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Potential Benefits of Effective Risk Communication and Shared Decision-Making

- Patients have <u>better understanding</u> of:
  - Disease consequences
  - Benefits of therapy
  - Potential harms of therapy
- Reduced mistrust and fear
- Better collaboration between provider and patient; improved patient experience
- Improved adherence with therapy
- Improved health outcomes and quality of life
- Possible reduced costs

EndoSHARE

www.endoshare.net

Stacey D, et. al. *Cochrane Database Syst Rev*. 2014;(1):CD001431.
O'Connor AM, et al. *Health Aff (Millwood)*. 2004;Suppl Variation:VAR63-72.
Wilson SR, et al. *Am J Respir Crit Care Med*. 2010;181(6):566-577.
Naik AD, et al. *Circulation*. 2008;117(11):1361-1368.
Clever SL, et al. *Med Care*. 2006;44(5):398-405.

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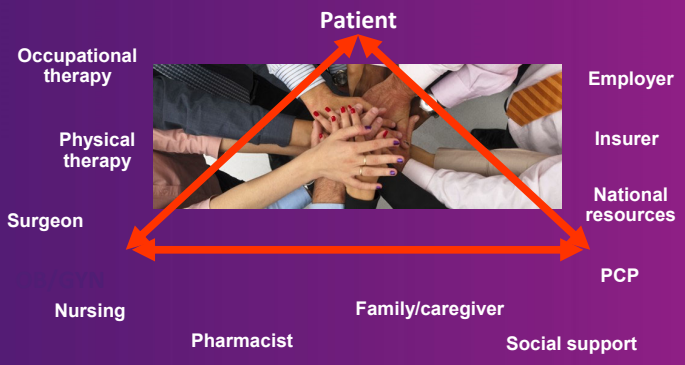
Endometriosis Management: A Team Approach Conclusion



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