

## CLINICAL PRACTICE

## Functional Hypothalamic Amenorrhea

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 16-year-old girl presents for evaluation of secondary amenorrhea. Her menarche was at the age of 12 years. Since she started running for exercise and sport at the age of 14 years, her menstrual periods have become lighter and less frequent. Her last menstrual period was 6 months ago. She has lost 2.3 kg (5 lb) over the past 3 months and reports a 2-week history of right foot pain. She typically runs 10 km (6 mi) per day, at least five times per week. On physical examination, her body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) is 19. There is pain on palpation along the fourth and fifth metatarsals; otherwise, the physical examination is normal. How should her case be evaluated and managed?**

## THE CLINICAL PROBLEM

Functional hypothalamic amenorrhea is a condition characterized by the absence of menses due to the suppression of the hypothalamic–pituitary–ovarian axis, in which no anatomical or organic disease is identified. Adolescents or young women with this condition typically present with amenorrhea of 6 months' duration or longer.<sup>1</sup> In adolescents, this condition may be difficult to differentiate from immaturity of the hypothalamic–pituitary–ovarian axis during the initial postmenarcheal years. However, several reports indicate that menstrual cycles in adolescents typically are no longer than 45 days, even during the first postmenarcheal year.<sup>2-4</sup>

Three main types of functional hypothalamic amenorrhea have been recognized, associated with stress, weight loss, or exercise.<sup>5</sup> These distinctions acknowledge that women who are either underweight or of normal weight may be affected, but in many cases, all three factors are present. Regardless of the specific trigger, functional hypothalamic amenorrhea is characterized by the suppression of gonadotropin-releasing hormone (GnRH) pulsatility. Many other physiological changes that occur in this condition have been described in detail previously.<sup>1,6-10</sup> These changes include overactivity of the hypothalamic–pituitary–adrenal axis (with increased secretion of corticotropin-releasing hormone, adrenocorticotropin hormone, cortisol, and endogenous opioids)<sup>5,11-13</sup> and disturbances of the hypothalamic–pituitary–thyroid axis (including a low-to-normal level of thyrotropin, an increased level of reverse triiodothyronine, and a low level of triiodothyronine),<sup>6</sup> representing a “euthyroid sick” pattern seen in chronic illness and starvation (Fig. 1). An energy deficit (which can occur independently of body weight) appears to be the critical factor in both weight-loss and exercise-induced forms of hypothalamic amenorrhea. Leptin appears to play a critical role in the regulation of hypothalamic dysfunction, and leptin administration has been shown to induce GnRH pulsatility and menstruation.<sup>9,10,14</sup>

Hypothalamic amenorrhea reflects a state of estrogen deficiency, which may

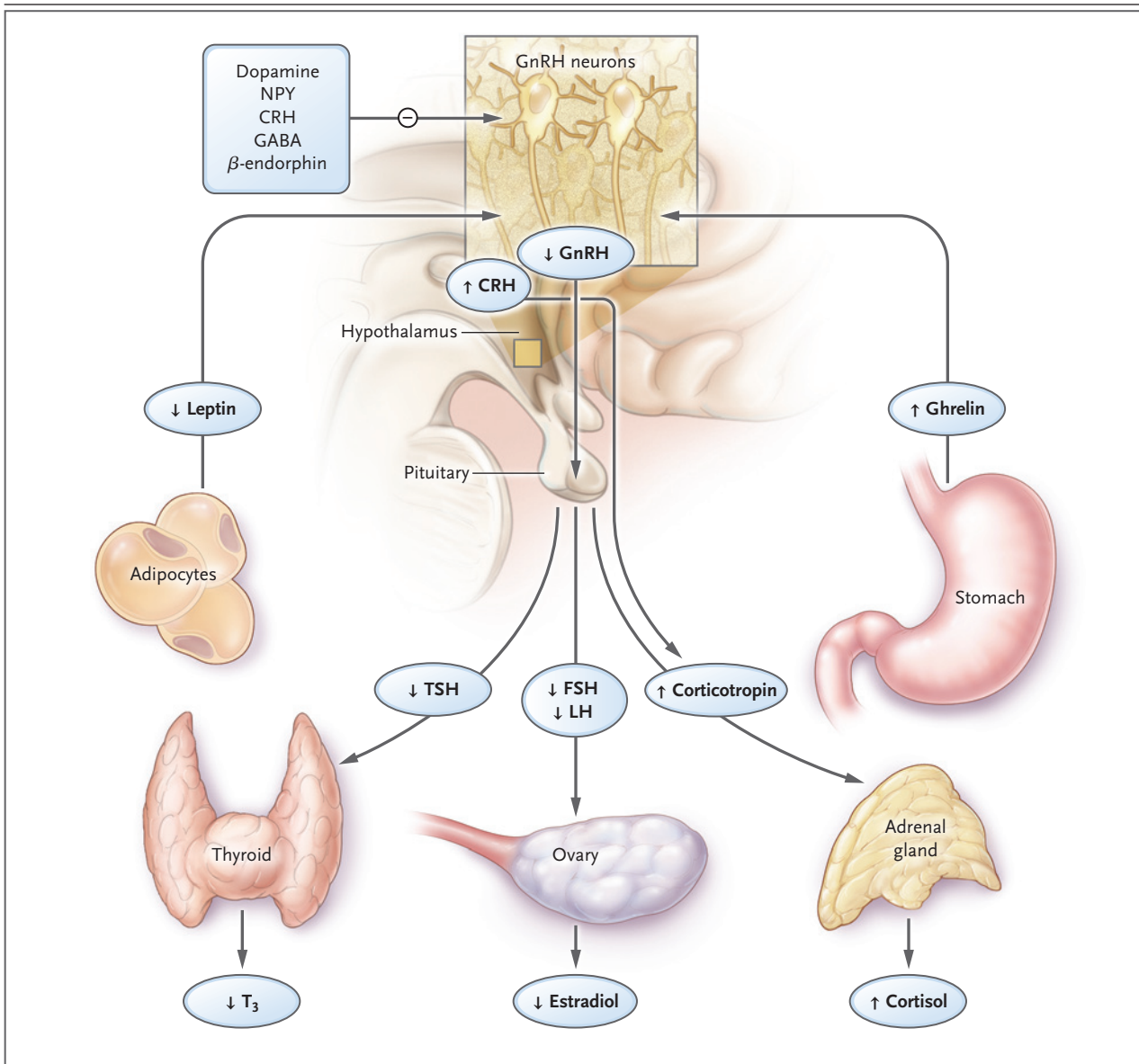
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**Figure 1. Hormonal and Other Changes in Patients with Hypothalamic Amenorrhea.**

In patients with hypothalamic amenorrhea, there are alterations of hormones and other factors that affect the secretion of gonadotropin-releasing hormone (GnRH), including low levels of leptin and high levels of both ghrelin and neuropeptide Y (NPY).  $\beta$ -endorphin, corticotropin-releasing hormone (CRH), dopamine, and  $\gamma$ -aminobutyric acid (GABA) are factors that negatively influence GnRH secretion. Some of these factors may also serve as hunger signals from the peripheral to the central nervous system and as links between nutrition and reproduction. Hallmark findings in adolescents and young women with hypothalamic amenorrhea include overactivity of the hypothalamic–pituitary–adrenal axis, suppression of the hypothalamic–pituitary–ovarian axis, and alterations in thyroid hormone regulation. FSH denotes follicle-stimulating hormone, LH luteinizing hormone, TSH thyrotropin, and T<sub>3</sub> triiodothyronine.

compromise peak bone mass attained in young women.<sup>15-17</sup> Exercise-induced benefits to the skeleton may be compromised if amenorrhea is present.<sup>18</sup> The term “female athlete triad” refers to the interplay among low energy availability (with or without an eating disorder), amenorrhea, and osteoporosis.<sup>19</sup>

## STRATEGIES AND EVIDENCE

### DIAGNOSIS

#### History

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have advocated for menstrual status to be

considered a “vital sign” at routine clinical visits, given the importance of estrogen for bone and other tissues.<sup>15,16</sup> In adolescents whose menstrual cycle assumed a regular pattern before the onset of amenorrhea, the evaluation does not differ substantially from that in adults.

Other than pregnancy, hypothalamic amenorrhea and the polycystic ovary syndrome are the most common causes of secondary amenorrhea.<sup>20</sup> The history taking should address whether weight loss, eating disorders, excessive exercise, and psychosocial stress are present. Patients should be queried about exercise and dietary habits, including any history of bingeing and purging, and recent stressors. Among high-school students,<sup>21</sup> girls who reported vomiting to control their weight even one to three times per month were 60% more likely than those who did not vomit to have irregular menses (after adjustment for BMI, age, and race or ethnic group). The 26-question Eating Attitudes Test is a validated tool that can be used to identify body-image or weight concerns.<sup>22</sup> However, eating disorders that are associated with hypothalamic amenorrhea require specific treatment that is beyond the scope of this article.

Attention should also be given to features suggesting alternative diagnoses, such as galactorrhea, headache, or visual changes (suggesting possible prolactinoma or other pituitary tumor) and symptoms of thyroid dysfunction or other chronic medical conditions. Mood disorders and other chronic psychiatric disorders may also be associated with amenorrhea. Women should also be queried about use of medications that may affect menses, in particular antipsychotic and contraceptive agents.<sup>23,24</sup> Among patients receiving antipsychotic medications, menstrual abnormalities develop in approximately 50%, and amenorrhea develops in about 12%.<sup>25</sup> Antipsychotic medications have antagonistic effects at pituitary dopamine receptors, which remove the inhibitory effect of dopamine on prolactin secretion; the resultant hyperprolactinemia then suppresses pulsatile GnRH release. Amenorrhea is also common in women using continuous combined oral contraceptive pills or depot medroxyprogesterone acetate injections.

#### *Physical Examination and Laboratory Testing*

Hypothalamic amenorrhea is ultimately a diagnosis of exclusion. The physical examination should rule out signs of hyperandrogenism (e.g.,

hirsutism and acne), which most often suggest the polycystic ovary syndrome but alternatively may indicate late-onset adrenal hyperplasia or androgen-secreting tumor, especially if signs of virilization are present (e.g., male pattern baldness, clitoromegaly, and voice change). Signs of vomiting should also be noted, including gingival abrasions, loss of dental enamel, and parotid swelling. The external gynecologic examination may reveal reddened, thin vaginal mucosa in estrogen-deficient young women. The bimanual examination should rule out a foreign body or adnexal mass; it is most critical in cases of primary amenorrhea to look for imperforate hymen, müllerian duct anomaly (with a shortened vagina and the absence of a uterus), or androgen insensitivity (blind vaginal pouch). Laboratory testing should include tests of the beta subunit of human chorionic gonadotropin, thyrotropin, and free thyroxine (to rule out both primary and central hypothyroidism), prolactin, follicle-stimulating hormone (to rule out ovarian insufficiency), and free testosterone and dehydroepiandrosterone sulfate (to rule out hyperandrogenism). It should be recognized that the results of thyroid-function tests in patients with eating disorders can resemble the pattern in those with central hypothyroidism. A complete blood count and blood chemistry panel should be considered to rule out chronic illness manifesting as amenorrhea. However, data in support of the cost-effectiveness of specific screening assessments are lacking.

Patients with hypothalamic amenorrhea characteristically have a low level of serum estradiol and low or low-to-normal levels of luteinizing hormone and follicle-stimulating hormone, whereas the gonadotropin response to GnRH stimulation is preserved. In a patient with presumed hypothalamic amenorrhea, the measurement of follicle-stimulating hormone alone generally provides adequate information to rule out ovarian insufficiency. Although estradiol assays continue to improve, such assessments can be limited by poor assay sensitivity, variation among assays, and the fact that a measurement reflects a single time point. Short-term administration of medroxyprogesterone acetate (10 mg for 10 days) may be useful in the evaluation; the onset of normal menstrual bleeding after cessation of this drug (usually within 1 to 3 days) suggests estrogen sufficiency. However, in rare cases, withdrawal bleeding occurs despite a pathologic cause of the amenorrhea, such as early ovarian insufficiency.<sup>26</sup>

Magnetic resonance imaging (MRI) of the brain is not routinely needed in patients with presumed hypothalamic amenorrhea. However, it is indicated in patients who have a history of severe or persistent headaches, persistent vomiting that is not self-induced, central hypothyroidism, hyperprolactinemia or galactorrhea, or a change in thirst, urination, or vision.

#### TREATMENT STRATEGIES

##### *Weight Gain and Exercise Reduction*

Less restrictive eating patterns with weight gain or a reduction in strenuous activity typically leads to restoration of menses. However, practical challenges can arise in convincing patients with hypothalamic amenorrhea to change long-standing behaviors. Many are elite athletes, and some participate in sports that promote leanness for optimal performance.<sup>19</sup> The American College of Sports Medicine advises that written contracts be developed between an athlete and the clinician that provide criteria for accepted weight and hemodynamic thresholds (e.g., heart rate and blood pressure) for continued training and competition.<sup>19</sup> Clinical experience suggests that a multidisciplinary approach — including the active involvement of a primary care physician (internist, pediatrician, or specialist in health issues of adolescents and young adults), nutritionist, and psychotherapist — can be helpful, although data regarding the long-term efficacy of this approach are lacking.

There is debate regarding whether a critical weight or percentage of body fat is necessary for resumption of ovulation and regular menses.<sup>27</sup> The fact that adrenal and ovarian androgens are converted to estradiol through aromatase activity within fat has suggested that there is a threshold level of body fat needed for menses to resume.<sup>28</sup> Yet data from a 2-year longitudinal study involving 100 adolescents with anorexia nervosa challenge this hypothesis.<sup>29</sup> In these girls, menses resumed at a mean standard body weight that was  $91.6 \pm 9.1\%$  of ideal body weight; within 6 months after achievement of that weight, menses resumed in 86% of the girls. However, there were no significant differences in weight, BMI, or body-fat percentage between those who had a resumption of menses by 1 year and those who did not. Of note, the weight needed for restoration of menses was 2.0 kg (4.4 lb) higher than the weight at which menses were lost. In a 1-year

follow-up study of 56 adolescents with amenorrhea, the mean BMI at menstrual resumption (which occurred in 64% of the subjects) was in the 27th percentile, and half of these subjects had a BMI between the 14th and 39th percentiles at the time of menstrual resumption.<sup>30</sup> However, subjects in whom menses did not resume had measures of weight gain and BMI that did not differ significantly from those of subjects in whom menses resumed. The majority of patients who gain weight have a resumption of menses over time. However, the clinical features that differentiate those who do and those who do not have menstrual restoration are unclear.

Data regarding the relative benefits of dietary regimens and exercise modification in adolescents and young women with hypothalamic amenorrhea are lacking. An uncontrolled study involving four athletes with amenorrhea who participated in a 20-week intervention involving diet and exercise training suggested that menstrual cycles may be restored with an increase in energy availability to more than 30 kcal per kilogram of fat-free body mass per day.<sup>31</sup> However, the study design made it impossible to determine whether the nutritional changes (vs. exercise modification or other factors) were responsible for the resumption of menses. Protein needs for athletes who are engaged in intensive exercise training may also be higher than those for age-matched control subjects (1.2 to 1.6 g per kilogram per day vs. 0.8 g per kilogram per day).<sup>19</sup> Adequate fat intake appears to be essential. In one study comparing eight female cyclers who had hypothalamic amenorrhea with eight control subjects who were matched according to age and BMI, the percentage of total calories derived from fat was 16.3% for the cyclers and 31.6% for the control subjects.<sup>32</sup> However, data regarding the effects of increased fat intake on the restoration of menses in women with hypothalamic amenorrhea are lacking.

##### *Psychosocial Approaches*

Uncontrolled observations of young women with hypothalamic amenorrhea have identified the following common features: perfectionism, a reported history of adverse childhood experiences, exposure to stressful events, a need for social approval, and altered eating attitudes.<sup>7</sup> Strategies to alleviate stress may lead to resumption of menses. In a 20-week randomized trial comparing

cognitive behavioral therapy with observation among 16 normal-weight women with hypothalamic amenorrhea (who did not report psychopathology or excessive exercise),<sup>33</sup> ovulation returned in 6 women assigned to cognitive therapy, as compared with 1 woman in the observational group. In an uncontrolled study, hypnotherapy was followed by menstrual restoration in 9 of 12 women with hypothalamic amenorrhea.<sup>34</sup> These observations require confirmation in large randomized trials.

#### *Interventions to Mitigate Bone Loss*

Most data guiding the therapeutic management of estrogen-deficient young women with amenorrhea are derived from studies involving patients with anorexia nervosa. Whereas oral contraceptive pills are commonly prescribed in practice with the goal of improving skeletal status, in several studies (including three randomized, controlled trials<sup>35-37</sup>), the provision of estrogen and progestin did not lead to a significant increase in bone density.<sup>35-38</sup> In one randomized, controlled trial, combination therapy with an oral contraceptive and subcutaneous insulin-like growth factor 1 in women with anorexia nervosa led to modest skeletal gains (a 1.8% increase in spinal bone mineral density) over a period of 9 months.<sup>39</sup> Limited data indicate that bisphosphonate treatment reduces bone turnover and increases bone density in adolescents and adults with anorexia nervosa.<sup>40,41</sup> However, given the potential risks (e.g., long-term skeletal retention of the drug and possibly teratogenic effects during pregnancy), more data are needed before the use of such drugs in this population can be endorsed. For sustained benefits with respect to bone health, nutritional rehabilitation and a decrease in strenuous activity are recommended strategies. An adequate intake of calcium (1300 mg of elemental calcium per day) and vitamin D (400 to 1000 IU per day) is recommended,<sup>19</sup> although appropriate supplementation doses are debated.

#### *Treatment for Infertility*

For women with hypothalamic amenorrhea who desire pregnancy, ovulation induction with pulsatile GnRH or injectable gonadotropins is the treatment of choice. A retrospective analysis of 30 women receiving gonadotropin therapy and 41 receiving pulsatile GnRH therapy showed ovulatory rates of 93 to 97%; GnRH therapy was

associated with a lower rate of multiple gestation than gonadotropin therapy.<sup>42</sup> Estrogen-deficient women with hypothalamic amenorrhea often have a poor response to ovulation induction with clomiphene citrate. In one study involving eight women, priming with estrogen plus progestin appeared to improve the ovulation rate after the administration of clomiphene,<sup>43</sup> although this approach requires further study. The pattern of hypogonadotropic hypogonadism is not fixed in such patients, and responses may vary, depending on weight and estrogen status. Data are needed regarding the association between weight gain or reduced exercise and the restoration of ovulation and fertility.

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#### AREAS OF UNCERTAINTY

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The pathophysiology underlying hypothalamic amenorrhea is not fully understood. Exercise reduction and nutritional rehabilitation are recommended to restore menses and improve skeletal health, but research is needed on strategies to facilitate lifestyle changes in patients with hypothalamic amenorrhea and on the long-term outcomes of these approaches.

Limited data indicate that leptin and opioid antagonists may restore ovulation in women with hypothalamic amenorrhea,<sup>14,44,45</sup> although the effects of such drugs in adolescents have not yet been studied. In a pilot study of leptin therapy in women with hypothalamic amenorrhea,<sup>14</sup> three of eight women ovulated after treatment. In two trials of naltrexone in women with hypothalamic amenorrhea, ovulation occurred in 3 of 3 women in one trial<sup>44</sup> and in 12 of 24 women in the other.<sup>45</sup> Data correlating bone-density measurements by dual-energy x-ray absorptiometry (DXA) with the risk of fracture in adolescents and young women are sparse. More research is needed to understand the benefits and risks of estrogen therapy and other treatments (e.g., dehydroepiandrosterone, insulin-like growth factor 1, and bisphosphonates) on bone mineral density, especially in adolescents who are accruing their peak bone mass.

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#### GUIDELINES

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Task forces that have been organized through the International Society for Clinical Densitometry have published guidelines for DXA screening

in adolescents and young women,<sup>46,47</sup> including the recommendation that clinicians consider obtaining baseline DXA scans in adolescents with anorexia nervosa who have amenorrhea. The American College of Sports Medicine has recommended the consideration of bone density screening, nutritional support, and strategies for stress reduction in female athletes with hypothalamic amenorrhea.<sup>19</sup>

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#### CONCLUSIONS AND RECOMMENDATIONS

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The patient in the vignette has secondary amenorrhea that is associated with an increased level of exercise and weight loss. Detailed dietary and exercise histories should be obtained, with attention to attitudes toward eating and body image, and the patient should be asked about psychosocial stressors. Basic testing should include an assessment of thyroid function, prolactin, and follicle-stimulating hormone. A thorough physical examination is needed to ensure that there are no physical stigmata of a chronic disease or self-induced vomiting, and pelvic examination should assess estrogen status and rule out abnormalities. Plain radiographs would be appropriate, given the new-onset foot pain, to look for possible stress fracture, and bone density testing is warranted, given the duration of the amenorrhea. A progestin challenge could be considered to as-

sess estrogen status. Brain MRI would not be indicated in the absence of neurologic symptoms or other evidence to suggest hypothalamic or pituitary dysfunction.

If no other cause of amenorrhea is identified, the patient should be educated regarding the effect of excessive exercise and weight loss on menstrual cycles and the risks of associated bone loss. Documentation of a stress fracture would warrant temporary cessation of or a marked reduction in exercise, but some reduction should be recommended in any case, since such a cutback in exercise and adequate caloric intake are likely to result in a resumption of menses. Consultation with a nutritionist and mental health provider should be encouraged, and nutritional intake, exercise levels, and the presence or absence of menstrual periods should be followed closely over time. An oral contraceptive pill should not be provided for the purpose of improving bone density, since several studies have indicated that this therapy does not attenuate bone loss in such patients.

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