

Individualizing Management of Endometriosis Pain: Current Evidence, Potential New Strategies, and Ongoing Research

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Conflict of Interest Disclosure

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Learning Objectives

At the end of this presentation, the participant will be able to

- Identify clinical practices that support the accurate and timely diagnosis of endometriosis
- Assess benefits and challenges of various medical therapies for initial and ongoing care of women with endometriosis
- Evaluate recent clinical trial and real-world data about the medical management of endometriosis

Endometriosis

- Endometriosis is a chronic inflammatory disorder that substantially reduces women's quality of life¹
- Technically defined as ectopic presence of glandular and stromal endometrial tissue with hemosiderin-laden macrophages
- Molecular differences exist between those endometriotic implants and normal endometrium¹
- Influenced by genetic, environmental, epidemiologic, inflammatory, immunologic, and angiogenic factors²
 - Even microbiome implicated³

Epidemiology

- Recent estimates: endometriosis affects 10% of reproductive-age women¹
 - ~ 190 million women worldwide
- Prevalence varies among different groups¹
 - 2%-11% asymptomatic women
 - 21%-47% women with subfertility
 - 71%-87% women with chronic pelvic pain
- Prevalence in young women is underappreciated²
- 75% of those unresponsive to medical therapy for pelvic pain have endometriosis³

Clinical Presentation of Endometriosis

- Average age of diagnosis – 28 years¹
 - 52% diagnosed between ages 18-29 years
- 86% symptomatic for 7-8 years on average before diagnosis made¹
 - Symptoms: dysmenorrhea (73%); pelvic pain (57%); dyspareunia (43%)²
- Women with endometriosis
 - 2.7 times more likely to have severe symptoms of other pains³
 - More likely to have co-existing conditions

Risk Factors for Endometriosis

- Family history¹
 - RR 7- to 10-fold higher if first-degree relative affected
- Early menarche¹
- Frequent or heavy menses¹
- Nulliparity¹
- Low BMI, alcohol use, autoimmune disease²
- Common genetic variants being identified²
- Uterine fibroids³

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2. Shigesu N, et al. *Hum Reprod Update.* 2019;25(4):486-503.
3. Lin KY, et al. *PLoS One.* 2021;16(8):e0256772.

Special Case: Endometriosis in Teens

- Signs and symptoms differ from adults¹
 - 90.6% acyclic pain +/- cyclic (62.5%)
 - >50% GI symptoms, GU symptoms²
- Migraines more prevalent in teens with endometriosis vs other teens³
- 1/3 of teens said dysmenorrhea and pain started before age 15⁴

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3. Miller JA, et al. Fertil Steril. 2018;109(4):685-690.
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Endometriosis Impacts

- Two important impacts: pain and infertility¹
- Costs similar in magnitude to costs for type 2 DM, Crohn's disease, rheumatoid arthritis²
- The cost of care to manage the spectrum of symptoms is much greater
 - Affects physical, mental, sexual, and social well-being as well as productivity³
 - Societal burden of endometriosis: \$49 billion per year if indirect costs and productivity losses are included⁴
- Pain is intense: opiate use 3x higher than controls³ and used by 2/3⁵

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2. Simoens D, et al. Hum Reprod. 2012;27(5):1292-1299.
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Endometriosis-Related Symptoms

- Chronic pelvic pain (acyclic)
- Dysmenorrhea
- Deep dyspareunia
- Dysuria
- Dysphasia
- Fatigue
- Infertility
- Somatosensory amplification

Significant decrease in quality of life

Manifestations of Endometriosis

- Superficial peritoneal lesions
 - Various colors (clear, yellow, red, brown, blue-black)
 - Various locations
- Ovarian endometrioma
- Deep infiltrative endometriosis
 - Vascularization of lesions
 - Innervation of lesions
 - Scarring or adhesions within the pelvic cavity
 - Extra-pelvic lesions

Pathophysiology Then and Now

- Classical Sampson's theory
 - Retrograde menstruation
 - Coelomic metaplasia
 - Lymphatic and vascular metastasis
- Newer, much more complex process envisioned
 - Immune factors
 - Hormonal factors
 - Inflammatory response
 - Heritable factors

Endometriosis as a Public Health Problem

- Major impact on QOL and economic cost
- Diagnosis now based on structural process of patient interview, clinical examination, and imaging
- Need to rethink old approach with immediate surgery
 - Consider patient's "endometriosis life"
- Medical management is first-line therapeutic option for women with pelvic pain and no desire for immediate pregnancy
- Modern endometriosis care should be individualized with patient-centered, multimodal, and interdisciplinary integrated approach

Challenges in Making the Diagnosis

- Patient hesitancy to bring up due to past disappointments, stigma
 - Diagnosis missed, treatment incomplete
- Varied physical manifestations, superficial lesions, deep infiltrative disease, endometrioma, severe dysmenorrhea
- Nonspecific or no symptoms, dyspareunia, chronic pelvic pain, infertility, dysphasia. . .
- Past reliance on surgical diagnosis
- Lack of public (and professional) awareness of the problem

Differential Diagnoses for Endometriosis (Level A)

- Adenomyosis
- Interstitial cystitis
- GYN, GU, GI malignancy
- Ovarian retention syndrome
- IBD, IBS
- Constipation, celiac disease, diverticulosis
- Pelvic adhesions
- Fibromyalgia, myofascial syndromes
- Neurological disorders, depression, anxiety

Key Considerations for Patient Care Strategies

- Acute symptoms and problems patient is dealing with
 - Impacts on her quality of life and relationships
- Comorbidities
- Reproductive life plans
- Longer-term health consequences
- Patient preferences
- Expectation of patient: treatment vs cure

Women's Emerging Reliance on Social Media

- Social media increasingly becoming a health resource for people with complex or debilitating health conditions
- Reproductive health-related concerns make up 90% of social media health inquiries made by women
- Women with pain are almost twice as likely to use social media to understand or manage their GYN conditions
- Women with pain are almost twice as likely to trust the information they find on social media

Current Approaches

- Endometriosis is now a clinical diagnosis initially; a complete pelvic exam is needed
 - Surgery can be reserved for cases that do not respond to medical therapy, pelvic masses, and acute presentation
 - Other individualized indications
- Design therapies that address woman's current complaint but also bridge to long-term suppression to reduce risk of recurrences

Imaging Studies

- Transvaginal ultrasound
 - Identify endometrioma (93% sensitive; 96% specification)
 - Addition of color flow Doppler studies may improve its otherwise limited value
 - 3D imaging holds some promise
- Transrectal ultrasound
 - Enables visualization of rectal regions, bowel wall infiltrates
- MRI

Classic Medical Treatments of Endometriosis

- One of two effects desired
 - Pseudo-decidualization and atrophy of implants (pseudopregnancy)
 - Progestin-only therapies
 - Progestin-dominant combined hormonal therapy
 - Pseudo-menopause to suppress estrogen
 - Androgens
 - GnRH agonists
 - Aromatase inhibitors
- Combine with inhibition of inflammation and pain
 - NSAIDs, opioids
- Important point: these are all treatments, not cures

Combined Oral or Vaginal Contraceptives as First-Line Therapy

- Progestational effects are key to success
 - 2/3 of women have relief from pain and have improvement in QOL
- Continuous use superior to cyclic use¹
 - After surgery, less recurrence of:
 - Dysmenorrhea
 - Nonspecific pelvic pain
 - Endometrioma
- Progestin resistance can develop

Combined Oral Contraceptives Lessons

- Cochrane – insufficient evidence that treatment with COCs is superior to placebo¹
 - High degree of bias in studies
- Desogestrel in multiphasic pills as effective as GnRH analogues^{2,3}
- 25%-30% of women may have or develop progesterone resistance⁴

Progestin-Only Treatments

- Progestin-only pills may be better than combined therapies
- Dienogest 2 mg/day shrunk implants and reduced pain¹
 - Antiangiogenic properties important
- LNG-IUS 20 vs ENG implant²
 - 42.5% and 55.6% reduction in pain scores, respectively
- LNG IUS 20 effective in pain suppression following surgery³
- LNG IUS 20 vs depot GnRH analogue for CPP⁴

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4. Petta CA, et al. Hum Reprod. 2005;20(7):1993-1998.

Progestin-Only Treatments

- DMPA vs continuous COC postoperatively
 - DMPA reduced pain more¹
- SQ DMPA vs GnRH agonist
 - Equivalent symptom relief²
 - FDA-approved for treatment of pain symptoms of endometriosis

Medical Therapies for Endometriosis

Other

- Older treatments
 - GnRH agonists
 - Leuprolide depot, Goserelin, Nafarelin +/- add-back
 - Androgenic steroids
 - Danazol – infrequently used due to side effects
- Emerging options
 - GnRH antagonists
 - Aromatase inhibitors (off-label)
 - Selective progesterone receptor modulators (not in USA)

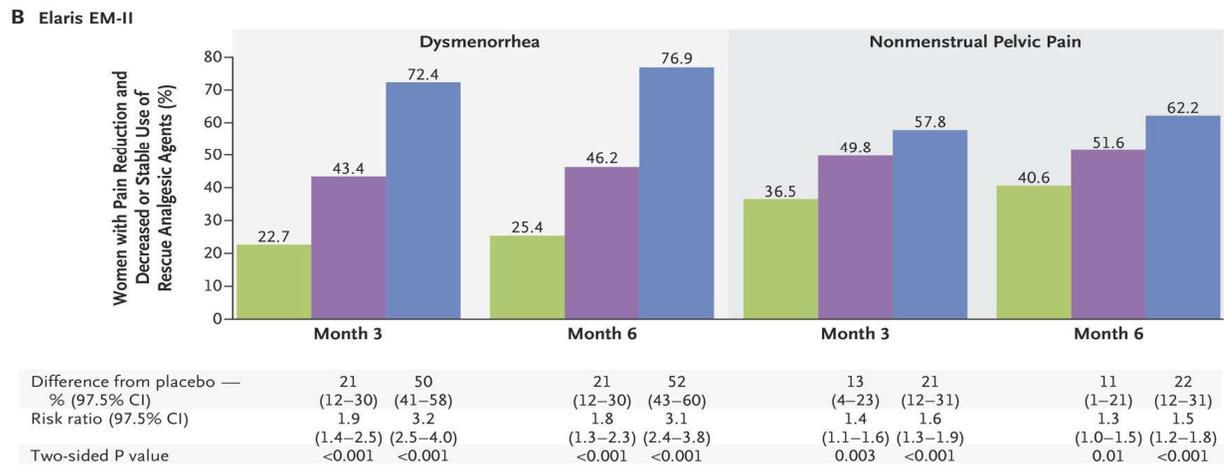
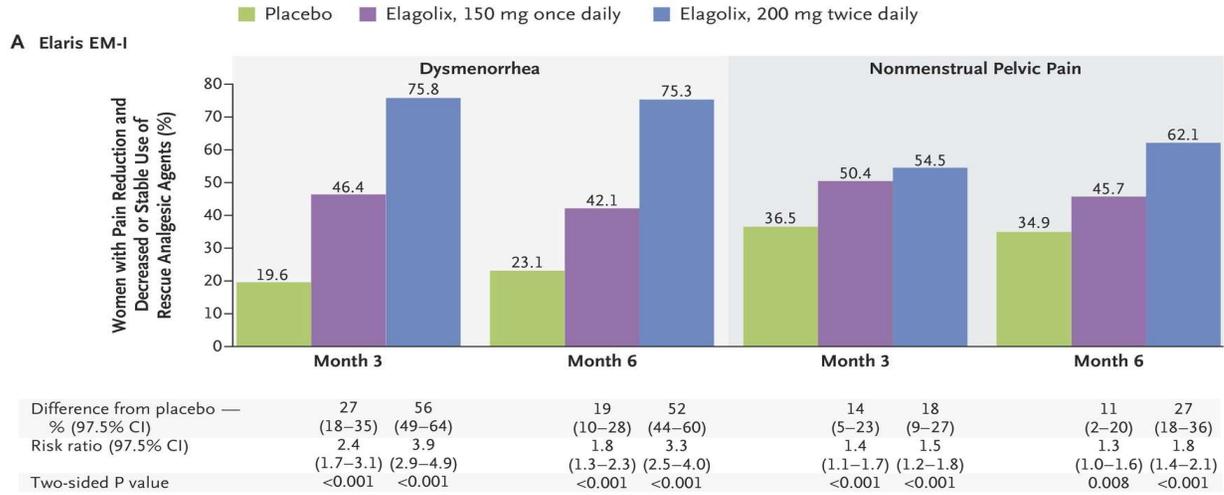
Treatment of Endometriosis-Associated Pain: Elagolix

- 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.
- Supporting clinical trial data came from 2 similar double-blind studies:
 - Elaris EM-I (EM-I) and Elaris EM-II (EM-II)

Elagolix: EM-I and EM-II (Taylor and colleagues, 2017)

- Both randomized, 6-month, phase 3 trials in endometriosis
- Evaluated elagolix as:
 - Low dose, 150 mg q.d.
 - High dose, 200 mg BID
- 872 women were randomized in EM-I; 817 in EM-II, resulting in evaluation of 653 and 632 women, respectively
- Endpoints: clinical response to dysmenorrhea and nonmenstrual pelvic pain at 3 months
 - Endpoints also assessed at 6 months

Results from EM-I and EM-II



Elagolix 6-Month Endometriosis Extensions (EM-III and EM-IV)

- Evaluated efficacy and safety of elagolix over 12 months
 - An additional 6-month treatment for women in EM-I and EM-II phase 3 trials
- Same 2 elagolix doses tested: 150 mg q.d and 200 mg BID
- Endpoints: clinically meaningful pain reduction and nonmenstrual pelvic pain scores
 - Data on dyspareunia were also reported

EM-III and EM-IV Results: Proportion of Responders

| Responders* | Elaris EM-III | | Elaris EM-IV | |
|---------------------------------|--------------------|---------------------|--------------------|---------------------|
| | Elagolix 150 mg QD | Elagolix 200 mg BID | Elagolix 150 mg QD | Elagolix 200 mg BID |
| Dysmenorrhea | | | | |
| 6 mo of treatment [†] | 60/149 (40.3) | 109/136 (80.1) | 72/142 (50.7) | 107/140 (76.4) |
| 12 mo of treatment [‡] | 61/117 (52.1) | 86/110 (78.2) | 62/122 (50.8) | 88/116 (75.9) |
| Nonmenstrual pelvic pain | | | | |
| 6 mo of treatment [†] | 74/149 (49.7) | 96/136 (70.6) | 82/142 (57.7) | 89/140 (63.6) |
| 12 mo of treatment [‡] | 79/117 (67.5) | 76/110 (69.1) | 81/122 (66.4) | 78/116 (67.2) |
| Dyspareunia | | | | |
| 6 mo of treatment [†] | 42/113 (37.2) | 54/92 (58.7) | 47/108 (43.5) | 62/100 (62.0) |
| 12 mo of treatment [‡] | 38/84 (45.2) | 42/70 (60.0) | 39/85 (45.9) | 43/74 (58.1) |

QD, once daily; BID, twice daily.

Data are n/N (%).

Between-group comparisons were not predefined and not performed. Data are observed, nonmissing data.

* Responders had a clinically meaningful reduction in the respective type of pain and stable or decreased rescue analgesic use.

[†] Month 6 in the preceding double-blind, placebo-controlled trials; data are from women who enrolled in the extension studies.

[‡] After an additional 6 months of treatment in the extension study; some women received greater than 6 months of additional elagolix treatment while individual eligibility for extension study enrollment was assessed (see Materials and Methods).

Elagolix Impact on Non-Pain Symptoms in Endometriosis

- HRQoL was assessed using the 30-item Endometriosis Health Profile (EHP-30) score
- Assessed 5 core domains:
 - Pain (11 questions)
 - Control and powerlessness (6 questions)
 - Emotional well-being (6 questions)
 - Social support (4 questions)
 - Self-image (3 questions)
- Also added intercourse as the 6th domain (5 questions)
- Elagolix therapy over the 6-month period significantly reduced EHP-30 scores across all domains
- The higher 200-mg dose BID was more effective than the lower 150-mg dose q.d.

Relugolix: FDA Status for Endometriosis and ASRM 2021

- Relugolix, an oral GnRH antagonist, is currently under review at the FDA for the treatment of moderate to severe pain associated with endometriosis
- The NDA submission is based on data from SPIRIT 1 and SPIRIT 2 clinical trials, in addition to the phase 3 SPIRIT extension study
 - PDUFA date for relugolix is May 6, 2022
- At ASRM, the effect of Rel-CT on health-related quality of life (QoL) was evaluated; 1,261 women were randomized 1:1:1 to once-daily Rel-CT, placebo, or delayed Rel-CT (relugolix 40 mg monotherapy then Rel-CT for 12 weeks each)
- With Rel-CT vs placebo, the proportions of dysmenorrhea and of NMPP responders were 74.9% vs 28.6% and 62.2% vs 41.1%, respectively (both $P < 0.0001$)

SPIRIT 1 and 2 Composite Findings at 24 Weeks: Presented at ASRM 2021 (EHP-30 Total Score Outcomes)

| | Rel-CT (n = 411) | Placebo (n = 412) | Change from Baseline to Week 24 | | P value (Rel-CT vs Placebo) at Week 24 |
|----------------------------------|---------------------|----------------------|---------------------------------|----------------------|---|
| | | | Rel-CT (n = 343) | Placebo (n = 327) | |
| Total Score | 56.9 (0.9) | 54.4 (0.9) | -29.9 (1.2) | -17.7 (1.2) | <0.0001 |
| Pain | 58.3 (0.9) | 56.2 (0.9) | -33.0 (1.2) | -19.2 (1.2) | <0.0001 |
| Emotional Well-Being | 51.0 (1.2) | 47.7 (1.2) | -23.3 (1.3) | -14.6 (1.3) | <0.0001 |
| Control and Powerlessness | 65.2 (1.2) | 61.9 (1.2) | -37.4 (1.4) | -22.6 (1.4) | <0.0001 |
| Self-Image | 51.9 (1.4) | 48.8 (1.4) | -23.3 (1.5) | -12.2 (1.5) | <0.0001 |
| Social Support | 54.0 (1.4) | 52.6 (1.4) | -24.7 (1.4) | -15.3 (1.5) | <0.0001 |

Linzagolix Findings in Endometriosis (in Clinical Trials)

- Linzagolix is a GnRH antagonist being studied for the management of endometriosis pain
- The phase 2b EDELWEISS 1 study has been completed
- Evaluated 75, 100, and 200 mg doses for 24 weeks, with possible extension to 52 weeks
- Primary endpoint was proportion of patients with $\geq 30\%$ reduction in pelvic pain over 28 days
- At week 12, significant reductions were observed at ≥ 75 mg and maintained through to 52 weeks

Linzagolix Findings in Endometriosis (con't.)

- Pivotal phase 3 clinical trials have been initiated
- EDELWEISS 2 (US, since discontinued due to pandemic)
- EDELWEISS 3 (US and EU); anticipated completion 4Q 2021
 - Will enroll approx. 450 patients
 - Co-primary endpoints of reductions in dysmenorrhea/menstrual pain and nonmenstrual pelvic pain
 - Study includes patients receiving 200 mg linzagolix with or without add-back therapy
 - For patients completing the 6-month course, a 6-month extension study will be offered

New Developments in Endometriosis

- New appreciation that this is a chronic, progressive inflammatory process that has systemic health impacts
- New understanding that adolescent and young women are frequently affected
 - Recognition that a delay in diagnosis of 7+ years persists
- New practice approaches for diagnosis are minimizing role of surgery
- New medical therapies to treat and suppress condition

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

Challenges in Shared Decision-Making

- Physicians typically spend less than 1 minute out of a 20-minute office visit discussing treatment and plans¹
- Average duration of an office visit is 7½ minutes²
- Informed decision-making occurs in only 9% of office visits²
- Physicians ask patients if they have questions in less than half of office visits²
- Patients recall only a fraction of the information presented^{3,4}

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Potential Benefits of Effective Risk Communication and Shared Decision-Making

- Patients have better understanding 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

The image displays two versions of the EndoSHARE 'Recommended action plan' form. The left version is a printed form with sections for 'TODAY'S DATE', 'GOALS' (Short term and Long term), 'CURRENT RECOMMENDED MANAGEMENT', 'Future insulin and other management', 'FUTURE MANAGEMENT OPTIONS', 'FOLLOWUP VISIT DATE', and 'NOTES'. The right version is a digital form with sections for 'START DATE', 'GOALS', 'CURRENT RECOMMENDED MANAGEMENT', 'Future insulin and other management', 'FUTURE MANAGEMENT OPTIONS', 'FOLLOWUP VISIT DATE', 'NOTES', and 'Management status in collaboration' (with sub-sections for Address, Safety, and Other). Both forms include a header with the EndoSHARE logo and title.

EndoSHARE

www.endoshare.net

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