Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy

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Endometriosis can recur after either surgical or medical therapy. Long-term medical therapy is implemented to treat symptoms or prevent recurrence. Dienogest and gonadotropin-releasing hormone (GnRH) analogues with hormone add-back therapy seem to be equally effective for long-term treatment of pain symptoms associated with endometriosis. There is insufficient evidence to support the superiority of one therapy over the other. However, add-back hormone therapy (HT) is recommended for patients using GnRH agonists. The treatment selection depends on therapeutic effectiveness, tolerability, drug cost, the physician's experience, and expected patient compliance. (Fertil Steril® 2017;107:537–48. ©2017 by American Society for Reproductive Medicine.)
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Endometriosis is a common gynecologic condition with a reported prevalence of 2% to 10% in the general population, up to 50% in the infertile patients (1, 2), and more than 60% in patients with chronic pelvic pain (3). Endometriosis and its associated infertility and chronic pelvic pain (CPP) represents a challenge to health-care providers and a significant burden on the health-care system.

The choice of medical management for endometriosis-associated pelvic pain depends on the patient's age and pain symptoms, the extent of the disease, the patient's reproductive plans, and the treatment risks, side effects, and cost considerations. In most cases, women with CPP due to presumptive endometriosis are initially treated empirically with nonsteroidal anti-inflammatory drugs (NSAIDs) and combined estrogen-progestin contraceptives (COCs). There is one placebo-controlled double-blind, randomized controlled trial (RCT) to support the beneficial effects of COCs on dysmenorrhea (4). However, there is limited evidence to support a beneficial effect on COCs on noncyclic pelvic pain.

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Suppression of endogenous estrogen production is important for the successful treatment of endometriosis-associated pain (5). Suppression of ovulation will in turn induce amenorrhea, thereby creating a relatively hypoestrogenic environment that will inhibit ectopic endometrial growth and prevent disease progression (5). Discontinuation of the hormone suppressive therapy is usually followed by recurrence of pain symptoms due to the return of hormone stimulation of the endometriotic implants. Endometriosis can recur after either surgical or medical therapy, with reported recurrence rates of up to 45% after 5 years (6). This rate is even higher reaching 56% for young women under the age of 21 years with surgically confirmed endometriosis (7). Hence the need for long-term medical therapy.

Dienoogest (DNG), a fourth generation progestin, and gonadotropin-releasing hormone agonists (GnRH-a)

are frequently used medical treatment options. This article reviews the use of DNG and GnRH-a with hormone add-back in the medical management of endometriosis-associated pain.

DIENOGEST

Progestin therapy is frequently used for patients with symptomatic endometriosis, and is typically considered when combined hormone contraceptives are contraindicated, lead to intolerable side effects, or fail to improve pain. A wide variety of oral, parenteral, intrauterine systems, and implantable progestins have been used for this purpose. Progestins inhibit the growth of endometriotic tissue by inducing decidualization followed by atrophy of the endometriotic implants and decreased peritoneal inflammatory markers (8). Additional proposed mechanisms of action include anovulation with reduced serum estrogen levels, suppression of matrix metalloproteinases–mediated growth and implantation of ectopic endometrium (9), inhibition of angiogenesis and immunomodulation (10). Dienogest (DNG) is the most recent member of this family, and its use in various countries has increased exponentially over the past decade. We will discuss clinically useful, evidence-based details about DNG pharmacotherapy for endometriosis-associated pain.

Pharmacology and Mechanism of Action

Dienogest is a steroidal fourth-generation selective progestin that combines the pharmacologic properties of 19-nortestosterone and derivatives of progesterone. A nonethinylated progestin that is structurally related to testosterone (11), DNG has antiandrogenic activity and thus can improve androgenic skin-related side effects (12).

At the pharmacokinetic level, DNG is absorbed rapidly after oral intake with approximately 90% bioavailability (13), and it is exclusively bound to albumin (90%) and not to sex hormone-binding globulin or corticoid binding globulin (13). Only 10% of absorbed DNG remains free, with a terminal half-life of 10 hours reaching a steady-state concentration after 2 days' administration (13). It is metabolized in the liver mainly by cytochrome P450 isoform 3A4 (CYP3A4) followed by rapid excretion of its inactive metabolites, and does not accumulate in the body (13).

Dienogest has a profound local effect on endometriotic lesions, with little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity and minimal impact on metabolic parameters (14). Studies have shown that DNG has both an anovulatory and an antiproliferative effect, while inhibiting the secretion of cytokines in the stroma of endometrial cells (15).

A systematic review evaluated 15 studies of the inflammatory response of endometriotic tissue to DNG therapy (16). Dienogest modulated prostaglandin (PG) production and metabolism (PGE2, PGE2 synthase, cyclooxygenase-2, and microsomal PGE synthase-1) in a way that is anti-inflammatory. In addition, its use was associated with proinflammatory cytokine and chemokine production: interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor-α, monocyte chemoattractant protein-1, and stromal cell-derived factor-1. Moreover, it was associated with growth factor biosynthesis (vascular endothelial growth factor and nerve growth factor) and signaling kinases, responsible for the control of inflammation. There is evidence to support the anti-inflammatory effect of DNG at the epithelial and the stromal cell levels. This was mediated via progesterone receptor (PR) in PR-expressing epithelial cells; whether this is via a PR-mediated mechanism in stromal cells has yet to be determined (16, 17).

Efficacy

Dienogest monotherapy. Treatment with DNG reduces endometriosis disease activity as measured by pretreatment and posttreatment surgical staging, and subjectively decreases pelvic pain as shown in multiple studies (Table 1). As an example, in an open-label, randomized, multicenter, 24-week comparative dose-finding trial, women with histologically confirmed endometriosis were assigned to 1, 2, or 4 mg of DNG. The efficacy of DNG was evaluated by second-look laparoscopy and patient-reported symptoms. The 1-mg dose arm was discontinued due to insufficient bleeding control. Dienogest reduced the mean revised American Fertility Society (AFS) scores from 11.4 to 3.6 in the 2-mg group and from 9.7 to 3.9 in the 4-mg group.

Dienogest at 2 and 4 mg/day was also associated with symptom improvement in a substantial proportion of 54 women who completed the study. The rates of dyspareunia statistically significantly decreased from 51.7% at baseline to 6.9% at week 24 in the 2-mg group, and from 57.1% to 5.7% in the 4-mg group. Similar decreases were observed in both groups for diffuse pelvic pain, dysmenorrhea, and premenstrual pain. Consequently 2 mg daily was recommended as the optimal dose (14), and that has been the dose of DNG used in most of the subsequent studies. However, reducing the revised AFS score is of limited clinical validity due to its poor correlation with pelvic pain.

The 2-mg dose was shown to be effective in improving symptoms in another prospective observational study in 135 patients with endometriosis. The proportion of patients who showed marked or moderate improvement in their global scores went from 72.5% at 24 weeks to 90.6% (106 of 117 cases) at 52 weeks, indicating a cumulative response (30). Dienogest was also shown to be superior to placebo in controlling pain symptoms in two independent studies (18, 19).

When compared with prior use of norethindrone acetate (NETA) at 2.5 mg, DNG at 2 mg produced comparable improvements of symptoms and health-related quality of life (23). Given the higher cost of DNG compared with NETA, the investigators suggested that DNG should be used in women who do not tolerate NETA. However, this study was limited by its serial design rather than head-to-head comparison, its relatively small sample size, and the variability of the medication cost in various settings.

A recent systematic review of eight RCT between 2002 and 2011 comparing DNG with placebo or GnRH-a included 1,273 patients with symptomatic endometriosis. This review showed that DNG at 2 mg/day was superior to placebo in reducing pelvic pain, with results equivalent to GnRH agonists (buserelin, leuprorelin, leuprolide acetate, and triptorelin) in controlling the pain symptoms associated with endometriosis. Dienogest was also effective when used for prolonged durations up to 52 weeks with tolerable side effects (31).

TABLE 1

Summary of clinical trials where dienogest was used to treat endometriosis-associated pain compared with no treatment, placebo, or other hormone treatment regimens.

Study	Design	n	Intervention	Duration	Comments
Köhler et al. 2010 (14)	Open-label, multicenter RCT	68	[1] DNG, 1 mg/d (n = 4) [2] DNG, 2 mg/d (n = 29) [3] DNG, 4 mg/d (n = 35)	24 wk	At 1 mg, associated with irregular vaginal bleeding that led to discontinuation. In both 2- and 4-mg groups, statistically significant and equivalent reduction in clinical symptoms (dyspareunia, pelvic pain, dysmenorrhea) and revised ASRM score. Both 2 and 4 mg associated with irregular vaginal bleeding, which improved over time. Lowest effective dose is 2 mg/d.
Strowitzki et al. 2010 (18)	Double-blind, placebo-controlled, multicenter RCT	198	[1] DNG, 2 mg/d (n = 102) [2] Placebo (n = 96)	12 wk	Significantly superior to placebo in reduction of pelvic pain, dysmenorrhea, dyspareunia, and pelvic tenderness with remarkable improvement in QoL. Greater episodes of spotting associated with DNG.
Petraglia et al. 2012 (19)	Extension for placebo-control study	152	DNG, 2 mg/d	36 wk (n = 17) vs. 52 wk (n = 135)	Improvement in pain for both groups previously treated with DNG or placebo. Adverse effects reported in 27 of 168 women, including breast discomfort, nausea, and irritability.
Harada et al. 2009 (15)	Prospective observational	132	DNG, 2 mg/d	52 wk	Further reduction in VAS score for pelvic pain noted after 52 weeks of treatment. All patients experienced side effects as vaginal bleeding, headache, constipation, nausea, and hot flushes. Statistically significant reduction in BMD after 24 to 52 weeks of treatment.
Strowitzki et al. 2015 (20)	RCT	332	DNG, 2 mg/d	65 wk	Well tolerated, with a favorable safety profile extending over a period up to 65 weeks. Adverse events were generally of mild-to-moderate intensity (headache, breast discomfort, depressed mood, and acne), each occurring in <10% of women. Bleeding pattern associated with DNG was well tolerated. Estradiol levels maintained within the low-physiologic range
Angioni et al. 2015 (21)	Pilot study	6	DNG, 2 mg/d	12 mo	Improvement of pain symptoms, QoL, and decreased nodule size.
Cosson et al. 2002 (22)	Multicenter, open, randomized trial	147	[1] DNG, 2 mg/d (n = 68) [2] Triptorelin, 3.75 mg IM every 28 d (n = 74)	16 wk	Similar reduction in revised ASRM implants and adhesion scores. Irregular vaginal bleeding more frequent in the DNG group (61.6% vs. 25.4%); hot flushes more frequent in the triptorelin group (61.2% vs. 9.6%).
Vercellini et al. 2016 (23)	Before and after study	180	[1] DNG, 2 mg/d (n = 90) [2] NETA, 2.5 mg/d (n = 90)	24 wk	Similar improvement in both groups for pain scores, with statistical significance in favoring DNG. Side effects associated at a higher rate with NETA versus DNG: weight gain (32% vs. 16%), spotting (22% vs. 13%), and decreased libido (14% vs. 9%). Statistically significantly better tolerability with DNG, assessed by the numeric rating scale. Higher proportion of patient satisfaction with DNG.

Bedaiwy. Dienogest, an GnRH analogue for endometriosis. Fertil Steril 2017.

TABLE 1

Continued.

Study	Design	n	Intervention	Duration	Comments
Strowitzki et al. 2010 (24)	Randomized, multicenter, open-label trial	229	[1] DNG, 2 mg/d (n = 109) [2] LA, 3.75 mg/mo (n = 120)	24 wk	Reduction in pelvic pain assessed by VAS similar between both groups. Main side effects were similar in both groups: headache, weight gain, and depression. Increased episodes of hot flushes in first week of treatment in LA group. Number of episodes per day of vaginal bleeding showed a tendency to decrease during treatment in both groups. Greater loss of BMD after treatment in LA group.
Harada et al. 2009 (15)	Double-blind, multicenter RCT	271	[1] DNG, 2 mg/d (n = 137) [2] BA, 900 mg/d intranasal (n = 134)	24 wk	DNG and BA showed similar results in reducing VAS scores. Frequency of reported adverse events similar in both groups. Statistically significant reduction in BMD in BA group.
Granese et al. 2015 (25)	Multicenter RCT	78	[1] E2V/DNG (n = 39) [2] GnRH-a (n = 39)	[1] 9 mo [2] 6 mo	VAS and QoL improved with both treatments (no statistical significant difference).
Morelli et al. 2013 (26)	Prospective study	92	[1] E2V + DNG (n = 48) [2] LNG-IUD (n = 44)	24 mo	Statistically significant improvement in VAS score in group 1; however, satisfaction rate higher in group 2 after 24 months of treatment. No difference in recurrence rate after laparoscopic surgery in either group.
Grandi et al. 2015 (27)	Prospective observational study	34	[1] E2V/DNG (n = 19) [2] NSAID (n = 15)	24 wk	Greater reduction in VAS scores for dysmenorrhea, intermenstrual pain, and dyspareunia with only minor adverse events, which did not cause withdrawal of treatment. in E2V/DNG group. No changes observed in NSAID group.
Caruso et al. 2015 (28)	Placebo-control study	92	[1] DNG, 2 mg/d (n = 54) [2] NSAID (n = 48)	6 mo	Statistically significant improvement in QoL, VAS, Female Sexual Function Index (FSFI), and Female Sexual Distress Scale (FSDS) after 6 months of treatment with DNG. No changes observed in NSAID group.
Caruso et al. 2016 (29)	Open label prospective study	99	COC: DNG, 2 mg + EE, 30 μg, continuous (n = 63); 21/7 regimen (n = 33)	6 mo	With continued administration of COC, remarkable improvement of QoL, VAS, FSFI, and FSDS scores at 3 month follow-up visit. However, 21/7 regimen group had similar scores at 6 mo follow-up visit.

Note: ASRM = American Society for Reproductive Medicine; BA = buserelin acetate; BMD = bone mass density; COC = combined oral contraceptive; DNG = dienogest; E2V = estradiol valerate; EE = ethinyl estradiol; FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index; GnRH-a = gonadotropin-releasing hormone agonist; LA = leuprolide acetate; LNG-IUD = levonorgestrel intrauterine device; NETA = norethindrone acetate; NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; RCT = randomized controlled trial; VAS = visual analogue scale.

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In another study, statistically significant improvement in pain and health-related quality of life (QoL) was observed at 3 and 6 months in patients treated with DNG (54 women) compared with those treated with NSAIDs (48 women). The DNG group experienced an improvement in pain syndrome and QoL at the first follow-up evaluation, and in sexual life by the second follow-up evaluation of DNG usage as compared with the NSAIDs group. The women treated with DNG continued to improve over the treatment period (28).

Dienogest-estradiol combination therapy. Dienogest alone is available for the treatment endometriosis in Europe, Australia, Canada, and Japan but not in the United States. In combination with estradiol valerate (E2V) and ethinyl estradiol (EE), DNG is used as a contraceptive in the United States. Few studies have evaluated DNG containing combined oral contraceptives for treatment of endometriosis. In a multicenter RCT, DNG + E2V was compared with GnRH-a in patients with chronic pelvic pain due to laparoscopically diagnosed and treated endometriosis. Both therapies were shown to be equally efficacious in preventing pain recurrence in the first 9 months of follow-up observation (25).

In a retrospective study, DNG + E2V was found to be statistically significantly more effective than a levonorgestrel intrauterine device (LNG-IUD) in reducing pelvic pain and more effective in reducing recurrence rate but not at a statistically significant level. However, LNG-IUD has statistically significantly higher patient satisfaction (26). In another prospective observational study, 24-week administration of the association of DNG-E2V decreased pelvic pain and improved quality of life in patients with endometriosis compared with NSAIDs (27).

A recent study showed that DNG-EE combined continuous therapy led to a statistically significant reduction of endometriosis-associated pelvic pain. In addition, the improvement in sexual activity and QoL was better in the continuous than the 21/7 conventional regimen (29).

Dienogest for Extragenital Endometriosis

Dienogest was reported to be successful in patients with deep infiltrating endometriosis with or without visceral involvement. In a pilot study, the efficacy of DNG was assessed in six patients with bladder endometriosis. The treatment was well tolerated for 1 year with a very quick improvement of urinary and pain symptoms and remarkable reduction of the size of the endometriotic nodules. The investigators suggested that DNG could be used as a first-line treatment for similar cases (21). A similar effect was reported in a patient with bladder endometriosis and a large vaginal fornix implant (32) and in a patient with a rectosigmoid nodule (33). A properly designed trial comparing DNG to placebo or to other medical options for extragenital endometriosis has yet to be performed.

Side Effects

Progestins used for contraception may cause several unwanted side effects due to their nonspecific binding to androgen and glucocorticoid receptors. New generation progestins such as DNG tend to have greater specificity in binding to progesterone receptors (34). The side effects associated with DNG are similar to those expected of a progestogen, such as weight gain, increased blood pressure, breast tenderness, and nausea (12). It produces no androgenic side effects and has little effect on metabolic and lipid parameters (35). In one observational study, all patients treated with DNG experienced some side effects, such as vaginal bleeding, headache, constipation, nausea, and hot flushes. In addition, a slight reduction in bone mass after 24 to 52 weeks of treatment was observed (30).

The safety and tolerability of DNG was assessed in a pooled analysis from four European RCTs. At 2 mg, DNG was shown to be well tolerated, with a favorable safety profile extending over a period up to 65 weeks in 332 women with endometriosis. The most common adverse drug reactions were mild to moderate headache, breast discomfort, depressed mood, and acne. Each side effect was reported in $<10\%$ of women, with an overall low discontinuation rates. Only 0.6% of patients reported bleeding events as the primary reason for premature discontinuation. Unlike treatment with GnRH-a, this analysis showed that estradiol levels were maintained within the low-physiologic range, confirming therapeutic efficacy without inducing hypoestrogenism (20).

GnRH AGONISTS

Pharmacology and Mechanism of Action

Gonadotropin-releasing hormone agonists (GnRH-a) are available via intramuscular, subcutaneous, or intranasal routes. Leuprolide acetate (parenteral), nafarelin acetate (intranasal), goserelin acetate (subcutaneous implant), and triptorelin are the most commonly used compounds (Table 2). They are manufactured by substituting a D-amino acid for the native L-amino acid at position 6 of the native GnRH. Unlike native GnRH, this substitution makes the agonist resistant to degradation by endopeptidases and give it a longer half-life, with resulting prolonged receptor occupancy (37).

With the initiation of treatment and during the first few days, a pituitary flare effect occurs. This is the result of the binding to the pituitary GnRH receptor. This will in turn provoke the pituitary to secrete both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Because this initial flare effect can be associated with exacerbated endometriosis pain or even obstructive symptoms, it should be avoided if possible. It can be blunted or prevented by treatment with aromatase inhibitors during the first 7 to 10 days of therapy (38). Alternatively, the initial injection can be given in the luteal phase of the cycle. Prolonged treatment with GnRH-a leads to down-regulation of the pituitary GnRH receptor with a subsequent decrease in pituitary secretion of LH and FSH. This will in turn suppresses ovarian follicular growth and ovulation, resulting in very low levels of circulating estradiol and progesterone. Within 1 month of GnRH use, the circulating estradiol concentrations will be in the menopausal range.

Like DNG, GnRH agonists may have direct effects on the endometrium and endometriotic implants. There are GnRH

TABLE 2

Common gonadotropin-releasing hormone agonists used for the management of endometriosis associated pain.

Type	Dose	Duration of treatment	Expected pain reduction
Leuprolide acetate	3.75 mg once per mo (Lupron depot) 11.25 mg every 3 mo (Lupron depot)	6 mo	Per randomized trials superior to placebo and similar to dienogest, danazol, and DMPA
Nafarelin acetate	1 spray (200 μg) every morning and evening (total daily dosage: 400 μg)	6 mo	Similar effect to medroxyprogesterone acetate and goserelin
Goserelin acetate	3.6 mg every 4 wk	6 mo	More effective than oral contraception
Triptorelin	3.75 mg every 4 wk	6 mo	Similar to placebo in terms of pain recurrence after surgical treatment of endometriosis

Note: Data from Streuli et al., 2013 (36). DMPA = depot preparation of medroxyprogesterone acetate.

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receptors present in endometrial cells, and a study in cultured endometrioma cell lines showed increasing concentrations of leuprolide (1,000 ng/mL) resulted in inhibition of cell growth (39) and induced endometrial epithelial cell apoptosis (40).

Three neuropeptides—kisspeptin, neurokinin B (NKB), and dynorphin, collectively termed KNDy neurons—have been characterized. They interact to affect pulsatile GnRH release where kisspeptin stimulates, NKB modulates, and the opioid dynorphin inhibits the pulsatile release of GnRH (41). This has led to the establishment of the KNDy hypothesis, which suggests that KNDy neurons in the arcuate nucleus may interact to control the release and pulsatility of GnRH (42).

In one study, LH was used as a surrogate marker to elucidate the interactions of KNDy signaling in regulating GnRH release and pulsatility (43). In addition, we have shown that kisspeptin is differentially expressed at the level of the endometrium in patients with and without endometriosis. Kisspeptin expression was statistically significantly lower in deep infiltrating endometriosis compared with superficial peritoneal disease (44). Taken together, these findings add to our understanding of the role of GnRH-a in the treatment of endometriosis.

Efficacy

Gonadotropin-releasing hormone agonists represent a second or a third line of effective medical treatment of endometriosis-associated pain. Most clinical trials have shown good relief of pain, ranging between 50% and 90% (Table 3). Some of these RCTs have shown that GnRH agonists are superior to placebo (47) and as effective as other medical therapies in relieving pain and reducing the progression of endometriotic implants (61). However, one small RCT showed that triptorelin treatment after operative laparoscopy for stage III/IV endometriosis was not superior to expectant management in terms of prevention of symptoms, recurrence, and endometrioma relapse, and had no influence on pregnancy rate in endometriosis-associated infertility (49).

In a systematic review of 41 studies published until 2010 with a total of 4,935 women with endometriosis, the effectiveness and safety of different GnRH-a in the treatment of endometriosis-associated pain was evaluated (62). This review showed that GnRH-a are superior to placebo or no treatment at relieving different types of endometriosis-associated pain. In addition, GnRH-a are as effective as any other alternative treatments including danazol, combined oral contraceptives (COCs), and the levonorgestrel intrauterine system (LNG-IUS).

An earlier Cochrane database systematic review of 15 RCT that compared GnRH agonists to danazol showed that both treatments were equally effective, with similar symptom relief and reduction of the disease load (61). The same comparison was addressed by another trial of 81 patients with endometriosis where both treatments had similar improvement of endometriosis-associated pain. However, statistically significantly higher patient compliance was observed with the GnRH-a treatment, more hypoestrogenic side effects were observed with leuprolide, and more androgenic side effects were seen with danazol (48). These findings are to the advantage of GnRH-a because the associated hypoestrogenic side effects can be mitigated by add-back HT while danazol androgenic side effects are difficult to treat. Only one study compared GnRH-a to aromatase inhibitors. No difference was observed in the endometriosis recurrence rate and pregnancy rate when 144 patients with surgically confirmed endometriosis received triptorelin, letrozole, or no treatment (50).

Perioperative GnRH-a treatment. In a three-arm RCT, endometriosis patients were randomly assigned to laparoscopy alone, combined laparoscopy, or one of two GnRH-a (leuprolide acetate or goserelin) treatments. Combined laparoscopy with both GnRH-a compounds was statistically significantly more effective than laparoscopy alone in treating endometriosis-associated pain. In addition, a statistically significantly higher recurrence at 1 year was observed in the laparoscopy-alone group (33%) compared with 13% in the leuprolide acetate group and 12% in the goserelin acetate group. After 2 years of follow-up observation, the pregnancy rate was 62% in the leuprolide acetate group, 60% in the goserelin acetate group, and only 39% in the laparoscopy group. However, this difference did not reach statistical significance, and the study was not powered to evaluate pregnancy as a primary outcome (46).

TABLE 3

Summary of clinical trials where gonadotropin-releasing hormone agonists with and without add-back hormone therapy were used to treat endometriosis-associated pain compared with no treatment, placebo, or other hormone treatment regimens.

Study	No. of patients	Intervention	Duration	Outcomes
Tahara et al. 2000 (45)	15	[1] Nafarelin (200 μg BID) (n = 7) [2] Nafarelin (200 μg BID) for 4 wk followed by half-dose nafarelin treatment (200 μg/d) for 20 wk (n = 8)	24 wk	Half-dose administration of nafarelin after pituitary down-regulation with full-dose nafarelin ("draw-back" therapy) associated with similar bone relief and less negative effect on BMD.
Song et al. 2013 (46)	198	[1] Laparoscopy [2] Laparoscopy + LA (3.75 mg/mo) [3] Laparoscopy + goserelin (3.6 mg/mo)	1 y	Compared with laparoscopy alone, laparoscopy combined with GnRH-a more effective in symptom relief with lower recurrence rate, higher pregnancy rate, and fewer adverse reactions.
Ling 1999 (47)	100	[1] Leuprolide depot (3.75 mg/mo) (n = 49) [2] Placebo (n = 46)	3 mo	Leprolide superior to placebo and effective for treating CCP.
Rotondi et al. 2002 (48)	81	[1] LA depot (3.75 mg every 28 d) [2] Danazol (200 mg 3 times d)	24 wk	Better patient compliance in group 1. Symptoms statistically significantly improved in both groups (no statistically significant difference). Higher patient's compliance in group 1 Hypoestrogenic side effects with LA, and more androgenic side effects with danazol.
Loverro et al. 2008 (49)	60	[1] Triptorelin depot (3.75 IM) [2] Placebo	3 mo	No statistically significant differences in pain recurrence or pregnancy rate between the two groups.
Alborzi et al. 2011 (50)	144	[1] Letrozole [2] Triptorelin [3] No treatment	12 wk	No difference in symptom recurrence rate. Cyst formation found in the letrozole group.
Tsai et al. 2016 (51)	107	GnRH-a combined with [1] E2V (1 mg) + MPA (2.5 mg BID) [2] E2V (1 mg) + MPA (2.5 mg once daily)	20 wk	Better patient compliance in group 2. Incidence of hypoestrogenic side effects lower in group 2 compared with the group 1 (including hot flashes and insomnia) with no statistically significant difference. Statistically significant, comparable loss of mean BMD in both groups with better results in group 2.
Gallagher et al. 2016 (52).	50	[1] LA depot (3 mo) + NETA (5 mg/d) + conjugated estrogens (0.625 mg/d) [2] LA depot (3 mo) + NETA (5 mg/d) + placebo	1 y	Greater improvements in pain, vitality, and physical health subscales in group 1. No changes in depression or menopause-like symptoms in either group.
Bergqvist et al. 1997 (53)	49	[1] Nafarelin (200 μg/d intranasal) [2] Nafarelin (400 μg/d intranasal) [3] Nafarelin (200 μg/d intranasal) + norethisterone (1.2 mg)	6 mo	Better bleeding control and fewer episodes of hot flushes in group 3. Nafarelin at 200 and 400 μg/d have similar effect on endometriosis symptoms. Endometriosis score statistically significantly decreased in groups 2 and 3.
Freundl et al. 1998 (54)	27	[1] Leuprorelin acetate depot (3.75 mg IM/mo) with ethinylestradiol (20 mg) + desogestrel (0.15 mg oral) for 3 wk (n = 14) [2] Leuprorelin acetate depot (3.75 mg IM/mo) with placebo (n = 13)	6 mo	Statistically significant decrease in revised AFS scores in both groups. Hypoestrogenic adverse drug reactions (e.g., hot flushes, sweating, sleeplessness) more frequently reported in group 2. Add-back HT led to a reduction in hypoestrogenic adverse drug reactions and mostly preserved agonist efficacy with the chance of treatment prolongation.
Surrey and Hornstein 2002 (55)	201	LA combined with: [1] Placebo [2] NETA (5 mg/d) [3] CEE (0.625 mg/d) [4] NETA (5 mg) + CEE (1.25 mg)	52 wk	Pain symptoms statistically significantly improved in all groups with comparable results. Add-back HT groups has less BMD effect compared with placebo.
Franke et al. 2000 (56)	41	[1] Goserelin (3.6 mg) + placebo [2] Goserelin (3.6 mg) + continuous estradiol-NETA	24 wk	Add-back HT maintained BMD with no changes in the treatment outcome regarding pain or reduction of endometrial implants.

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TABLE 3

Continued.

Study	No. of patients	Intervention	Duration	Outcomes
Hurst et al. 2000 (57)	13	[1] LA + estradiol (1 mg/d) [2] LA + placebo	6 wk	Estrogen added in the last 3 mo of treatment. Mean pain scores of the oral estrogen group tended to be higher than the placebo group, and hot flushes tended to be less severe with estrogen treatment.
Fernandez et al. 2004 (58)	78	Leuprorelin (3.75 mg/mo), after the third injection combined with: [1] Promegestone (0.5 mg) + estradiol [2] Promegestone (0.5 mg) + placebo [3] Estradiol 2 mg/d	1 y	All groups had similar clinical improvement in pain symptoms. Group 1 had fewest BMD changes followed by group 3 then group 2.
DiVasta et al. 2015 (59)	34	GnRH-a combined with: [1] NETA (5 mg/d) + CEE (0.625 mg/d) [2] NETA (5 mg/d) + placebo	12 mo	BMD increase in group 1 but not group 2. Improvement in QoL assessment greater in group 1. No differences at the hip or lumbar spine by dual-energy X-ray absorptiometry.
Ferrero S. 2011 (65)	35	[1] Letrozole (2.5 mg/d) + NETA (2.5 mg/d) [2] Letrozole (2.5 mg/d) + triptorelin (11.25 mg every 3 mo)	6 mo	Statistically significant reduction in the volume of endometriosis and satisfaction rate in group 2. No difference in VAS scores in either group. Statistically significantly decreased BMD in group 2 but not group 1.
Wang et al. 2009 (60)	28	[1] Goserelin (3.6 mg/every 4 wk) [2] Goserelin (3.6 mg/4 wk) + half-hydrate estradiol/wk + oral medroxyprogesterone (6 mg/d)	12 wk	Level of E_2 higher and FSH lower in group 2 than group 1. Basal vaginal exfoliate cell proportion (66.2% ± 29.0%) statistically significantly lower in group 1 than group 2. Statistically significant decrease in VAS scores in both groups. No difference in bone gla protein before and after treatment in either group. Fewer hot flash episodes in group 2.

Note: BID = twice per day; BMD = bone mass density; CCP = chronic pelvic pain; CEE = conjugated equine estrogens; E_2 = estradiol; E2V = estradiol valerate; FSH = follicle-stimulating hormone; GnRH-a = gonadotropin-releasing hormone agonist; HT = hormone therapy; LA = leuprolide acetate; MPA = medroxyprogesterone acetate; NETA = norethindrone acetate; QoL = quality of life; RCT = randomized controlled trial; revised AFS = revised American Fertility Society classification; VAS = visual analogue scale.

Bedaiwy. Dienogest, an GnRH analogue for endometriosis. Fertil Steril 2017.

Along the same line, another trial compared GnRH-a treatment, laparoscopy, and combined medical/surgical treatment. All three groups were found to have comparable results, with a reported pain relief rate of ≥50%. The lowest incidence of recurrence and the highest cure rate were observed with combined surgical and medical treatment (63).

GnRH-A for Extragenital Endometriosis

Extragenital endometriosis has been reported in other pelvic organs, including the bladder and the colon, the upper abdomen, diaphragm, abdominal wall including the umbilicus and surgical scars, perineum, and chest, with a wide variety of catamenial symptoms. Hormone suppression with GnRH agonists is usually the first-line treatment with or without surgery because they are highly effective at suppressing ovarian hormone production and inhibiting the growth of the extrapelvic endometrial tissue (64). In a randomized, prospective, open-label design, the efficacy and tolerability of letrozole combined with either NETA or triptorelin were evaluated in 35 women with pain symptoms caused by rectovaginal endometriosis. Patients were treated with letrozole (2.5 mg/day) and were randomized to also receive either oral NETA (2.5 mg/day) or intramuscular injections of triptorelin (11.25 mg every 3 months) for 6 months. Letrozole reduced the intensity of endometriosis-related pain symptoms. Combining letrozole with oral NETA was associated with a lower incidence of adverse effects and a lower discontinuation rate than combining letrozole with triptorelin (65).

Side Effects and Add-back HT

Hypoestrogenic side effects. Hypoestrogenism associated with GnRH-a therapy often leads to hot flushes, bone loss, vaginal dryness, decreased libido, mood swings, and headache. Adequate add-back HT is indicated to treat the immediate side effects and prevent long-term sequelae. Common regimens include either progestin-only, typically NETA, or a combination estrogen/progestin in a dose used for HT (8). Add-back HT does not interfere with the GnRH agonist's efficacy for pain symptoms (66), and its use is recommended.

Duration of HT add-back and HT rationale. Typically, GnRH-a therapy is continued for 3 to 6 months and could be extended to 1 year. However, treatment discontinuation is associated with recurrence of pain (67). Extended therapy is safe if the appropriate add-back preparation is used concomitantly. There are some reports about the use of a GnRH agonist with add-back HT for up to 10 years with adequate pain relief and bone sparing (68). High-dose NETA (5 mg orally daily) is the most widely used agent for add-back HT, and it is approved by the U.S. Food and Drug Administration for treatment of endometriosis-associated pelvic pain in conjunction with leuprolide (69).

Add-back HT regimens. Several trials have confirmed the therapeutic benefits and decreased side effects of using various add-back HT regimens of progestin alone or combined with an estrogen (Table 3) (54–56,58). In a study to evaluate the efficacy of add back with transdermal estrogen and medroxyprogesterone acetate during goserelin treatment of surgically confirmed endometriosis, it was found to be safe and effective (60). However, when low-dose estrogen replacement alone was used as an add-back HT in another RCT, endometriosis-related pain increased, and the study was terminated prematurely after the first 13 patients due to the concerning trend toward recurrent symptoms (57).

Therapy with HT add-back should be started concomitantly with GnRH-a therapy. This will minimize the associated vasomotor symptoms and maximize bone density preservation. In addition, patients treated with a GnRH-a should ensure adequate calcium and vitamin D intake in addition to HT.

HT add-back regimen modifications. In an observational cohort study for patients on GnRH-a, a once-a-day dose of 1 mg E2V and 2.5 mg medroxyprogesterone acetate could effectively ameliorate hypoestrogenic side effects and simultaneously maintain the therapeutic response of GnRH-a treatment compared with double the dose of the same combination. The treatment dropout was lower in the low-dose group compared with the high-dose group. Therefore, low-dose add-back HT can be considered a treatment choice during postoperative GnRH agonist treatment (51).

Patients who cannot use HT add-back could benefit from nonhormonal alternatives such as herbal remedies, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors. Alternatively, decreasing doses of GnRH-a (70) or increasing the interval between doses (71) has been shown to be as effective and less costly, and to result in a hypoestrogenic environment like that achieved by the conventional regimen. An earlier longitudinal prospective study showed that half-dose administration of nafarelin after pituitary down-regulation with full-dose nafarelin ("draw-back" therapy) was associated with similar pain relief and less adverse effect on bone mass density (45).

LONG-TERM MEDICAL MANAGEMENT OF ENDOMETRIOSIS IN ADOLESCENTS AND YOUNG ADULTS

Endometriosis is encountered in up to 73% of adolescents and young adults with a history of severe and primary dysmenorrhea (72). Combined estrogen-progestin contraceptives are the first-line treatment when NSAIDs are not effective (73). Prior use of COCs for dysmenorrhea has been shown in a cohort of approximately 1,000 women to be a surrogate marker of severe endometriosis (74). Despite the lack of evidence to support a cause–effect relationship, this implies that COCs treatment for severe dysmenorrhea may not be satisfactory. There is a need for early diagnosis of endometriosis and prevention of disease progression to improve quality of life and preserve fertility. There are no studies where DNG was used solely to treat adolescent endometriosis, but there are several studies where GnRH-a with HT add-back were implemented.

In a recent RCT, 51 adolescents and young women on GnRH-a therapy for endometriosis were randomly assigned to HT add-back with NETA (5 mg/day) + CEE (0.625 mg/day) or NETA + placebo for 12 months. The HT add-back

maintained bone health and improved QoL for the duration of the study. Combination therapy with NETA and CEE was more effective for increasing total body bone mineral content, density, and lean mass than monotherapy with NETA (59). These findings were substantiated in another RCT where NETA + CEE was superior to NETA alone for improving physical health-related QoL in 50 adolescent aged 15–22 years with surgically confirmed endometriosis (52).

PRACTICAL CONSIDERATIONS

When long-term medical treatment of endometriosis is contemplated, a few practical considerations are noteworthy. First, surgical confirmation of the diagnosis is preferred before considering long-term medical treatment or initiating medications with significant cost and side effects, such as GnRH agonists. However, many guidelines support treatment initiation with NSAIDs and hormone treatment without a laparoscopic diagnosis, after appropriate counseling (8,75–77).

Second, medical suppressive therapy for endometriosis-associated pain is contraceptive in nature and has no fertility benefit. In a systematic review of 25 trials, there is no evidence of benefit in the use of ovulation suppression in subfertile women with endometriosis who wish to conceive (78). However, for women desirous of pregnancy who have endometriosis-associated pain, and where in vitro fertilization for treatment of infertility may be required, GnRH-a with add-back HT is an appropriate choice. A GnRH agonist can be used during gonadotropin stimulation to prevent a premature LH surge, thus simplifying the in vitro fertilization stimulation process and potentially improving pregnancy rates, as shown by a meta-analysis of implantation rates in women with endometriosis (79).

Third, GnRH-a treatment has demonstrated efficacy in treating endometriosis-associated pain in the presence of endometriomas without the risks or negative impact of surgery on ovarian reserve. In a pooled analysis of 237 patients to investigate the impact of surgery for endometriomas on ovarian reserve as determined by serum antimüllerian hormone, there was a statistically significant postoperative fall of antimüllerian hormone concentration with weighted mean difference −1.13 ng/mL (80). To protect ovarian reserve, there is an increasing trend toward conservative or medical management of ovarian endometriomas, particularly when they are asymptomatic.

Fourth, there is enough evidence to support the notion that GnRH agonist treatment should be the first-line agents for extrapelvic disease. This is because it provides effective hormone suppression within a few weeks of treatment initiation and inhibits the growth of the extrapelvic endometrial tissue (64). Of note, DNG has shown promise for this disease phenotype as well, and it may be the preferred first-line therapy in countries where it is available.

CONCLUSION

Endometriosis is a chronic disease that requires a long-term management plan. Both DNG and GnRH-a with hormone add-back HT seem to be equally effective for long-term treatment of pain symptoms associated with endometriosis. A GnRH agonist and add-back HT is usually initiated in patients who do not respond to the first-line regimens or have symptom recurrence. These two options have different costs and side-effect profiles. There is insufficient evidence to support the superiority of one therapy over the other. Symptom severity, disease location, and reproductive plans play a key role in treatment selection. It is important to consider the patient's preference in the treatment approach and to provide appropriate counseling on the risks, side effects, and cost.

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