

AOGS COMMENTARY

Women with anorexia nervosa should not be treated with estrogen or birth control pills in a bone-sparing effect

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Eating disorders are prevalent, serious conditions that affect mainly the identity-building part of life. The serious somatic condition of anorexia nervosa has a prevalence of 0.3–1.0% (1). With less stringent criteria for diagnosis, the prevalence is likely to be much higher. People with anorexia nervosa often have long periods of illness and this affects their education and career. The condition often fluctuates with periods of remission and relapses, which could result from either low food intake or high energy expenditure due to extensive training, both of which disrupt the hypothalamic signals to the pituitary

Abstract

Eating disorders are prevalent, serious conditions that affect mainly young women. An early and enduring sign of anorexia is amenorrhea. There is no evidence for benefits of hormone therapy in patients with anorexia; however, hormone medication and oral contraceptives are frequently prescribed for young women with anorexia as a prevention against and treatment for low bone mineral density. The use of estrogens may create a false picture indicating that the skeleton is being protected against osteoporosis. Thus the motivation to regain weight, and adhere to treatment of the eating disorder in itself, may be reduced. The most important intervention is to restore the menstrual periods through increased nutrition. Hormone and oral contraceptive therapy should not be prescribed for young women with amenorrhea and concurrent eating disorders.

Abbreviations: BMD, bone mineral density; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; IUS, intrauterine system; LH, luteinizing hormone.

gland. These disruptions lead to a suppression of the menstrual cycle. The consequence is a lowering of estrogen levels and infrequent or even a near complete lack of ovulation (1). An early and enduring sign of anorexia is amenorrhea. Long periods of starvation have a negative impact on underweight individuals since virtually every organ in the body is exposed to a high degree of somatic stress. One of the consequences is the loss of bone mineral density (BMD), which leads to a low BMD for age and an increased risk for osteoporosis later in life. Measured with dual x-ray absorptiometry, the annual loss is

reported to be up to 2.5% (1,2). Patients with anorexia will have a threefold risk of fractures compared with age-matched controls (3). The reason for bone density loss is considered to be related to the low body mass index, a low caloric intake, a low intake of calcium and vitamin D, low estrogen levels, low insulin-like growth factor 1 (IGF-1) levels and cortisone supplements (4,5).

The reason why many physicians treat young women with anorexia and menstrual loss with estrogens is probably in part because it is believed through this that the woman will avoid BMD loss. A recent article published in the journal *Metabolism* highlights this issue (1). Since estrogens have a positive effect on bone metabolism, several studies have evaluated the role of estrogen treatment on bone density in women with anorexia, primarily in the form of oral contraceptives. The results, however, have been discouraging (1,6,7). To further exemplify this, the study of Viapiana et al. can be referred to (3), showing that prevention of bone density loss after 2 years of treatment could not be obtained with hormone therapy. The return of menstruation and weight gain were the two main factors leading to an increase of BMD in the hip and lumbar spine. The same conclusion was also reached by Legroux-Gerot et al. in 2008 (8). Miller et al. made regular assessment of BMD over a period of 6 months in 75 women with anorexia who had amenorrhea (2). The women, who received oral contraceptives and did not gain weight, lost BMD. The BMD remained unchanged in those who received oral contraceptives, even when they had a 10% weight increase. The women without medication who regained their menses and/or increased their weight, showed an increase in BMD (2). According to a meta-analysis based on two prospective cohort studies and four randomized clinical trials, estrogens had a significant but moderate effect on BMD in the lumbar spine [0.33 effect size; 95% confidence interval (CI) 0.09–0.56] but did not reduce the loss of BMD at the femoral neck (0.13 effect size; 95% CI 0.09–0.43). The conclusion was that estrogens had uncertain benefits, but that improved nutrition was the most important factor for bone health in these patients (9).

The reason for the lack of effect of estrogens on bone density in women with anorexia may be due to oral estrogens depressing the levels of insulin-like growth factors in these patients, who already have low IGF-1 levels. IGF-1 is a nutritionally dependent bone tropic factor (1). However, in one randomized trial including 110 adolescent girls with anorexia, where 100 µg of transdermal estradiol with cyclic progesterone were given for 18 months, significant increases in spine and hip BMD Z-scores were demonstrated in comparison with placebo (10).

Another reason could be that the bone density loss in women with anorexia is due not only to an increased

osteoclast activity, i.e. similar to the resorption activity in postmenopausal women, but also to a decreased osteoblast activity, i.e. bone formation activity (11). A decrease in bone formation is not seen in postmenopausal women. Estrogens mainly regulate resorption activity, but in women with anorexia the anabolic osteoblast activity is also suppressed. Nutritional rehabilitation leads to a powerful anabolic effect on bone, as measured with bone markers. The increased resorption activity found in patients with anorexia is normalized when menstruation has returned (12). In a study from 2012, Legroux-Gerot et al. concluded that the most predictive factor for improvement in BMD at the hip and lumbar spine was weight gain. There is a strong correlation between weight gain after 1 year and an increase of BMD in the hip and lower back after 2 years (13). In contrast, Divasta et al. (14), in a double-blind, placebo-controlled, randomized trial in 60 young women with anorexia, have recently evaluated the effect of 18 months of combined treatment with dehydroepiandrosterone (DHEA) and estrogen/progestins where both groups gained weight, which alone should lead to improvements in skeletal health in patients with anorexia. However, in this study after weight-adjusted results, the combination of gonadal and adrenal steroid therapy was still effective in preserving skeletal health compared with the placebo group (14).

Despite the lack of evidence for benefits from hormone therapy and oral contraceptives in anorexia, these medications are often prescribed for young women with anorexia to try to prevent and treat low bone mineral density. In a study in 2000, when clinicians were asked about their opinion regarding hormone treatment for enhancement of BMD in anorexia patients, 78% reported that they prescribed hormone treatment to prevent bone loss in women with anorexia (6). The use of estrogens may create a false impression that the skeleton is protected against osteoporosis. The induced regular menstrual cycles may create a false sense of health and hereby the motivation to regain weight and adhere to treatment of the eating disorder may be disturbed (4). There are many indications to show that the most important intervention is to restore the periods through increased nutrition. Studies show that to regain a normal menstrual cycle, the patient should weigh 2.05 kg more than she did when she lost her periods over a range of 1.2–17.6 months (15).

There is currently conflicting evidence in young women with amenorrhea and concurrent eating disorders that estrogens are an effective treatment or will prevent osteoporosis. Therefore hormone or oral contraceptive therapy should be avoided for this group of patients. However, it is estimated that approximately 20% of women with anorexia have a chronic course and poor outcome. This group of patients, with a chronic disease, will presumably

be better off with hormone therapy, preferably transdermal treatment, since the study of Misra *et al.* (10) showed a positive effect on BMD with transdermal estradiol and cyclic progesterone. Women with eating disorders often consult a gynecologist because of the amenorrhea. Hormone investigation in this type of secondary amenorrhea usually shows a typical hypothalamic inhibition with low levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estradiol. By describing the mechanisms leading to this, the gynecologist can make the woman understand why menstruation has stopped. It is important that the woman becomes aware that weight gain is the prime factor that mediates the onset of menses. Prescribing hormones or oral contraceptives creates a false sense of security for the woman and can reduce her motivation to seek full recovery from the eating disorder. One study also showed that women with anorexia who took the oral contraceptives had higher C-reactive protein levels. The authors calculate a 20% risk of developing future cardiovascular disease for this group of patients (16).

The follow-up visit can serve as an instrument to follow recovery. The patient should be encouraged to attend for such a visit after 3–6 months. If she begins to gain weight, the LH, FSH and estradiol levels will rise. During the gynecologic examination, increased discharge but also healthy mucous membranes in the vagina may be found and commented on. Ultrasound demonstration of a thickened endometrium and more visible follicles in the ovary, with a possible ovulation can be shown. These findings may motivate the woman to continue on her way to becoming healthy and resume her periods by gaining weight. The oral contraceptive pill is only justified if the woman needs contraception. A combined oral contraceptive pill should then be prescribed. The gestagen alternative depo-medroxyprogesterone acetate reduces BMD by inducing an imbalance between bone resorption and bone formation in favor of bone resorption, which is accompanied by significant bone loss (17). However, there are reports to show that levonogestrel appears to decrease bone turnover markers (17).

Regular periods are an indication of a balanced hormonal status. With the hormonal intrauterine system (IUS), menstruation will disappear and this hampers the possibility of following up the menstrual pattern that might be normalized by an improved nutritional status. Therefore the hormonal IUS is not advisable for this group of women.

We hope that all care providers will feel able to contribute to the rehabilitation of patients with anorexia and communicate a similar message to our patients. By providing a unanimous message, we can improve credibility which might lead to better treatment regimes and

patient compliance that will result in better health and hopefully a full remission in these women.

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