Remarks

The absence of menses or by irregular menstrual cycles due to insufficient stimulation and/or suppression of the HPO axis is characteristic of FHA. It can be related to stress, anxiety, weight change, energy imbalance, and/or excessive exercise.

1.3 We suggest screening patients with FHA for psychological stressors (patients with FHA may be coping with stressors, and stress sensitivity has multiple determinants). (2l⊕⊕⊕○)

Evidence

Available evidence suggests that psychogenic stimuli, both external and internal, activate the HPA axis. Any psychogenic event (*e.g.,* start of college, profound grief, loss of weight) that may elicit an increase in cortisol secretion results in metabolic adaptation. Likewise, metabolic adaptations engender psychogenic concomitants. Although the blend of psychological and metabolic factors associated with FHA may vary, the final common pathway is suppression of GnRH drive (13, 17, 20, 21, 87, 101, 102). Studies have also suggested that energy imbalance sensitizes the HPO axis to psychological stress (21, 103). Both animal and human studies have shown that an actual stressor (*e.g.,* psychological stress, decreased energy availability, drive for thinness), as well as perception or anticipation of a threat, may elicit similar endocrine consequences to alter menses (104–111). Data indicate that women who exercise or are under dietary restriction develop FHA as an adaptive response to chronic metabolic energy deficiency (33, 112). The physiological process of adaptation diverts energy and other resources (*e.g.,* emotion, vigilance) to systems needed for survival (101). The HPA axis in women who exercise regularly and present with amenorrhea is activated, which helps to mobilize glucose. Furthermore, neuroendocrine adaptations in the hypothalamic–pituitary–thyroid axis minimize energy expenditure [*i.e.,* the pattern of low thyrotropin-releasing hormone, normal/low TSH, and decreased triiodothyronine (T3) and T4 indicates an increased negative feedback of thyroid hormones at the hypothalamus level and reduced thyroidal responsivity to TSH] (5, 24, 65).

There are two major hypotheses to explain the mechanism by which negative energy balance causes FHA. The metabolic fuel hypothesis posits that peripheral tissues (*e.g.,* liver, adipose tissue, pancreas, stomach, duodenum, and hindbrain) detect short-term reduced amounts of fuels available for oxidation (*e.g.,* oxidizable glucose, fatty acids, or ketone bodies) through neural or humoral afferents (with the hindbrain being the main detection site) (113–115). Subsequently, numerous hormones and neuropeptides are secreted that alter feedback sensitivity in the hindbrain. A second hypothesis (the critical body fat hypothesis) posits that a minimum amount of adipose tissue is necessary for the onset of puberty and for the preservation of reproductive function (116). These findings were not conclusively confirmed (17, 117–119) and are not mutually exclusive, as body fat is a reflection of energy stores. Adipose tissue likely participates in the pathogenesis of FHA via adipokines, such as leptin and adiponectin (120, 121). Recovery from FHA associated with CBT resulted in reduced nocturnal cortisol secretion and increased leptin and TSH without weight gain, suggesting that reducing stress corrects the neuroendocrine and metabolic signature independent of weight gain *per se* (24, 35).

1.4 Once clinicians establish the diagnosis of FHA, we suggest they provide patient education about various menstrual patterns occurring during the recovery phase. We suggest clinicians inform patients that irregular menses do not require immediate evaluation and that menstrual irregularity does not preclude conception. (Ungraded Good Practice Statement)

Evidence

Adolescents and women who are recovering from a restrictive eating disorder and/or female athletes can exhibit a larger spectrum of hypogonadotropic hypogonadism in addition to amenorrhea. Women recovering from anorexia nervosa, as well as some female athletes, may go through a stage of inadequate luteal phase (with disordered folliculogenesis and follicular dynamics), exhibiting elements of the "female athlete triad" (*i.e.,* decreased energy availability, menstrual dysfunction, and low bone density) as they modify their caloric intake and/or activity level (95).

Some women may have a mild hypogonadotropic state that persists for many years with lower gonadotropin and sex steroid concentrations than would be expected for their age. Clinically, these patients may present with a luteal phase defect phenotype (*i.e.,* long menstrual cycles with prolonged follicular phases and short luteal phases with premenstrual spotting or early arrival of menses due to reduced progesterone secretion) (95, 122). In one study of eumenorrheic runners, a larger proportion of the women had anovulatory cycles or a shortened luteal phase compared with sedentary women (99). The long-term clinical significance of these milder menstrual abnormalities, especially with respect to risk for low bone density, cardiovascular disease, and fertility, is unknown.

2.0 Evaluation

2.1 In patients with suspected FHA, we recommend obtaining a detailed personal history with a focus on diet;