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The Effects of GnRHa plus Add-Back Therapy on Quality of Life for Adolescents with Endometriosis: A Randomized Controlled Trial

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Abstract

Study Objective—Use of gonadotropin-releasing hormone agonist (GnRHa) to treat endometriosis can cause mood and vasomotor side effects. “Add-back therapy,” the addition of low dose hormones, limits side effects but research is limited to adults. We sought to characterize quality of life (QOL) before treatment and to compare an add-back regimen of norethindrone acetate (NA) + conjugated estrogens (CEE) to NA alone for preventing side effects of GnRHa therapy in adolescents with endometriosis.

Design—12-month double-blind, placebo-controlled trial.

Setting—Pediatric Gynecology clinic in Boston, Massachusetts.

Participants—50 females (age 15–22y) with surgically-confirmed endometriosis initiating treatment with GnRHa.

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Intervention—Subjects were randomized to: NA (5 mg/d) + CEE (0.625 mg/d) or NA (5 mg/d) + placebo. All subjects received leuprolide acetate depot every 3 months.

Main Outcome Measures—The Short Form 36-v2 Health Survey, Beck Depression Inventory-II, and Menopause Rating Scale were completed at repeated intervals.

Results—At baseline, subjects reported impaired physical health-related QOL when compared to national norms (all $p < 0.0001$). Over 12 months, these SF-36 scores improved (all $p < 0.05$). Subjects receiving NA+CEE showed greater improvements in Pain, Vitality, and Physical Health subscales ($p_{\text{between}} < 0.05$) than those receiving NA alone, as well as better Physical Functioning ($p < 0.05$). There were no changes in depression or menopause-like symptoms in either group.

Conclusion—Adolescents with endometriosis initiating GnRHa therapy have impaired QOL. Treatment with GnRHa plus add-back led to improved QOL, with no worsening of mood or menopausal side effects. NA+CEE was superior to NA alone for improving physical health-related QOL.

Keywords

endometriosis; adolescence; gonadotropin releasing hormone agonist; add-back therapy; quality of life

Introduction

Endometriosis is a disease associated with chronic pain that may lead to decreased occupational and social success. In adults, endometriosis is associated with decreased quality of life (QOL); impairment is attributed to experiences of bodily pain and decreased physical and social functioning.^{1,2} Adults report significant financial burden,^{1,3} losses in work productivity,^{1,2} and increased work absenteeism.^{1,2} Less is known about the adolescent and young adult experience of endometriosis,^{1,4} despite increasing incidence rates and frequent reports of symptom onset during adolescence.⁴

Adolescents with endometriosis tend to present to clinicians with pelvic or abdominal pain which is often related to their menstrual cycle. This pain may initially be misclassified as a normal menstrual symptom or attributed to non-gynecologic disease, causing a delay in diagnosis and leaving the adolescent to suffer with untreated pain, potentially for years.^{4,5} Patients are often trialed on combined oral contraceptives or progesterone-only therapy to regulate or suppress the menstrual cycle. Many patients find relief with this treatment. However, approximately 70% of patients with persistent pelvic pain despite hormonal therapy will be found to have endometriosis.⁶ Surgery remains the gold standard for diagnosis of endometriosis. Adolescents with a surgical diagnosis of endometriosis who do not find relief from combined oral contraceptives or progesterone-only therapy may be prescribed gonadotropin-releasing hormone agonists (GnRHa) to suppress the hypothalamic-pituitary-ovarian axis, inducing a hypogonadal hypoestrogenic state and reducing pain and bleeding of estrogen-sensitive endometrial lesions.^{5,6}

Use of GnRHa in adults with endometriosis is associated with menopausal side effects including hot flashes, vaginal dryness, mood changes, and sleep disturbance.^{6,7} Depression

is also reported as an adverse event in 23% of adult women treated with GnRHa.⁶ These side effects are widely recognized and may contribute towards providers' hesitancy to prescribe and patients' unwillingness to initiate treatment with this medication. "Add-back therapy," where low doses of hormone are taken concurrently with GnRHa, is a promising adjunct to help mitigate these treatment side effects. With add-back therapy, patients receive sufficient hormone to prevent somatic and psychological complaints, as well as to protect bone health, while still preserving the efficacy of the GnRHa.⁵⁻⁷ Hornstein et al. successfully used GnRHa plus add-back in adults, demonstrating both prevention of vasomotor symptoms and reduction in pelvic pain.⁷ We previously reported the efficacy of add-back therapy in adolescents for preservation of bone density during 12 months of GnRHa treatment.⁸ To our knowledge, there is no existing literature discussing the impact of GnRHa plus add-back therapy on QOL in adolescents.

The purpose of this study was 1) to characterize QOL before treatment, and 2) to determine whether an add-back regimen of norethindrone acetate (NA) + conjugated estrogens (CEE) or NA alone was superior for prevention of side effects in adolescents with endometriosis receiving treatment with GnRHa. We hypothesized that all patients would show improved QOL during 12 months of GnRHa treatment, and that patients receiving NA+CEE add-back would exhibit fewer menopause-like symptoms than those receiving NA alone.

Materials and Methods

We conducted a 12 month, randomized, double-blind, placebo-controlled trial. Full details of the trial design have previously been published.⁸ Briefly, eligible females were aged 15 to 22 years, at least 2 years post-menarche, with surgically-confirmed endometriosis and a decision to begin treatment with leuprolide acetate depot (Lupron Depot® 11.25 mg IM; Abbvie Inc., Chicago, IL). The Boston Children's Hospital Institutional Review Board approved the protocol. Informed consent was obtained, with parental consent/subject assent for subjects <18 years (clinicaltrials.gov NCT00474851). Group 1 received two drug add-back: NA (Aygestin® 5 mg PO daily; Teva Pharmaceuticals, Sellersville, PA) + CEE (Premarin® 0.625 mg PO daily; Wyeth Pharmaceuticals, Philadelphia, PA). Group 2 received NA (5 mg daily) + placebo. Neither study staff nor patients were aware of drug assignment. Add-back therapy was started for all subjects 21 days after the first injection of GnRHa, which is the standard of care at our institution for patients currently using other hormonal therapies. Medication compliance was assessed at each study visit.

Subjects completed three questionnaires at their baseline visit and then at scheduled intervals during the trial. The Short Form-36 v2 (SF-36) is a general measure of health-related QOL that includes 8 subscales (Table 1).⁹ Raw scores were transformed into normed scores (mean = 50; SD = 10; range 0–100); normed scores are reported here unless otherwise noted. Two composite scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), were calculated from the transformed subscale scores.⁹ For all scales, lower scores indicate a greater degree of impairment. Baseline scores (obtained prior to administration of the first dose of GnRHa) were compared to published norms for age-matched (18–24 years old), healthy United States females.¹⁰

The Menopause Rating Scale (MRS) measures health-related QOL with a focus on psychological, somato-vegetative, and urogenital symptoms associated with menopause. The MRS is validated as an outcome measure for trials of hormone therapy.¹¹ Three subscale scores and a total MRS score (range 0–44) can be calculated, with higher scores indicating more severe symptoms. Baseline scores were compared to a published sample of 1400 U.S. women aged 40–70 years, as age-matched norms are not available.¹²

The Beck Depression Inventory-II (BDI) is widely used with adults and adolescents to measure depressive symptoms. Scores range from 0–63, with higher scores indicating more severe symptoms. A cut-off score of 14 or greater was adopted to identify clinically significant depressive symptoms.¹³ The SF-36 and BDI were repeated at 6 month intervals. The MRS was repeated every 3 months.

We compared baseline characteristics of the two study arms by Student t, Wilcoxon rank-sum, or Fisher exact test as appropriate. We compared baseline mean scale scores to the fixed national norm (50) by one-sample t-test and to normative samples of age-matched females by two-sample t-test.

The time course of each scale between baseline, 6 months, and 12 months was analyzed by repeated-measures analysis variance (ANOVA), with an autoregressive covariance structure to account for within-subject correlation over the three time points. Contrasts were constructed from parameters of the fitted ANOVA to test for significant divergence in time course between the two study arms by Fisher F-test (p_{between}). To summarize the overall change in each group, we report the estimated mean change between baseline and 12 months, constructed from parameters of the ANOVA model and assessed for significance by Student t-statistic (p_{within}).

To test whether the effects of treatment varied according to age or body-mass index (BMI), we added appropriate interaction terms to the ANOVA model. Where the interaction was significant, we stratified the effect modifier and report stratum-specific estimates for the mean change between baseline and 12 months.

Significance was set at $p < 0.05$. We followed the intention-to-treat principle, and all data were attributed to the subject's assigned treatment group regardless of whether treatment was delivered or completed. SAS software (version 9.4, Cary, NC) was used for all computations.

Results

Mean age at baseline was 17.9 ± 1.7 y (mean $\pm$ SD; Table 2). All patients had ASRM Stage 1 or Stage 2 endometriosis at the time of their diagnostic laparoscopy, which occurred at a mean age of 16.3 ± 2.1 y. Most (49/50) were using some type of medical therapy at baseline: continuous combination hormonal therapy $n=27$ (54%), NA monotherapy $n=20$ (40%), or depot medroxyprogesterone (DMPA) $n=2$ (4%). The trial arms did not differ in baseline demographic characteristics (Table 2). Reported medication compliance did not vary between trial arms ($p=0.77$).

SF-36

At baseline, before initiating GnRHa plus add-back therapy, scores for all 8 subscales fell below the population mean of 50, indicating impairment (Figures 1a, 1b). Scores for all physical health domain subscales (Physical Functioning, Role Limitation-Physical, Bodily Pain, General Health), the PCS, and the Social Functioning subscale were also lower than age-matched mean scores ($p < 0.0001$; Figures 1a,b). Scores for Vitality, Role Limitation-Emotional, Mental Health and MCS did not differ from age-matched norms ($p > 0.05$; Figure 1b). Subjects' method of hormonal treatment at baseline (continuous combination hormonal therapy or NA monotherapy) did not affect QOL scores. When compared to published scores for adolescents and young adults with cystic fibrosis,¹⁴ juvenile rheumatoid arthritis,¹⁵ and polycystic ovary syndrome,¹⁶ adolescents with endometriosis had lower scores on both physical health and mental health subscales (Table 3).

Treatment with GnRHa plus add-back led to improvements in physical health-related QOL over the 12-month investigation for both trial arms. However, the time course of changes in the PCS summary score differed according to add-back assignment ($p_{\text{between}} = 0.005$; Figure 2a). Subjects receiving NA+CEE sustained greater increases in PCS score between baseline and 12 mo ($+10 \pm 3$, adjusted mean $\pm$ standard error; $p_{\text{within}} = 0.0008$) than those receiving NA alone ($+6 \pm 3$; $p_{\text{within}} = 0.05$). Similarly, while both groups demonstrated improvements on the Bodily Pain subscale, the time course differed ($p_{\text{between}} = 0.008$; Figure 2a). Subjects who received NA+CEE had greater improvements ($+12 \pm 3$, $p_{\text{within}} = 0.0004$) than those who received NA alone ($+8 \pm 3$; $p_{\text{within}} < 0.015$). The Physical Functioning Subscale improved in those adolescents randomized to NA+CEE ($+7 \pm 3$, $p_{\text{within}} = 0.002$); no improvements were seen in the NA group ($+2 \pm 2$, $p_{\text{within}} = 0.42$). Equal changes on the Role-Physical subscale were found in the NA+CEE group ($+11 \pm 3$, $p_{\text{within}} = 0.002$) and the NA group ($+8 \pm 3$, $p_{\text{within}} = 0.017$; $p_{\text{between}} = 0.22$). No changes in General Health scores were observed ($p_{\text{between}} = 0.10$).

Mental Health scales also changed over time. Subjects showed comparable improvement in Vitality scores (NA+CEE: $+7 \pm 3$, $p_{\text{within}} = 0.015$ versus NA: $+6 \pm 3$, $p_{\text{within}} = 0.04$), although the trajectory of change differed between groups ($p_{\text{between}} = 0.02$; Figure 2b). Greater increases in Social Functioning were seen in the NA+CEE group ($+12 \pm 3$, $p_{\text{within}} = 0.0006$) than the NA group ($+4 \pm 3$, $p_{\text{within}} = 0.21$; Figure 2b). There were no changes in Role-Emotional ($p_{\text{between}} = 0.69$), Mental Health ($p_{\text{between}} = 0.89$) or MCS summary scores ($p_{\text{between}} = 0.87$) during the trial.

Age did not have an impact on the SF-36 scales. Significant interactions of BMI with treatment effect were found for PCS ($p = 0.03$) and two subscales: Bodily Pain ($p = 0.03$) and Role-Physical ($p = 0.04$). For each of these scales, stratified analysis indicated that among subjects in the highest quartile of BMI (BMI ≥ 27.1 kg/m²) the NA+CEE group showed greater increases from baseline to 12 months than the NA group. In contrast, in the lowest quartile (BMI < 21.9 kg/m²) the NA group showed greater increases.

Beck Depression Inventory

At baseline, the mean BDI score in the combined study arms was 10.2 ± 8.0 (mean $\pm$ SD). Aberrant mood was prevalent; over one quarter of subjects (26%) scored ≥ 14 on the BDI, suggesting a mild or greater level of depression.¹³ There were no differences at baseline by current hormonal treatment group. No significant changes in BDI score occurred during 12 months of treatment ($p_{\text{between}}=0.66$; Table 4).

Menopause Rating Scale

At baseline, teens with symptomatic endometriosis reported a moderate level of menopause-like symptoms (9.1 ± 6.8 , mean $\pm$ SD). This score is not significantly different from a published sample of U.S. females 40–70 years ($p>0.05$).¹² There were no differences at baseline by current hormonal treatment group. MRS scores did not change during the trial in either arm ($p_{\text{between}}=0.21$; Table 3).

Discussion

The lack of knowledge about the impact of endometriosis and its treatments on adolescents' lives may prevent clinicians and families from adequately meeting these teens' needs. To address this issue, we first sought to characterize the degree of impact that symptomatic endometriosis had on QOL and mood for these adolescents. Second, we sought to determine whether an add-back regimen of NA+CEE was superior to NA alone when used in conjunction with GnRHa therapy.

Prior to initiating treatment with GnRHa, physical health-related QOL for these young women was impaired, evidenced by SF-36 physical health subscale scores and a PCS summary score that were significantly lower than those of age-matched healthy females. Only one subscale within the mental-health component of the SF-36, the Social Functioning subscale, was impaired at baseline. The Social Functioning subscale is unique in that it refers to both physical health and emotional problems. As such, it factors into the MCS, but is also recognized to correlate with PCS.⁸ Subjects also reported menopausal symptoms at the level of perimenopausal and menopausal adult women, as well as aberrations in mood. This impaired QOL occurred despite 98% of patients receiving commonly used hormonal treatments (combined oral contraceptives, NA monotherapy) for endometriosis. Our cohort includes patients whose endometriosis pain was refractory to these first line therapies.

Although 26% of subjects in our sample scored at or above a “mild depression” level on the BDI, and scores on the psychological subscale of the MRS were above the adult norm (indicating greater impairment), these young women did not perceive their mental health to have a negative impact on their QOL. This finding speaks to a potential unidentified and unmet need for mental health counseling. With this result in mind, providers making referrals for counseling should present it as adjunct to, not a replacement for, continued medical management of the disease. This distinction may be important to stress to patients, many of whom will have been referred to a mental health provider before a gynecologist for treatment of their pain, contributing to their diagnostic delay and protracted pain experience, and for others who may not recognize the disease's impact on their mental health.

As the SF-36 is a general measure of health-related QOL, scores between disease groups can be compared to better understand the level of impairment each disease produces. At baseline, teens with endometriosis fared worse than adolescents and young adults with cystic fibrosis,¹⁴ juvenile rheumatoid arthritis,¹⁵ and polycystic ovary syndrome,¹⁶ three chronic conditions considered to have profound impact on QOL, providing further evidence of the substantial impact of endometriosis.

Twelve months of treatment with GnRHa plus add-back appears to address these QOL deficits by lessening endometriosis-associated pain and controlling other physical symptoms. Subjects demonstrated significant improvements in their physical health (PCS), as well as specific measures of Pain, Social Functioning, Physical Functioning, Physical Health, and Vitality. For the first time, we were able to show the effectiveness of GnRHa plus add-back for improving adolescent patient QOL outcomes, replicating Hornstein et al.'s work in adults.^{7,17}

While the NA group initially showed greater improvement, perhaps due to a greater decrease in circulating hormone levels, an add-back regimen of NA+CEE was superior for improving self-reported QOL over 12 months. Only those patients receiving NA+CEE achieved normative scores on the Bodily Pain subscale. In contrast, adolescents receiving NA alone continued to have impairment due to Bodily Pain at 12 months. The NA+CEE treatment group also showed greater improvements in Physical Health and Vitality.

The addition of low-dose estrogen to the add-back regimen may allow these patients to reach an "estrogen threshold," described by Barbieri as a level at which hypoestrogenic side effects are prevented without activating the disease itself, leading to more positive treatment outcomes.⁷ Subjects randomized to NA+CEE may have reached this threshold, with the result being improved physical health-related QOL, whereas subjects receiving NA alone began to struggle with the effects of their hypoestrogenic state. These results should be taken in the context of our previous study, in which we demonstrated that NA+CEE was superior to NA monotherapy for protecting bone health in adolescents.⁸

Our results did not vary by age. We did find evidence of an interaction effect for BMI. Subjects in the lowest BMI quartile ($\text{BMI} < 21.9 \text{ kg/m}^2$) showed different responses than those in the highest quartile ($\text{BMI} > 27.1 \text{ kg/m}^2$). Those adolescents with low BMI reported greater improvement with NA alone than with NA+CEE on Bodily Pain and Role-Physical SF-36 subscales. We hypothesize that the lower BMI cohort may have less body fat, and therefore less aromatization to estrogen. As such, these girls with low BMI may be more sensitive to the additional estrogen replacement and may feel greater somatic side effects as a result. The more estrogen replete, higher BMI girls tolerated the combination therapy better as they were potentially more estrogen replete upon initiation of the combination therapy. These are merely hypotheses, and we recognize that this finding is an area for further research.

Both add-back regimens were efficacious in preventing potential mental health and menopausal symptoms associated with GnRHa use, such as mood and vasomotor changes. Subjects did not report an increase in depressive symptoms as measured by the BDI, SF-36

MCS, or MRS psychological subscale.⁷ These findings are reassuring evidence that treatment with GnRHa plus add-back did not lead to adverse mental health changes in adolescents. We did not see group differences in MRS scores. While the MRS has been validated as an outcome measure in hormone therapy trials in adults,¹¹ it may not be able to detect treatment-related changes in the adolescent population. Scores on the MRS could also have been affected by the young age of our sample who are less likely to be sexually active, and for whom the urogenital subscale may have been irrelevant.

Study limitations should be acknowledged. Our cohort consists of adolescents with symptomatic endometriosis who were scheduled to begin treatment with a GnRHa. These patients represent a small proportion of our clinic population; results may not generalize to patients whose endometriosis symptoms were successfully treated by initial medical therapy. In addition, there may be variation among patients with comorbidities or with more diverse personal and demographic characteristics; our sample predominantly identified as white. Finally, the SF-36 normative data and MRS data that were used for comparison were not collected concurrently with our sample data and may be impacted by secular trends. Seventeen subjects withdrew from the trial due to a clinical decision to discontinue treatment with leuprolide acetate depot. Sixteen subjects cited lack of pain relief or inability to tolerate treatment side effects. There were no differences in baseline characteristics between those who terminated and those who completed the trial, but our results may only generalize to patients who find success with long term (> 6 month) GnRHa therapy.

In summary, adolescents with symptomatic endometriosis have impaired QOL when compared to scores for healthy age-matched females or to adolescents suffering from other chronic diseases. Adolescents with endometriosis perceive that their physical health has a significant impact on their QOL; they do not attribute poor QOL to problems with mental health. An add-back regimen of NA+CEE appears superior for addressing QOL deficits, and led to greater improvements in QOL over 12 months of therapy than did NA alone. Larger studies are needed to further understand the life-long trajectory and holistic impact of this disease. Focus on adolescent patients is critical to understanding the impact of the disease during adolescence and the impact of intervention during adolescence on outcomes in adulthood.

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Figure 1.

Figure 1a. Scores on the Physical Health indices of the SF-36 v2 from 50 adolescents with surgically-confirmed endometriosis compared to 1998 age-matched national norms.

Figure 1b. Scores on the Mental Health indices of the SF-36 v2 from 50 adolescents with surgically-confirmed endometriosis compared to 1998 age-matched national norms.

Figure 2.

Figure 2a: SF-36 Physical Component Summary (PCS) and physical component subscale scores over 12 months of treatment with a GnRH agonist plus add-back therapy. Dotted line represents the 1998 age-matched national norms.

● = Norethindrone acetate + Conjugated estrogens; × = Norethindrone acetate + Placebo

Figure 2b: SF-36 Mental Component Summary (MCS) and mental health subscale scores over 12 months of treatment with a GnRH agonist plus add-back therapy. Dotted line represents the 1998 age-matched national norms.

● = Norethindrone acetate + Conjugated estrogens; × = Norethindrone acetate + Placebo

Table 1

Subscales of the Short Form-36 measure of quality of life

Physical Health	
Physical Functioning	Ability to perform physical activities
Role Limitation–Physical	Problems with work or other daily activities due to physical health
Bodily Pain	Limitations due to pain
General Health	Evaluation of personal health
Mental Health	
Vitality	Level of energy/fatigue
Social Functioning	Interference with social activities due to physical and emotional problems
Role Limitation–Emotional	Problems with work or other daily activities due to emotional health
Mental Health	Feelings of anxiety and depression

Table 2

Baseline Participant Demographic Characteristics by Study Arm

	All (n=50)		NA + CEE (n=24)		NA + Placebo (n=26)		P*
	Mean ± SD	Min—Max	Mean ± SD	Min—Max	Mean ± SD	Min—Max	
Age, yr	17.9 ± 1.7	15.4—22.6	17.7 ± 1.4	15.4—22.6	18.1 ± 1.9	15.4—22.6	0.41
Height, cm	163.8 ± 4.8	155.6—176.6	162.9 ± 4.3	155.6—176.6	164.7 ± 5.2	155.6—176.6	0.19
Weight, kg	67.8 ± 13.4	50.9—116.6	66.7 ± 12.6	50.9—116.6	68.9 ± 14.3	50.9—116.6	0.55
BMI, kg/m ²	25.2 ± 4.6	19.7—41.3	25.1 ± 4.3	19.7—41.3	25.4 ± 4.9	19.7—41.3	0.82
	Median (Q1–Q3)	Min—Max	Median (Q1–Q3)	Min—Max	Median (Q1–Q3)	Min—Max	
Months since diagnosis	15 (9–24)	1—124	12 (9–20)	1—124	20 (8–30)	1—124	0.30
	N (%)		N (%)		N (%)		
White	49 (98)		23 (96)		26 (100)		0.24

* Student t, Wilcoxin rank-sum, or Fisher Exact test comparing distribution in NA+CEE and NA+P arms.

NA, norethindrone acetate; CEE, conjugated equine estrogens; BMI, body mass index

Table 3

Raw Scores for the Short Form-36 subscales for subjects with endometriosis compared to other disease groups.

	Endometriosis (n=50)		Cystic Fibrosis (n=70)		Juvenile Rheumatoid Arthritis (n=258)		Polycystic Ovary Syndrome (n=50)	
	mean $\pm$ SD		mean $\pm$ SD	p-value *	mean $\pm$ SD	p-value *	mean $\pm$ SD	p-value *
Physical Functioning	46.3 $\pm$ 8.6		79.5 $\pm$ 22.6	<0.0001	85.2 $\pm$ 18.4	<0.0001	Data not available	-
Role – Physical	39.8 $\pm$ 12.1		67.5 $\pm$ 37.7	<0.0001	78.9 $\pm$ 32.9	<0.0001	71 $\pm$ 37	<0.0001
Bodily Pain	35.6 $\pm$ 9.3		78.5 $\pm$ 26.3	<0.0001	75.6 $\pm$ 23.5	<0.0001	73 $\pm$ 30	<0.0001
General Health	39.0 $\pm$ 10.1		44.1 $\pm$ 22.3	0.09	69.9 $\pm$ 22.5	<0.0001	Data not available	-
Vitality	43.5 $\pm$ 11.0		56.0 $\pm$ 18.5	<0.0001	Data not available	-	43 $\pm$ 20	0.88
Social Functioning	38.9 $\pm$ 10.9		80.7 $\pm$ 23.0	<0.0001	Data not available	-	66 $\pm$ 30	<0.0001
Role-Emotional	47.8 $\pm$ 11.6		90.5 $\pm$ 22.8	<0.0001	Data not available	-	49 $\pm$ 44	0.85
Mental Health	45.8 $\pm$ 10.5		71.4 $\pm$ 16.2	<0.0001	82.4 $\pm$ 16.2	<0.0001	53 $\pm$ 20	0.02

* p-value is from the comparison of the disease group mean to the endometriosis group mean.

Disease data published by Goldbeck and Schmitz,¹⁴ Flato et al.¹⁵ and Elsenbruch et al.¹⁶

Changes in Beck Depression Inventory (BDI) and Menopause Rating Scale (MRS) scores over 12 months of treatment with a GnRH agonist plus add-back therapy.

Table 4

	Group	Baseline mean $\pm$ SD	Adjusted mean change				<i>P</i> (within group)	<i>P</i> (between groups)
			3 mo	6 mo	9 mo	12 mo		
Beck Depression Inventory	NA+CEE	9 $\pm$ 6	—	-2	—	-3	0.27	0.66
	NA+Placebo	12 $\pm$ 10	—	-2	—	-1	0.42	
Menopause Rating Scale	NA+CEE	8 $\pm$ 6	0	1	1	0	0.66	0.21
	NA+Placebo	10 $\pm$ 8	2	1	1	1	0.23	

NA, norethindrone acetate; CEE, conjugated equine estrogens