Published in final edited form as:

Obstet Gynecol. 2015 September ; 126(3): 617–627. doi:10.1097/AOG.0000000000000964.

Hormonal Add-Back Therapy for Females Treated With Gonadotropin-Releasing Hormone Agonist for Endometriosis: A Randomized Controlled Trial

Amy D. DiVasta, MD, MMSc^{1,2,3}, Henry A. Feldman, PhD⁴, Jenny Sadler Gallagher, BA^{1,3}, Natalie A. Stokes, BA⁵, Marc R. Laufer, MD^{2,3,6}, Mark D. Hornstein, MD^{3,6}, and Catherine M. Gordon, MD, MSc⁷

¹Division of Adolescent Medicine, Children's Hospital Boston

²Division of Gynecology, Children's Hospital Boston

³Boston Center for Endometriosis

⁴Clinical Research Program, Children's Hospital Boston

⁵University of Pennsylvania School of Medicine

⁶Department of Obstetrics and Gynecology, Brigham and Women's Hospital

⁷Divisions of Adolescent Medicine and Endocrinology, Hasbro Children's Hospital

Abstract

Objective—To assess whether add-back therapy with norethindrone acetate (n. acetate) or n. acetate plus conjugated equine estrogens is superior to maintain bone health in adolescents and young women using gonadotropin-releasing hormone agonists (GnRHa) for endometriosis. GnRHa are associated with deleterious effects on bone. Hormonal add-back may mitigate these effects.

Methods—Adolescents and young women (n=51) received a random, double-blind assignment to add-back with n. acetate (5 mg/d) plus conjugated equine estrogens (0.625 mg/d) or n. acetate plus placebo for 12 months. Body composition, bone mineral content, and bone mineral density (BMD) were obtained by dual-energy X-ray absorptiometry (DXA) every 6 months. Quality-of-life measures were collected every 3 months. Intention-to-treat comparison of outcomes was conducted by repeated-measures ANOVA.

Results—Thirty-four adolescents and young women completed the trial; dropouts did not differ from. BMD was normal at baseline. At 12-months, total body bone mineral content and BMD had increased in the n. acetate plus conjugated equine estrogens group (bone mineral content +37g, $p<0.001$ and BMD +0.012 g/cm², $p=0.05$), but not in those receiving n. acetate plus placebo (bone mineral content $p=0.19$ and BMD $p=0.95$). Lean mass increased only in those receiving

Corresponding Author: Amy D. DiVasta, MD, MMSc, Division of Adolescent Medicine, Boston Children's Hospital, 333 Longwood Avenue, Boston, MA 02115, Phone:617-355-3792, amy.divasta@childrens.harvard.edu.

Presented at the 2015 meetings of the Society for Adolescent Health and Medicine (March 18–21 2015, Los Angeles, CA), North American Society for Pediatric and Adolescent Gynecology (April 16–18 2015, Orlando, FL), and Pediatric Academic Societies (April 25–28 2015, San Diego, CA).

conjugated equine estrogens (+1.4kg, $p=0.001$). Improvements in physical functioning domains of quality-of-life assessments were greater with n. acetate plus conjugated equine estrogens ($p=0.005$). No differences were seen at the hip or lumbar spine by DXA. No significant adverse events occurred.

Conclusions—Hormonal add-back successfully preserved bone health and improved quality of life for adolescents and young women with endometriosis during 12 months of GnRHa therapy. Combination n. acetate plus conjugated equine estrogens add-back appears to be more effective for increasing total body bone mineral content, areal BMD, and lean mass than n. acetate monotherapy.

Clinical Trial Registration—[ClinicalTrials.gov](https://clinicaltrials.gov); www.clinicaltrials.gov, NCT00474851.

Introduction

Endometriosis commonly begins during adolescence,¹ and can be a debilitating disease complicated by pain and activity limitation. Appropriate management involves prompt initiation of therapy and often maintenance of therapy over the long term.

Gonadotropin releasing hormone agonists (GnRHa) are commonly used for patients who fail first-line therapies. GnRHa relieve symptoms and reduce endometrial lesions seen on laparoscopy.² Long-term GnRHa use is problematic due to deleterious effects on bone mineral density (BMD).³ Adults lost 5%–8% of spine BMD after only 3–6 months of GnRHa therapy.^{4–6} BMD may not return to baseline after cessation of treatment.^{7,8}

Add-back therapy with daily low doses of steroid hormone appears promising.^{4,5,9} Hornstein et al followed adults treated with GnRHa for one year.⁴ Patients receiving no add-back lost 6.3% of BMD while BMD was preserved in all 3 studied add-back groups. The benefits of add-back extended for at least 8 months after completion of therapy.⁸ However, the significant BMD loss in the placebo group had not returned to baseline by 24 months after therapy.

The efficacy of add-back therapy must be studied in adolescents and young women, given this critical time window for the attainment of peak bone mass.¹⁰ Any interference with this process puts patients at risk for lifelong low BMD and possibly increased fracture risk.^{11,12} However, GnRHa therapy remains the only option to relieve debilitating pain for many young patients. Current care for these adolescents and young women includes the use of add-back based on adult experience.¹³ We were unable to find any data regarding GnRHa use with add-back for adolescents and young women (PubMed search, conducted from inception through April 2015, search terms “add-back”, “adolescents”, “endometriosis”).

Thus, our objective was to assess whether norethindrone acetate (n. acetate) + conjugated equine estrogens or n. acetate + placebo (P) was superior for maintaining BMD in adolescents and young women with endometriosis treated with a GnRHa.

MATERIALS AND METHODS

From 2003 to 2008, 65 young women were screened for study eligibility (Figure 1). Eligible females were aged 15 to 22 years, at least 2 years post-menarche, and had surgically-confirmed endometriosis diagnosed on the basis of visual inspection¹⁴, with the clinical decision made to initiate treatment with leuprolide acetate depot (Lupron Depot 11.25 mg IM) every 3 months. Patients were excluded for other medical diagnoses (e.g., celiac disease, diabetes mellitus) or medications (eg, glucocorticoids) known to affect BMD. The treating provider made the decision to offer GnRHa therapy to each patient on the basis of ongoing pain or intolerance of other medications. First, the patient had to agree to begin GnRHa therapy; patients were then approached and enrolled into the trial. Treatment assignment was determined before baseline measurements for logistical reasons. Fifty-three patients underwent randomization; 51 completed baseline measurements and were included in the intention-to-treat analysis. Prior to initiation of the GnRHa, patients were treated with varied medical therapies: combination oral contraceptives n=27 (53%), n. acetate monotherapy n=20 (39%), depot medroxyprogesterone n=2 (4%), no medical therapy n=2 (4%). Patients were not required to undergo a “wash out” prior to beginning the GnRHa. The Boston Children’s Hospital institutional review board approved the protocol. Informed consent was obtained, with parental consent or subject assent for patients <18 years ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00474851) NCT00474851).

The study was a single site, randomized, double-blind, placebo-controlled 12-month trial conducted at Boston Children’s Hospital. A permuted-block randomization design was used to prevent prediction of assignments while preserving balanced allocation of treatments. Treatment allocation was governed by a sequential list of study ID’s and corresponding random assignments, prepared in advance by the study statistician and followed by the pharmacy as each new participant enrolled and was assigned the next study ID. Only the statistician and pharmacy staff were privy to the assignments until after the trial was completed. The PI, study staff, and patients were blinded throughout the trial. Group 1 received two drug add-back: oral n. acetate (Aygestin 5 mg daily) plus conjugated equine estrogens (Premarin 0.625 mg daily). Group 2 received n. acetate plus placebo. The conjugated equine estrogens and placebo were dispensed by our pharmacy in a gelatin capsule, and were identical in appearance. Add-back therapy started 21 days after the first injection of GnRHa. All patients were advised to consume the recommended daily intake of calcium and vitamin D.

The primary study outcomes were areal BMD of the total hip, lumbar spine (L1–L4), and whole body by dual-energy X-ray absorptiometry (DXA; Hologic Discovery A, Hologic, Inc., Waltham, MA), measured at 0, 6, and 12 months. Measurements were compared with age- and gender-matched norms. Average *in vivo* precision for areal BMD (expressed as percent coefficient of variation) was 0.62% at the spine and 0.72% at the total hip. Body composition (lean body mass, fat mass) was also measured by DXA.

After randomization, participants returned for assessments at 3, 6, 9, and 12 months. Medication compliance was measured at each visit with pill counts. Pain symptoms were graded using the Pain scale from the Short Form-36 v2 (SF-36). Height was measured in a

standardized fashion, using the same wall-mounted stadiometer. Weight was obtained on the same digital scale, with patients clothed in a hospital gown, after voiding. Measures of quality of life (QOL) and mood were obtained. The SF-36 measures health-related QOL under 2 domains, physical and mental, with lower scores indicating more disability.¹⁵ The Beck Depression Inventory-II (BDI) measures depressive symptoms.¹⁶ The Menopausal Rating Scale (MRS) measures health-related QOL with a focus on psychological, somato-vegetative, and urogenital symptoms.¹⁷

Fasting venous blood samples were collected at the baseline, 6 month, and 12 month study visit for measurement of hormone concentrations [estradiol (E2, high-performance liquid chromatography tandem mass spectrometry)] and safety monitoring studies (liver function tests, lipid profiles). Samples were assayed at a central reference laboratory.

The trial was designed with 80% power to detect a rate of change of 0.017 g/cm²/yr in hip BMD. Baseline comparison of continuous measures between trial arms was made by Student t-test, corroborated by Wilcoxon two-sample test for variables with skewed distribution. Dichotomies were compared by Fisher exact test. Analysis followed the intention-to-treat principle, with all data attributed to the patient's assigned treatment group regardless of whether treatment was delivered or completed. The time course of each measurement from baseline to 3, 6, 9, and 12 months was compared between arms by repeated-measures analysis of variance (RM-ANOVA), with an autoregressive covariance model to account for visit-to-visit correlation within patients. The primary test of treatment efficacy was time by treatment interaction. Adjusted changes over time and differences between trial arms were constructed from parameters of the RM-ANOVA. Outcome variables with highly skewed distributions were log-transformed for analysis and retransformed for reporting, with changes and differences expressed multiplicatively. SAS software (version 9.2, Cary, NC) was used for all computations. $p=0.05$ or below was considered a statistically significant difference.

RESULTS

Among the 53 patients randomized, 2 (1 n. acetate plus conjugated equine estrogens, 1 n. acetate plus placebo) became ineligible or withdrew before completing baseline measurements (Fig. 1), resulting in a final sample of 51 participants (25 n. acetate plus conjugated equine estrogens, 26 n. acetate plus placebo) aged 17.9 ± 1.7 y (mean $\pm$ SD). The groups did not differ in baseline demographic characteristics (Table 1). All patients had American Society for Reproductive Medicine Stage 1 or 2 endometriosis at the time of diagnostic laparoscopy. Vitamin D concentrations were measured at baseline; if deficient or insufficient, patients were supplemented to achieve normal levels.¹⁸

Seven patients receiving n. acetate plus conjugated equine estrogens and 10 patients receiving placebo discontinued participation (Fig. 1). Of those terminating study participation, 15/17 (88%) did so because of a decision to stop GnRHa therapy altogether. Reasons for discontinuation are presented in Table 2. Dropouts did not differ from completers with respect to baseline characteristics.

Twenty-eight percent of patients reported missing at least one dose of add-back medication before the 3-month visit; 33% at 6 months; 26% at 9 months; and 21% at 12 months. Reported compliance did not vary between visits ($p=0.67$) or between trial arms ($p=0.77$). During study participation, seven patients were evaluated in the emergency room for complaints of abdominal pain. Thirty-four adolescents and young women completed the trial.

At baseline, the two study groups had similar, normal measurements of BMD and BMD Z-scores at all measured sites (Table 1; $p>0.50$). During 12 months of GnRHa therapy, participants receiving n. acetate plus placebo exhibited stabilization of total body, lumbar spine, and hip BMD and BMD Z-scores (Table 3; $p_{\text{within}}>0.30$ for all measures). With n. acetate plus conjugated equine estrogens, total body BMD showed a marginally significant increase over time (Figure 2; Table 3, adjusted mean change $+0.012 \text{ g/cm}^2$ at 12 months, $p_{\text{within}}=0.05$). No losses in BMD at the lumbar spine and hip, as well as BMD Z-scores, were seen over time ($p_{\text{within}}>0.21$ for all). No between group differences were seen for any BMD or BMD-Z measures. BMD Z-scores remained within the normal range at all sites in both groups throughout the 12-month trial.

Bone mineral content changed in similar ways to BMD (Table 3). With n. acetate plus conjugated equine estrogens, total body bone mineral content increased over time (Figure 2; Table 3, mean adjusted change $+37$ at 12 months; $p_{\text{within}}<0.001$), while not significantly changing in the n. acetate plus placebo group ($p_{\text{within}}=0.31$), a significant between-arm difference in time course ($p_{\text{between}}=0.02$). At the hip and spine, bone mineral content remained stable throughout the trial in both groups (Table 3).

Both groups were overweight at baseline (BMI mean $\pm$ SD $25.2 \pm 4.6 \text{ kg/m}^2$), and gained weight at a non-significant rate during the 12-month study (Table 4). Patients receiving n. acetate plus conjugated equine estrogens gained $3.4 \pm 1.7 \text{ kg}$ by 12 months (mean $\pm$ SE, $p_{\text{within}}=0.24$) while those receiving n. acetate plus placebo gained $2.3 \pm 1.8 \text{ kg}$ over the same time period (mean $\pm$ SE, $p_{\text{within}}=0.73$; $p_{\text{between}}=0.77$). BMI did not change significantly in either group.

Body composition as measured by DXA did vary over the 12 month study (Figure 2). Lean mass increased only in those receiving n. acetate plus conjugated equine estrogens (Table 4, adjusted mean change $+1.4 \text{ kg}$ at 12 months, $p_{\text{within}}=0.001$), while remained unchanged in the n. acetate plus placebo arm ($p_{\text{within}}=0.07$, $p_{\text{between}}=0.006$). Fat mass increased similarly over time in both groups ($p_{\text{between}}=0.44$).

At baseline, serum estradiol (E2) concentrations are difficult to interpret, as the majority of participants were receiving hormonal therapy at the time of the blood draw. E2 concentrations did not change significantly during treatment within ($p>0.29$) or between the trial arms ($p=0.46$). E2 concentrations remained in the menopausal range starting 12 weeks after first GnRHa injection for the course of the study.

Pain Subscale scores on the SF-36 improved in both trial arms over time. In patients receiving n. acetate plus placebo, pain scores improved at 6 months (adj mean change $+14$), then declined slightly by 12 months ($+8$, $p_{\text{within}}=0.001$). Recipients of n. acetate plus

conjugated equine estrogens had sustained improvements in pain scores to 12 months (+12, $p_{\text{within}}=0.002$), leading to a significant difference between the treatment groups ($p_{\text{between}}=0.008$).

At baseline these young women reported depressed mood and poor quality of life related to physical functioning. Overall scores for physical health (Physical Summary Score, PCS) were significantly lower than the United States mean for both add-back groups at baseline, indicating impairment. While both groups improved (Figure 3; $p_{\text{within}} 0.003$), patients in the n. acetate plus conjugated equine estrogens group showed greater increases in PCS score than the n. acetate plus placebo group ($p_{\text{between}}=0.005$). Mental Summary Scores (MCS) for both groups were not lower than the US mean at baseline. Neither group showed significant changes in MCS over time ($p_{\text{within}} 0.49$). Neither add-back regimen was associated with changes in scores on the BDI or MRS ($p_{\text{within}} 0.20$).

Mean ALT and AST were similar between groups at trial initiation, and remained normal throughout (Figure 4). Only one subject (randomized to n. acetate plus placebo) developed a transaminase elevation (ALT>100 IU/L) while on study. The elevation occurred at her 12-month visit and was thought related to a concurrent viral illness (Table 5). The ALT spontaneously resolved within the next 4 weeks. Neither add-back regimen led to deleterious changes in lipid profiles. Seven patients had an elevated total cholesterol >200 mg/dL at baseline; in every case, the total cholesterol decreased over time while the HDL rose. Total cholesterol and triglycerides declined similarly in the two trial arms (Figure 4; $p_{\text{between}} 0.34$).

DISCUSSION

In this randomized trial, add-back therapy with either regimen successfully preserved skeletal health in young women with endometriosis treated with one year of GnRHa. However, combination therapy with oral n. acetate plus conjugated equine estrogens appears to be superior to n. acetate plus placebo. Patients randomized to n. acetate plus conjugated equine estrogens had increases of total body bone mineral content and areal BMD, while those receiving n. acetate plus placebo showed no changes. No BMD losses were noted at the hip or lumbar spine with either add-back.

The rationale for add-back is based on the “estrogen threshold hypothesis”.¹⁹ Endometriotic tissue growth is stimulated by estrogen. Low circulating E2 concentrations cause regression of estrogen-sensitive tissues like endometrial implants. Adding back small amounts of hormone increases circulating E2 levels enough to maintain bone integrity and prevent menopausal symptoms while suppressing other tissues, like the endometrium. Norethindrone acetate has been the most widely-studied adjunctive therapy in adults.⁴ N. acetate inhibits pituitary gonadotropin secretion which prevents follicular maturation and ovulation. In vivo, n. acetate is converted into ethinyl estradiol after oral ingestion, such that 20 mg n. acetate may be equivalent to taking a pill containing 30 µcg of ethinyl estradiol.²⁰ This conversion may be partly responsible for the n. acetate’s efficacy for preserving bone health.

The addition of low-dose conjugated equine estrogens add-back appears to offer additional benefit. Estrogen deficiency reduces bone accrual during adolescence and bone loss after achievement of peak bone mass.²¹ Estrogen deficiency may also slow growth in axial bone size during adolescence, a time when truncal growth typically accelerates.²² Low estrogen states, such as anorexia nervosa or the menopause, are characterized by increased bone resorption.²³ In other patient groups, estrogen decreases accelerated bone resorption.²⁴ Unlike n. acetate plus placebo, combined n. acetate plus conjugated equine estrogens not only preserves but also increases areal BMD and bone mineral content during this important time for bone accrual.

We can only hypothesize regarding the mechanism of action behind the preservation of areal BMD noted in our study. Estrogens inhibit bone resorption, while decreasing bone formation.²⁵ Androgens stimulate bone formation.²⁶ N. acetate is an “estrogen precursor” and is converted in vivo into estrogen. Given the potentially synergistic mechanisms of action, we explored the effect of combination n. acetate plus conjugated equine estrogens during GnRHa treatment in adolescence. With dual add-back, both bone formation and resorption may be affected to attenuate bone loss. Interestingly, total body BMD, a site composed primarily of cortical bone rather than trabecular-rich spinal BMD, responded to the n. acetate plus conjugated equine estrogens. Trabecular bone is typically more hormonally responsive, and hypothetically should have been more sensitive to these hormonal regimens. Our findings did not support that hypothesis, and bear further study.

Participants reported significant disability related to their physical health prior to initiating GnRHa. Over time, improvements in self-perceived physical health were seen, as demonstrated by increases in SF-36 PCS scores. While improvements occurred in both trial arms, patients receiving n. acetate plus conjugated equine estrogens maintained greater increases at 12 months than those receiving n. acetate plus placebo. Minimal changes were seen in mental health measures, but patients did not report impairments in this area at baseline. Reassuringly, neither depressed mood nor menopausal symptoms worsened over the trial.

Potential adverse effects of treatment were monitored closely. In adults, treatment with GnRHa without add-back led to LDL cholesterol elevations and increased LDL and HDL cholesterol ratios.²⁷ GnRHa plus progestin add-back has negatively impacted lipid profiles²⁸; these adverse effects were minimized in patients taking lower doses of steroid hormones, such as those utilized in the current study.^{4,28} We did not find negative changes in lipid profiles nor elevation in liver enzymes associated with our hormonal therapy.

Study limitations should be acknowledged. Our sample was limited to women at least 18–24 months post-menarche since further skeletal growth is minimal and skeletal maturity is complete²⁹; results may not be generalizable to younger females with open epiphyses. Our study was not powered to determine the effects of add-back therapy on BMI, quality of life, estradiol, or safety measures. Measurements of areal BMD provide two-dimensional measurements of BMD, and do not yield information regarding skeletal strength or microarchitecture. Our future work will explore the effects of this treatment on the

peripheral skeleton, a common fracture site among youth, and use more sophisticated assessment tools to explore mechanisms of action and effects on bone strength.

In summary, a combination regimen of oral n. acetate plus conjugated equine estrogens appears to be safe and effective for increasing areal BMD and bone mineral content in young women with endometriosis during one year of GnRHa treatment, and superior to n. acetate plus placebo. Monitoring of clinical and biochemical safety parameters yielded reassuring results. Given the increasing prevalence of endometriosis, these data suggest n. acetate plus conjugated equine estrogens to be a useful adjunctive therapy to prevent bone loss while these adolescents and young women receive appropriate medical treatment for their underlying disease.

Acknowledgments

Supported by NICHD T32 HD043034, NICHD K23 HD060066, NIH UL1 RR-025758 (Harvard Clinical and Translational Science Center), McCarthy Family Foundation, Thrasher Research Fund, and the Boston Children's Hospital Department of Medicine and Clinical and Translational Study Unit (CTSUS). Study medications were donated from Abbott Pharmaceuticals, Duramed Pharmaceuticals, and Wyeth Pharmaceuticals.

The authors thank Jamie Nydegger, Yailka Cardenas, Alicia McAllister, and Ashley Quach for technical assistance; the excellent care of the CTSU nurses; and our patients and their families, who made this research possible.

References

1. Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol.* 1997; 10(4):199–202. [PubMed: 9391902]
2. Steingold KA, Cedars M, Lu JK, Randle D, Judd HL, Meldrum DR. Treatment of endometriosis with a long-acting gonadotropin-releasing hormone agonist. *Obstet Gynecol.* 1987; 69(3 pt 1):403–11. [PubMed: 2950349]
3. Surrey ES. Gonadotropin-releasing hormone agonist and add-back therapy: what do the data show? *Curr Opin Obstet Gynecol.* 2010; 22(4):283–288. [PubMed: 20498596]
4. Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Lupron Add-Back Study Group. Obstet Gynecol.* 1998; 91(1):16–24. [PubMed: 9464714]
5. Surrey ES, Judd HL. Reduction of vasomotor symptoms and bone mineral density loss with combined norethindrone and long-acting gonadotropin-releasing hormone agonist therapy of symptomatic endometriosis: a prospective randomized trial. *J Clin Endocrinol Metab.* 1992; 75(2):558–563. [PubMed: 1386374]
6. Matsuo H. Prediction of the change in bone mineral density induced by gonadotropin-releasing hormone agonist treatment for endometriosis. *Fertil Steril.* 2004; 81(1):149–153. [PubMed: 14711558]
7. Revilla R, Revilla M, Hernandez ER, Villa LF, Varela L, Rico H. Evidence that the loss of bone mass induced by GnRH agonists is not totally recovered. *Maturitas.* 1995; 22(2):145–150. [PubMed: 8538483]
8. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol.* 2002; 99(5 Pt 1):709–719. [PubMed: 11978277]
9. Kiesel L, Schweppe KW, Sillem M, Siebzehrubl E. Should add-back therapy for endometriosis be deferred for optimal results? *Br J Obstet Gynaecol.* 1996; 103(Suppl):15–17. [PubMed: 8916982]
10. DiVasta AD, Gordon CM. Bone health in adolescents. *Adolesc Med Clin.* 2006; 17(3):639–52. abstract xi. [PubMed: 17030283]

11. Golden NH, Abrams SA. Optimizing bone health in children and adolescents. *Pediatrics*. 2014; 134(4):e1229–43. [PubMed: 25266429]
12. Bonjour J-P, Chevalley T. Pubertal timing, bone acquisition, and risk of fracture throughout life. *Endocr Rev*. 2014; 35(5):820–47. [PubMed: 25153348]
13. ACOG Committee Opinion. Number 310, April 2005. Endometriosis in adolescents. *Obstet Gynecol*. 2005; 105(4):921–7. [PubMed: 15802438]
14. Becker CM, Laufer MR, Stratton P, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype data collection in endometriosis research. *Fertil Steril*. 2014; 102(5):1213–22. [PubMed: 25150390]
15. Ware, JE. SF-36 Health Survey Update. In: Manish, ME., editor. *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment*. 3rd. Vol. 3. Lawrence Erlbaum Associates; 2004. p. 693-718.
16. Beck, AT.; Brown, G.; Steer, RA. *Beck Depression Inventory II Manual*. San Antonio, TX: The Psychological Corporation; 1996.
17. Schneider HP, Heinemann LA, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): comparison with Kupperman index and quality-of-life scale SF-36. *Climacteric*. 2000; 3(1):50–58. [PubMed: 11910610]
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011; 96(7):1911–1930. [PubMed: 21646368]
19. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. *Am J Obstet Gynecol*. 1992; 166(2):740–745. [PubMed: 1536260]
20. Chu MC, Zhang X, Gentzsch E, Stanczyk FZ, Lobo Ra. Formation of ethinyl estradiol in women during treatment with norethindrone acetate. *J Clin Endocrinol Metab*. 2007; 92(6):2205–7. [PubMed: 17341557]
21. Gordon CM, Nelson LM. Amenorrhea and bone health in adolescents and young women. *Curr Opin Obstet Gynecol*. 2003; 15(5):377–384. [PubMed: 14501240]
22. Seeman E, Karlsson MK, Duan Y. On exposure to anorexia nervosa, the temporal variation in axial and appendicular skeletal development predisposes to site-specific deficits in bone size and density: a cross-sectional study. *J Bone Miner Res*. 2000; 15(11):2259–2265. [PubMed: 11092408]
23. Gordon CM, Goodman E, Emans SJ, Grace E, Becker KA, Rosen CJ, Gundberg CM, Leboff MS. Physiologic regulators of bone turnover in young women with anorexia nervosa. *J Pediatr*. 2002; 141(1):64–70. [PubMed: 12091853]
24. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA*. 2002; 287(20):2668–2676. [PubMed: 12020302]
25. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. *Br J Sports Med*. 2006; 40(1):11–24. [PubMed: 16371485]
26. Gordon CM, Grace E, Emans SJ, Goodman E, Crawford MH, Leboff MS. Changes in bone turnover markers and menstrual function after short-term oral DHEA in young women with anorexia nervosa. *J Bone Miner Res*. 1999; 14(1):136–145. [PubMed: 9893076]
27. Al-Omari WR, Nassir UN, Izzat B. Estrogen “add-back” and lipid profile during GnRH agonist (triptorelin) therapy. *Int J Gynaecol Obstet*. 2001; 74(1):61–62. [PubMed: 11430944]
28. Surrey ES, Fournet N, Voigt B, Judd HL. Effects of sodium etidronate in combination with low-dose norethindrone in patients administered a long-acting GnRH agonist: a preliminary report. *Obstet Gynecol*. 1993; 81(4):581–586. [PubMed: 8459971]
29. Chevalley T, Bonjour JP, Ferrari S, Rizzoli R. The influence of pubertal timing on bone mass acquisition: a predetermined trajectory detectable five years before menarche. *J Clin Endocrinol Metab*. 2009; 94(9):3424–3431. [PubMed: 19531591]

Figure 1.
Patient recruitment, enrollment, and disposition.

Figure 2.

Longitudinal measurement of total body bone mineral density and bone mineral content and body composition in adolescent females with endometriosis randomized to 12 months of treatment with norethindrone acetate and conjugated equine estrogens or norethindrone acetate and placebo. The bars represent the 25th to 75th percentiles for the measure at each time point. Total body bone mineral density (g/cm²) (A); total body bone mineral content (grams) (B); lean mass (grams) (C); fat mass (grams) (D).

Figure 3.

Changes in quality of life over time in adolescent females with endometriosis randomized to 12 months of treatment with norethindrone acetate and conjugated equine estrogens or norethindrone acetate and placebo. The dashed line at 50 represents the United States mean score for each measure. The bars represent the 25th to 75th percentiles for the measure at each time point. Physical Summary Score (**A**); Mental Summary Score (**B**).

Figure 4.

Safety measures (aspartate aminotransferase, alanine aminotransferase, total cholesterol, and triglycerides) in adolescent females with endometriosis randomized to 12 months of treatment with norethindrone acetate and conjugated equine estrogens or norethindrone acetate and placebo. The bars represent the 25th to 75th percentiles for the measure at each time point. Aspartate aminotransferase (international units per liter) (A); alanine aminotransferase (international units per liter) (B); total cholesterol (mg/dL) (C); triglycerides (mg/dL) (D).

Table 1

Baseline Participant Characteristics by Study Arm

	All (51)		N, Acetate + CEE Arm (25)	N, Acetate + Placebo Arm (26)	P*
	Mean ± SD	Minimum — Maximum			
Age, yr	17.9 ± 1.7	15.4 — 22.6	17.7 ± 1.4	18.1 ± 1.9	0.41
Height, cm	163.8 ± 4.8	155.6 — 176.6	162.9 ± 4.3	164.7 ± 5.2	0.19
Weight, kg	67.8 ± 13.4	50.9 — 116.6	66.7 ± 12.6	68.9 ± 14.3	0.55
BMI, kg/m ²	25.2 ± 4.6	19.7 — 41.3	25.1 ± 4.3	25.4 ± 4.9	0.82
25(OH)D, ng/mL	29.2 ± 10.8	13 — 59	27.7 ± 9.5	30.7 ± 11.8	0.32
AST, IU/L	18.3 ± 4.7	9 — 31	17.7 ± 5.0	18.9 ± 4.3	0.35
ALT, IU/L	17.6 ± 7.9	5 — 35	16.9 ± 7.5	18.3 ± 8.4	0.51
Total cholesterol, mg/dL	188.4 ± 36.4	108 — 284	191.5 ± 37.3	185.5 ± 36.0	0.56
HDL cholesterol, mg/dL	47.0 ± 16.2	22.1 — 95	49.3 ± 17.0	44.8 ± 15.3	0.33
LDL cholesterol, mg/dL	121.9 ± 38.2	55.6 — 227.4	122.3 ± 42.2	121.5 ± 34.9	0.94
Triglycerides, mg/dL	97.7 ± 34.5	48 — 174	99.8 ± 36.5	95.6 ± 33.0	0.67
Total body BMD Z-score	−0.5 ± 0.8	−2.1 — 1.9	−0.4 ± 0.8	−0.6 ± 0.8	0.51
Hip BMD Z-score	−0.0 ± 0.9	−1.4 — 2.0	0.1 ± 0.9	−0.2 ± 0.9	0.23
Lumbar spine BMD Z-score	0.2 ± 1.0	−1.5 — 2.6	0.3 ± 1.0	0.1 ± 1.1	0.51
	Median (Q1–Q3)	Minimum–Maximum	Median (Q1–Q3)		
Months since diagnosis	15 (9 – 24)	1 — 124	12 (9 – 20)	20 (8 – 30)	0.30
Estradiol, pg/mL [†]	18.9 (10.0 – 29.3)	3.5 — 159.6	22.7 (11.3 – 36.0)	12.2 (8.0 – 22.6)	0.05
	N (%)		N (%)		
Stage 1 endometriosis	33 (64.7)		15 (60)		0.56
Stage 2 endometriosis	18 (35.3)		10 (40)		
White	49 (96)		23 (92)		0.24
Hispanic	0 (0)		0 (0)		—
Total body BMD Z-score:					
−2 < Z −1	14 (27)		6 (24)		0.76
Z −2	1 (2)		0 (0)		1.00

	All (51)		N. Acetate + CEE Arm (25)	N.Acetate + Placebo Arm (26)	P*
	Mean ± SD	Minimum — Maximum			
Hip BMD Z-score:					
–2 < Z	–1	6 (12)	2 (8)	4 (16)	0.67
Z	–2	0 (0)	0 (0)	0 (0)	—
Lumbar spine BMD Z-score:					
–2 < Z	–1	7 (14)	4 (16)	3 (12)	1.00
Z	–2	0 (0)	0 (0)	0 (0)	—

* Student t, Wilcoxon rank-sum, or Fisher Exact test comparing distribution in n. acetate plus CEE and n. acetate plus placebo arms.

† At baseline, most study patients were receiving hormonal therapy making the baseline estradiol concentration difficult to interpret.

N. acetate, norethindrone acetate; CEE, conjugated equine estrogens; BMI, body mass index; 25(OH)D, 25-hydroxy-vitamin D; BMD, bone mineral density

Table 2

Reasons for discontinuation of study participation by study arm

	N. acetate plus conjugated equine estrogens	N. acetate plus placebo
Abdominal or pelvic pain	3	4
Joint aches or pains	1	1
Memory or mood changes	1	2
Acne	0	1
Constipation or bowel symptoms	1	1
Other or unrelated	1	1

N. acetate, norethindrone acetate

Table 3

Measurements of Bone Mineral Density and Bone Mineral Content at baseline and during 12 months of GnRHa treatment and add-back therapy in adolescents and young women with endometriosis*

Measure	Location	Arm	Baseline Mean $\pm$ SD	Adjusted mean change		<i>P</i> (within group)	<i>P</i> (between groups)
				6 mo	12 mo		
BMD Z-score	Total body	NA+CEE	-0.45 $\pm$ 0.82	-0.07	0.01	0.21	0.10
		NA+P	-0.60 $\pm$ 0.76	-0.01	-0.11	0.30	
	Lumbar spine	NA+CEE	0.28 $\pm$ 0.99	-0.03	-0.06	0.73	0.87
		NA+P	0.09 $\pm$ 1.10	-0.06	-0.11	0.33	
	Hip	NA+CEE	0.11 $\pm$ 0.87	0.02	0.00	0.84	0.80
		NA+P	-0.20 $\pm$ 0.91	-0.00	0.03	0.90	
BMD, g/cm²	Total body	NA+CEE	1.052 $\pm$ 0.061	0.001	0.012	0.05	0.10
		NA+P	1.045 $\pm$ 0.061	0.003	-0.000	0.65	
	Lumbar spine	NA+CEE	1.029 $\pm$ 0.105	-0.001	-0.002	0.94	0.96
		NA+P	1.014 $\pm$ 0.128	-0.003	-0.002	0.88	
	Hip	NA+CEE	0.973 $\pm$ 0.099	0.007	0.004	0.34	0.32
		NA+P	0.940 $\pm$ 0.103	0.001	0.008	0.41	
BMC, g	Total body	NA+CEE	2019 $\pm$ 181	2	37	0.0001	0.02
		NA+P	2021 $\pm$ 219	11	15	0.31	
	Lumbar spine	NA+CEE	57 $\pm$ 7	-2	-2	0.11	0.48
		NA+P	56 $\pm$ 13	0	0	0.92	
	Hip	NA+CEE	30 $\pm$ 4	1	0	0.09	0.53
		NA+P	30 $\pm$ 5	0	1	0.32	

BMD, bone mineral density; BMC, bone mineral content; NA, norethindrone acetate; CEE, conjugated equine estrogens; P, placebo

* Baseline value is unadjusted group mean. Changes at 6–12 mo are contrasts with baseline, from repeated-measures analysis of variance. P-values test for within-group change and between-group difference in change (group $\times$ time interaction).

Anthropometry at Baseline and During 12 Months of Gonadotropin-Releasing Hormone Agonist Treatment and Add-Back Therapy in Young Women With Endometriosis*

Table 4

	Group	Baseline	Adjusted mean change				<i>P</i> (within group)	<i>P</i> (between groups)
			3 mo	6 mo	9 mo	12 mo		
Weight, kg	NA+CEE	66.7 ± 12.6	1.6	2.3	2.9	3.4	0.24	0.77
	NA+P	68.9 ± 14.3	0.1	0.7	1.8	2.3	0.73	
Height, cm	NA+CEE	162.9 ± 4.3	-0.2	0.3	0.1	0.5	0.59	0.73
	NA+P	164.7 ± 5.2	0.4	0.5	0.3	0.6	0.72	
BMI, kg/m²	NA+CEE	25.1 ± 4.3	0.7	0.8	1.1	1.1	0.06	0.26
	NA+P	25.4 ± 4.9	-0.1	0.1	0.6	0.7	0.47	
Lean mass, kg	NA+CEE	40.2 ± 5.0	— [†]	1.0	—	1.4	0.001	0.006
	NA+P	41.9 ± 4.6	—	-0.6	—	0.1	0.07	
Fat mass, kg	NA+CEE	24.7 ± 8.2	—	1.4	—	1.8	0.02	0.44
	NA+P	25.4 ± 10.2	—	0.7	—	1.8	0.08	

NA, norethindrone acetate; CEE, conjugated equine estrogens; P, placebo

* Baseline value is simple group mean ± SD. Changes at 3–12 mo are contrasts with baseline, from repeated-measures analysis of variance. *P*-values test for within-group change and between-group difference in change (group x time interaction).

[†] Lean mass and fat mass not measured at 3 mo and 9 mo.