Estrogen Supplementation in Amenorrheic, Weight-Recovered Women with Anorexia Nervosa and Osteopenia

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A. Study Purpose and Rationale

The purpose of this study is to investigate whether women with Anorexia Nervosa (AN) and osteopenia who have recovered at least 90% of their ideal body weight (IBW), based on the 1959 Metropolitan Life Insurance Tables, and who remain amenorrheic after recovery of this weight will benefit, with respect to bone turnover parameters, from estrogen supplementation.

Osteopenia and osteoporosis are well-documented complications of AN. Bone density has been found to be reduced by more than 1.0 SD in 92% of women with AN (Grinspoon et al. 2000). These complications result in an increased risk of fractures. The mechanism for osteopenia and osteoporosis in women with AN has been investigated but is still not well understood. Proposed mechanisms have included hypoestrogenism, hypercortisolism, low serum levels of IGF-1 and low serum DHEA and DHEA-S levels. Studies have shown that providing women with AN with estrogen supplementation does not improve bone density, except in females in the lowest weight group (initial body weight of less than 70% of IBW) (Klibanski et al. 1995).

Recent data has proposed a possible biphasic model for osteopenia in AN. Dominguez et al. recently presented data that appears to indicate that women with AN need to recover both weight as well as their menstrual cycle in order to normalize their bone turnover parameters (2003). Dominguez et al. followed women in a recovery program for AN at Columbia-Presbyterian Medical Center (2003). Serum osteocalcin levels, a marker of bone formation, and urine NTX levels, a marker of bone resorption, were measured in the subjects at their admission weight as well as when they reached 90% of their IBW. Serum osteocalcin and urine NTX were also measured in normal controls that weighed between 90-100% of their IBW. The data showed that women who regained 90% of their IBW and also regained their menses normalized their levels of serum osteocalcin (which were initially low) and urine NTX (which were initially elevated). Yet women who regained 90% of their IBW and did not regain their menses had normal serum osteocalcin levels but their urine NTX levels remained elevated (indicating normal bone formation but increased bone resorption).

Given that estrogen is believed to suppress bone resorption, this study will be undertaken to investigate whether providing weight-recovered AN women with estrogen supplementation will improve their bone turnover parameters. This is clinically very important in order to increase an individual's peak bone mass and to decrease the risk of pathologic fractures.

B. Study Design and Statistical Analysis

This is a prospective, double-blind, randomized study that will take place over a 6-month period. Females who are admitted to the inpatient Eating Disorders Unit at Columbia-Presbyterian Medical Center who meet the DSM IV-R criteria for AN will be approached to enroll in the study. Any subjects who are taking, or have taken within the previous 3 months, medications known to affect reproductive function, the HPO or HPA axis, including thyroid hormone, estrogen or oral contraceptives, or any women who are pregnant will be excluded from the study. After the subjects achieve at least 90% of their IBW and maintain this weight for 2 weeks they will be divided into 2 groups, those who have regained their menses and those who remain amenorrheic. The women in the group who continue to be amenorrheic will then be randomly assigned into 2 groups, the oral contraceptive arm and the placebo arm and they will be followed for 3 months while taking the oral contraceptive or the placebo.

The study requires a total of 12 subjects, 6 in each arm. Statistical analysis will be performed using an unpaired t-test with alpha of 0.05 and beta of 0.80.

C. Study Procedure

Females admitted to the inpatient Eating Disorders Unit at Columbia-Presbyterian Medical Center who meet the DSM IV-R criteria for AN will be approached to enroll in the study. Upon admission to the Eating Disorders Unit, the subjects will provide a urine sample and blood samples. The subjects will need to provide blood and urine samples for their routine clinical care, in order to evaluate for abnormal thyroid function and pregnancy, and an additional blood and urine sample will be added to these initial tests to measure serum osteocalcin and urine NTX levels. The women will also undergo a screening DEXA scan to assess bone mineral density at the time of admission as part of the study protocol. Only subjects who meet criteria for osteopenia, as defined by the World Health Organization (T score of –1.0 or less at the AP spine) will be eligible for the study. The subjects will then undergo treatment as an inpatient and upon recovery (defined as achieving at least 90% of IBW and maintaining this weight for 2 weeks), those individuals who have not regained their menses will be asked to provide a urine sample to assess for pregnancy as part of the study protocol. At this time the subjects will be randomized into the 2 arms of the study, the oral contraceptive group and the placebo group. The subjects will then provide a urine sample and a blood sample will be drawn on day 5/28 of each of the months the subjects will be taking the placebo or oral contraceptive, as part of the protocol. The subjects will all be provided with counseling instructing them to use at least one other form of birth control, as there is a 50% chance that they are not taking an oral contraceptive. The subjects will also be provided with weekly nutrition counseling in addition to their outpatient follow-up counseling through the Eating Disorders Unit, to prevent relapse. At the end of the 3-month period, the subjects will again undergo a DEXA scan to assess bone mineral density, as part of the study protocol. During the study all women will be provided with supplements and will be instructed to take 1500mg of calcium and 400IU of vitamin D per day.

D. Study Drugs

An approved oral contraceptive formulation will be used in this study. Oral contraceptives are considered a safe and effective way in which to provide women with estrogen in that they also provide progesterone to prevent excessive growth of the uterine lining. The route of administration will be by mouth. The drug or placebo (to be designed by the company manufacturing the oral contraceptive) will be ingested once a day, at the same time each day (standard for this drug). The side effects of oral contraceptives include bloating, nausea, breast tenderness, and mood changes which usually subside in several months. Side effects also include breakthrough bleeding and amenorrhea. There is also an increased risk of myocardial infarction (MI) in women, greater than 35 years of age, who smoke. There is also an increased risk of MI in hypertensive women. Oral contraceptives may also cause an elevation in blood pressure and may slightly increase the incidence of stroke. Oral contraceptives have also been shown to increase the risk of venous thromboembolic disease. Oral contraceptives may cause a mild insulin resistance and may increase serum triglyceride levels slightly. They may alter HDL and LDL profiles. There is an increased risk of developing cervical cancer. There is conflicting data regarding the risk of developing breast cancer in women taking oral contraceptives with a family history of breast cancer, but the risk may be increased in these women. There is conflicting data regarding an increased incidence of melanoma in women taking oral contraceptive pills. There is conflicting data regarding the increased risk of developing inflammatory bowel disease in women taking oral contraceptives. There may be an increased risk of developing cerebral thromboembolism in women with a history of migraine headaches. Oral contraceptives may also induce or exacerbate symptoms of hereditary angioedema.

E. Medical Device

None

F. Study Questionnaires

None

G. Study Subjects

a. Inclusion Criteria

Female subjects, between 18 and 30 years of age, entering the inpatient Eating Disorders Unit at Columbia-Presbyterian Medical Center who meet the DSM IV-R criteria for Anorexia Nervosa and who meet the World Health Organizations definition of osteopenia (T score of 1.0 or less at the AP spine) at the time of the screening DEXA scan will be eligible for the study.

b. Exclusion Criteria

Individuals who are taking, or have taken within the past 3 months, medications known to affect reproductive function, the HPO or HPA axis, including thyroid hormone, estrogen or oral contraceptives, or any women who are pregnant will be excluded from the study. Also individuals taking, or who have taken within the past 3 months, medications known to affect bone mineralization, including bisphosphonates and glucocorticoids will be excluded.

Individuals who have a history of a thromboembolic event or have an inherited or acquired thrombophilia will also be excluded from the study given the potential risks of using oral contraceptives in this population, as will women with a history of migraine headaches.

H. Recruitment of Subjects

Individuals qualifying for inclusion will be approached and asked if they wish to enroll in the study at the time of admission to the Eating Disorders Unit, by the study investigators. Great emphasis will be placed on the fact that the care they receive will not be affected in any way if they choose not to enroll. Similarly, they may choose to withdraw from the study at any time, again without their care being affected.

I. Confidentiality of Study Data

Study data will be coded and stored in a secure location, in accordance with IRB regulations.

J. Potential Conflict of Interest

None.

K. Location of Study

This study will be conducted in the Eating Disorders Unit at Columbia-Presbyterian Medical Center.

L. Potential Risks

The risks involved in this study include the potential risks of taking oral contraceptive pills (see **Study Drug** above). These risks will be carefully discussed with the study participants prior to enrollment.

M. Potential Benefits

Potential benefits of oral contraceptive pills include a decreased risk of developing non-heritable forms of ovarian cancer as well as a decreased risk of developing endometrial cancer. While there may or may not be a potential benefit with respect to the subject's osteopenia, the potential benefit of this study is that it will provide new information and provide us with a greater understanding of the mechanisms leading to osteopenia/osteoporosis in women with AN.

N. Alternative Therapies

No alternative therapies have been approved for the improvement of bone mineral density in females with AN. There is currently an ongoing experimental trial for a potential therapy in the treatment of osteopenia in women with AN. The investigators are attempting to assess whether administering IGF-1 and actonel (risedronate sodium), a pyridinyl bisphosphonate, to women with AN improves bone density. This study is being performed at MGH in low weight women, not women who have achieved 90% of their IBW, and therefore involves a different study population.

O. Compensation to Subjects

While direct payment will not be provided to the subjects, they will be provided with free weekly psychiatric and nutritional counseling during the study period. The DEXA scan will also be performed at no cost to the participant and the placebo/oral contraceptive will be provided at no cost.

P. Costs to Subjects

None.

Q. Minors as Research Subjects

No minors will participate in this study.

R. Radiation or Radioactive Substances

A Dexa scan will be performed at the beginning of the study and at the completion of the study. A Dexa scan is associated with minimal radiation exposure (less than that of a chest x-ray) and is clinically indicated for women at risk for osteoporosis.

S. References

Dominguez JE, Lee KK, Mayer L, Glasofer D, Walsh BT, Wang J, Pierson R, Heymsfield S, Ferin M and MP Warren 2003 BMD recovery in anorexia nervosa: A biphasic model. Presented at *The Endocrine Society's 85th Annual Meeting*, Philadelphia.

Grinspoon S, Thomas E, Pitts S, Gross E, Mickley D, Miller K, Herzog D, Klibanski A 2000 Prevalence and predictive factors for regional osteopenia in women with anorexia nervosa. *Annals of Internal Medicine* 133: 790-794.

Klibanski A et al. 1995 The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. *Journal of Clinical Endocrinology and Metabolism* 80(3): 898-904.