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GnRH Agonists in the Treatment of Symptomatic Endometriosis: A Review

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Abstract

The development of highly potent gonadotropin releasing hormone agonists (GnRHa) allowed for a significant addition to options for 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 impact 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.

The majority of 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. Hypoestrogenic side-effects including bone mineral density loss and vasomotor symptoms have limited duration of use of these agents alone to six months. The use of an appropriate add-back allows for mitigation of side-effects, while maintaining efficacy and allowing extension of use to for up to 12 months. There is a limited amount of data regarding use of GnRHa in adolescents out of concern for impact 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. The development of oral GnRH antagonists with short half-lives, variable dosing, and decreased side-effects represents an exciting alternative.

Key words: GnRH agonist, endometriosis, add-back therapy

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Endometriosis is a disorder which can have a devastating impact 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, non-menstrual pelvic pain, dyschezia, dysuria, and dyspareunia, but a host of 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 of which 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 initiation of treatment without prior surgery (4). Those who have classic symptoms and fail to respond to an initial course of combination oral contraceptives (typically administered continuously) and non-steroidal 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 1990's centered on 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 in the medical management of this disease (5). The hypoestrogenic state induced by these agents due to 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 publication of several small series demonstrating efficacy, a variety of 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 extent of disease regression as documented by pre- and post-therapy laparoscopy, an approach which is not employed in trials today. In addition, evaluation of symptoms varied significantly in that no standardized scales were used. Similarly, impact on quality of life was not evaluated. This review will be limited primarily to a discussion of randomized trials which are summarized in Table 1.

The GnRHa nafarelin acetate administered by nasal spray in doses of 400 or 800 mcg per day was compared to 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 more than 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 noted that estradiol levels and LH pulse amplitude were more significantly suppressed with nafarelin, particularly at an 800 mcg dose, in comparison to danazol (8). In a 6-month trial of 300 patients with a one-year follow-up, symptoms returned in each group, but severity remained significantly lower than at baseline at all time points ($p \leq 0.016$) (9).

Another GnRHa, buserelin, administered daily in either subcutaneous (0.2 mg) or intranasally (1.2 mg) preparations was compared to danazol employing both sequential laparoscopy and symptom scores as outcome parameters in a similarly designed prospective randomized open labelled 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 which was developed in a sustained release depot preparation administered 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 lesions was reduced by 50% with the agonist in comparison to a 17% increase in patients receiving placebo. Pain symptoms were more significantly reduced after 2 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 3 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 to 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 which has been formulated as a subcutaneous implant administered in a 3.6 mg dose every 28 days. Two large randomized multicenter 24-week studies evaluated a total of 622 patients with symptomatic endometriosis using danazol 600 or 800 mg daily as controls (13,14). Both studies required follow-up laparoscopy. Extent of symptom improvement and disease regression were 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 the fact that bone mineral density decreased by 5.4% in the goserelin group vs. 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 impact was noted after 6 months of depot leuprolide acetate in a follow-up of 270 patients from 22 centers, although there was a trend towards return to baseline (15).

Interestingly, Vercellini et al noted similar improvements in dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain in women receiving goserelin in comparison to a low-dose oral contraceptive administered continuously (16). 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 contractive therapy (either with or without a non-steroidal 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 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 to nafarelin 200 mcg administered intranasally twice daily (17). Both agents were equally effective in treating symptoms, but bone mineral density loss was greater and the incidence as well as intensity of vasomotor symptoms were greater in the leuprolide group which would be explained by consistently lower estradiol levels.

The U.S. Food and Drug Administration has approved the use of leuprolide acetate in a depot preparation, goserelin implant, and intranasal nafarelin for up to 6 months when administered alone for the treatment of symptomatic endometriosis. The potential benefit of shorter courses of GnRHa may allow for decrease in side-effects and the possibility for retreatment. A multicenter trial addressed this issue demonstrating that reduction in pain scores and symptom recurrence rates were similar after 3 vs. 6 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 3 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 3 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 use of these agents. As described above, there appears to be short-term symptom recurrence to levels below baseline in those studies in which this parameter was evaluated, although most trials limited their assessment to 12-24 weeks post-therapy. Waller and Shaw evaluated 130 endometriosis patients retrospectively who had been treated with a variety of GnRHa (20). 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.

All of the aforementioned trials 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 feel that such patients had a high likelihood of having the disease. Pain improvement after twelve weeks was significantly greater in those receiving GnRHa compared to placebo ($p \leq 0.001$). Follow-up laparoscopy revealed the presence of endometriosis in 78% of patients administered leuprolide acetate and 87% of those receiving 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 impact of the secondary hypoestrogenic state caused by pituitary down-regulation. However, a variety of investigators have suggested that these agents may have a direct effect on cytokine release, angiogenesis, and cell proliferation, although further investigation is clearly needed (3,22). A full discussion of theses proposed mechanisms is beyond the scope of this manuscript.

Post-operative GnRHa Therapy

Classically, treatment of symptomatic endometriosis has been exclusively medical or surgical. However, the concept of using GnRHa post-operatively has been investigated. A six-month course of postoperative therapy with nafarelin after cytoreductive laparoscopic surgery for endometriosis significantly decreased recurrence rates in comparison to placebo in a large multicenter trial of 109 women (23). This impact has been demonstrated with other GnRHa as well (24). Endometrioma recurrence rates have also been shown to decrease in comparison to expectant management subsequent to 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

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" (27). Unfortunately, although logical, there is limited data to define a single estradiol level that should be reached to achieve this goal and it would be expected that there would 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 the use of 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 in an effort 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 amongst each of these trials making comparisons amongst the regimens virtually impossible.

Currently, a single add-back regimen has been approved by the U.S. Food and Drug Administration for use in conjunction with a depot preparation of leuprolide acetate when therapy is to be extended beyond 6 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 (28). Patients were divided into one of 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 amongst 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 in comparison to 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 actually experienced 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 (26).

A pharmacy claims analysis of 1285 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 6 months. The benefits of relieving hypoestrogenic side-effects, maintaining painful symptom relief, and enhancing compliance makes 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 at least 18 years old. Younger girls are in a state of rapid bone development so that one should have a greater degree of concern in administering an agent that could impact this development. It is also unclear whether add-back as administered to older women would allow for bone development and not just act as bone sparing agents in this population.

DiVasta et al 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%) (30). All patients received GnRHa for 12 months and were randomized to norethindrone acetate 5 mg daily alone or in combination with conjugated equine estrogens 0.625 mg daily as add-back. The mean age was 17.9 ± 1.7 years but did include women up to 22.5 years of age which would represent 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 as well as parameters of physical functioning were also greater in the combination add-back group. These findings were confirmed with long-term follow-up assessment of 61% of these patients (31). Clearly, other forms of medical therapy should be used first in this patient populations e.g., combination oral contraceptives or progestins. However, use of 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 which established this efficacy are fraught with a significant degree of heterogeneity and inconsistent means of evaluating outcome parameters. The emphasis on post-therapy surgical analysis of disease regression is not considered to be as significant a concern today as are improvement 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 a 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 impact 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 which can allow for symptom relief and amelioration of many hypoestrogenic side-effects for up to one 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, efficacy of the medical management of this devastating disease.

Table 1: Selected prospective randomized trials evaluating GnRHa as therapy for symptomatic endometriosis

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

[a] IN = Intranasal
SC = Subcutaneous
IM = Intramuscular

[b] OC=Monophasic oral contraceptive (ethinyl estradiol 0.02 mg and desogestrel 0.15 mg)

[c] BMD = Bone mineral density

Table 2: Evaluated add-back therapies with GnRHa for symptomatic endometriosis – Adapted from Surrey (Table 1) (22)

	6 months only	Up to 12 months
Medroxyprogesterone acetate (MPA)	+	
Medrogesterone	+	
Ethinyl estradiol + desogestrel	+	
17β estradiol (E2) + MPA	+	
Conjugated equine estrogens (CEE) + MPA	+	
Norethindrone acetate (NETA)		+[a]
NETA + sodium etidronate		+
17β E2 + NETA		+
CEE + NETA		+
17β E2 + promegestrone		+
Tibolone		+

[a] FDA approved for use in a 5 mg daily dose with depot leuprolide acetate for up to one year of therapy

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Essential points: 1) Gonadotropin releasing hormone agonists (GnRHa) are effective in treating the symptoms associated with endometriosis.

2) Post-operative 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 6 months.

4) Hypoestrogenic side-effects can be minimized while maintaining efficacy of GnRHa and allowing extension of therapy for up to 12 months with use of an appropriate add-back.