Impact of Physiologic Estrogen Replacement on Anxiety Symptoms, Body Shape Perception, and Eating Attitudes in Adolescent Girls With Anorexia Nervosa: Data From a Randomized Controlled Trial

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ABSTRACT

Objective: Anorexia nervosa is characterized by low weight, aberrant eating attitudes, body image distortion, and hypogonadism. Anxiety is a common comorbid condition. Estrogen replacement reduces anxiety in animal models, and reported variations in food intake across the menstrual cycle may be related to gonadal steroid levels. The impact of estrogen replacement on anxiety, eating attitudes, and body image has not been reported in anorexia nervosa. We hypothesized that physiologic estrogen replacement would ameliorate anxiety and improve eating attitudes without affecting body image in anorexia nervosa.

Method: Girls 13–18 years old with anorexia nervosa (*DSM-IV*) were randomized to transdermal estradiol (100 µg twice weekly) with cyclic progesterone or placebo patches and pills for 18-months, between 2002 and 2010. The State-Trait Anxiety Inventory for Children (STAIC), the Eating Disorders Inventory-2 (EDI-2), and the Body Shape Questionnaire (BSQ-34) were administered. 72 girls completed these measures at baseline (n = 38 [girls receiving estrogen] and n = 34 [girls receiving placebo]) and 37 at 18 months (n = 20 [girls receiving estrogen] and n = 17 [girls receiving placebo]). The primary outcome measure was the change in these scores over 18 months.

Results: Estrogen replacement caused a decrease in STAIC-trait scores (−3.05 [1.22] vs 2.07 [1.73], $P = .02$), without impacting STAIC-state scores (−1.11 [2.17] vs 0.20 [1.42], $P = .64$). There was no effect of estrogen replacement on EDI-2 or BSQ-34 scores. Body mass index (BMI) changes did not differ between groups, and effects of estrogen replacement on STAIC-trait scores persisted after controlling for BMI changes ($P = .03$). Increases in serum estradiol were significantly associated with decreases in STAIC-trait scores (Spearman $\rho = -0.45$, $P = .03$).

Conclusions: Estrogen replacement improved trait anxiety (the tendency to experience anxiety) but did not impact eating attitudes or body shape perception.

Trial Registration: ClinicalTrials.gov identifier: NCT00088153

J Clin Psychiatry 2013;74(8):e765–e771

Submitted: *January 11, 3013; accepted March 22, 2013 (doi:10.4088/JCP.13m08365).*
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Anorexia nervosa is reported in 0.2%–1% of all adolescent girls and is characterized by low weight, aberrant eating attitudes and behavior (restriction, binge/purge behaviors), body image disturbance, and hypothalamic amenorrhea. Anxiety is a common comorbid condition[1–3] and is reported in as many as two-thirds of women presenting with anorexia nervosa[3]; when present, it precedes the diagnosis of the eating disorder in 69%.[4] Levels of gonadal steroids, both estrogen and testosterone, are low in anorexia nervosa[5,6] and contribute to pathology associated with anorexia nervosa, such as low bone density. We have shown that physiologic estrogen replacement is effective in increasing bone density and maintaining bone density *Z* scores in adolescent girls with anorexia nervosa.[7] Studies indicate that estrogen status may also impact cognitive function,[8] mood and anxiety,[9,10] body shape perception, and eating behavior.[11,12] However, the effect of physiologic estrogen replacement on these end points has not been assessed in anorexia nervosa.

Estrogen acting through estrogen receptor-β is anxiolytic in animals,[9] and levels of anxiety change across the estrus cycle.[10] Ovariectomized, hypogonadal rats treated with estrogen perform better than controls who do not receive estrogen during a forced swim test and the open field test.[13,14] Additionally, women are more likely to develop anxiety disorders than men.[15] Of note, adolescents and adults with Turner syndrome or premature ovarian failure (hypogonadal conditions) have higher anxiety levels than controls,[16–18] although anxiety symptoms do not improve with estrogen administration.[17] Estrogen may also be involved with perception of body shape and may account for greater body shape concerns in females than in males. Additionally, caloric intake is lower during the follicular phase, when estrogen levels are low, than in the luteal phase, suggesting that variations in food intake across the menstrual cycle may be related to levels of gonadal hormones.[11,12]

Few studies have assessed the impact of estrogen status on cognitive and psychiatric outcomes in adolescents or adults with anorexia nervosa. One study reported an improvement in certain cognitive measures in adult women with a history of anorexia nervosa who spontaneously resumed menses or were treated with estrogen-progesterone combination pills, whereas this was not observed in women who recovered weight alone without resuming menses. These data suggest that gonadal steroid status, rather than weight recovery alone, is important for improving cognitive function in anorexia nervosa.[8] Another study reported an improvement in anxiety trait scores, with weight recovery

Clinical Points

- Physiologic estrogen replacement in the form of transdermal estrogen patch improves trait anxiety (the tendency to experience anxiety) but not state anxiety, eating attitudes, or body shape perception in adolescent girls with anorexia nervosa.
- Further studies in adolescents and adults with anorexic samples are necessary to understand the impact of other forms and doses of estrogen administration.

in anorexia nervosa.[2] However, the impact of estrogen replacement on anxiety, body image, and eating attitudes and behavior has not been assessed in patients with anorexia nervosa, specifically adolescents, and therefore merits investigation.

We assessed changes in anxiety scores, perception of body shape, and eating attitudes and behavior in adolescent girls with anorexia nervosa randomized to physiologic estrogen replacement or placebo. We hypothesized that physiologic estrogen replacement in adolescents with anorexia nervosa would ameliorate anxiety and improve eating behavior, without affecting body image.

METHOD

Subject Selection and Protocol

Girls with anorexia nervosa who were 13–18 years old and a bone age of at least 15 years were randomized for 18 months to physiologic estrogen replacement or placebo by the Massachusetts General Hospital (MGH) Research Pharmacy based on a predetermined computer-generated randomization sequence. The study was carried out between 2002 and 2010 (ClinicalTrials.gov identifier: NCT00088153). We have previously published data regarding effects of estrogen replacement on bone density in adolescent girls with anorexia nervosa, but not related to the psychiatric outcome being reported in this article.[7] Inclusion criteria were a diagnosis of anorexia nervosa based on *DSM-IV* criteria and a chronological age between 13–18 years. Exclusion criteria included (1) active suicidality, psychosis, or substance abuse and (2) hematocrit < 30%, potassium < 3.0 mmol/L, or glucose < 50 mg/dL. Because the larger randomized controlled trial examined effects of physiologic estrogen replacement on bone density, additional exclusion criteria included use of prescription medications within 3 months of study participation known to affect bone metabolism and other diseases known to affect bone metabolism.

All subjects with anorexia nervosa from this larger cohort (n = 110) who had a bone age of at least 15 years and completed psychiatric questionnaires at baseline were included in the current analysis. Seventy-two girls with anorexia nervosa completed the questionnaires at baseline (38 randomized to estrogen and 34 to placebo), and 37 at 18 months' follow-up (20 randomized to estrogen and 17 to placebo). The remainder of the girls either were lost to follow-up or did not complete the questionnaires at 18 months. The completers and noncompleters did not differ at baseline with regard to body mass index (BMI) and questionnaire scores for anxiety symptoms, eating attitudes and behavior, and body image. Subjects were recruited at MGH, Boston, and the Hospital for Sick Children (Sick-Kids), Toronto. Recruitment strategies and inclusion and exclusion criteria for the study have been previously reported.[7] Use of psychiatric medications was not an exclusion criterion for study participation. All girls with anorexia nervosa had multidisciplinary treatment teams in place. The study team did not assume clinical care of these subjects. The study was approved by the Partners Health Care Institutional Review Board (for MGH) and the Research Ethics Board (for Sick-Kids), and informed consent and assent were obtained from parents and subjects.

The diagnosis of anorexia nervosa was confirmed by the study psychiatrist or psychologist. Girls with anorexia nervosa received either (1) transdermal 17β-estradiol (100 μg twice weekly; Novartis Pharmaceuticals, Inc) with cyclic progesterone (2.5 mg of medroxyprogesterone acetate given each day for the first 10 days of every month) or (2) placebo patches and cyclic placebo pills for the study duration. Progesterone or placebo pills were taken during the first 10 days of each month to prevent unopposed estrogen stimulation of the uterus. We assessed compliance with study medications every 2 months using verbal questionnaires and calendars given to subjects to record any missed study medication doses. All used and unused medications were collected. Groups did not differ in compliance with study medications.

To investigate the effects of physiologic estrogen on anxiety symptoms, eating attitudes and behavior, and body image, we administered the State-Trait Anxiety Inventory for Children (STAIC),[19] the Eating Disorders Inventory-2 (EDI-2),[20] and the 34-item Body Shape Questionnaire (BSQ-34)[21] at baseline and 18 months. On the STAIC,[19] the state-anxiety scale includes 20 statements that measure transitory anxiety states or subjective, consciously perceived feelings of apprehension, tension, and worry that vary in intensity and fluctuate over time.[22] The trait-anxiety scale includes 20 statements that measure relatively stable individual differences in anxiety proneness or differences between children in the tendency to experience anxiety states. The statements are assessed on a 3-point rating scale. The EDI-2 is a measure of eating disorder attitudes and behaviors used to diagnose eating disorders and evaluate treatment success in intervention studies.[20] It includes 91 questions divided into 11 subscales. Answers for each question are structured on a 6-point scale (ranging from "always" to "never") and rated 0–3. The score for each subscale is then summated. The EDI-2 subscales include drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation, and social insecurity. The BSQ-34 asks 34 questions related to body shape perception with scores that range from 1 to 6. Higher scores on these scales indicate greater psychopathology.

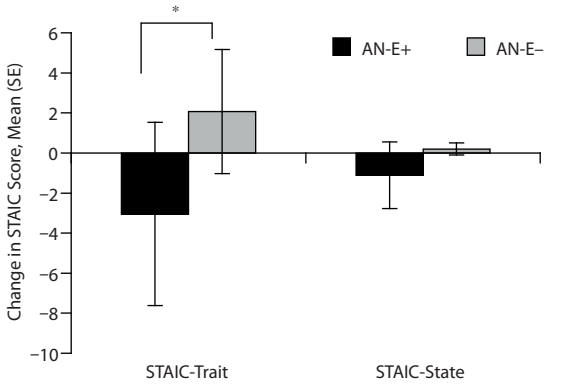
Subjects were weighed in a hospital gown on an electronic scale (to the nearest 0.1 kg) and measured on a single wall-

Table 1. Baseline Characteristics of Girls With Anorexia Nervosa Randomized to Physiologic Estrogen With Cyclic Progesterone or Placebo Patches and Cyclic Placebo Pills

Characteristic	AN-E+ (n = 38), Mean (SE)	AN-E– (n = 34), Mean (SE)	*P*
Age, y	16.9 (0.2)	16.6 (0.2)	.39
Bone age, y	16.7 (0.1)	16.4 (0.2)	.10
BMI (kg/m^2)	17.2 (0.2)	17.5 (0.2)	.34
Ideal body weight (for height), %	79.1 (1.6)	82.1 (2.0)	.25
Ideal body weight (based on height and 50th percentile of BMI for age), %	83.0 (1.1)	84.8 (1.1)	.25
Body fat, %	18.6 (0.8)	17.2 (0.9)	.27
Age at menarche, y	12.3 (0.2)	12.2 (0.2)	.79
Duration since diagnosis, mo	14.5 (2.8)	13.6 (2.6)	.82
EDI-2 score			
Drive for thinness	11.7 (1.2)	13.2 (1.2)	.39
Bulimia	1.7 (0.5)	0.9 (0.2)	.23
Body dissatisfaction	15.2 (1.6)	15.9 (1.5)	.77
Ineffectiveness	9.4 (1.2)	8.7 (1.3)	.69
Perfectionism	7.7 (0.9)	7.3 (0.8)	.75
Interpersonal distrust	6.3 (0.8)	5.4 (0.8)	.42
Interoceptive awareness	7.1 (1.0)	7.4 (1.1)	.83
Maturity fears	7.3 (0.5)	7.6 (0.7)	.69
Asceticism	7.8 (0.9)	8.6 (1.1)	.58
Impulse regulation	3.7 (0.7)	3.0 (0.8)	.56
Social insecurity	7.4 (0.8)	7.7 (0.9)	.82
BSQ-34 score	119.8 (7.3)	129.8 (7.8)	.35
STAIC-state score	36.2 (1.1)	36.7 (1.2)	.77
STAIC-trait score	43.0 (1.5)	41.6 (1.4)	.49
Estradiol, pg/mL	43.2 (7.6)	32.3 (6.3)	.28
Testosterone, ng/dL	43.0 (6.4)	36.8 (5.7)	.47
Free androgen index	3.1 (0.5)	2.6 (0.5)	.57

Abbreviations: AN-E– = girls with anorexia nervosa receiving placebo, AN-E+ = girls with anorexia nervosa receiving estrogen, BMI = body mass index, BSQ-34 = 34-item Body Shape Questionnaire, EDI-2 = Eating Disorders Inventory-2, SE = standard error, STAIC = State-Trait Anxiety Inventory for Children.

Figure 1. Change in STAIC-Trait (left) and -State (right) Scores in Girls With Anorexia Nervosa Randomized to Physiologic Estrogen With Cyclic Progesterone or Placebo Patches and Cyclic Placebo Pills[a]



[a]Physiologic estrogen replacement led to a significant decrease in anxiety trait (but not state) scores.
*$P < .05$.
Abbreviations: AN-E– = girls with anorexia nervosa receiving placebo, AN-E+ = girls with anorexia nervosa receiving estrogen, SE = standard error, STAIC = State-Trait Anxiety Inventory for Children.

mounted stadiometer (average of 3 measurements to the nearest 0.1 cm) at the Clinical Research Center at MGH or the Clinical Investigation Unit at Sick-Kids. Blood samples were drawn for estradiol, testosterone, and sex hormone binding globulin levels at these visits. We assessed compliance with study medications every 2 months by using verbal questionnaires and by collecting calendars provided to subjects to record missed study medications. We also collected used and unused patches and pills. Groups did not differ in compliance with study medications.

Biochemical Analysis

We used a radioimmunoassay to measure estradiol (Diagnostic Systems Laboratories, Inc, Webster, Texas; limit of detection, 2.2 pg/mL, intra-assay coefficient of variation [CV], 6.5%–8.9%). The Access chemiluminescent immunoassay (Beckman Coulter, Fullerton, California) was used to measure testosterone (limit of detection, 10 ng/dL; intra-assay CV, 1.67%–3.93%) and sex hormone binding globulin (limit of detection, 0.33 nmol/L; intra-assay CV, 4.5%–4.8%). Free androgen index was calculated with the following formula: (total testosterone × 3.47)/sex hormone binding globulin. Data at 18 months were available for 27 subjects for gonadal steroids. Samples were stored at −80°C until analysis and run in duplicate.

Statistical Methods

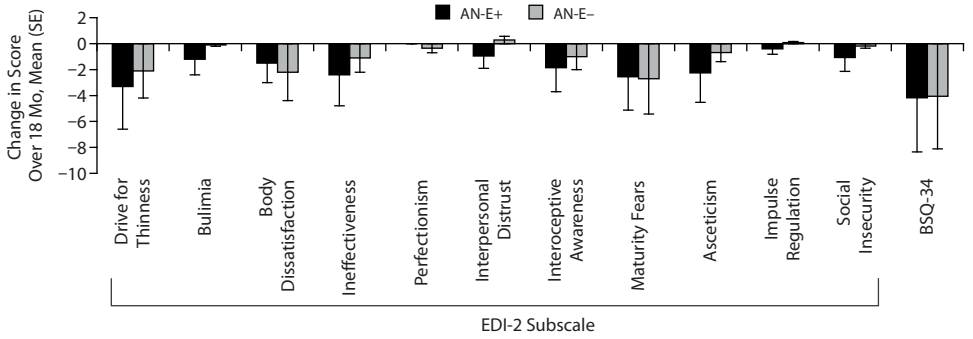
Data are reported as mean (standard error [SE]). A *P* value of < .05 on a 2-tailed test was used to indicate significance. Our primary end point was the prospective change in questionnaire scores in AN-E+ versus AN-E– subjects over 18 months. Baseline characteristics of AN-E+ versus AN-E– and the difference in questionnaire scores between the 2 groups from baseline to 18 months (18 months – baseline) was compared by using the Student *t* test. In comparing AN-E+ versus AN-E–, we controlled for weight and BMI changes over 18 months using analysis of covariance, given that these are known determinants of prospective changes in certain questionnaire measures over time.[2] We also used correlation analysis to determine associations of changes in weight, BMI, and estradiol levels with changes in questionnaire scores over 18 months, and we performed multivariate analysis to control for potential confounders of these associations. We used Spearman (nonparametric) correlations when determining associations for data that were not normally distributed and Pearson (parametric) correlations when data were normally distributed. Baseline data are provided for all subjects who completed the questionnaires at baseline, and follow-up data are provided for those who also completed the questionnaires at 18-month follow-up.

RESULTS

Baseline Characteristics

Girls with anorexia nervosa randomized to physiologic estrogen replacement did not differ from those randomized to placebo for age, bone age, height, weight, BMI, baseline STAIC-state and -trait scores, EDI-2 and BSQ-34 scores, and estradiol and testosterone levels (Table 1). At baseline, 52.6% of girls with anorexia nervosa receiving estrogen (AN-E+) and 50.0% of the girls with anorexia nervosa receiving placebo

Figure 2. Changes in EDI-2 Subscale Scores and BSQ-34 Scores in Girls With Anorexia Nervosa Randomized to Physiologic Estrogen With Cyclic Progesterone or Placebo Patches and Cyclic Placebo Pills[a]



[a]Physiologic estrogen replacement had no significant impact on these scores.
Abbreviations: AN-E– = girls with anorexia nervosa receiving placebo, AN-E+ = girls with anorexia nervosa receiving estrogen, BSQ-34 = 34-item Body Shape Questionnaire, EDI-2 = Eating Disorders Inventory-2, SE = standard error.

Table 2. Changes in Body Composition Parameters and Hormones Over 18 Months in Girls With Anorexia Nervosa Randomized to Physiologic Estrogen With Cyclic Progesterone or Placebo Patches and Cyclic Placebo Pills

Variable (18 mo – baseline)	AN-E+ (n = 20), Mean (SE)	AN-E– (n = 17), Mean (SE)	*P*
Weight, kg	3.8 (1.1)	3.3 (1.1)	.73
Body mass index (kg/m^2)	1.36 (0.45)	1.19 (0.42)	.79
Percentage body fat	2.8 (1.5)	4.1 (1.0)	.48
Estradiol, pg/mL	117.0 (28.0)	22.4 (18.8)	.01
Testosterone, ng/dL	−15.2 (9.4)	−16.6 (11.8)	.93
Free androgen index	−0.6 (0.5)	1.2 (1.8)	.28

Abbreviation: AN-E– = girls with anorexia nervosa receiving placebo, AN-E+ = girls with anorexia nervosa receiving estrogen, SE = standard error.

(AN-E–) were taking psychotropic medication ($P = 1.0$). Additionally, AN-E+ and AN-E– groups did not differ in the use of SSRIs/SNRIs (44.7% vs 44.1%, $P = 1.00$), atypical antipsychotics (21.1% vs 14.7%, $P = .55$), or benzodiazepines (13.2% vs 5.9%, $P = .43$). Girls who did or did not complete the questionnaires at follow-up or were lost to follow-up did not differ in baseline characteristics, including use of psychotropic medication.

Changes in STAIC, EDI-2, and BSQ-34 Scores

Estrogen replacement in girls with anorexia nervosa led to a significant decrease in the STAIC-trait scores (−3.05 [1.22] vs 2.07 [1.73], $P = .02$), without impacting STAIC-state scores (−1.11 [2.17] vs 0.20 [1.42], $P = .64$) (Figure 1). AN-E+ and AN-E– groups did not differ for changes in EDI-2 subscale scores or BSQ-34 scores over 18 months (Figure 2).

The groups did not differ in changes in weight, BMI, or percentage of body fat over 18 months (Table 2). Estradiol levels, as expected, increased significantly in the AN-E+ group compared with the AN-E– group; however, changes in total testosterone levels and the free androgen index did not differ between groups. Differences between AN-E+ and AN-E– with regard to change in STAIC-trait scores remained significant after controlling for changes in weight or BMI over the 18 months ($P = .02$ and $P = .03$, respectively).

An inverse association between change in estradiol and change in STAIC-trait scores over the study duration was found for the group as a whole, such that an increase in estradiol levels was associated with a decrease in STAIC-trait scores (Spearman $\rho = -0.45$, $P = .03$). This inverse association was even more marked in the AN-E+ group (Spearman $\rho = -0.60$, $P = .03$). The association persisted after controlling for change in BMI for the group as a whole ($P = .002$) and within AN-E+ ($P = .0007$). No associations were found regarding changes in testosterone or the free androgen index and the questionnaire scores. The decrease in STAIC-trait scores in the AN-E+ compared with the AN-E– group remained significant after controlling for baseline estradiol and baseline STAIC-trait scores ($P = .01$).

Only 8 subjects were assessed at follow-up on days during which they were on progesterone or placebo. Differences between the groups remained significant after these subjects were excluded in a subgroup analysis ($P = .02$). None of the girls in the AN-E– group resumed regular menses (although about 50% had irregular cycles or spotting), and we were thus unable to assess the impact of spontaneous menstrual recovery on questionnaire scores.

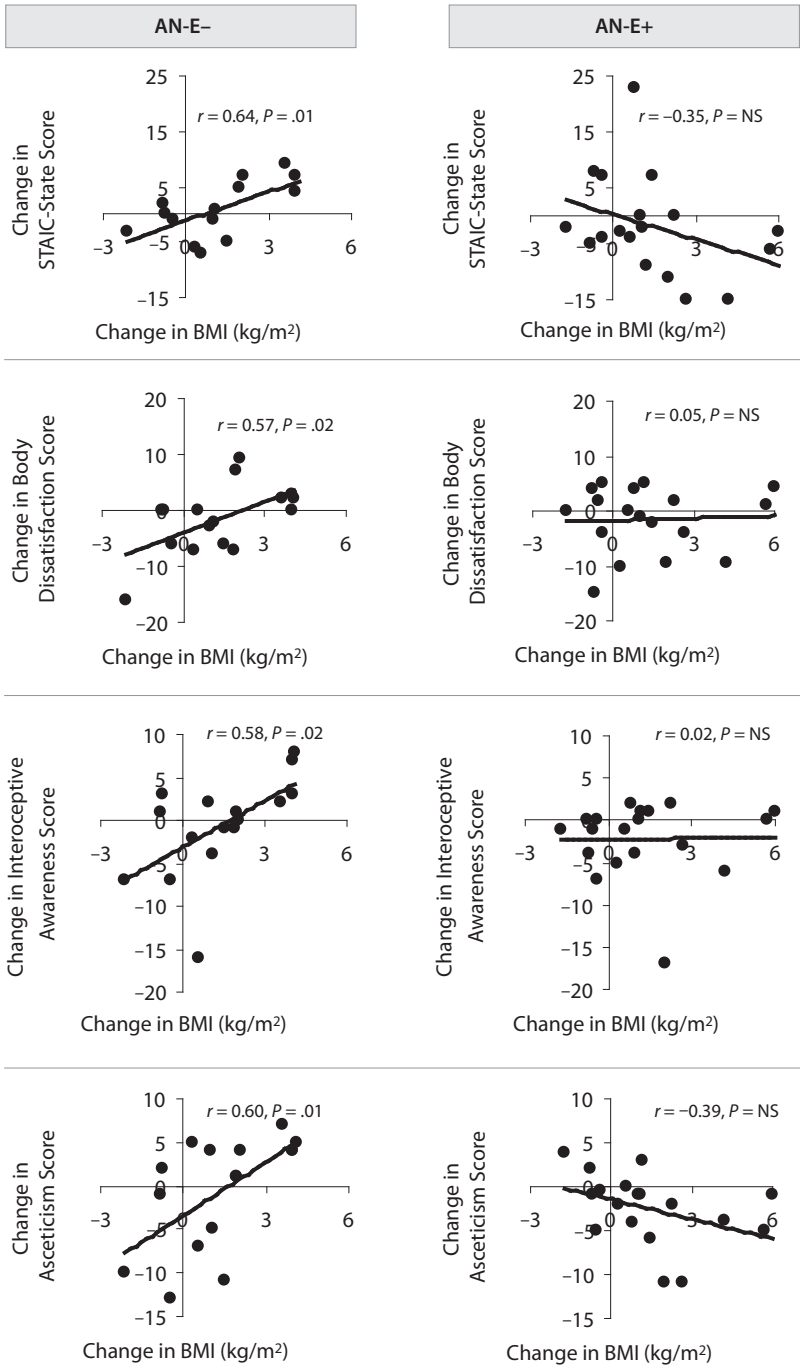
Other Determinants of Changes in EDI-2, BSQ-34, and STAIC Scores

In the AN-E– group, changes in weight or in BMI were associated positively with changes in the STAIC-state scores ($r = 0.64$; $P = .01$ for both) and the following EDI-2 subscale scores: body dissatisfaction ($r = 0.59$ and 0.57; $P = .01$ and $P = .02$), interoceptive awareness ($r = 0.58$ for both; $P = .01$ and $P = .02$) and asceticism ($r = 0.58$ and 0.60; $P = .01$) (Figure 3). However, these associations were not observed in the AN-E+ group. In contrast, there was an inverse association between change in BMI and change in ineffectiveness (EDI-2 subscale) in the AN-E+ group ($r = -0.46$, $P = .048$).

DISCUSSION

We demonstrate a reduction in trait anxiety (the tendency to experience anxiety) with estrogen replacement in adolescent

Figure 3. Associations of Changes in BMI Over 18 Months With Changes in STAIC-State Scores and With Changes in Body Dissatisfaction, Interoceptive Awareness, and Asceticism Subscale Scores on the EDI-2 in Girls With Anorexia Nervosa Randomized to Physiologic Estrogen With Cyclic Progesterone or Placebo Patches and Cyclic Placebo Pills[a]



[a]Positive associations of changes in these scores over 18 months were noted with changes in BMI in AN-E–, but not in AN-E+.
Abbreviations: AN-E– = girls with anorexia nervosa receiving placebo, AN-E+ = girls with anorexia nervosa receiving estrogen, BMI = body mass index, EDI-2 = Editing Disorders Inventory-2, STAIC = State-Trait Anxiety Inventory for Children.

girls with anorexia nervosa independent of weight changes in a randomized placebo-controlled study. However, estrogen replacement did not directly impact eating attitudes and behaviors, body shape perception, or state anxiety.

Our findings are consistent with data from animal experiments that report a decrease in depressive behavior and anxiety in animal models of hypogonadism following estrogen replacement.[13,14,23] Ovariectomy leads to hypoestrogenism and has been shown to be anxiogenic in rats.[13,14] However, ovariectomized rats treated with estrogen performed better than those treated with a vehicle during a forced swim test by swimming more and struggling less.[13,23] Following estrogen administration, when exposed to a circular open field, ovariectomized rats tend to be less immobile, venture

more often into the center of the field, and spend more time there.[14,23] Estrogen replacement also results in less anxiety-like behavior on the mirror maze test and with light-dark transition tasks.[23] In our study, use of physiologic replacement doses of the 17β-estradiol transdermal patch was associated with a reduction in trait anxiety scores, and this effect persisted after controlling for weight changes. We also found correlations between increases in estradiol and decreases in trait anxiety scores over 18 months, and this association remained significant after controlling for weight changes. In addition, the impact on trait anxiety scores was not related to progesterone intake, as differences between groups persisted after excluding subjects who were assessed during the days they were taking progesterone/placebo pills. The fact that "trait" rather than "state" anxiety was impacted by estrogen replacement is most likely related to trait reflecting a pattern of responding or proneness to respond or to feel a certain way, whereas state reflects feelings at any given moment. Our data suggest that estrogen replacement improves chronic patterns of anxiety rather than feelings at any given moment, which may be more likely to be impacted by coincident triggers and stimuli. Of note, although the constructs of state and trait anxiety are the same across the age spectrum, the language in the child measure (used in this study) is simplified. Future studies should include use of the STAI rather than the STAIC in this adolescent age group. We did not assess depressive symptoms in our subjects in this study, and this will be important to evaluate in future studies.

Estrogen replacement was not associated with a decrease in scores on the EDI-2 subscales or on the BSQ-34, suggesting that estrogen replacement does not improve eating attitudes and behavior or body shape perception in anorexia nervosa. However, girls with anorexia nervosa randomized to placebo had a positive association between changes in weight or BMI and (1) changes in various subscale scores of the EDI-2, including body dissatisfaction, interoceptive awareness, and asceticism, and (2) changes in STAIC state scores. These data suggest that, when estrogen levels are low, an increase in weight or BMI alone is associated with an increase in eating disorder psychopathology and state anxiety. Importantly, this association was not evident in girls with anorexia nervosa randomized to transdermal estradiol, indicating that in an estrogen-replete state, an increase in weight or BMI is reassuringly not associated with an increase in psychopathology or state anxiety. In fact, in girls with anorexia nervosa randomized to transdermal estradiol, an increase in weight/BMI was associated with a decrease in feelings of ineffectiveness on correlation analysis. This has implications for better chances at sustaining recovery in an estrogen-replete than an estrogen-deficient state.

Estrogen administration has been associated with improved cognitive performance in ovariectomized rats.[23] In addition, in women with anorexia nervosa, spontaneous resumption of menses, use of oral estrogen, or both are associated with improvement in certain cognitive measures.[8] We did not assess cognitive function following transdermal estradiol use in our study, and this will be important to evaluate.

A limitation of the study is our reliance on self-report questionnaires. Although study participants were aware that the questionnaires were for research purposes only, there may be a bias toward underreporting psychopathology. However, this bias would be expected to be distributed equally across the randomization groups. Also, these questionnaires have been validated for assessing anxiety, eating attitudes and behavior, and body shape perception.[19,20] An additional limitation is that multiple factors, such as weight changes over time, may mediate longitudinal changes in anxiety, self-body image, and eating attitudes and behavior. Controlling for such covariates in multivariate models is 1 strategy to assess whether effects of estrogen replacement on prospective changes in questionnaire scores are independent of other confounders. Indeed, differences between treatment groups persisted for STAIC-trait scores even after controlling for changes in weight or BMI over the study duration. Additionally, the groups did not differ in changes in weight or BMI over time.

Another study limitation is that treatment status and current emotional and physical state of the subject may impact performance on questionnaires, as may comorbid conditions such as anxiety and depression. Although we had complete information about our study subjects' use of psychotropic drugs, they were not always clear about specific indications for these drugs, which limited our ability to determine effects of specific comorbidities. Again, in a randomized trial, these modifiers would be evenly distributed across groups. Finally, a higher retention rate would have been desirable over the study duration. Our attrition rate was comparable to other reports in anorexia nervosa,[24] although a recent study in adolescents reported significant success with retention.[25] This finding may relate to perceived benefits from study participation, with studies involving treatment of the state of anorexia nervosa being perceived as more beneficial than those involving treatment of associated morbidities such as low bone density. Importantly, girls who did or did not complete the study did not differ in baseline characteristics, including use of psychotropic medications.

We thus demonstrate an improvement in trait anxiety in girls with anorexia nervosa randomized to physiologic replacement doses of transdermal estradiol, even after controlling for weight changes. We also demonstrate that associations of increases in weight with increase in eating disorder psychopathology and state anxiety (observed in estrogen-deficient girls with anorexia nervosa) are not evident in those who receive estrogen replacement. Further studies are necessary to confirm these findings, to assess the impact of physiologic estrogen replacement on long-term cognitive outcomes and depressive symptoms in anorexia nervosa, and to assess the effect of other forms of estrogen administration (such as estrogen-progesterone combination pills) not considered physiologic replacement on anxiety, cognitive outcomes, and depressive symptoms.

Drug names: estradiol (Vivelle-Dot and others), medroxyprogesterone acetate (Provera).

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Potential conflicts of interest: The authors report no financial or other relationship relevant to the subject of this article.

Funding/support: This work was supported by National Institutes of Health grants R01 DK 062249, M01-RR-01066, and 1 UL1 RR025758-03.

Acknowledgments: The authors thank the skilled nursing and bionutrition staff of the Clinical Research Center of Massachusetts General Hospital, Boston, and the Clinical Investigation Center of the Hospital for Sick Children, Toronto, Ontario, Canada, for their help with carrying out this study. They also thank their subjects, without whom this study would not have been possible.

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