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Long-Term Effects of Gonadotropin-Releasing Hormone Agonists and Add-Back in Adolescent Endometriosis

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Abstract

Study Objective—To explore the potential occurrence of long-term side effects and tolerability of gonadotropin-releasing hormone agonist (GnRHa) plus 2 different add-back regimens in adolescent patients with endometriosis

Design—Follow-up questionnaire sent in 2016 to patients who participated in a drug trial between 2008–2012

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A portion of these results were presented on a poster at the World Congress of Endometriosis May 17–20, 2017 in Vancouver, Canada and were accepted for a poster presentation at the North American Society of Pediatric and Adolescent Gynecology ACRM meeting April 12–14 in West Palm Beach, Florida.

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Setting—Tertiary care center in Boston, MA.

Participants—Females with surgically confirmed endometriosis (n=51) who enrolled in a GnRHa plus add-back trial as adolescents

Interventions—Leuprolide depot 11.25 mg intramuscular injection every 3 month, plus oral norethindrone acetate 5 mg daily or oral norethindrone acetate 5 mg daily plus oral conjugated equine estrogens 0.625 mg daily.

Main Outcome Measure(s)—Side effects during and after treatment, irreversible side effects, changes in pain, overall satisfaction

Results—The response rate was 61%. Almost all (96%) reported side effects during treatment; 80% reported side effects lasting > 6 months after stopping treatment. Almost half (45%) reported side effects they considered irreversible, including memory loss, insomnia, and hot flashes. Despite side effects, subjects rated GnRHa plus add-back as the most effective hormonal medication for treating endometriosis pain; two thirds (16/25) would recommend it to others. More subjects who received a modified two drug add-back regimen versus standard one drug add-back would recommend GnRHa and felt it was the most effective hormonal medication.

Conclusion—Subjects felt GnRHa plus add-back was effective and would recommend it to others, despite significant side effects. Those who received two drug add-back reported more success than those who received standard add-back. A subset of patients reported irreversible side effects.

Clinical Trial registration—ClinicalTrials.gov, NCT00474851

Keywords

endometriosis; adolescence; GnRHa; add-back

INTRODUCTION

Despite evidence that gonadotropin-releasing hormone agonists (GnRHa) such as leuprolide acetate are effective at controlling pain associated with endometriosis,^{1,2} there is controversy in the lay media surrounding these medications. Major media outlets publish stories of women with long-term, debilitating health problems that they attribute to use of leuprolide.^{3–5} Online petitions and forums to remove this drug from the market have received thousands of signatures and comments from dissatisfied patients and family members,^{6–9} citing irreversible health consequences.

Leuprolide acetate was approved by Food and Drug Administration for treatment of endometriosis in 1990.¹⁰ GnRHa suppress the hypothalamic-pituitary-ovarian axis, resulting in a hypoestrogenic state that can induce amenorrhea, relieve pelvic pain, and reduce the size of endometriosis lesions.^{2,11} Common side effects of this low estrogen state include bone density loss, hot flashes, depression, and memory loss.^{2,11–13} To minimize these side effects, “add-back therapy,” a low dose of hormone taken daily, is often prescribed as an adjunct to GnRHa treatment.^{12–15} The manufacturer’s website¹³ states side effects resolve within 3–6 months after stopping treatment. Patients and providers considering treating endometriosis

with GnRHa plus add-back weigh the potential benefits (pain reduction) against the potential side effects of treatment.

Less is known about the potential long-term side effects that persist > 6 months after GnRHa use. Drug trials do not always have long-term follow-up of patients, and those that do focus on fertility outcomes or recurrence of endometriosis symptoms^{16,17} rather than on treatment side effects. The purpose of this study was to explore the potential occurrence of long-term side effects of GnRHa plus add-back in patients known to have used this regimen during adolescence, as well as to assess patients' satisfaction with this treatment.

MATERIALS AND METHODS

From 2008 to 2012, 51 subjects aged 15–22 years enrolled in a 12 month longitudinal treatment trial of leuprolide depot (Lupron Depot ®) 11.25 mg intramuscular injection every 3 months. Full trial details have been previously published.¹⁴ Subjects were randomized to receive an add-back regimen of 1) oral norethindrone acetate (Aygestin®) 5 mg daily or 2) oral norethindrone acetate 5 mg daily plus oral conjugated equine estrogens (Premarin®) 0.625 mg daily. All subjects had surgically confirmed endometriosis treated with ablation and/or excision of lesions at the time of surgery, and had subsequently made the clinical decision to begin treatment with GnRHa for pelvic pain that was persistent despite oral hormonal therapies such as oral contraceptive pills. Of the 51 subjects enrolled in the study, 34 completed the 12-month trial and received 4 injections of GnRHa between baseline and study completion. Some subjects continued receiving additional doses of GnRHa after participation in the trial was over. Seventeen subjects withdrew from the study early and received between 1 and 4 GnRHa injections during participation; reasons for early termination are detailed elsewhere.¹⁴ Demographic information was collected at baseline. Subjects were asked to report treatment side effects and changes in endometriosis-associated pain at regular intervals during the trial.

In April 2016, we identified all 51 subjects who had enrolled in the treatment trial and had received at least one dose of GnRHa. We attempted to re-contact each subject by telephone, email, and/or mail. Subjects were asked to complete a 27 question follow-up survey online or on paper. Due to the lack of endometriosis measures validated for use in the adolescent age group, a study-specific survey was created. Subjects were given a list of potential side effects, based on the manufacturer's drug information,¹⁸ plus room to write in additional side effects. They were asked to report which symptoms, if any, they experienced in the short-term (during treatment), long-term (persisting for > 6 months after discontinuing treatment), or as an irreversible side effect (still experiencing).

To assess treatment satisfaction and effectiveness, subjects were asked to compare their endometriosis-related pain *before* initiating GnRHa plus add-back to their pain both *during* and *after* treatment. Subjects used a 0–10 scale to assess the direction in which their pain changed, where 0 = pain was much worse, 5 = no change in pain, and 10 = pain was much better. Scores were grouped into 3 categories: pain was worse (score = 0, 1, 2, or 3), pain was the same (score = 4, 5, or 6), or pain was better (score = 7, 8, 9, or 10). Subjects were asked to identify what medication was most effective for treating their endometriosis pain

(“Think about all the hormonal medications that you have ever used to treat your endometriosis. What medication do you think has helped the most with your endometriosis pain?”). Subjects were asked if their GnRHa dose or dose frequency had changed at any point, what medication they used after stopping GnRHa plus add-back, and if they had additional surgeries for endometriosis since stopping GnRHa plus add-back. Study data were collected and managed using REDCap electronic data capture tools hosted at Boston Children’s Hospital.¹⁹ Surveys completed on paper were entered into the REDCap database by a trained research assistant. Double data checks were performed. The study was approved by the Boston Children’s Hospital Institutional Review Board. Completion of the survey was taken as consent to participate. Subjects were not compensated for completing the survey.

RESULTS

Ten of the original 51 study subjects could not be re-contacted by phone, email, or mail (Figure 1). Of the 41 that could be reached, 25 completed the follow up survey online or on paper (61% response rate). Respondents and non-respondents were predominantly non-Hispanic whites; mean age at follow up was 22.4 years (SD = 2.0) for respondents and 23.1 years (SD = 2.4) for non-respondents (Table 1). Time elapsed from study termination/completion to the time of the follow up survey ranged from 21–65 months for respondents and 29–86 months for non-respondents. Time elapsed from stopping use of GnRHa to completion of the follow-up survey ranged from 0–82 months for respondents; data could not be collected from non-respondents. The survey response rate was greater among subjects who completed the trial: 56% of trial completers filled out the survey vs. 35% of participants who terminated study participation early. The response rate was also higher among those who enrolled in the study more recently (60% response rate for those enrolled 2010–2012 vs. 38% response rate for those enrolled 2008–2010), despite the same trial completion rate (64%) during the two time periods. The response rate did not differ between add-back treatment groups (44% Group 1 vs. 50% Group 2).

Of the 25 respondents, about half (12/25) continued treatment with GnRHa plus add-back after the 12-month randomized trial ended. Of these 12 subjects, 5 reported current use of GnRHa plus add-back at the time of survey completion and were excluded from analyses of long-term and irreversible side effects. Seven had discontinued GnRHa plus add-back between the end of the treatment trial and the time of the follow-up survey. Among those who discontinued GnRHa plus add-back at any point, the most common reasons for termination of therapy were medication side effects (65%), lack of improvement in pain (25%), and cost/insurance problems (20%) (Table 2). Reasons for stopping GnRHa plus add-back were similar for those who completed the trial and those who terminated early.

The vast majority (96%) of subjects reported experiencing at least one side effect during use of GnRHa plus add-back, similar to the 100% reporting of side effects collected prospectively during the trial. The most common side effects were those commonly associated with low estrogen states, including hot flashes/sweating, weight gain, mood swings/irritability, and breast changes/tenderness/pain, as well as reaction/pain at the injection site (Table 3).

Of those who terminated GnRHa plus add-back therapy, eighty percent reported experiencing at least one long-term side effect (lasting for >6 months after discontinuation). Long-term side effects included migraines, hot flashes/sweating, joint pain, and decreased libido (Table 3). Nearly half (45%) of subjects reported side effects that they considered to be “irreversible,” including bone density loss, memory loss, decreased libido, insomnia, anxiety, hypertension, hot flashes, headache, acne, trouble sleeping, nerve pain, joint pain, and weight gain. Reporting of irreversible symptoms was similar between the two add-back regimen groups and did not differ between those who terminated the trial early and those that completed the trial.

When asked to compare their endometriosis pain *during* treatment with GnRHa plus add-back to their pain *before* treatment with this regimen, 63% (15/24; 1 missing) said their pain was better while using GnRHa plus add-back, 28% (7/24) said pain was the same, and 8% (2/24) said pain was worse while using GnRHa plus add-back. Retrospective responses are similar to reports given during the trial; 60% (15/25) subjects contemporaneously reported improved pain during the study.^{14,15} When asked to compare their endometriosis pain *after* GnRHa treatment to their pain *prior* to GnRHa use, 52% of subjects (11/21, excluding 5 still using GnRHa plus add-back) said their pain was better after treatment, 19% (4/21) said it was the same, and 29% (6/21) said it was worse.

When asked to think about all the hormonal medications they had ever used to treat endometriosis (including those used before or after treatment with GnRHa plus add-back), 12 subjects (48%) rated GnRHa plus add-back as the hormonal medication that helped the most with their endometriosis pain, followed by progestin-only therapy (24%), hormonal IUD (12%), combination hormonal pill (8%), nafarelin acetate nasal spray (4%), and aromatase inhibitor (4%). Nearly 70% of subjects who received a combined add-back regimen of norethindrone acetate plus estrogens rated GnRHa plus add-back as the best treatment for reducing pain, versus 25% of subjects who received norethindrone acetate add-back alone.

Most subjects (64%) would recommend use of GnRHa to a friend or family member who had painful endometriosis, including one third (3/9) of subjects with irreversible side effects who would still recommend its use (Figure 2). When stratified by the type of add-back therapy received during trial participation, 85% of subjects who received add-back therapy with norethindrone acetate plus estrogens would recommend GnRHa plus add-back, versus only 42% of subjects who received GnRHa plus norethindrone acetate alone.

DISCUSSION

In this study of patient reported side effects of GnRHa plus add-back treatment for endometriosis and treatment satisfaction, this treatment regimen was beneficial for many. Sixty-three percent saw pain reduction during treatment, and 52% percent saw continued pain reduction after stopping treatment. Two thirds would recommend GnRHa plus add-back therapy to a friend or family member who had painful endometriosis, and almost half felt that GnRHa plus add-back was the best hormonal treatment they had tried for addressing endometriosis pain.

Reports of treatment success were associated with the type of add-back subjects received. Willingness to recommend GnRHa therapy to others was a more common response among subjects who received a modified add-back regimen of norethindrone acetate plus low dose estrogens rather than the more common add-back regimen of norethindrone acetate alone, suggesting this combination regimen was better tolerated by patients. Additionally, a greater proportion of those who received the modified two drug add-back regimen rated GnRHa plus add-back as the most effective hormonal therapy they had used. These results provide further support for the previously published outcomes from this patient cohort; a two-drug add-back regimen was found to be superior for preserving bone mineral density¹⁴ and preventing menopausal side effects during treatment.¹⁵

Almost all subjects (96%) reported experiencing at least one side effect during GnRHa plus add-back treatment, which is not surprising as the potential side effects of GnRHa use are well-established and well-advertised.^{13,18} In aggregate, our current results were consistent with data prospectively collected during the trial, suggesting that as a group, patients were able to accurately remember and report the side effects they experienced up to six years prior.

It is perhaps more surprising that 80% of subjects experienced side effects that persisted for > 6 months after terminating leuprolide plus add-back that they still attributed to the GnRHa. The leuprolide pharmaceutical insert¹⁸ and patient website¹³ state most side effects will disappear within 3 to 6 months of discontinuing treatment. Many of the long-term side effects reported, such as migraines, hot flashes, and decreased libido, suggest persistence of a hypoestrogenic state, although we do not have laboratory tests to confirm this hypothesis. This may suggest that for some patients, the GnRHa's effects on the body may not resolve within 3–6 months of discontinuing the medication.

We identified a subgroup of 9 subjects (5 received norethindrone acetate add-back and 4 received combined add-back) who experienced what they considered to be irreversible side effects that persisted for at least 2.5 years – 6 years after terminating GnRHa treatment. The current literature does not present the existence of these irreversible side effects. Among this subset, 2 reported bone density loss, a known side effect of treatment which should be monitored closely,¹⁸ however review of these 2 subjects' medical records showed either no loss or clinically insignificant decreases in bone density for age as measured by dual-energy x-ray absorptiometry. Neither subject identified bone density loss as a reason for terminating GnRHa treatment, and 1 continued using GnRHa plus add-back after the trial. We hypothesize that the results of bone density tests may have resulted in a more conservative course of treatment due to the age of the adolescent patient and the importance of bone development during this time, leading patients to believe there was a problem.¹⁴ Two subjects reported persistent memory loss, a recognized side effect of GnRHa that was generally thought to be reversible after discontinuation.¹³ Both subjects with continued memory complaints received norethindrone acetate alone for add-back. In another study, estrogen add-back treatment was shown to improve memory when used in conjunction with GnRHa.²⁰ This finding may provide further support of the benefits of a two-drug add-back regimen, although the sample size is small and we do not have results of objective memory tests to quantify or validate this subject-perceived decline in memory.

We recognize there are limitations of this study. While subjects were instructed to think specifically about side effects they associated with GnRHa plus add-back treatment, we cannot discount that side effects reported may have been a result of initiating a new treatment regimen after discontinuing GnRHa plus add-back. We also focused on patient-reported outcomes that could not be corroborated by physical exam or other diagnostic measures. Additionally, the response rate was greater for those who participated in the trial more recently which may bias the outcomes toward recent use, however those who most recently completed the trial finished at least 21 months prior to questionnaire completion. Additionally, the lack of long-term follow up data on the side effects of other hormone-altering medications in adolescents makes it difficult to compare these results to those of other treatments for endometriosis. This study also focused specifically on adolescent patients and may not generalize to adults with endometriosis.

Among patients who used GnRHa plus add-back for treatment of endometriosis during adolescence, long-term side effects of treatment were common. There appears to be a group who experienced pain remediation and tolerable side effects, and a small subset who experienced long-lasting side effects that outweigh any benefits achieved. These may be the stories that draw attention from the media. Other scientific investigations have also identified a subgroup of women who experience side effects of GnRHa above and beyond what is expected.²¹ We did not find demographic differences between those who succeeded with this treatment regimen and those who were dissatisfied and moved on to other medications. An important goal for our future work is to phenotype more extensively these patients to explore whether endometriosis staging, lesion location, lesion appearance, or presenting symptoms have a relationship with treatment success. Considering the general lack of endometriosis research that includes adolescents,²² this study provides important information for patients and providers about the use of GnRHa plus add-back in adolescents with endometriosis, and provides further support for a combined add-back regimen.

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Figure 1.
Patient enrollment and survey completion details

Figure 2.

Percentage of adolescents with endometriosis who would recommend GnRHa + add-back therapy to a friend or family member who had painful endometriosis, by add-back group
NETA plus CEE – norethindrone acetate 5mg daily plus 0.625mg conjugated equine estrogens daily; NETA – norethindrone acetate 5mg dail

Table 1

Demographic characteristics of survey respondents (n= 25) versus non-respondents plus those that could not be contacted (n=26)

Characteristic	Survey Respondents (N = 25)	Non-Respondents/Could not be Contacted (N = 26)
Age at time of survey, years	22.4 ± 2.0	23.1 ± 2.4
ASRM stage		
ASRM stage 1 endometriosis	15 (60%)	18 (69%)
ASRM stage 2 endometriosis	10 (40%)	8 (31%)
Race: white	23 (92%)	26 (100%)
Ethnicity: non-Hispanic	25 (100%)	26 (100%)
Time since ending trial, months	21–65	29–86
Time since stopping GnRHa + add-back, months	0–82	N/A

GnRHa: gonadotropin releasing hormone agonist; ASRM – American Society for Reproductive Medicine; N/A: not available from non-respondents

Data are mean ± SD, n (%), or minimum – maximum

Table 2

Reasons for stopping GnRHa plus add-back therapy, by add-back group

Reason for stopping GnRHa	N (%) [*]	NETA	NETA + CEE
Didn't like the side effects	13 (65%)	9	4
Didn't help with my endometriosis pain	5 (25%)	2	3
Too expensive/insurance problems	4 (20%)	1	3
Didn't need it anymore	2 (10%)	2	0
Didn't like injections	2 (10%)	2	0
Switched doctors	2 (10%)	2	0
Other: bone density concerns	2 (10%)	0	2
Still using GnRHa	5	1	4

GnRHa: gonadotropin-releasing hormone agonist; NETA – norethindrone acetate 5mg daily; NETA + CEE – norethindrone acetate 5mg daily plus 0.625mg conjugated equine estrogens daily

* Percentages are based on a group size of 20, excluding 5 subjects still using GnRHa + add-back at the time of survey. Subjects were asked to report all reasons for stopping.

Table 3

Patient reported side effects of GnRHα plus add-back treatment for endometriosis

Symptom	Data collected during trial			Data collected on follow-up survey		
	Non-responsive to follow up survey (N=23)*	Responded to follow up survey (N=24)†	N (%)	During treatment (N=25)	> 6 months after treatment (N=20)‡	Irreversible (N=20)§
CARDIOVASCULAR						
Hot flashes/sweating	23 (100%)	21 (88%)	22 (88%)	6 (30%)	3 (15%)	
High blood pressure	N/A	N/A	0	0	1 (5%)	
GI SYSTEM						
Constipation	N/A	N/A	9 (36%)	4 (20%)	0	
Bloating	N/A	N/A	8 (32%)	5 (25%)	0	
Nausea/vomiting	N/A	N/A	8 (32%)	4 (20%)	0	
Increased appetite	N/A	N/A	6 (24%)	3 (15%)	0	
Diarrhea	N/A	N/A	5 (20%)	2 (10%)	0	
Loss of appetite	N/A	N/A	3 (12%)	1 (5%)	0	
CONSTITUTIONAL						
Weight gain	N/A	N/A	15 (60%)	5 (25%)	1 (5%)	
Weight loss	N/A	N/A	3 (12%)	2 (10%)	0	
Lack of energy,§	20 (87%)	20 (83%)	10 (40%)	5 (25%)	0	
Memory loss			3 (12%)	4 (20%)	2 (10%)	
General body pain			8 (32%)	5 (25%)	0	
Whole body weakness	N/A	N/A	7 (28%)	4 (20%)	0	
ENDOCRINE SYSTEM						
Hair loss	N/A	N/A	6 (24%)	4 (20%)	0	
Acne	N/A	N/A	5 (20%)	5 (25%)	1 (5%)	
Unwanted hair growth	N/A	N/A	0	2 (10%)	0	
MUSCULOSKELETAL SYSTEM						
Reaction/pain at injection site	N/A	N/A	12 (48%)	1 (5%)	1 (5%)	

Symptom	Data collected during trial			Data collected on follow-up survey		
	Non-responsive to follow up survey (N=23) [*]	Responded to follow up survey (N=24) [†]	N (%)	> 6 months after treatment (N=25)	Irreversible (N=20) [‡]	
Muscle pain [§]	15 (65%)	18 (72%)	6 (24%)	4 (20%)	0	
Joint pain			4 (16%)	6 (30%)	1 (5%)	
Bone pain	N/A	N/A	2 (8%)	3 (15%)	0	
Muscle spasms	N/A	N/A	2 (8%)	2 (10%)	0	
Bone density loss	N/A	N/A	0	0	2 (10%)	
NERVOUS SYSTEM						
Mood swings/irritability [§]	17 (74%)	22 (88%)	16 (64%)	4 (20%)	1 (5%)	
Depression			7 (28%)	2 (10%)	0	
Insomnia/trouble sleeping	20 (87%)	22 (88%)	7 (28%)	3 (15%)	2 (10%)	
Headache (not migraine)	N/A	N/A	7 (28%)	3 (15%)	1 (5%)	
Migraine	N/A	N/A	6 (24%)	7 (35%)	0	
Nervousness/anxiety	16 (70%)	19 (76%)	6 (24%)	3 (15%)	1 (5%)	
Dizziness	N/A	N/A	4 (16%)	1 (5%)	0	
Tremors/shaking	N/A	N/A	3 (12%)	0	0	
Tingling in hands/feet	N/A	N/A	1 (4%)	1 (5%)	0	
UROGENITAL SYSTEM						
Breast changes/tenderness/pain	N/A	N/A	12 (48%)	3 (15%)	0	
Pain during sex	N/A	N/A	7 (28%)	4 (20%)	0	
Decreased interest in sex	8 (35%)	5 (20%)	6 (24%)	6 (30%)	1 (5%)	

GnRHa: gonadotropin-releasing hormone agonist; N/A – not available

^{*} Percentages are based on a group size of 23, excluding 3 subjects who only had baseline data obtained before beginning GnRHa therapy

[†] Percentages are based on a group size of 24, excluding 1 subject who only had baseline data obtained before beginning GnRHa therapy

[‡] Percentages are based on a group size of 20, excluding 5 subjects still using GnRHa + add-back at the time of survey

[§] These pairs of items are grouped together on the standardized Menopausal Rating Scale (MRS) which was utilized prospectively during the clinical trial, but were asked about separately on the follow-up survey