EndoShare: Personalizing Treatment of Endometriosis

Introduction

Endometriosis is defined as a chronic inflammatory disease characterized by the presence of endometrial tissue outside the uterus that results in pelvic pain and infertility,[1] both of which diminish patient quality of life. Typical symptoms of endometriosis include dysmenorrhea, dyspareunia, menorrhagia, non-menstrual cycle pelvic pain, dysuria, chronic fatigue, and infertility.[2,3] Levels of both estrogen and progesterone play a role in the pain associated with endometriosis; endometriotic lesions display variable levels of estrogen and progesterone receptors, influencing hormonal responsiveness.[4]

Clinical practice guidelines for the treatment of endometriosis and pain associated with endometriosis suggest that endometriosis is best viewed as a chronic medical disease requiring lifelong management through the optimal use of medical treatment and avoidance of repeated surgical procedures (e.g., laparoscopic ablation and excision).[5] Importantly, pain associated with endometriosis may involve different mechanisms; thus, selection of treatment is best individualized,[5] with consideration toward desired pregnancy if applicable. The three most common mechanisms for pain associated with endometriosis include: 1) production of growth factors and cytokines; 2) effects of active bleeding from endometriotic implants; and 3) irritation of pelvic floor muscles.[5] Since pain and pelvic adhesions relapse when medical therapy is discontinued, treatment is long term; side effects, costs, and complexities of regimens must be taken into account when selecting treatment.

Treatment Options for Endometriosis

Treatment options for endometriosis may be classified as hormonal, non-hormonal, non-pharmacological, and surgical. Evidence-based data is greatest for hormonal therapies as there is limited data on non-hormonal (e.g., magnesium, minerals, and vitamins B1 and B6) and non-pharmacological (e.g., acupuncture, psychological, and transcutaneous electrical nerve stimulator) therapies.[6] Of note, data suggest that nearly 25% of OB-GYN clinicians prescribe opioid therapy for endometriosis, and nearly 20% prescribe opioid therapy for chronic pelvic pain of unknown cause;[7] the use of opioids for chronic pelvic pain (e.g., endometriosis and interstitial cystitis) should be avoided due to the limited evidence of their effectiveness in these pain states.[8] Laparoscopic surgery (e.g., ablation and excision) may significantly improve pain associated with endometriosis as well as increase clinical pregnancy rates in women with endometriosis.[9,10]

Currently available hormonal therapies include, but are not limited to:[6,11]

- **NSAIDs (e.g., ibuprofen and celecoxib)**: Lower inflammatory markers (e.g., COX and prostaglandin); while effective for treatment of primary dysmenorrhea,[12] a Cochrane analysis found insufficient evidence that NSAIDs significantly reduce pain associated with endometriosis.[13]
- **Combination oral contraceptives**: Combined oral contraceptives, especially those with more androgenic progestogens (derivatives of 19-nortestosterone) have been used to treat symptoms of endometriosis; desogestrel (progestin) is also effective.[14]Continuous low-dose oral

contraceptives vis-à-vis cyclic combination oral contraceptives may be more effective for controlling symptoms of endometriosis after surgical treatment; this is not an FDA-approved indication for most combined oral contraceptives.[15]

- **Progestins/progestogens (medroxyprogesterone, levonorgestrel, norethindrone acetate, dienogest)**: Levonorgestrel-releasing intrauterine system has been shown to be an effective post-operative maintenance therapy of endometriosis pain relief, while preventing recurrence of dysmenorrhea;[16,17] superior to danazol and comparable to GnRH agonists for pain relief;[16] may be associated with higher vaginal bleeding compared to GnRH agonists.[16]

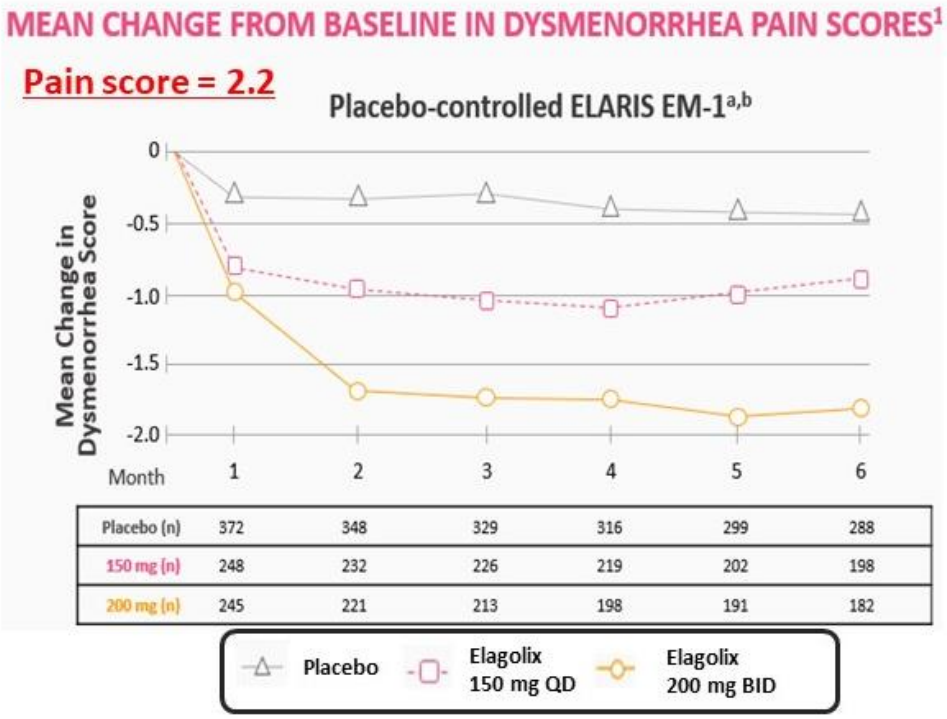
- **Danazol**: Acts by inhibiting the surge in luteinizing hormone (LH) and steroidogenesis while increasing free testosterone;[18]danazol may be associated with hirsutism, acne, and weight gain.[19]

- **Gonadotropin-releasing hormone (GnRH) agonists (e.g., nafarelin, leuprolide, buserelin, goserelin, and triptorelin—not all are FDA-approved for endometriosis)[10]**: GnRH agonists bind to receptors in the pituitary, resulting in downregulation of the pituitary-ovarian axis and hypoestrogenism.[5] GnRH agonists likely relieve the pain of endometriosis through the induction of amenorrhea and progressive endometrial atrophy through initial super-stimulation of pituitary receptors, producing high levels of LH and FSH and temporarily increasing FSH and LH; this is otherwise known as the "flare response."[11,18] With pituitary fatigue comes decreased estrogen and progesterone. Side effects of GnRH agonists include hot flashes, headache, vaginal dryness, mood swings, and depletion of bone mineral.[20] Long-term data suggest a 53% recurrence of disease/symptoms after 2 years following 6 months of treatment with GnRH agonist monotherapy.[21] Use of "add-back" therapy with norethindrone acetate may reduce bone loss and other hypoestrogenic symptoms.[5]

- **GnRH antagonists (e.g., elagolix, ganirelix, and cetrorelix)** – GnRH antagonists suppress pituitary gonadotropin in a dose-dependent manner. Unlike GnRH agonists, GnRH antagonists produce a more immediate impact on estrogen and progesterone levels and do not activate pituitary receptors, thus avoiding the flare response. Ganirelix and cetrorelix are parenteral formulations, while elagolix is an oral formulation; only elagolix is approved by the FDA for use in endometriosis.

Elagolix is a non-peptide, oral, GnRH receptor antagonist approved for the management of moderate to severe pain associated with endometriosis.[22] Elagolix suppresses LH and FSH in a dose-dependent manner, with suppression beginning within hours of administration, which results in decreased serum estradiol and progesterone.[23] Both doses of elagolix are effective in improving dysmenorrhea pain scores (see Figure 1) and non-menstrual pelvic pain in women with endometriosis-associated pain.[24]In the Elaris EM-I study, clinical response related to dysmennorhea was 46.4%, 75.8%, and 19.6% with elagolix 150mg daily, elagolix 200 mg BID, and placebo, respectively. In Elaris EM-II, the corresponding percentages were 43.3%, 72.4%, and 22.7%, respectively (P<0.001 for all comparisons).[24] With respect to clinical response in non-menstrual pelvic pain, the percentages in Elaris EM-I were 50.4%, 54.5%, and 36.5%, respectively, and in Elaris EM-II, the percentages were 49.8%, 57.8%, and 36.5%, respectively. The response was sustained at 6 months for both outcomes.[24]

Figure 1. Dysmenorrhea pain scores from Elaris EM-I.[24]



Investigational Therapies

Efforts are continuing to find more effective and favorably tolerated treatment options for endometriosis and/or the pain associated with endometriosis. Such agents may include, but are not limited to:[11]

- Aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane) – inhibit extra-ovarian synthesis of estrogen[2]
- Selective progesterone receptor modulators[18]
- Immunomodulators
- Angiogenesis inhibitors[18]
- Metalloproteinase inhibitors[18]
- Estrogen receptor inhibitors[18]
- Next-generation GnRH antagonists (e.g., linzagolix, opigolix, and relugolix)

Shared Decision Making

Shared decision making is a process emphasizing collaborative interaction between the patient and physician in arriving at informed treatment decisions. Data indicate that shared decision making can

improve patient adherence to treatment and improve outcomes as well.[25-27] Through this process, patients have a better understanding of disease consequences, benefits of therapy, and potential risks associated with treatment. Indeed, better collaboration between the patient and physician results in improved patient experience. For patients with endometriosis, that includes discussions about infertility and risk communication.

Conclusions

Endometriosis is a chronic disease associated with significant morbidity, which is why it necessitates long-term treatment. Medical therapy and surgical approach are recommended by clinical practice guidelines for its management, with medical therapy recommended as a first option in most cases. Medical therapy should be individualized based on patient symptoms and the severity of disease in the context of quality of life.

References:

1. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol*. 2019;15(11):666-682.
2. Slopien R, Meczekalski B. Aromatase inhibitors in the treatment of endometriosis. *Prz Menopauzalny*. 2016;15(1):43-47.
3. Fuldeore MJ, Soliman AM. Prevalence and symptomatic burden of diagnosed endometriosis in the United States: national estimates from a cross-sectional survey of 59,411 women. *Gynecol Obstet Invest*. 2017;82(5):453-461.
4. Donnez J, Gillet N, Nisolle M, Beguin S, Smoes P, Casana-Roux F. Peritoneal endometriosis and "endometriotic" nodules of the rectovaginal septum are two different entities. *Fertil Steril*. 1996;66(3):362-368.
5. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertil Steril*. 2014;101(4):927-935
6. Hirsch M, Begum MR, Paniz E, Barker C, Davis CJ, Duffy JMN. Diagnosis and management of endometriosis: a systematic review of international and national guidelines. *BJOG*. 2018;125(5):556-564.
7. Madsen AM, Stark LM, Has P, Emerson JB, Schulkin J, Matteson KA. Opioid knowledge and prescribing practices among obstetrician-gynecologists. *Obstet Gynecol*. 2018;131(1):150-157.
8. Steele A. Opioid use and depression in chronic pelvic pain. *Obstet Gynecol Clin North Am*. 2014;41(3):491-501.
9. Jacobson TZ, Duffy JMN, Barlow D, Koninckx PR, Garry R. Laparoscopic surgery for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev.* 2009;4:CD001300.
10. Brown J, Farquhar C. An overview of treatments for endometriosis. *JAMA.* 2015;313(3):296-297.
11. Cohen S, Singer AJ. EndoShare 2019: Personalizing Treatment Choices. Presented at Women's Health 15th Anniversary Annual Visit. Presented October 11, 2019, New York, New York.
12. Marjoribanks J, Proctor ML, Farquhar C. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhea. *Cochrane Database Syst Rev*. 2003;(4):CD001751.
13. Allen C, Hopewell S, Prentice A, Gregory D. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev*. 2009;(2):CD004753.
14. Razzi S, Luisi S, Ferretti C, et al. Use of a progestogen-only preparation containing desogestrel in the treatment of recurrent pelvic pain after conservative surgery for endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2007;135(2):188-190.
15. Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. *Fertil Steril* 2003;80(3):560-563.

16. Song SY, Park M, Lee GW, et al. Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2018;231:85-92.
17. Taneja A, Kaur S, Soni RK, Bhanupriya, Kaur J, Singla L. Evaluating the efficacy of levonorgestrel intrauterine system and danazol for relief of postoperative pain in endometriosis. *J Clin Diagn Res*. 2017;11(7):QC10-QC12.
18. Olive DL. Medical therapy for endometriosis. *Semin Reprod Med*. 2003;21(2):209-222.
19. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev*. 2001(4):CD000068.
20. Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotropin-releasing hormone analogues for endometriosis: bone mineral density. *Cochrane Database Syst Rev*. 2003(4):CD001297.
21. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis. *Fertil Steril.* 1993;59(3):511-515.
22. Orilissa (elagolix) prescribing information [package insert], revised August 2019. AbbVie, Inc., North Chicago, Illinois 60064. Available at https://www.rxabbvie.com/pdf/orilissa_pi.pdf.
23. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab*. 2017;102(5):1683-1691.
24. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377(1):28-40.
25. Wilson SR, Strub P, Buist AS, et al; Better Outcomes of Asthma Treatment (BOAT) Study Group. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med*. 2010;181(6):566-577.
26. Naik AD, Kallen MA, Walder A, Street RL Jr. Improving hypertension control in diabetes mellitus: the effects of collaborative and proactive health communications. *Circulation*. 2008;117(11):1361-1368.
27. Clever SL, Ford DE, Rubenstein LV, et al. Primary care patients' involvement in decision-making is associated with improvement in depression. *Med Care.* 2006;44(5):398-405.