Reviews

Menses Requires Energy: A Review of How Disordered Eating, Excessive Exercise, and High Stress Lead to Menstrual Irregularities

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ABSTRACT

Purpose: Functional hypothalamic amenorrhea secondary to low weight, excessive exercise, and/or high levels of stress is common among young women. Adolescence is a time in development that a positive energy balance is crucial for puberty, menarche, and regular menstruation. Disordered eating and eating disorders are the third most common chronic illness and tend to start during puberty. High-level athletes, specifically young girls participating in ballet, running, gymnastics, and figure skating, are at risk of developing hypothalamic amenorrhea from excessive exercise and inability to meet the energy needs of the body. Dysfunction of the hypothalamic–pituitary–ovarian axis leads to a hypoestrogenic state. Low levels of estrogen have a negative effect on bone health, sexual maturation, sexual function, and fertility. Puberty has the highest rate of bone accrual in a female's life. Adequate nutrition, physical activity, and estrogen are crucial for bone development and prevention of osteoporosis. Recognition and early intervention are necessary to limit the irreversibility of some of these effects.

Methods: A review of literature was completed to gather epidemiologic data, pathophysiology, diagnostic criteria, recommended laboratory/imaging, and approaches to treatment.

Findings: According to the American College of Obstetricians and Gynecologists, 16% to 47% of slender female athletes have disordered eating, which makes them at risk for functional hypothalamic amenorrhea (FHA). Most women present with previously regular menstrual cycles until there was a change in one or multiple factors, including weight, stress, and/or exercise. Athletes have a higher incidence, stemming from the synergistic relationship that exercise and low weight have on puberty and the menstrual cycle. FHA is a diagnosis of exclusion; therefore, eating disorders and other etiologies of menstrual irregularity need to be ruled out first.

Implications: Hypothalamic dysfunction leads to a hypoestrogenic state within the body. Low levels of estrogen manifest in multiple ways: amenorrhea, low bone mineral density, vaginal and breast atrophy, infertility, and dyspareunia. The goal of treatment of FHA and these downstream symptoms is weight gain with spontaneous resumption of menses, as this is the best indicator that the hypothalamic dysfunction and hypoestrogenic state have been resolved. In refractory cases of FHA, it may be necessary to replace hormones with physiologic dosing of transdermal estrogen and cyclic progesterone for the benefit of the young woman's bone health (*Clin Ther*. 2020;42:XXX–XXX) © 2020 Elsevier HS Journals, Inc. (*Clin Ther*. 2020;42:401–407) © 2020 Elsevier Inc.

Key words: Amenorrhea, Functional amenorrhea, Menstrual irregularity, Adolescent gynecology, Menstrual cycle.

INTRODUCTION

Adolescence is a vulnerable time magnified by social pressures to look and/or perform a certain way. These stresses contribute to the development of disordered eating, the third most common chronic illness among adolescents that tends to develop

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during puberty.[1] According to the American College of Obstetricians and Gynecologists, 16%− to 47% of slender female athletes have disordered eating, whereas the general population's rate of disordered eating is 0.5% to 10%.[2] Anorexia nervosa has a prevalence of 1% to 4% and is the most fatal psychiatric illness with a mortality rate of 5% to 6%. Aside from mortality, there are numerous comorbid conditions associated with anorexia nervosa, including cardiovascular disease, bone health, reproductive issues, and gastrointestinal complications. Eating disorders, as with many chronic medical conditions, are hereditable. Specifically, anorexia nervosa has a 33% to 84% heritability, whereas the heritability of bulimia nervosa ranges from 28% to 83%.[1]

Well-rounded nutrition is necessary for physical development, pubertal growth, and prevention of chronic illness. Creating a solid nutritional foundation early-on is important because puberty starts around age 8 to 13 years with the presence of breast budding. About 2 years later, menarche is expected and correlates with stage 3 to 4 breast development on the sexual maturity rating scale (synonymous with Tanner staging). This time period is the highest rate of bone accrual in a female individual's life. It is crucial for bone development and the prevention of osteoporosis. Nutritional elements such as calcium, vitamin D, and phosphorus are key components to good bone health. However, estrogen and regular physical activity are large contributors as well.

A functioning hypothalamic−ovarian axis influences the production of estrogen during puberty. Balanced nutrition is a major building block for proper functioning of this axis. The United States dietary guidelines endorse the My Plate standard of nutrition. The typical American diet, especially for adolescents, rarely adheres to these recommendations, however. My Plate suggests that one half of the plate be filled with fruits or vegetables while the other half is filled with protein and grains, one half of which should be whole grains. Dairy items are encouraged to be low-fat or fat-free milk or yogurt. Sodium, saturated fats, and added sugars should be limited.[3] In addition to healthful eating choices, adolescents should be participating in at least 60 min of physical activity each day.

Adhering to these recommendations provides the body with the optimal energy for growth and development. The estimated energy needs of an active female subject aged 12 to 18 years are ~2200 to 2400 kcal per day. Activity is defined as participation in 60 min of moderate-intensity exercise each day. Adequate protein, carbohydrates, fat, and vitamins play an important role in creating a positive energy balance. Protein promotes linear growth and aids in pubertal development. The most critical time of adequate protein is during the peak growth phase, between 11 and 14 years of age. Adolescents who are food insecure, follow restrictive diets, or are vegan have increased risk of delayed puberty, reduction in linear growth, and diminished lean body mass.[1] Carbohydrates encompass nearly one half of our diet (ie, 45%−65%). To reduce the risk of cardiometabolic disease and excessive weight gain, carbohydrates should consist mostly of whole grains and vegetables as well as limiting added sugars and sugar-sweetened beverages to <10% of all carbohydrate intake. Fats are another key component of balanced nutrition. Polysaturated fats found in fish, nuts, avocados, and vegetable oil are the best. Less than 10% of the diet should consist of saturated fat (butter and shortening). Preferred saturated fats are liquid forms (olive oil, sesame oil, or canola oil). The avoidance of trans fat, such as hydrogenated vegetable oils, reduces the risk of cardiometabolic disease.[1]

In addition, vitamins provide support to the body's function and development. Fat-soluble vitamins (vitamins A, D, E, and K) are necessary for fat absorption. Vitamin A aids in visual health, vitamin E is essential for immunity and prevention of cardiovascular disease, and vitamin C repairs oxidative stress. Folate, iron, and zinc boost red blood cell health. As mentioned previously, calcium and vitamin D are vital for strong bones.[1]

When the body is devoid of adequate nutrition and energy, the expected maturation and growth during adolescence fail to meet their full potential. This is largely due to hypothalamic suppression and affects the individual's health for the remainder of their life. Correction of unbalanced habits and energy reserve allows for catch-up but does not always lead to full recovery. For this reason, it is imperative to educate about optimal energy, nutrition and exercise, and to intervene early on.

Pathophysiology

Functional hypothalamic amenorrhea (FHA) is the absence of menstruation that results from low

weight, excessive exercise, and/or stress. It is a diagnosis of exclusion and most commonly presents as a loss of menstruation. FHA accounts for ~25% to 35% of all secondary amenorrhea and only 3% of primary amenorrhea. Athletes have a higher incidence stemming from the synergistic relationship that exercise and low weight have on puberty and the menstrual cycle. To achieve menarche, there is a minimum fat storage requirement of 17%, whereas regular menses requires 22%.[4] Not all exercise is treated equally. Runners, dancers, gymnasts, and figure skaters have a higher incidence of FHA due to the importance of lean-ness associated with success in these sports. Swimming, a non–weight-bearing sport, has a lower risk because lean-ness plays a smaller role.

FHA manifests from many factors influencing the complex hypothalamic–pituitary–ovarian axis. When energy stores fail to meet the energy requirements of the body, there are numerous downstream effects. At the level of the hypothalamus, gonadotropin-releasing hormone (GnRH) secretion decreases, leading to less follicle-stimulating hormone (FSH), luteinizing hormone (LH), follicular development, and estrogen secretion.[5–7] Serum testing of FSH and LH levels in a female with FHA falls in the low-normal to pre-pubertal range reflecting this physiologic change. Cortisol and stress affect this axis, as increasing levels of cortisol inhibit GnRH secretion. This action helps to explain why times of high stress can lead to irregular menses and amenorrhea.[4]

Multiple factors within the body's circulation associated with fat and energy also influence the hypothalamic axis. Leptin, secreted by fat cells, is found to be low in low-energy states. Studies have shown that with weight gain and higher fat mass, leptin levels increase and menses resume.[8,9] However, the relation between leptin and the menstrual cycle is much more complex than a unilateral relation to fat stores. As seen in exercising amenorrheic women compared with menstruating women, leptin lacks the typical diurnal rhythm and provides feedback on the hypothalamus that is not completely explained by fat content alone.[4] Ghrelin is an appetite-stimulating hormone secreted from the gastric fundus. Higher levels are seen in low-weight conditions and impair FSH and LH secretion from the pituitary gland.[10,11] Peptide YY is secreted by the gut and suppresses appetite. It is elevated in patients with anorexia nervosa but unexpectedly does not normalize with weight gain.[12,13] The reason for this phenomenon is not well understood. In this population, growth hormone is higher while insulin-like growth factor (IGF) is decreased. IGF is of major importance and works synergistically with sex steroids in bone accrual. Thyroid hormone is also affected. During low-energy states, T3 is reduced whereas TSH and free T4 are in the low–normal to normal range. This may be partially explained by brown adipose tissue, which is reduced in low-energy states. Typically, brown adipose is positively associated with T3. Lower amounts of brown adipose tissue associated with low T3 is a process that allows the body to conserve energy by reducing daily expenditures.[14,15]

Diagnosis

The diagnosis of FHA is based on amenorrhea with low levels of FSH, LH, and estradiol, in the absence of an identifiable underlying cause. Typically, these changes are associated with a precipitating factor such as stress, exercise, and low weight. FHA requires eating disorders and other etiologies of menstrual irregularity to be ruled out before reaching a diagnosis, making it a diagnosis of exclusion. Female athlete triad is another form of FHA that more specifically defines the population and etiology. This condition is seen in physically active females in which FHA results from low energy and leads to low bone density.[2] Ultimately, these are 2 similar conditions with comparable long-term risks and treatment.

The typical patient scenario presenting with FHA is a female subject who previously had regular menstrual cycles until there was a change in one or multiple factors, including weight, stress, and/or exercise. A thorough history specifically asking about weight loss, dieting, excessive exercise, and stress is helpful in making the diagnosis. The health care provider must also consider alternative diagnoses such as celiac disease, inflammatory bowel disease, thyroid disease, polycystic ovarian syndrome, and pregnancy. In general, laboratory evaluation includes a pregnancy test, prolactin, thyroid-stimulating hormone and T4, follicle-stimulating hormone, LH, and estradiol. Testosterone levels should be added if there are clinical signs of hyperandrogenism (hirsutism and/or severe acne). If the history is

concerning for inflammatory conditions such as inflammatory bowel disease and celiac disease, additional laboratory tests that include a complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, basic metabolic panel, and celiac panel should be obtained.[16]

Imaging studies are only necessary in specific circumstances. A pelvic ultrasound is useful in cases in which a uterine anomaly or outflow obstruction is suspected. This scenario is more likely to be seen in situations of primary amenorrhea and/or pelvic pain that have progressed from cyclic to persistent. Magnetic resonance imaging of the sella is recommended in all cases of hypothalamic hypogonadotropic amenorrhea unexplained by weight loss, stress, and decreased energy reserve.

Low bone density is a concern in this population, especially adolescents, because estrogen aids in bone health by balancing the osteoclast and osteoblast activity.[2] Puberty is the main time of bone accrual in female adolescents. By 18 years of age, a female has already achieved 92% of her total bone mineral content. A dual-energy X-ray absorptiometry (DEXA) scan is helpful in assessing the bone density and reports a *Z* and *T* score. The *Z* score compares bone mineral densities based on age and sex, whereas the *T* score compares values versus those of a 30-year-old woman. In premenopausal women, especially adolescents, the *Z* score is much more meaningful. Young women with a *Z* score between –1.0 and –1.9 have low bone density. The term low bone density is preferred over osteopenia in this population. Osteoporosis is defined as a *Z* score greater than –2. Approximately 22% to 50% of elite female athletes meet criteria for low bone density.[2]

Bone health is one of the major long-term risks associated with FHA. However, not all women require a DEXA scan, and actually most transient cases do not. Before obtaining a DEXA scan, the woman should meet criteria for bone mineral density screening. One criterion includes women with >6 months of amenorrhea and presence of severe weight loss or a stress fracture. If the bone mineral density is low, vitamin D deficiency should be ruled out by obtaining 25-hydroxyvitamin D levels. Another group of women recommended to undergo DEXA scan monitoring are those with ongoing FHA. This population should have a DEXA scan every 1 to 2 years.

The female athlete triad coalition guidelines make recommendations for bone density monitoring for exercising amenorrheic women based on high and moderate risk factors.[17] A DEXA scan is recommended when one or more high-risk factors or two or more moderate-risk factors are present. High-risk factors (one or more) include the following: (1) a history of eating disorder diagnosed per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; (2) body mass index (BMI) $\leq$17.5 kg/m^2; (3) less than 85% of expected weight, or recent weight loss of $\geq$10% in 1 month; (4) menarche at 16 years of age or older; (5) fewer than 6 menses in 12 months (in the past or current); (6) two previous stress fractures, one high-risk stress fracture, or history of low-energy nontraumatic fracture; and (7) a prior *Z* score of less than –2. Moderate-risk factors (two or more) include the following: (1) history of disordered eating for $\geq$6 months (in the past or current); (2) BMI between 17.5 and 18.5 kg/m^2, between 85% and 90% of expected weight, or recent weight loss of 5% to 10% in 1 month; (3) menarche between 15 and 16 years; (4) history of 6 to 8 menses in 12 months (in the past or current); (5) one previous stress fracture; and (6) prior *Z* score between –1 and –2.

A DEXA scan is additionally recommended if there is a history of $\geq$1 nonperipheral or $\geq$2 peripheral long bone fractures or a traumatic fracture in the presence of one moderate risk factor. DEXA imaging ought to be considered in an amenorrheic athlete taking medications, for at least 6 months, that could affect bone development such as oral steroids.[17]

According to the 2013 International Society for Clinical Densitometry guidelines, the age of the patient dictates the preferred part of the body to scan for bone density.[18] In children, adolescents, and women <20 years old, the lumbar spine or a whole-body scan is recommended. Adult women aged >20 years should have the lumbar spine, total hip, and femoral neck assessed by DEXA scanning.

Clinical Manifestations

Hypothalamic dysfunction results from suboptimal available energy and leads to a hypoestrogenic state within the body. Low levels of estrogen manifest in multiple ways: amenorrhea, low bone mineral

density, vaginal and breast atrophy, infertility, and dyspareunia. In the treatment of FHA and these downstream clinical symptoms, the goal is weight gain with spontaneous resumption of menses. Spontaneous menstruation is an indicator that the hypothalamic dysfunction and hypoestrogenic state have been resolved. Menstrual resumption takes an average of ~9 months at the 90th or higher percentile of ideal body weight. The individual is typically about 2 kg heavier in weight than when she initially became amenorrheic.[19] These patients should be followed up closely (every 3–6 months). If menses still have not returned with lifestyle modifications by the first follow-up visit, a DEXA scan should be obtained to assess bone density.

Low bone density is initially treated with nonpharmacologic options such as weight-bearing exercise, achieving the recommended daily calcium intake of 1200 to 1500 mg, and supplementing vitamin D to maintain a serum level between 32 and 50 ng/mL (~1000–2000 IU/d).[1,16] These strategies are in combination with weight gain. The current recommendations state that female with low bone density should be encouraged to gain weight and use nonpharmacologic options to enhance bone health for 1 year. If menses still have not resumed spontaneously over that time, hormone replacement is indicated.[16] Bisphosphonates are not recommended in the treatment of low bone density and osteoporosis in this population because bisphosphonates linger in the bones for at least 10 years after use, and little is known about the effect on fetal development. Most females undergoing treatment for FHA are adolescents or young women planning childbearing during that time frame. Despite nonpharmacologic and hormone treatments, bone density is not guaranteed to fully recover.[20]

When using hormones, physiologic replacement is preferred over hormonal contraceptives because the bone accrual is more significant with physiologic hormones. Transdermal estrogen is preferred over oral due to the avoidance of first-pass metabolism. Oral routes are metabolized through the liver, which decreases the production of insulin-like growth factor 1 (IGF1). IGF1 has a trophic effect on bone and is already present in reduced levels in low-weight individuals. The use of transdermal estrogen avoids first-pass metabolism and suppression of IGF1. The recommended replacement of estrogen is transdermal 17-beta-estradiol (100 μg). Because these patients typically have a uterus, cyclic progesterone is required for uterine protection. There are multiple progesterone formulations, including Prometrium 200 mg, medroxyprogesterone 5 to 10 mg, or norethindrone acetate 5 mg. Each can be used for 10 to 12 consecutive days each month.

Adolescents and adults diagnosed with anorexia nervosa exhibited higher rates of bone accrual over an 18-month period when using physiologic dosing of estrogen over combined oral contraceptive pills.[21–23] Bone accrual is still limited by overall low levels of IGF1, decreased leptin, and high levels of cortisol, showing that hormonal replacement is helpful; weight gain and spontaneous menstruation, however, continue to be the main goal of treatment.

In patients at risk for pregnancy, contraception may be necessary and is not provided by physiologic dosing of estrogen with cyclic progesterone. For those not receiving any hormonal replacement, a nonhormonal copper intrauterine device is a great option for contraception because it does not mask menses. Progesterone-only methods (levonorgestrel intrauterine device, etonogestrel implant, and depot medroxyprogesterone injection) are choices that would allow contraceptive benefit and uterine protection while using physiologic estrogen. However, these progesterone-only options may "mask" the resumption of spontaneous menses. Estrogen-containing combined contraceptive options are not recommended in those with already established low bone density or osteoporosis because the peak bone accrual is reduced.

Lifestyle modifications, weight gain, and changes in exercise require a team approach consisting of cognitive behavioral therapy, internal medicine physicians, nutrition, family, and coaches. Family-based therapy is the most efficacious for adolescents. During the 3 phases of family therapy, the control over meals gradually shifts from being completely controlled by the parent back to the adolescents as they work to establish their own healthy identity. This approach has shown improved rates of weight gain and lower rates of relapse.[1] Family mealtime is encouraged and is protective against the development of eating disorders, mental health conditions, risk-taking behaviors (including drugs and alcohol use), and obesity.

As mentioned previously, stress can compound hypothalamic dysfunction. Anxiety and mood disorders can be a product or etiology of high levels of stress. Cognitive behavioral therapy is useful in treating these conditions and decreases the perceived level of stress.

Women struggling with sexual function from vaginal atrophy can use topical estrogen cream until the body recovers from the hypoestrogenic state. Young adult women diagnosed with FHA may desire pregnancy. Hypothalamic dysfunction hinders follicular development and ovulation, both of which are necessary for a pregnancy. Women should be encouraged to obtain a healthy weight (BMI $\geq$18.5 kg/m^2) before undergoing infertility treatments. Low maternal weight increases the risk of preterm birth, low birth weight infants, and spontaneous abortion. As with most women with infertility, starting with oral ovulation induction is reasonable.

These techniques and team-based approaches can achieve a healthy weight gain, a positive energy balance in the body, and resumption of menses. The negative effects on the bone can be improved but not always fully recovered. Recognizing the lifestyle patterns leading to FHA can be preventative for future relapses. Disordered eating, eating disorders, excessive exercise, and stress are often chronic conditions with significant relapse rates. The rate of relapse for anorexia nervosa is 35% to 65% and bulimia is 42%.[1] Therefore, long-term continuity is important for continued education, recognition of relapse, and early intervention.

CONCLUSIONS

FHA results from a combination of low weight, low energy, and/or increased stress. This condition specifically seen within elite athletes is called the female athlete triad. Amenorrhea occurs due to hypothalamic suppression of GnRH, FSH, LH, and estrogen. The development of low bone density and osteoporosis is very concerning in the adolescent population with FHA because the largest amount of bone accrual occurs during puberty and adolescence. Encouraging the young female and her family to develop a positive energy balance by increasing weight, decreasing exercise, or reducing stress is the mainstay of treatment. This approach will allow for spontaneous resumption of menses, meaning resolution of the hypothalamic suppression, hypoestrogenic state, and negative effect on bone health. Despite lifestyle modifications, FHA may be prolonged. In these cases, hormone replacement with physiologic estrogen and cyclic progesterone may be necessary to support bone health during the recovery period. Once spontaneous menstruation resumes, the young woman should be monitored closely because relapse is common. Education about FHA, recognition of relapse, and early intervention are key components to long-term health.

DISCLOSURES

The author has indicated that she has no conflicts of interest regarding the content of this article.

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