Update on pharmacologic treatment for endometriosis-related pain

By Caitlin Henderson, MSN, RN, WHNP-BC, and Jennifer Hofmann, MS, PA-C

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners and other healthcare providers who provide primary care for women.

CE approval period: Now through June 30, 2022

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit, including 0.5 contact hours of pharmacology content

Goal statement: Nurse practitioners and other healthcare providers who provide primary care for reproductive-aged women will increase their knowledge about pharmacotherapeutic options and nonpharmacologic approaches for the management of endometriosis-related pelvic pain.

Needs assessment: Endometriosis is one of the most common causes of chronic pelvic pain in reproductive-aged women. It can adversely affect quality of life, daily activities, work and school productivity, and both sexual and nonsexual relationships. Nurse practitioners and other healthcare providers who provide primary care for reproductive-aged women need to be knowledgeable about and able to make appropriate choices regarding pharmacotherapeutic options and nonpharmacologic therapy for individualized care of women suffering from endometriosis-related pelvic pain.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Identify risk factors, common symptoms, and physical examination findings associated with endometriosis.
2. Describe indications, mechanism of action, efficacy, adverse effects, and contraindications for pharmacologic options in treating endometriosis-related pelvic pain.
3. Discuss nonpharmacologic treatments for endometriosis-related pelvic pain.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH) and has been approved for 1.0 contact hour of CE credit, including 0.5 hours of pharmacology credit.

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Caitlin Henderson, MSN, RN, WHNP-BC, has no actual or potential conflicts of interest in relation to the contents of this article.
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Endometriosis is one of the most common causes of chronic pelvic pain in reproductive-aged women. Treatment for endometriosis can be pharmacologic, surgical, or both. In this article, the authors focus on current pharmacologic options for endometriosis-related pelvic pain and also discuss nonpharmacologic approaches.

KEY WORDS: **endometriosis-related pelvic pain, NSAID, hormone therapy, gonadotropin-releasing hormone agonist, aromatase inhibitor, gonadotropin-releasing hormone antagonist**

Endometriosis, characterized by the appearance of endometrial implants outside the uterine cavity, is one of the most common causes of chronic pelvic pain (CPP), affecting 5% to 10% of reproductive-aged women.[1] More than half of women with CPP and 15% to 50% of those with infertility have endometriosis.[2] Endometriosis-related pelvic pain (ERPP) can adversely affect quality of life, daily activities, work and school productivity, and both sexual and nonsexual relationships. Endometriosis can be treated pharmacologically, surgically, or with both medication and surgery. In this article, the authors focus on pharmacologic options for ERPP and discuss drug efficacy, safety, contraindications, tolerability, and cost-effectiveness.

Background

Endometriosis is a chronic inflammatory disorder that is estrogen dependent and commonly associated with dysmenorrhea, dyspareunia, and infertility in addition to CPP.[3] The etiology of endometriosis is not well understood. The disorder is characterized by growth of endometrial cells or implants outside the uterus, usually on pelvic structures and most commonly on the ovaries. Suggested mechanisms by which these endometrial implants cause pain include local overproduction of prostaglandins as a result of activated macrophages and increased cyclooxygenase-2 activity, direct and indirect effects of active bleeding from the implants, and irritation of pelvic floor nerves.[4,5]

Risk factors

These include early menarche; nulliparity; family history of endometriosis, especially in first-degree relatives; and low body mass index.[6] This disorder primarily affects reproductive-age females, including adolescents. In fact, endometriosis is the most common cause of secondary dysmenorrhea among adolescents.[7]

Diagnosis

The gold standard for diagnosis of endometriosis is direct laparoscopic visualization of characteristic lesions and/or excision of lesions for histologic evaluation. Lesions can be subtle and may be missed by laparoscopy, and surgical evaluation may not be feasible for or desired by some women.[8] Although not definitively diagnostic of endometriosis, common symptoms include dysmenorrhea, CPP, and dyspareunia. Common physical examination findings include uterosacral nodularity, fixed retroverted uterus, and adnexal enlargement. Pelvic ultrasonography may help rule out other causes of these symptoms and exam findings.

Pharmacotherapy

First-line treatments

Low-risk first-line pharmacotherapy may be initiated based on the presence of mild-to-moderate symptoms and examination and ultrasound

First-line pharmacotherapy for pain management can be initiated based on the presence of mild-to-moderate symptoms and examination and ultrasound findings that rule out other potential causes.

findings suggestive of endometriosis.[9] Choice of pharmacotherapy for ERPP is based on patient preference and reproductive plans, as well as medication efficacy, safety, side effects, and cost. First-line options for mild-to-moderate ERPP include nonsteroidal anti-inflammatory drugs (NSAIDs), combined hormonal contraceptives (CHCs), and progestin-only contraceptives (POCs).

NSAIDs

The primary mechanism of action of NSAIDs is inhibition of prostaglandin production. Data are inconclusive regarding whether NSAIDs are effective in relieving ERPP or whether any particular NSAID is more effective than others.[10,11] NSAIDs have been shown to be effective in treating mild-to-moderate primary dysmenorrhea, however, and are generally well tolerated and cost effective.[6] Although no specific NSAID dosages are recommended for treating endometriosis-associated dysmenorrhea, those recommended for treating primary dysmenorrhea include ibuprofen 800 mg initially, followed by 400 to 800 mg every 8 hours; naproxen sodium 440 to 550 mg initially, followed by 220 to 550 mg every 12 hours; and mefenamic acid 500 mg initially, followed by 250 mg every 6 hours.[7,12] NSAID use may be most effective when started 1 to 2 days before menses onset and continued through the first 2 to 3 days of bleeding.[7]

Contraindications to NSAID use include a history of gastrointestinal bleeding, other bleeding disorders, cardiovascular disease, hepatic disease, renal impairment, and aspirin-sensitive asthma.[10] The most common adverse effects are nausea, indigestion, headache, drowsiness, dizziness, and mouth dryness.[10] Although NSAIDs can ease dysmenorrhea, they do not suppress estrogen-dependent endometrial growths and are often combined with hormone treatment.

Combination hormonal contraceptives

CHCs containing estrogen and a progestin suppress ovarian function, leading to atrophy of endometrial tissue and a reduction in estrogen-induced production of prostaglandins. CHCs are available in oral pill, transdermal patch, and vaginal ring delivery systems and are dosed continuously or cyclically. Although the mechanism of action of hormones delivered orally, transdermally, or vaginally is essentially the same, most available studies have focused on combination oral contraceptives (COCs). Multiple clinical trials have demonstrated the superior efficacy of COCs versus placebo in reducing ERPP.[9] No available evidence supports the superiority of one COC formulation over another in reducing dysmenorrhea. In some studies, however, continuous-dose COC regimens, as compared with cyclic-dose regimens, have been shown to provide quicker effects and greater pain score reductions.[13,14] Although COCs are effective in treating ERPP, recurrence rates following treatment discontinuation are high.[4,5]

All of the CHCs are generally well tolerated. The most common side effects are nausea, bloating, breast tenderness, and unscheduled/breakthrough bleeding, which often resolve after the initial few months of treatment. Contraindications to CHC use for treatment of ERPP are the same as those when CHCs are considered for use as contraceptives.[15]

Progestin-only contraceptives

Depot medroxyprogesterone acetate (DMPA) and the etonogestrel subcutaneous implant have been shown to be effective in reducing ERPP and are useful in women who cannot tolerate or have contraindications to estrogen.[5,16] The main mechanism of action of these POCs in terms of their ability to reduce ERPP is prevention of endometrial proliferation and ovulation, which results in reduction in the production of prostaglandins. Amenorrhea is common with ongoing use of POCs.[4,5] DMPA is administered intramuscularly (IM) or subcutaneously (SC) every 3 months. The subcutaneous DMPA injection product was approved by the US Food and Drug Administration (FDA) for the treatment of ERPP in 2005. The etonogestrel implant is placed SC under the skin of the upper inner arm and may be used for up to 3 years. This product has not been FDA approved to treat ERPP.

Common adverse effects of DMPA include irregular spotting/bleeding, mood changes, and weight gain. Reversible bone loss has been reported with long-term use of DMPA. The most commonly reported adverse effect of the etonogestrel implant is irregular spotting/bleeding. Contraindications to use of DMPA and the etonogestrel implant for treatment

of ERPP are the same as those listed for these agents if they were to be considered for use as contraceptives.[15] Women considering a pregnancy in the near future may not want to use DMPA because of the potential for a 9- to 10-month delay in return to fertility. By contrast, return to fertility after discontinuation of the etonogestrel implant is generally immediate.

Another POC option for relieving ERPP is the levonorgestrel intrauterine system (LNG-IUS). A few small studies have shown LNG-IUS 52 mg to have efficacy similar to that of DMPA and gonadotropin-releasing hormone (GnRH) agonists in reducing ERPP.[17–19] LNG suppresses endometrial proliferation, and amenorrhea is common during use. Common adverse effects include irregular spotting/bleeding, breast tenderness, mood changes, and acne. Contraindications to use of LNG-IUS for treatment of ERPP are the same as those if the product were being considered for use as a contraceptive.[15]

Second-line treatments

If first-line pharmacotherapies are not effective after at least a 3-month trial, second-line pharmacologic options may be considered. These second-line pharmacotherapies, however, are associated with potentially more problematic short- and long-term adverse effects.[4]

GnRH agonists

These agents are FDA approved for up to 12 months of use for treatment of ERPP.[5] They bind to GnRH receptors on the anterior pituitary, causing a down-regulation of the pituitary–ovarian axis and profound but reversible hypoestrogenism (iatrogenic menopause).[4,5] Progressive endometrial atrophy and amenorrhea are the result. Efficacy of GnRH agonists in different doses, regimens, and routes of administration has been demonstrated in multiple clinical trials.[20] Overall, these agents have been found to be more effective than placebo or no treatment in relieving ERPP.[20]

The most commonly used GnRH agonists are goserelin 3.6 mg SC every 28 days, leuprolide 3.75 mg IM every month or 11.25 mg IM every 3 months, or nafarelin 400 to 800 mcg/day given as a nasal spray twice daily. Disadvantages of GnRH agonists include cost and the non-oral route of administration. If these agents are initiated in the follicular phase of a menstrual cycle, women may experience an initial 2- to 3-week flare of symptoms due to a temporary increase in ovarian hormones. If initiated during the luteal phase after ruling out pregnancy, this flare is avoided, with suppression of hormonal levels and amenorrhea occurring more quickly.[21] Menopausal symptoms, including hot flashes, mood swings, vaginal dryness, diminished sex drive, and headaches, are common.

Bone loss occurs when GnRH agonists are used for longer than 6 months. Add-back therapy is used to diminish the risk of bone loss.[4,5] Of note, women need not wait until 6 months of GnRH agonist use to initiate add-back therapy, which has not been shown to diminish the efficacy of pain relief but does increase treatment cost.[5] Add-back therapies include progestins, either alone or with an estrogen formulation or a bisphosphonate. A daily calcium supplement, usually elemental calcium 1,200 mg/day, is recommended.[5] Use of GnRH agonists is contraindicated during pregnancy.

Nonpharmacologic approaches to therapy can be considered as needed. Referrals should be made to reproductive endocrinology specialists when fertility is a concern or when first-line pharmacotherapies are not effective in reducing pain.

GnRH antagonist

In 2018, the FDA approved elagolix sodium, the first GnRH antagonist indicated for moderate-to-severe ERPP (dysmenorrhea, dyspareunia, and noncyclic pelvic pain).[22] Elagolix is not associated with an initial flare of symptoms because, as an antagonist, it suppresses follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen effects immediately.

Elagolix is an oral tablet available in two dosages, 150 mg once daily or 200 mg twice daily. The higher dosage is more effective for all types of ERPP but is associated with more bone loss. Efficacy of elagolix was demonstrated in two phase III trials, with a significant dose-dependent reduction in dysmenorrhea and noncyclic pelvic pain by 3 months; efficacy was sustained in an extension trial at 12 months.[22] The higher dosage was associated with a decrease in dyspareunia.

Elagolix is indicated for short-term use (6 months for the higher dosage and 24 months for the lower dosage) because of the risk of bone loss. Studies have shown that bone loss is dose dependent, with a significant decrease in lumbar spine bone mineral density (BMD) by 6 months with the higher dosage.[22] Adverse effects of elagolix, including hot flashes, headaches, nausea, insomnia, and mood changes, are also dose dependent. Contraindications to elagolix use are pregnancy and hepatic dysfunction.

Elagolix has been directly compared with other hormonal therapies for ERPP. In a randomized controlled trial (RCT), elagolix 150 mg/day or 75 mg bid was similar to DMPA in reducing ERPP, and both treatments had minimal adverse effects on BMD.[23] In the phase II Tulip PETAL trial, elagolix 150 mg/day or 250 mg/day was similarly effective as the GnRH agonist leuprorelin acetate in reducing ERPP and had a slightly less adverse effect on BMD.[24]

Danazol

This oral synthetic androgen was approved for the treatment of endometriosis more than 2 decades ago. Although shown to be effective, danazol is no longer commonly used because of its androgenic effects and the availability of other options.[25] Danazol produces a high androgen environment, suppresses FSH and LH, and lowers estrogen levels, causing atrophy of endometrial implants and a resulting pseudomenopause. Danazol 400 to 800 mg/day is initiated during menses, continued for 3 to 6 months, and extended for up to 9 months.[26] Adverse effects include acne, weight gain, muscle cramps, hirsutism, decreased breast size, and deepening of the voice.[27]

Aromatase inhibitors

Although not FDA approved for this indication, aromatase inhibitors (AIs) such as oral anastrozole (1 mg/day) and oral letrozole (2.5 mg/day) are used off label for severe ERPP refractory to other pharmacotherapies.[5] Overexpression of the aromatase enzyme is one of the main factors responsible for estrogen synthesis in endometrial lesions. AIs suppress extraovarian estrogens, stopping endometrial lesion proliferation and prostaglandin-mediated inflammation and pain.[4,27] AIs may be an important option for women with endometriosis whose symptoms persist after menopause because most estrogens are made outside the ovaries.[28] In premenopausal women, AIs are often combined with progestins or GnRH analogs to suppress both ovarian and extraovarian estrogens.

Small studies in both premenopausal and postmenopausal women taking letrozole or anastrozole for an average of 6 months have shown decreased pain, reduction of extrauterine endometrial growths, and improved quality of life.[29] A randomized 6-month clinical trial showed that goserelin plus anastrozole increased pain-free intervals and decreased recurrence of pain in patients with severe endometriosis.[30] No significant bone loss was noted with this regimen. AIs are generally well tolerated, although musculoskeletal complaints such as arthralgias, joint stiffness, and bone pain are fairly common and can lead to discontinuation. With long-term use, AIs may increase risk of osteoporosis and bone fracture.[31] Because AIs can reactivate ovarian cysts and follicular function in reproductive-age women, they are prescribed

with hormonal contraceptives or GnRH agonists to suppress follicular development.[32] AIs are contraindicated in women who are or may become pregnant.

Nonpharmacologic treatments

Women with mild-to-moderate ERPP may benefit from nonpharmacologic approaches, alone or with pharmacotherapy. In a small randomized trial, use of a heating pad in patients with primary dysmenorrhea was as effective as ibuprofen 400 mg 3 times daily.[33] Massage therapy just prior to menses onset may alleviate menstrual pain associated with endometriosis.[34] A small placebo-controlled trial demonstrated that oral melatonin significantly reduced pain and endometriosis-related dysmenorrhea.[35]

In vitro studies with endometrial cells have indicated that turmeric and omega-3 fatty acids may inhibit endometrial growths via reduction of estradiol production.[36] Dietary changes such as increasing consumption of green vegetables and fruit and limiting ingestion of red meats may decrease the risk of endometriosis. Data on the effect of diet on the course of endometriosis, however, are limited.[37] Few conclusive data exist regarding the effect of physical activity on the course of endometriosis or on ERPP.[38]

A meta-analysis of acupuncture showed a statistically significant reduction in ERPP.[39] A randomized, single-blind, placebo-controlled trial is under way to assess the efficacy of acupuncture on ERPP.[40] A component of myofascial pain often accompanies ERPP; therefore, pelvic floor physical therapy (PT) may provide relief of this type of pain.[41] A few small studies have suggested the effectiveness of pelvic floor PT in this regard, but no RCTs have been reported to date.

Implications for practice

Nurse practitioners must be able to inform women with ERPP about the advantages and disadvantages of all the pharmacotherapeutic options so that they can make informed choices that best meet their needs. First-line pharmacotherapy for pain management can be initiated based on the presence of mild-to-moderate symptoms and examination and ultrasound findings that rule out other potential causes. Nonpharmacologic approaches to therapy can be considered as needed. Referrals should be made to reproductive endocrinology specialists when fertility is a concern or when first-line pharmacotherapies are not effective in reducing pain. ●

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References

1. Schrager S, Falleroni J, Edgoose J. Evaluation and treatment of endometriosis. *Am Fam Physician*. 2013;87(2):107-113.
2. Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. *J Assist Reprod Genet*. 2010;27(8):441-447.
3. 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.
4. American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertil Steril*. 2015;101(4):927-955.
5. American College of Obstetricians and Gynecologists. Practice bulletin number 114: management of endometriosis. 2010; (reaffirmed 2018):1-14. acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Management-of-Endometriosis.
6. Hediger ML, Hartnett HJ, Louis GM. Association of endometriosis with body size and figure. *Fertil Steril*. 2005;84(5):1366-1374.
7. American College of Obstetricians and Gynecologists. ACOG committee opinion: dysmenorrhea and endometriosis in adolescence. *Obstet Gynecol*. 2018;132(6):e249-e257.
8. Pugsley Z, Ballard K. Management of endometriosis in general practice: the pathway to diagnosis. *Br J Gen Pract*. 2007;57(539):470-476.
9. Barcellos MB, Lasmar B, Lasmar R. Agreement between the preoperative findings and the operative diagnosis in patients with deep endometriosis. *Arch Gynecol Obstet*. 2016;293(4):845-850.
10. Marjoribanks J, Proctor M, Farquhar C, Derks RS. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Systematic Rev*. 2010;1:CD001751.
11. Brown J, Crawford TJ, Allen C, et al. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev*. 2017;1:CD004753.
12. Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacologic treatments and management strategies. *Expert Opin Pharmacother*. 2012;13(2):157-170.
13. Dmitrovic R, Kunselman AR, Legro RS. Continuous compared with cyclic oral contraceptives for the treatment of primary dysmenorrhea: a randomized controlled trial. *Obstet Gynecol*. 2012;119(6):1143-1150.
14. Vercellini P, Eskenazi B, Consonni D, et al. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. *Hum Reprod Update*. 2011;17(2):159-170.
15. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Cri-

teria for Contraceptive Use, 2016. *MMWR Recomm Rep.* 2016;65(3):1-103.

16. Walch K, Unfried G, Huber J, et al. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis – a pilot study. *Contraception.* 2009;79(1):29-34.
17. Lockhat FB, Emembolu JO, Konje JC. The efficacy, side-effects, and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen (levonorgestrel): a 3 year follow-up. *Hum Reprod.* 2005;20(3):789-793.
18. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod.* 2005;20(7):1993-1998.
19. Bayoglu T, Dilbaz B, Altinbas S, et al. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. *Fertil Steril.* 2011;95(2):492-496.
20. Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev.* 2010;12:CD008475.
21. Advincula A, Truong M, Lobo R. Endometriosis etiology, pathology, diagnosis, management. In: Lobo R, Gershenson D, Lentz G, Valea F, eds. *Comprehensive Gynecology.* 7th ed. Philadelphia, PA: Elsevier; 2017:423-442.
22. Orilissa. Prescribing information. North Chicago, IL: AbbVie; July 2018.
23. Carr B, Dmowski WP, O'Brien C, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. *Reprod Sci.* 2014;21(11):1341-1351.
24. Ács N, O'Brien C, Jiang P, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist: results from a phase 2, randomized controlled study. *J Endometriosis Pelvic Pain Dis.* 2015;7(2):56-62.
25. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev.* 2007;4:CD000068.
26. Danazol. Prescribing information. Philadelphia, PA: Lannett; November 2006.
27. Zito G, Luppi S, Giolo E, et al. Medical treatments for endometriosis-associated pelvic pain. *Biomed Res Int.* 2014:1-12.
28. Słopień R, Męczekalski B. Aromatase inhibitors in the treatment of endometriosis. *Prz Menopauzalny.* 2016;15(1):43-47.
29. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis. *Fertil Steril.* 2012;98(6):1370-1379.
30. Soysal S, Soysal ME, Ozer S, et al. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. *Hum Reprod.* 2004;19(1):160-167.
31. Polyzos NP, Fatemi HM, Zavos A, et al. Aromatase inhibitors in postmenopausal endometriosis. *Reprod Biol Endocrinol.* 2011;9:90.
32. Amsterdam LL, Gentry W, Jobanputra S, et al. Anastrozole and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril.* 2005;84(2):300-304.
33. Akin MD, Weingand KW, Hengehold DA, et al. Continuous low-level topical heat in the treatment of dysmenorrhea. *Obstet Gynecol.* 2001;97(3):343-349.
34. Valiani M, Ghasemi N, Bahadoran P, Heshmat R. The effects of massage therapy on dysmenorrhea caused by endometriosis. *Iran J Nurs Midwifery Res.* 2010;15(4):167-171.
35. Schwertner A, Conceição Dos Santos CC, Costa GD, et al. Efficacy of melatonin in the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled trial. *Pain.* 2013;154(6):874-881.
36. Zhang Y, Cao H, Yu Z, et al. Curcumin inhibits endometriosis endometrial cells by reducing estradiol production. *Iran J Reprod Med.* 2013;11(5):415-422.
37. Parazzini F, Chiaffarino F, Surace M, et al. Selected food intake and risk of endometriosis. *Hum Reprod.* 2004;19(8):1755-1759.
38. Bonocher CM, Montenegro ML, Rosa E Silva JC, et al. Endometriosis and physical exercises: a systematic review. *Reprod Biol Endocrinol.* 2014;12:4.
39. Mira TA, Buen MM, Borges MG, et al. Systematic review and meta-analysis of complementary treatments for women with symptomatic endometriosis. *Int J Gynecol Obstet.* 2018;143(1):2-9.
40. Liang R, Li P, Peng X, et al. Efficacy of acupuncture on pelvic pain in patients with endometriosis: study protocol for a randomized, single-blind, multi-center, placebo-controlled trial. *Trials.* 2018;19(1):314.
41. Bedaiwy MA, Patterson B, Mahajan S. Prevalence of myofascial chronic pelvic pain and the effectiveness of pelvic floor physical therapy (PT). *J Reprod Med.* 2013;58(11-12):504-510.