(Excerpt from Needs Assessment)

Management of Pain Associated With Endometriosis: An Update on Hormonal Therapies

BACKGROUND

Endometriosis is one of the most common causes of chronic pelvic pain in women.[1,2] This chronic condition affects 6% to 10% of women of reproductive age and nearly 90% of women with chronic pelvic pain.[2-4] Endometriosis is characterized by the presence of endometrial-like tissue outside of the uterus.[5,6] The resulting inflammatory reaction is mediated by the overproduction of cytokines and prostaglandins in the peritoneal fluid.[2,5] While some women are asymptomatic, many others are affected by pelvic adhesions, scarring, and pain.[2,5]

Medical suppressive therapy is effective in managing pain associated with endometriosis.[2,5] Suppression of estrogen production inhibits endometrial tissue growth and prevents progression of the disease.[5] Hormonal therapies available for the management of pain associated with endometriosis include combined oral contraceptives (COC), progestins, androgens, and gonadotropin-releasing hormone (GnRH) agonists.[2,5]

Current hormonal options improve pain during treatment, but recurrence of symptoms is common after the medication is discontinued.[2,5] In addition, side effects, such as irregular uterine bleeding and loss of bone mineral density (BMD), limit their long-term use on some patients.[2,5,6]

In July of 2018, elagolix, a GnRH antagonist, was approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe pain associated with endometriosis.[7] This is the first FDA-approved oral treatment for this indication in over a decade. However, similar to other suppressive therapies, elagolix treatment is associated with hypoestrogenic adverse events.[6,8]

Chronic pelvic pain can decrease a patient's quality of life and result in a substantial economic burden.[9,10] Many women with endometriosis report lack of support from healthcare providers in regards to the management of pain.[11] Clinicians would benefit from additional education on the efficacy and safety data of established and novel treatments for management of pain associated with endometriosis.

EDUCATIONAL ANALYSIS

Gap #2: Clinicians may not be familiar with the limitations and safety concerns of established and new therapies for the management of pain associated with endometriosis.

Hormonal treatment results in improvement of pain associated with endometriosis, but pain recurrence is common after the medication is discontinued.[2,5] In addition, side effects associated with hormonal options often limit their long-term use.[2,5,6] Their main mechanism of action, suppression of estrogen production, makes hormonal medications contraindicated in patients actively attempting pregnancy.[5] With new therapies available, clinicians have a greater need for education on the safety data of current and novel treatments for management of pain associated with endometriosis.

Long-term use of COC is effective and well tolerated by a large proportion of women with endometriosis.[2,13,23] However, women might experience irregular uterine bleeding when using an extended regimen.[13] Other less common side effects include headaches and bloating.[13]

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The main safety concern with the use of COC is the risk of venous thromboembolism (VTE), which is increased among users of COC compared to nonusers.[23,24] However, the overall risk of VTE during COC use is low and much lower than the risk of VTE during pregnancy and the immediate postpartum.[24] Clinicians should consider the patient's risk factors and refer to the "U.S. Medical Eligibility Criteria for Contraceptive Use", issued by the Centers of Disease Control and Prevention, when prescribing COC.[25]

Prolonged hypoestrogenic state can lead to BMD loss.[2] Treatment with subcutaneous DMPA results in less BMD loss compared with leuprolide acetate (an injectable GnRH agonist).[19,20] In prior studies, BMD loss associated with DMPA returned to pretreatment levels by 12 months.[19,20] Treatment with DMPA is associated with a delay in resumption of ovulation, which limits its use to those not desiring pregnancy soon after treatment.[2]

Side effects associated with the use of a GnRH agonist include hot flushes, increased lipid levels, BMD loss, vaginal dryness, and mood swings.[1,2] Treatment is usually limited to 12 months due to the impact on BMD, but guidelines by ACOG indicate that longer treatment can be considered in patients with good response.[2] Norethindrone acetate is FDA approved as an add-back therapy, which protects against BMD loss, during treatment with a GnRH agonist.[1,2]

Danazol, an androgenic drug, is effective for the management of pain associated with endometriosis.[2,21] However, it is not as well tolerated as other options due to side effects such as acne, hirsutism, and myalgias.[2]

In phase 3 trials evaluating elagolix, the incidence of hot flushes, described by most participants as mild to moderate, was significantly higher with both doses of elagolix compared with placebo ($P < .001$).[6] More patients reported headaches with 200 mg twice daily dose of elagolix compared with placebo ($P < .05$).[6] After 12 months of treatment, a greater percentage of women in the 200-mg twice-daily group had a decrease of more than 5% in baseline lumbar spine BMD.[8] After treatment was discontinued, an improvement of lumbar spine BMD was observed.[8]

CONCLUSION

Endometriosis is a chronic gynecologic disorder affecting a substantial number of women of reproductive age. Chronic pelvic pain, a common symptom associated with endometriosis, can decrease the patient's quality of life and result in a significant economic burden. Hormonal suppressive therapies, while effective in managing pain, are associated with side effects that can limit their use on some patients. With new therapies available, clinicians have a greater need for education on the safety data of current and novel treatments for management of pain associated with endometriosis.

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Clinical Practice Gap	Educational Need	Learning Objective	Type of Gap	ACGME Competencies
Clinicians may not be familiar with the limitations and safety concerns of established and new therapies for the management of pain associated with endometriosis	To improve patient outcomes, clinicians need to be familiar with the limitations and safety concerns of the available hormonal treatment options for the management of pain associated with endometriosis	Discuss the limitations and safety concerns of the available hormonal treatments for the management of pain associated with endometriosis	Competence	Medical knowledge Practice-based learning and improvement

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