GnRH agonists in the treatment of symptomatic endometriosis: a review

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The development of highly potent gonadotropin-releasing hormone agonists (GnRHa) allowed for a significant addition to options for the medical management of symptomatic endometriosis. Pituitary GnRH receptor down-regulation leads to a hypogonadotropic and secondary hypoestrogenic state resulting in lesion regression and symptom improvement. There may be an additional effect of these agents on the inflammatory processes associated with endometriosis as well. This is a review of critical milestones in the clinical application of these agents.

Most initial trials of various GnRHa employed danazol as a control and demonstrated general equivalence in reducing symptoms and extent of lesions but without hyperandrogenic side effects and adverse metabolic changes induced by the latter. Short-acting GnRHa is administered intranasally or subcutaneously. Longer-acting preparations are administered intramuscularly or as subcutaneous implants. GnRHa also decrease symptom recurrence rates after surgical management. The hypoestrogenic side effects, including bone mineral density loss and vasomotor symptoms, have limited the duration of use of these agents alone to six months. The use of an appropriate add-back allows for the mitigation of side effects while maintaining efficacy and allowing extension of use for up to 12 months. There is a limited amount of data regarding the use of GnRHa in adolescents out of concern for the effect on developing bone. These agents should be used with caution in this group. The lack of dose flexibility, need for parental administration, and side effect profiles represent drawbacks to GnRHa use. The development of oral GnRH antagonists with short half-lives, variable dosing, and decreased side effects represents an exciting alternative. (Fertil Steril Rep® 2023;4:40–5. ©2022 by American Society for Reproductive Medicine.)
Key Words: GnRH agonist, endometriosis, add-back therapy

ESSENTIAL POINTS

1 Gonadotropin-releasing hormone agonists (GnRHa) are effective in treating the symptoms associated with endometriosis.
2 Postoperative GnRHa administration decreases symptom recurrence rates after surgical treatment of endometriosis.
3 Secondary hypoestrogenic side effects limit the duration of use of GnRHa alone to six months.
4 Hypoestrogenic side effects can be minimized while maintaining the efficacy of GnRHa and allowing extension of therapy for up to twelve months with the use of an appropriate add-back.

Endometriosis is a disorder that can have a devastating effect on those afflicted with the disease, including deleterious effects on quality of life, productivity, and health care costs (1, 2). Although considered to have a prevalence of approximately 10% among reproductive age women, this figure is clearly an underestimate, given that patients with asymptomatic disease and those with symptoms who have not had a surgical diagnosis have not been included in these estimates. Classic symptoms include dysmenorrhea, nonmenstrual pelvic pain, dyschezia, dysuria, and dyspareunia, but other symptoms and comorbidities may also be associated. Infertility is also associated with the disorder and may occur in asymptomatic individuals. Endometriosis is thought to be an estrogen-sensitive disease, but a host of investigators have suggested that there is also an association with profound alterations in peritoneal inflammatory processes and cytokine expression, a discussion that is beyond the scope of this review (3).A definitive diagnosis has traditionally been made based on surgical visualization and histologic confirmation. More recently, the concept of making a presumptive diagnosis of "clinically suspected endometriosis" in patients who have undergone a thorough history, physical examination, and imaging studies has led to the initiation of treatment without prior surgery (4). Those who have classic symptoms and fail to respond to an initial course of

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combination oral contraceptives (typically administered continuously) and nonsteroidal anti-inflammatory drugs would be appropriate candidates for more aggressive interventions.

Treatment of symptomatic endometriosis has typically been either surgical, medical, or a combination of the two. Despite somewhat vociferous opinions that have been expressed, there are few, if any, well-designed studies to compare these approaches. Given the estrogen-sensitive nature of this disorder and the fact that most women with endometriosis who conceive become asymptomatic, most medical therapies administered until the 1990s centered on the administration of high-dose oral contraceptives and progestins to create a "pseudo-pregnancy" state. Synthetic androgens such as danazol were also used extensively. Unfortunately, these approaches achieved variable outcomes and are associated with significant side effect profiles.

The development of gonadotropin-releasing hormone agonists (GnRHa), as described elsewhere in this issue, led to a new approach to the medical management of this disease (5). The hypoestrogenic state induced by these agents because of GnRH receptor down-regulation would theoretically impede stimulus for the proliferation of endometriosis and could theoretically lead to disease regression and symptom suppression. This manuscript will review salient investigations addressing the clinical use of GnRHa in the treatment of symptomatic endometriosis.

GnRHa AS MONOTHERAPY FOR SYMPTOMATIC ENDOMETRIOSIS

After the publication of several small series demonstrating efficacy, various randomized trials were published using different GnRHa and control groups in the treatment of symptomatic endometriosis. It is important to note that a primary outcome parameter for many of these early studies was the extent of disease regression as documented by pre- and post-therapy laparoscopy, an approach that is not employed in trials today. In addition, the evaluation of symptoms varied significantly in that no standardized scales were used. Similarly, the effect on the quality of life was not evaluated. This review will be limited primarily to a discussion of randomized trials, summarized in Table 1.

The GnRHa nafarelin acetate administered by nasal spray in doses of 400 or 800 μg per day was compared with danazol 800 mg daily in a double-blind, multicenter trial of 213 women with symptomatic endometriosis in a seminal 6-month trial (6). Statistically significant disease reduction occurred in >80% of women with no differences among the groups, although the value of laparoscopic scoring systems has more recently been called into question. Severely painful symptoms decreased in all groups as well. Aberrant lipoprotein changes within the danazol group did not occur in those administered GnRHa, although these patients reported a higher incidence of vasomotor symptoms and decreased libido. These findings were confirmed by others using this same agent with a similar study design (7). Hickok et al. (8) noted that estradiol levels and luteinizing hormone pulse amplitude were more significantly suppressed with nafarelin, particularly at an 800 μg dose, in comparison to danazol. In a 6-month trial of 300 patients with a 1-year follow-up, symptoms returned in each group, but severity remained significantly lower than at baseline at all time points ($p \leq .016$) (9).

Another GnRHa, buserelin, administered daily in either subcutaneous (0.2 mg) or intranasally (1.2 mg) preparations, was compared with danazol employing both sequential laparoscopy and symptom scores as outcome parameters in a similarly designed prospective randomized open-labeled trial of 36 women with surgically diagnosed endometriosis (10). Symptom improvement and disease regression were similar among the groups as well.

The need to administer these agents daily is not ideal for patient compliance. Therefore, the development of several longer-acting depot preparations of GnRHa represented an important advance. Triporelin is a GnRHa developed in a sustained release depot preparation administered

TABLE 1

Selected prospective randomized trials evaluating GnRHa as therapy for symptomatic endometriosis

Reference	GnRHa	N	Dose	Route of Administration	Control	Duration	Follow-up
6	Nafarelin	213	400–800 μg	IN daily	Danazol 800 mg	6 mo	—
7	Nafarelin	82	400 μg	IN daily	Danazol 600 mg	6 mo	3 mo
9	Nafarelin	307	400 μg	IN daily	Danazol 600 mg	6 mo	1 y
10	Buserelin	36	0.2 mg 1.2 mg	SC daily IN daily	Danazol 800 mg	6 mo	—
11	Triptorelin	49	3.75 mg	IM every 4 wk	Placebo	6 mo	12 mo (5 patients)
12	Leuprolide	52	3.75 mg	IM every 4 wk	Placebo	6 mo	1 y (24 patients)
13	Goserelin	315	3.6 mg	SC every 4 wk	Danazol 800 mg	24 wk	48 wk BMD only (58 patients)
14	Goserelin	307	3.6 mg	SC every 4 wk	Danazol 600 mg	24 wk	24 wk
16	Goserelin	57	3.6 mg	SC every 4 wk	OC	24 wk	24 wk
17	Nafarelin	183	400 μg	IN daily	Leuprolide 3.75 mg	24 wk	24 wk BMD only

IN = intranasal, SC = subcutaneous, IM = intramuscular, OC = Monophasic oral contraceptive (ethinyl estradiol 0.02 mg and desogestrel 0.15 mg), BMD = bone mineral density.

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intramuscularly in a 3.75 mg dose every 28 days and was evaluated in a double-blind, placebo-controlled study involving 49 women (11). The extent of the lesions was reduced by 50% with the agonist compared with a 17% increase in patients receiving a placebo. Pain symptoms were more significantly reduced after two months of therapy. Vasomotor symptoms were significantly higher in the triptorelin group.

Leuprolide acetate has also been formulated into depot suspensions which can be administered either monthly (3.75 mg) or every three months (11.25 mg) to adult women with symptomatic endometriosis. An initial phase III randomized placebo-controlled multicenter 6-month trial evaluated a 3.75 mg monthly dose administered to women with symptomatic endometriosis (12). All patients had laparoscopically diagnosed endometriosis, but follow-up laparoscopy was not required. Scores for dysmenorrhea, pelvic pain, and tenderness all decreased significantly compared with the placebo. Estradiol levels reached menopausal ranges in those treated with the GnRHa, with vasomotor symptoms representing the most common adverse event.

Goserelin is a GnRHa formulated as a subcutaneous implant administered in a 3.6 mg dose every 28 days. Two large randomized multicenter 24-week studies evaluated 622 patients with symptomatic endometriosis using danazol 600 or 800 mg daily as controls (13, 14). Both studies required follow-up laparoscopy. The extent of symptom improvement and disease regression was similar among the groups. Hypoestrogenic side effects were common in those receiving the agonist, whereas androgenic side effects were more common in those receiving danazol, a group associated with a higher percentage of withdrawals. Of note is that bone mineral density decreased by 5.4% in the goserelin group versus a 1.0% increase in the danazol group as measured by dual photon absorptiometry of the lumbar spine. This loss appeared to be persistent in a more limited number of patients who underwent follow-up studies 24 and 48 weeks after study completion. A similar effect was noted after six months of depot leuprolide acetate in a follow-up of 270 patients from 22 centers, although there was a trend toward a return to baseline (15).

Interestingly, Vercellini et al. (16) noted similar improvements in dysmenorrhea, deep dyspareunia, and nonmenstrual pelvic pain in women receiving goserelin compared with a low-dose oral contraceptive administered continuously. Symptom recurrence rates were also similar between the groups. Although clearly oral contraceptives represent a less costly and more tolerable alternative to GnRHa, in current practice, most patients who are offered a GnRHa are those who have failed to respond to oral contraceptive therapy (either with or without a nonsteroidal anti-inflammatory drug) which was not the case in this study.

Very few trials have compared the clinical efficacy of different agonists. Agarwal et al. (17) published the results of a prospective randomized multicenter, double-blind double-placebo 6-month study comparing a depot preparation of leuprolide acetate 3.75 mg administered intramuscularly monthly with nafarelin 200 μg administered intranasally twice daily. Both agents were equally effective in treating symptoms, but bone mineral density loss was greater, and the incidence, as well as the intensity of vasomotor symptoms, were greater in the leuprolide group, which would be explained by consistently lower estradiol levels.

The US Food and Drug Administration has approved the use of leuprolide acetate in a depot preparation, goserelin implant, and intranasal nafarelin for up to six months when administered alone for the treatment of symptomatic endometriosis. The potential benefit of shorter courses of GnRHa may allow for a decrease in side effects and the possibility of retreatment. A multicenter trial addressed this issue, demonstrating that reduction in pain scores and symptom recurrence rates were similar after three versus six months of nafarelin therapy, with 26% of patients in each group requiring retreatment for recurrent symptoms (18). A second study evaluated 36 women from the initial investigation who had recurrent symptoms after either a three or 6-month initial course of nafarelin and were retreated for a second 3-month course (19). Significant symptom improvement was noted with recurrence to levels below baseline scores three months after completing therapy. Mean bone mineral density decreased by 0.56% after retreatment as measured by dual x-ray absorptiometry (DEXA) scanning of the lumbar spine.

There is limited information regarding long-term recurrence rates after using these agents. As described above, there appears to be short-term symptom recurrence to levels below baseline in those studies where this parameter was evaluated, although most trials limited their assessment to 12–24 weeks post-therapy. Waller and Shaw (20) evaluated 130 endometriosis patients retrospectively who had been treated with a variety of GnRHa. They reported an overall recurrence rate of 53.4% five years after completion of therapy. Interestingly, the recurrence rates were much higher for those with severe as opposed to minimal disease (74.4% vs. 36.9%), which could have been a function of the fact that adhesive disease and fibrosis associated with more extensive endometriosis would be less likely to respond to medical intervention.

The trials mentioned earlier required the presence of surgically symptomatic endometriosis as an inclusion criterion. Using an alternative approach, Ling and colleagues randomized 100 women with "clinically suspected endometriosis" to a 12-week course of depot leuprolide acetate or placebo (21). All patients had at least a 6-month history of moderate to severe pain and underwent physical examination, laboratory evaluation, and ultrasound examinations leading the investigators to consider that such patients had a high likelihood of having the disease. Pain improvement after twelve weeks was significantly greater in those receiving GnRHa compared with placebo ($P \leq .001$). Follow-up laparoscopy revealed the presence of endometriosis in 78% of patients administered leuprolide acetate and 87% of those receiving a placebo confirming the high degree of accuracy of the less invasive approach, which has been more widely adopted today.

It has been assumed that the primary mechanism of action for GnRHa in treating endometriosis is the effect of the secondary hypoestrogenic state caused by pituitary down-regulation. However, a variety of investigators have suggested that these agents may directly affect cytokine release, angiogenesis, and cell proliferation, although further

TABLE 2

Evaluated add-back therapies with GnRHa for symptomatic endometriosis—adapted from Surrey (Table 1) (22)

Add-back regimen	6 mo only	< 12 mo
Medroxyprogesterone acetate	+	
Medrogesterone	+	
Ethinyl estradiol + desogestrel	+	
17β estradiol + MPA	+	
CEE + MPA	+	
NETA		+[a]
NETA + sodium etidronate		+
17β E2 + NETA		+
CEE + NETA		+
17β E2 + promegestrone		+
Tibolone		+

MPA = Medroxyprogesterone acetate, E2 = 17β estradiol, CEE = conjugated equine estrogens, NETA = Norethindrone acetate.
[a] FDA approved for use in a 5 mg daily dose with depot leuprolide acetate for up to 1 year of therapy

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investigation is clearly needed (3, 22). A full discussion of these proposed mechanisms is beyond the scope of this manuscript.

POSTOPERATIVE GnRHa THERAPY

Classically, treatment of symptomatic endometriosis has been exclusively medical or surgical. However, the concept of using GnRHa postoperatively has been investigated. A six-month course of postoperative therapy with nafarelin after cytoreductive laparoscopic surgery for endometriosis significantly decreased recurrence rates compared with a placebo in a large multicenter trial of 109 women (23). This effect has been demonstrated with other GnRHa as well (24). Endometrioma recurrence rates have also been shown to decrease compared with expectant management after resection (25). This seems to be a reasonable approach for those patients who are not trying to conceive immediately after surgery, although the ideal duration of this therapy has not been established.

ADD-BACK THERAPY

The GnRHa achieve their efficacy, at least in part, by inducing a profound hypoestrogenic state. However, this also leads to a host of secondary side effects, which have been described earlier and include vasomotor symptoms, bone mineral density loss, vaginal dryness, decreased libido, depression, and joint pain (22). More prolonged courses of GnRHa (up to 12 months) may result in bone mineral density loss that does not return to baseline for up to 18 months after cessation of therapy. Unfortunately, GnRHa (unlike the newer oral GnRH antagonists) do not have the potential for dose adjustment. It has been proposed that there may be a way to give back hormone (add-back therapy) to raise estradiol levels to a sufficient level that hypoestrogenic side effects could be minimized but remain low enough to prevent simulation of disease—"the estrogen threshold hypothesis" (26). Unfortunately, although logical, there is limited data to define a single estradiol level that should be reached to achieve this goal, and there would be expected to be significant variation among individuals.

A variety of add-back regimens used with different GnRHa have been evaluated in 6 and 12-month trials (Table 2). A detailed analysis of these studies is beyond the scope of this review but has been described elsewhere (22). Initially, investigators tried to avoid estrogens as add-back altogether out of concern for disease stimulation, with studies focusing on using progestins and other synthetic steroids. Others have attempted to use low doses of either 17 β-estradiol, conjugated equine estrogens or ethinyl estradiol in conjunction with various progestins to achieve this goal. Unfortunately, as had been described previously, outcome parameters, including the way in which painful symptoms, disease state, vasomotor symptoms, and bone mineral density were assessed, varied significantly among each of these trials, making comparisons among the regimens virtually impossible.

Currently, a single add-back regimen has been approved by the US Food and Drug Administration for use in conjunction with a depot preparation of leuprolide acetate when therapy is to be extended beyond six months and up to 12 months: norethindrone acetate 5 mg daily. This agent is a highly potent oral progestin reported to have some metabolism to ethinyl estradiol. The approval was based on the results of a multicenter placebo-controlled double, blinded trial of symptomatic endometriosis patients who had a prior surgical diagnosis and were all administered this GnRHa monthly in a 3.75 mg dose for 12 months (27). Patients were divided into four add-back groups: placebo, norethindrone acetate (NETA) 5 mg daily, NETA and conjugated equine estrogens (CEE) 0.625 mg daily, or NETA 5 mg, and CEE 1.25 mg daily. Follow-up laparoscopy was not required. Symptom relief was similar among all the groups. Vasomotor symptom frequency and intensity, as well as bone mineral density loss of the lumbar spine as measured by serial DEXA scans, were equally suppressed among all three add-back groups compared with those receiving placebo as add-back. However, the higher 1.25 mg dose of CEE was less well tolerated leading to a greater degree of patient drop-out in this group. Those in the placebo group experienced a progressive decline in bone density in the second six months of therapy which, as described previously, had not returned to baseline within 12 months after discontinuation of therapy. This follow-up investigation also noted that symptom relief was maintained in all groups at least 12 months after discontinuation of therapy (28).

A pharmacy claims analysis of 1,285 women treated with depot leuprolide acetate reported that only 32% used any type of add-back, but those patients who did so remained on treatment to a significantly higher degree than those who did not (29). In summary, the use of an appropriate add-back, such as NETA 5 mg daily, should be considered mandatory for patients who are to be treated with GnRHa for more than six months. The benefits of relieving hypoestrogenic side effects, maintaining painful symptom relief and enhancing compliance make this approach logical in those being treated for a shorter treatment course as well.

ADMINISTRATION OF GnRHa TO ADOLESCENT ENDOMETRIOSIS PATIENTS

The unique situation of the adolescent with symptomatic endometriosis should be addressed separately. Virtually all studies assessing GnRHa alone or with add-back were performed in patients who were ≥18 years old. Younger girls are in a state of rapid bone development, so one should be more concerned about administering an agent that could affect this development. It is also unclear whether add-back, as administered to older women, would allow for bone development and not just act as a bone-sparing agent in this population.

DiVasta et al. (30) evaluated 24 adolescents and young women with symptomatic endometriosis who had failed combination oral contraceptives (53%), norethindrone acetate alone (39%), depot medroxyprogesterone acetate (4%) or no therapy (7%). All patients received GnRHa for 12 months and were randomized to norethindrone acetate 5 mg daily alone or in combination with CEE 0.625 mg daily as an add-back. The mean age was 17.9 ± 1.7 years but included women up to 22.5 years, representing a confounding variable. Total body bone mineral density increased in the combination add-back group only, although this difference was not noted at the hip or lumbar spine as evaluated by serial DEXA scans. Assessments of quality of life and parameters of physical functioning were also greater in the combination add-back group. These findings were confirmed with a long-term follow-up assessment of 61% of these patients (31). Clearly, other forms of medical therapy should be used first in this patient population eg, combination of oral contraceptives or progestins. However, using a GnRHa with appropriate add-back would represent an alternative for those who do not respond to these first-time therapies.

CONCLUSION

The development of highly potent GnRHa represented a significant addition to the armamentarium of agents available for the treatment of symptomatic endometriosis. Unfortunately, the studies that established this efficacy are fraught with significant heterogeneity and inconsistent means of evaluating outcome parameters. The emphasis on post-therapy surgical analysis of disease regression is not considered as significant a concern today as improvements in symptoms, comorbidities, quality of life, and functionality. The lack of consistent long-term follow-up is a major drawback, although recurrence rates appear to be no greater than those achieved with surgical intervention or other medical therapies. It would not be appropriate to consider these agents as the first line of therapy, but they do represent a reasonable second-line choice if primary approaches fail and if a thorough evaluation is highly suggestive of the diagnosis, which need not necessarily include surgical confirmation (4). The effect of these agents on infertility associated with endometriosis has been less carefully evaluated and is beyond the scope of this manuscript but has been addressed elsewhere (32).

There is little reason to fail to include an appropriate add-back that can allow for symptom relief and amelioration of many hypoestrogenic side effects for up to 1 year of agonist use. The potential for "pulse therapy" using serial shorter courses of these agents is not unreasonable but has not been sufficiently evaluated.

These agents do suffer from the need for parenteral or intranasal administration, inability to titrate dosing, slower onset of action, and delayed reversibility. The development of highly effective, short-acting, rapidly reversible, and orally administered GnRH antagonists in various dose regimens employed both with and without hormonal add-back, as discussed elsewhere in this issue, represents a major advance in enhancing tolerability and efficacy of the medical management of this devastating disease.

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