Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline

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Objective: To formulate clinical practice guidelines for the diagnosis and treatment of functional hypothalamic amenorrhea (FHA).

Participants: The participants include an Endocrine Society–appointed task force of eight experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Endocrine Society committees and members and cosponsoring organizations reviewed and commented on preliminary drafts of this guideline.

Conclusions: FHA is a form of chronic anovulation, not due to identifiable organic causes, but often associated with stress, weight loss, excessive exercise, or a combination thereof. Investigations should include assessment of systemic and endocrinologic etiologies, as FHA is a diagnosis of exclusion. A multidisciplinary treatment approach is necessary, including medical, dietary, and mental health support. Medical complications include, among others, bone loss and infertility, and appropriate therapies are under debate and investigation. **(*J Clin Endocrinol Metab* 102: 1–27, 2017)**

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Abbreviations: AMH, anti-Müllerian hormone; BMD, bone mineral density; BMI, body mass index; CAH, congenital adrenal hyperplasia; CBT, cognitive behavior therapy; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DXA, dual-energy X-ray absorptiometry; E2, estradiol; FHA, functional hypothalamic amenorrhea; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal; HPO, hypothalamic–pituitary–ovarian; IGF, insulin-like growth factor; LH, luteinizing hormone; MRI, magnetic resonance imaging; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome; rPTH, recombinant parathyroid hormone 1-34; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.

Summary of Recommendations

1.0 Diagnosis, differential diagnosis, and evaluation

1.1 We suggest that clinicians only make the diagnosis of functional hypothalamic amenorrhea (FHA) after excluding the anatomic or organic pathology of amenorrhea. (Ungraded Good Practice Statement)

1.2 We suggest diagnostic evaluation for FHA in adolescents and women whose menstrual cycle interval persistently exceeds 45 days and/or those who present with amenorrhea for 3 months or more. (2|⊕⊕◯◯)

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). (2|⊕⊕⊕◯)

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)

2.0 Evaluation

2.1 In patients with suspected FHA, we recommend obtaining a detailed personal history with a focus on diet; eating disorders; exercise and athletic training; attitudes, such as perfectionism and high need for social approval; ambitions and expectations for self and others; weight fluctuations; sleep patterns; stressors; mood; menstrual pattern; fractures; and substance abuse. Clinicians should also obtain a thorough family history with attention to eating and reproductive disorders. (Ungraded Good Practice Statement)

2.2 In a patient with suspected FHA, we recommend excluding pregnancy and performing a full physical examination, including a gynecological examination (external, and in selected cases, bimanual), to evaluate the possibility of organic etiologies of amenorrhea. (1|⊕⊕⊕◯)

2.3 In adolescents and women with suspected FHA, we recommend obtaining the following screening laboratory tests: β-human chorionic gonadotropin, complete blood count, electrolytes, glucose, bicarbonate, blood urea nitrogen, creatinine, liver panel, and (when appropriate) sedimentation rate and/or C-reactive protein levels. (1|⊕⊕⊕⊕)

2.4 As part of an initial endocrine evaluation for patients with FHA, we recommend obtaining the following laboratory tests: serum thyroid-stimulating hormone (TSH), free thyroxine (T4), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and anti-Müllerian hormone (AMH). Clinicians should obtain total testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels in patients with clinical hyperandrogenism and 8 AM 17-hydroxyprogesterone levels if clinicians suspect late-onset congenital adrenal hyperplasia (CAH). (1|⊕⊕⊕⊕)

2.5 After excluding pregnancy, we suggest administering a progestin challenge in patients with FHA to induce withdrawal bleeding (as an indication of chronic estrogen exposure) and ensure the integrity of the outflow tract. (2|⊕⊕⊕◯)

2.6 We recommend a brain magnetic resonance imaging (MRI) (with pituitary cuts and contrast) in adolescents or women with presumed FHA and a history of severe or persistent headaches; persistent vomiting that is not self-induced; change in vision, thirst, or urination not attributable to other causes; lateralizing neurologic signs; and clinical signs and/or laboratory results that suggest pituitary hormone deficiency or excess. (1|⊕⊕⊕◯)

2.7 We suggest that clinicians obtain a baseline bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA) from any adolescent or woman with 6 or more months of amenorrhea, and that clinicians obtain it earlier in those patients with a history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility. (2|⊕⊕⊕◯)

2.8 In cases of primary amenorrhea, we suggest evaluating Müllerian tract anomalies (congenital or acquired). Diagnostic options include physical examination, progestin challenge test, abdominal or transvaginal ultrasound, and/or MRI, depending on the context and patient preferences. (2|⊕⊕⊕◯)

2.9 In patients with FHA and underlying polycystic ovary syndrome (PCOS), we suggest:

- a baseline BMD measurement by DXA in those with 6 or more months of amenorrhea and earlier in those with history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility (2/⊕⊕◯◯); and
- clinical monitoring for hyperresponse in those treated with exogenous gonadotropins for infertility. (2|⊕⊕◯◯)

3.0 Treatment of functional hypothalamic amenorrhea and concomitant medical conditions

3.1 We recommend that clinicians evaluate patients for inpatient treatment who have FHA and severe bradycardia, hypotension, orthostasis, and/or electrolyte imbalance. (1|⊕⊕⊕◯)

3.2 In adolescents and women with FHA, we recommend correcting the energy imbalance to improve hypothalamic–pituitary–ovarian (HPO) axis function; this often requires behavioral change. Options for improving energy balance include increased caloric

consumption, and/or improved nutrition, and/or decreased exercise activity. This often requires weight gain. (1|⊕⊕⊕◯)

3.3 In adolescents and women with FHA, we suggest psychological support, such as cognitive behavior therapy (CBT). (2|⊕⊕◯◯)

3.4 We suggest against patients with FHA using oral contraceptive pills (OCPs) for the sole purpose of regaining menses or improving BMD. (2|⊕⊕◯◯)

3.5 In patients with FHA using OCPs for contraception, we suggest educating patients regarding the fact that OCPs may mask the return of spontaneous menses and that bone loss may continue, particularly if patients maintain an energy deficit. (2|⊕⊕◯◯)

3.6 We suggest short-term use of transdermal E2 therapy with cyclic oral progestin (not oral contraceptives or ethinyl E2) in adolescents and women who have not had return of menses after a reasonable trial of nutritional, psychological, and/or modified exercise intervention. (2|⊕◯◯◯)

3.7 We suggest against using bisphosphonates, denosumab, testosterone, and leptin to improve BMD in adolescents and women with FHA. (2|⊕⊕◯◯)

3.8 In rare adult FHA cases, we suggest that short-term use of recombinant parathyroid hormone 1-34 (rPTH) is an option in the setting of delayed fracture healing and very low BMD. (2|⊕◯◯◯)

3.9 In patients with FHA wishing to conceive, after a complete fertility workup, we suggest:

- treatment with pulsatile gonadotropin-releasing hormone (GnRH) as a first line, followed by gonadatropin therapy and induction of ovulation when GnRH is not available (2|⊕◯◯◯);
- cautious use of gonadotropin therapy (2|⊕◯◯◯);
- a trial of treatment with clomiphene citrate for ovulation induction if a woman has a sufficient endogenous estrogen level (2|⊕◯◯◯);
- against the use of kisspeptin and leptin for treating infertility (2|⊕◯◯◯); and
- given that there is only a single, small study suggesting efficacy, but minimal potential for harm, clinicians can consider a trial of CBT in women with FHA who wish to conceive, as this treatment has the potential to restore ovulatory cycles and fertility without the need for medical intervention. (2|⊕⊕◯◯)

3.10 We suggest that clinicians should only induce ovulation in women with FHA that have a body mass index (BMI) of at least 18.5 kg/m^2 and only after attempts to normalize energy balance, due to the increased risk for fetal loss, small-for-gestational-age babies, preterm labor, and delivery by Cesarean section for extreme low weight. (2|⊕⊕◯◯)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of the Endocrine Society deemed an enhanced understanding and management of FHA to be a priority area in need of practice guidelines and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group, an international committee with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of a recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that the task force considered in making the recommendation; in some instances, there are remarks, a section in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their values and preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of FHA treatment. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised, and thus considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles; one should not consider these statements as graded recommendations (3).

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The Clinical Guidelines Subcommittee reviews all conflicts of interest before the Society's Council approves the members to participate on the task force, and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and majority of these participants must be without any conflicts of interest. The Clinical Guidelines Subcommittee and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.,* stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Reviews

The task force developed *a priori* protocols for two systematic reviews to evaluate the effect of hormonal therapy and bisphosphonates in preventing bone loss in patients with FHA. After a comprehensive search of several databases for original controlled and non-controlled studies, nine were eligible (280 patients that received different hormonal therapies, none with bisphosphonate). None of the studies reported on fractures. Random-effects meta-analysis showed a statistically significant increase in BMD of the lumbar spine in patients receiving hormonal therapy compared with patients receiving control and no significant effect on BMD of the femoral neck. The quality of this evidence was low due to the high risk of bias, imprecision (very small sample size), and indirectness (for example, BMD is a surrogate outcome).

Background

FHA is a form of chronic anovulation that is not due to identifiable organic causes (4). The term "functional" implies that correction or amelioration of causal behavioral factors will restore ovulatory ovarian function. The proximate cause of the anovulation is a functional reduction in GnRH drive, which manifests as reduced LH pulse frequency (5). Reduced GnRH drive results in LH and FSH levels insufficient to maintain full folliculogenesis and ovulatory ovarian function. Providing exogenous GnRH or gonadotropins restores folliculogenesis (6, 7). Klinefelter *et al.* (8) originally used the term "hypothalamic hypoestrogenism" to describe this condition. Additionally, there may be a genetic predisposition for the development of FHA, such as heterozygosity for congenital hypogonadotropic hypogonadism (9).

The neuromodulatory signals that alter GnRH function are many and include both inhibitory and stimulatory inputs that align GnRH function with the internal and external milieu (Fig. 1) (10). There is a tight link between activation of the hypothalamic–pituitary–adrenal (HPA) axis and reduction in GnRH drive in those with FHA, including hypercortisolemia in both amenorrheic athletes and nonathletes (5, 11–16). Acute nutritional deprivation activates the HPA axis and reduces LH pulsatility (17). Given the energetic expense of reproduction, metabolic factors play a fundamental role in gating reproductive function. We commonly see this phenomenon in female athletes who may expend more calories through exercise than they consume in their diets. Military personnel who sustain grueling training regimens, or may have experienced traumatic brain injury, represent another example (18). Psychosocial influences, including externally imposed stressors and stressful attitudes toward commonplace conditions (19–21), also activate the HPA axis and alter the neuromodulatory cascade that modulates GnRH drive (22). Furthermore, exogenous endocrine-disrupting chemicals, such as bisphenol A and some polychlorinated biphenyls, may affect neuronal GnRH activity and kisspeptin systems through modulation of GnRH gene transcription and/or effects as an estrogen agonist or antagonist (23). Reversing amenorrhea by behavioral modifications (12) is associated with a reduction in cortisol levels (24) and resumption of ovarian function in some women with FHA (25). Kisspeptin is the G protein–coupled receptor ligand for its receptor, GPR54. Kisspeptin–GPR54 signaling plays a critical role in the initiation of GnRH secretion during puberty. Kisspeptin/neurokinin B/dynorphin neurons within the arcuate nucleus secrete kisspeptin, which stimulates GnRH neurons (26). Kisspeptin/neurokinin B/dynorphin neurons may be the final common pathway that integrates the other neuromodulatory signaling systems that are linked to reduced GnRH pulsatility (27) (Fig. 1).

Stressors, regardless of type, activate the HPA axis and autonomic nervous system, resulting in a constellation of neuroendocrine alterations, including hypothalamic hypothyroidism that conserves and diverts energetic expenditure (5, 11). The "stress system" in the brain includes corticotropin-releasing hormone neurons in the hypothalamic paraventricular nuclei, limbic lobe inputs to the paraventricular nucleus, other brain areas, the central sympathetic nervous system, and the locus ceruleus/norepinephrine system in the brainstem (28).

Many of the health consequences linked to FHA are likely due to the combined alterations in metabolism, neuroendocrine function, and anovulation classically associated with FHA (24). Available data suggest that appropriate behavioral interventions have the potential to foster ovarian, neuroendocrine, and metabolic recovery. Studies have demonstrated a higher prevalence of disordered eating patterns and food attitudes in females with FHA compared with controls (29–32). Studies reported that females with FHA had higher scores on scales of eating behavior, indicating a higher occurrence of dieting, bulimia, food preoccupation, and dietary

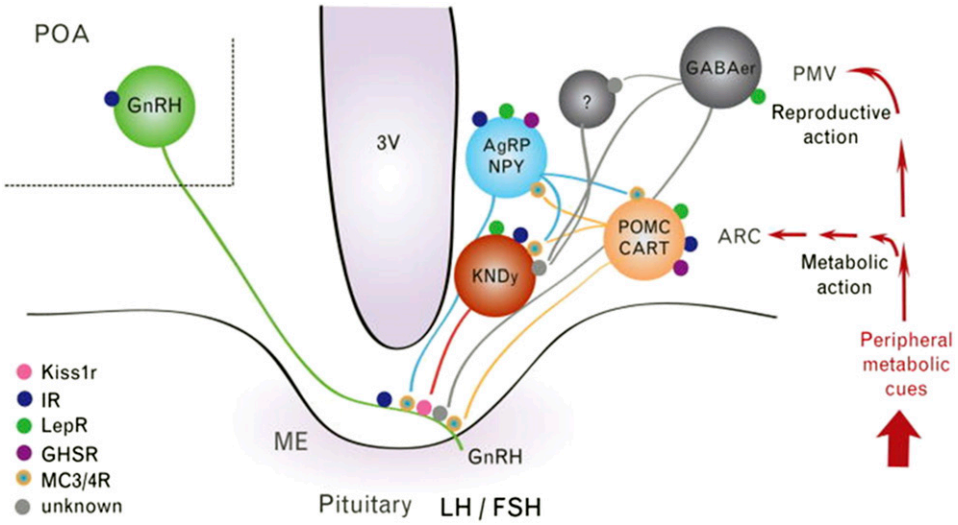

Figure 1. Schematic representation of neural interactions between metabolic and reproductive functions depicting likely sites of action of leptin, insulin, and ghrelin to control the release of gonadotropin-releasing hormone. Abbreviations: 3V, third ventricle; AgRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; GABA, γ-aminobutyric acid; GHSR, growth hormone secretagogue receptor; IR, insulin receptor; Kiss1r, kisspeptin receptor; KNDy, kisspeptin/neurokinin B/dynorphin; LepR, leptin receptor; MC3r, melanocortin receptor 3; MC4r, melanocortin receptor 4; ME, median eminence; NPY, neuropeptide Y; PMV, ventral premammillary nucleus; POA, preoptic area; POMC, pro-opiomelanocortin. [Reproduced from Navarro VM, Kaiser UB (10). Reproduced with permission of Lippincott, Williams & Wilkins].

restraint (33, 34). These findings build on an earlier study that showed altered diets in women runners (15). Additionally, women with FHA had higher measured serum 24-hour cortisol concentrations when compared with controls, similar to women with eating disorders (16, 33). A study using frequent nighttime sampling has also reported higher cortisol levels in adolescent and young adult athletes with amenorrhea, compared with eumenorrheic athletes and nonathletes (14). Preclinical evidence in primates suggests a synergy between metabolic and psychosocial stressors, which are additive and contribute to the reproductive dysfunction (22). Monkeys, similar to women, vary in their sensitivity to reproductive disruption when exposed to metabolic and psychosocial stressors. Researchers refer to monkeys that respond adversely to these stressors as "stress-sensitive," a term that could likely apply to the analogous group of women (35, 36). One study reported dysfunction of the serotonin system in stress-sensitive monkeys, and that administering the serotonin reuptake inhibitor (citalopram) reversed the effect, suggesting that the neurobiology is fundamentally different (37). Other studies have reported that socially subordinate monkeys develop reproductive dysfunction, which includes anovulation and luteal phase defects (shortened phase after ovulation), which can reflect underlying progesterone deficiency (36, 38–40).

The most significant acute risks of FHA include delayed puberty, amenorrhea, infertility, and long-term health consequences of hypoestrogenism. Generally, the infertility is due to anovulation, although patients might also experience prolongation of the follicular phase of the cycle or inadequate luteal phases (41, 42). Amenorrhea may be prolonged and associated risks may differ according to its etiology. Lack of menses may accompany weight loss from restrictive eating, and in some cases, indicates an eating disorder. Typically, a longer duration of insult will result in a longer time to reversal and return of normal menses. The most significant chronic risk is bone loss or inability to obtain peak bone mass (43–47). Women who have exercise-induced amenorrhea, especially those engaged in activities associated with restrictive eating habits and low weight, may have decreased bone density, in spite of the bone-building effect of weight-bearing exercise (48, 49). Some patients with FHA develop osteoporosis and fractures, particularly stress fractures (50, 51). Repeated stress fractures may occur in up to 30% of ballet dancers (50, 52) and also in other athletic activities where there is a high level of exercise (53). Repeated fractures can also be a sign of poor eating habits (54). The etiology is partly due to low bone mass, but researchers also think that it is related to a low-energy state, which leads to low bone formation and low bone turnover, favoring a resorptive state. This, in turn, impairs the normal mechanisms, which repair bone and injuries due to overuse. The uncoupling of bone turnover (including suppressed bone formation and increased resorption) is unique, and although it can be reproduced by short-term starvation in normal exercising women, it is not typical of estrogen loss but, rather, nutritional deprivation (55–57). Limited data support risks of fetal loss and small-for-gestation babies as possible consequences of FHA, particularly when

associated with eating disorders. Women with anorexia nervosa are also at risk for preterm labor and delivery by Cesarean section (58–60). Finally, although it is not known whether prolonged hypoestrogenism is associated with cardiovascular risk in premenopausal women, several studies using premenopausal monkeys have linked socially induced reproductive suppression to exacerbated coronary artery atherosclerosis (61, 62).

1.0 Diagnosis, differential diagnosis, and evaluation

1.1 We suggest that clinicians only make the diagnosis of FHA after excluding the anatomic or organic pathology of amenorrhea. (Ungraded Good Practice Statement)

Evidence

Clinicians can use the menstrual period in adolescent girls to recognize estrogen status and identify underlying problems (53, 63, 64). Absent or irregular menses and estrogen deficiency due to insufficient stimulation or suppression of the HPO axis in the absence of anatomic or organic pathology characterizes FHA. In this context, we use the term "organic" for those cases of amenorrhea with inappropriately low gonadotropin levels where a clear pathologic etiology exists (these might include cases where gonadotropin levels are within the laboratory reference range). We must consider a broad differential diagnosis in these cases to make certain that we have excluded underlying etiologies that may be manifesting as amenorrhea (Table 1) (65–69). Other than pregnancy, FHA and PCOS are the most common causes of secondary amenorrhea (65, 70).

Overall, we recognize three main underlying causes of FHA: weight loss, and/or vigorous exercise, and/or stress (5, 20, 21, 65, 71). These distinctions allow for the inclusion of underweight and normal-weight women and acknowledge that the etiology may vary and represent a combination of factors. Regardless of the trigger, FHA is characterized by abnormalities in GnRH secretion or dynamics (4, 33, 72). An energy deficit (which can occur independent of changes in body weight) appears to be the critical factor in both the weight loss and exercise-induced forms of FHA. In 2003, Loucks and Thuma (17) set the threshold for energy availability at 30 kcal/kg (in an acute setting), below which LH pulsatility is disrupted (73). Williams *et al.* (74) estimated that experimental reduction of energy by 470 and 810 kcal per day led to an increased frequency of menstrual disturbance. We need more studies to determine the average threshold below which women who exercise or have low dietary intake are at risk for developing menstrual disturbances. It is possible that energy thresholds vary among and

Table 1. Potential Etiologies of Amenorrhea

Congenital malformation
- Septo-optic dysplasia
- Holoprosencephaly
- Encephalocele

Constitutional delay

Genetic conditions
- Congenital deficiency of hypothalamic or pituitary transcription factors (gonadotropin deficiency)
- Single-gene mutations (hypogonadotropic hypogonadism)

Hyperprolactinemia

Pituitary gland or stalk damage
- Tumors and cysts [hypothalamic or pituitary tumor (hormone-secreting), craniopharyngioma, Rathke cleft cyst, other cysts, and tumors]
- Infiltrative disorders (germinoma, autoimmune hypophysitis, sarcoidosis, hemochromatosis, tuberculosis, Langerhans cell histiocytosis, IgG4-related hypophysitis)
- Irradiation
- Infarction [apoplexy in pre-existing pituitary tumors, or following postpartum hemorrhage (Sheehan syndrome)]
- Surgery
- Trauma

Others
- Eating disorders
- Competitive athletics
- Chronic disease
- Mood disorders
- Stress or psychiatric illness
- Drugs

Thyroid
- Hypothyroidism or hyperthyroidism

Adrenals
- Congenital adrenal hyperplasia (select types)
- Cushing syndrome
- Addison disease (adrenal insufficiency)
- Tumor (androgen-secreting)

Ovaries
- Associated with high levels of gonadotropins
  - Gonadal agenesis or dysgenesis (in the setting of Turner syndrome/other)
  - Ovarian insufficiency
  - Autoimmune oophoritis
  - Irradiation or surgery
- Not associated with high levels of gonadotropins
  - Polycystic ovary syndrome
  - Tumor (estrogen- or androgen-secreting)

Uterus (eugonadism)
- Müllerian anomalies (obstructive outflow anomalies)
- Asherman syndrome
- Synechiae (integral to Asherman syndrome)
- Pregnancy
- Infectious (*e.g.,* tuberculous endometritis)
- Agenesis (uterine or cervical)

Vagina (eugonadism)
- Agenesis
- Transverse septum

Hymen (eugonadism)
- Imperforate

within individuals, and that growing adolescents may require even more available energy than older women for normal HPO axis function.

Many studies have reported hormonal alterations among amenorrheic hyperexercisers compared with eumenorrheic hyperexercisers and nonexercisers, including: higher cortisol and ghrelin and lower leptin secretion accompanying lower LH secretion (14, 72, 75); a blunted elevation in FSH during the luteal–follicular transition, which may predispose to luteal phase defects (*i.e.,* luteal phase deficiency in progesterone secretion) (76); and abnormalities in peptide YY and other adipokines (Fig. 1) (77, 78). These hormonal changes occur as a consequence of low energy availability and can directly impact the HPO axis, thus disrupting menstrual function.

In adolescents or women with FHA manifesting an energy deficit, there is a spectrum of presentations and/or diseases. The spectrum ranges from those who inadvertently or knowingly consume insufficient calories to match their caloric expenditure to those who have eating disorders and are severely undernourished. These adolescents or women can thus range from normal-weight to severely underweight. Similarly, there is a spectrum of menstrual status that includes ovulatory eumenorrhea, subclinical menstrual dysfunction (luteal phase defects and anovulatory eumenorrhea), and amenorrhea. Among these young women, bone density ranges from normal to low. A higher prevalence rate of exercise-induced amenorrhea may occur in those sports and activities in which leanness may confer an advantage (*e.g.,* gymnastics, cheerleading, figure skating, running) (65, 79–81). When weight is near normal, amenorrhea may reverse during intervals when training is decreased or absent, suggesting that the energy demands of training cause the dysfunction (82, 83). The severity of the menstrual dysfunction has been shown to increase in proportion to indices of energy conservation in exercising women (84). One study suggested that increasing energy to >30 kcal/kg of fat free mass per day may reverse the amenorrhea, but more data are needed to confirm this finding (85). Another report on exercising women showed a reversal of amenorrhea in three of four amenorrheic athletes with nutritional intervention (86). Of note, some young women do not resume menses after a nutritional intervention, highlighting the underlying psychological issues that may be at play. Mood disorders and chronic diseases may be linked to amenorrhea, as associated behaviors (*e.g.,* hyperexercise, restricting eating) may reflect underlying obsessions and anxiety (20, 21, 87). Although subjects may initiate the behaviors to reduce stress, the behaviors often function as stress amplifiers. Thus, a psychological assessment to exclude or verify a mental disorder is critical (88). In the case of a DSM-5 diagnosis, we recommend referral to appropriate psychiatric care. In particular, it is important to determine the presence of modifiable Axis I (mood) disorders as contrasted with less easily modified Axis II (personality) disorders.

It is important to recognize that medications such as antipsychotics (typical and atypical), certain antidepressants, contraceptive agents, and opioids commonly alter menses (89, 90), and we should not confuse the consequent amenorrhea or irregular menses with FHA. In a study of 50 patients on antipsychotic medications, 90% reported eumenorrhea prior to the initiation of their treatment, whereas 54% and 12% reported menstrual abnormalities and amenorrhea, respectively, during antipsychotic usage (90). This is due to their antagonistic effects at pituitary dopamine receptors, which lessen the inhibitory effect of dopamine on prolactin secretion. Resultant hyperprolactinemia then suppresses pulsatile GnRH release. Continuous progesterone use, combined OCPs (as continuous extended preparations), depot medroxyprogesterone acetate injections, and long-term use of progesterone-releasing intrauterine devices can result in amenorrhea (91–93).

1.2 We suggest diagnostic evaluation for FHA in adolescents and women whose menstrual cycle interval persistently exceeds 45 days and/or those who present with amenorrhea for 3 months or more. (2l⊕⊕○○)

Evidence

Adolescents or young women with FHA typically report amenorrhea for 6 months or longer (35, 65, 94–96). In adolescents, this condition may be difficult to differentiate from delayed maturation of the HPO axis during the initial postmenarchal years. However, several reports indicate that menstrual cycles in adolescents typically do not exceed 45 days, even during the first postmenarchal year (71, 97, 98). Athletes may report varying durations of amenorrhea corresponding with intervals of intense physical activity followed by intervals of irregular menstrual cycles or eumenorrhea after training season ends (82, 83). Of note, FHA is at the extreme end of functional hypothalamic hypogonadism, which includes anovulatory eumenorrhea and eumenorrhea with luteal phase defects, both which may be associated with infertility (99). Women with functional hypothalamic hypogonadism may thus also present with eumenorrhea and infertility rather than amenorrhea. Lastly, it is noteworthy that as many as half of patients with PCOS with a nonhyperandrogenic PCOS phenotype (*i.e.,* oligomenorrhea and polycystic ovarian morphology on ultrasound) may have FHA (100).

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;

eating disorders; exercise and athletic training; attitudes, such as perfectionism and high need for social approval; ambitions and expectations for self and others; weight fluctuations; sleep patterns; stressors; mood; menstrual pattern; fractures; and substance abuse. Clinicians should also obtain a thorough family history with attention to eating and reproductive disorders. (Ungraded Good Practice Statement)

Evidence

In patients with suspected FHA, it is imperative to elicit a history of galactorrhea, severe or persistent headache, nausea, vomiting, or changes in vision, thirst, or urination (both volume and frequency), suggesting the possibility of a prolactinoma or other pituitary or intracranial tumor. Clinicians should also obtain a history of symptoms suggesting thyroid dysfunction (hypothyroidism or hyperthyroidism), symptoms suggesting androgen excess and PCOS, or those consistent with other chronic health conditions (123–125). In patients with primary amenorrhea, anosmia or hyposmia can indicate Kallmann syndrome, which is associated with a failure of GnRH neurons to migrate from the olfactory placode to the hypothalamus. Anxiety, depression, and chronic diseases may also be associated with amenorrhea, and clinicians should look for signs and symptoms of each of these conditions.

Clinicians should ask patients about recent exercise and dietary habits (and potential changes therein), including a history of binging and purging, current or recent weight changes, and stressors (126). A short, reliable tool (that corresponds to the patient's native language) can help clinicians better understand eating disordered cognitions and behaviors (127). Clinicians should also consider energy availability, which is defined as the energy remaining for normal body functioning after subtracting exercise energy expenditure from the energy ingested. There is no clear exercise threshold that leads to an energy deficit and eventual amenorrhea. Furthermore, some female athletes have energy deficits from increasing exercise energy expenditure more than energy intake, and others have energy deficits simply from reducing energy intake (45, 51, 64). Additionally, multiple seemingly insignificant stressors may be more disruptive to reproductive function than an easily identified stressor (22).

Medications, including antipsychotics, antidepressants, contraceptive agents, and opioids, can alter menses, as discussed (89, 90). Chronic illicit drug use is often a marker of stress and undernutrition. A patient may require a formal psychiatric evaluation, as conditions associated with inappropriate HPA axis activation can suppress GnRH drive, which might require management with medication.

Clinicians should obtain a full family history, including queries regarding eating disorders and/or reproductive endocrine issues among family members (65). Clinicians should ask about miscarriages and obstetrical complications, which are more common in women with a history of restrictive eating disorders (128). Many endocrine conditions are familial, which may affect age of menarche and menstrual function.

2.2 In a patient with suspected FHA, we recommend excluding pregnancy and performing a full physical examination, including a gynecological examination (external, and in selected cases, bimanual), to evaluate the possibility of organic etiologies of amenorrhea. (1|⊕⊕⊕◯)

Evidence

A full physical examination, including weight, height, and an external gynecologic and bimanual examination, enables a clinician to consider the broad differential diagnosis for adolescents and young women with FHA (65, 70). This should include evaluating fundi and visual fields (to rule out papilledema or visual field deficits) and examining for galactorrhea, thyromegaly, hirsutism, acne, or clitoromegaly. Lateralizing neurologic signs might indicate intracranial pathology. In addition to weight loss, FHA also manifests symptoms such as bradycardia, mottled, cool extremities, and dermal manifestations of hypercarotenemia (129). Signs of androgen excess (*e.g.*, acne, hirsutism, male pattern alopecia, clitoromegaly) and hyperinsulinism (*e.g.*, acanthosis nigricans and skin tags) should raise concerns of PCOS or other causes of androgen excess (*e.g.*, nonclassic CAH and virilizing ovarian and adrenal tumors) (130). Occasionally, young women with severe hyperandrogenism will present with amenorrhea, reflecting the atrophic effect of a sustained androgen load on the endometrium. The external gynecologic examination may reveal reddened, thin vaginal mucosa in estrogen-deficient young women, and a bluish bulge in patients with an imperforate hymen. The bimanual examination can be helpful in some cases, such as to rule out the presence of an adnexal mass. It is most critical in cases of primary amenorrhea, to evaluate for imperforate hymen, Müllerian anomaly (with a shortened vagina and absent or rudimentary uterus), or androgen insensitivity (blind vaginal pouch) (123–125). Depending on the skills of the clinician and the preference/cooperation of the patient, patients with amenorrhea (and some young adolescents) might consider a transabdominal or transvaginal pelvic sonogram on initial presentation instead of the bimanual examination.

2.3 In adolescents and women with suspected FHA, we recommend obtaining the following screening laboratory

tests: β-human chorionic gonadotropin, complete blood count, electrolytes, glucose, bicarbonate, blood urea nitrogen, creatinine, liver panel, and (when appropriate) sedimentation rate and/or C-reactive protein levels. (1|⊕⊕⊕⊕)

Evidence

General laboratory testing, beginning with a β-human chorionic gonadotropin to rule out pregnancy, initiates a comprehensive workup for the adolescent or young woman with FHA. Clinicians should obtain a complete blood count, chemistry panel, liver panel, sedimentation rate, and/or C-reactive protein level in those suspected to have a chronic illness manifesting as hypogonadism. An elevated random or fasting glucose level should prompt clinicians to measure hemoglobin A1C. A high sedimentation rate and/or C-reactive protein level suggests a chronic inflammatory condition. Studies have shown that liver function tests are altered in adolescents and young women with extreme energy restrictions (131–133). However, data to support the cost-effectiveness of specific screening assessments are lacking (65).

2.4 As part of an initial endocrine evaluation for patients with FHA, we recommend obtaining the following laboratory tests: serum TSH, free T4, prolactin, LH, FSH, E2, and AMH. Clinicians should obtain total testosterone and DHEA-S levels in patients with clinical hyperandrogenism and 8 AM 17-hydroxyprogesterone levels if clinicians suspect late-onset CAH. (1|⊕⊕⊕⊕)

Evidence

If properly interpreted, a panel that includes TSH, free T4, prolactin, FSH, E2, and total testosterone detects the most important causes of amenorrhea. The pattern of hormone levels is more critical than absolute values. Patients with FHA have characteristically low or low normal LH, normal FSH concentrations (which are usually higher than LH concentrations), E2 <50 pg/mL, and progesterone <1 ng/mL; the acute gonadotropin response to GnRH stimulation is preserved (defined as a twofold to threefold rise in LH and FSH compared with baseline levels). E2 measurements are typically limited by the fact that a measurement reflects a single time point, and no single E2 value can confirm a diagnosis of FHA. However, in patients whose E2 is persistently <20 pg/mL, the response to GnRH is the only feature that may differentiate FHA from hypogonadotropic hypogonadism. With the latter diagnosis, the acute LH response would be low, but normalizes with prolonged pulsatile GnRH therapy. For E2, clinicians should follow Endocrine Society guidelines to assure assay validity and reliability (134). In FHA, thyroid function is similar to that seen with any chronic illness, that is, TSH and free T4 levels in the lower range of normal, which generally reverse to normal with weight gain and psychological recovery (5, 24, 134). Testosterone will be in the lower range of normal, and prolactin will be in the low normal range (65).

In the absence of signs of androgen excess, measuring FSH, LH, prolactin, TSH, and free T4 will generally provide sufficient information to rule out organic causes of amenorrhea or irregular menstrual cycles, including ovarian insufficiency, hyperprolactinemia, and thyroid dysfunction (primary). Elevated FSH and LH levels with low E2 (<20 pg/mL) and progesterone (<1 ng/mL) indicate low or absent ovarian reserve consistent with complete or impending ovarian insufficiency. In contrast, high FSH and LH levels with E2 >150 pg/mL and progesterone <2 ng/mL indicate the midcycle gonadotropin surge. In FHA, LH and FSH are often normal, a confusing point to clinicians, as E2 levels are low and LH/FSH ratios may be elevated when a patient has underlying PCOS. Very low and often undetectable LH and FSH levels suggest organic hypothalamic amenorrhea due to genetic mutations affecting GnRH ontogeny and function or central causes, such as pituitary, hypothalamic, or other brain tumors, and infiltrative lesions (Table 2). Evaluating basal pituitary hormones is usually sufficient to establish hypopituitarism, and pituitary stimulation tests often do not determine the causes of the pituitary hypofunction.

Assessing thyroid function and prolactin levels is important in adolescents and women with FHA (65). Food, sleep, exercise, coitus, nipple stimulation, breast examination, lactation, and many medications can elevate prolactin concentrations. If a patient has more profound hyperprolactinemia (serum prolactin >100 ng/mL), she will require additional evaluation that is beyond the scope of this guideline. If TSH is low, one should consider a diagnostic assessment for thyrotoxicosis, especially if the free T4 is high. Similarly, if TSH is high, and free T4 is low or in the lower range of normal, then clinicians must consider subclinical hypothyroidism or hypothyroidism. Conversely, a normal or minimally elevated TSH with a low free T4 may indicate central hypothyroidism.

In the workup for hyperandrogenism, familiarity with local reference ranges is important, as assays are not standardized across laboratories. Clinicians should obtain total or free testosterone levels (depending on assay reliability and noting that the former is usually more accurate) (135). Clinicians should also consider measuring serum DHEA-S to rule out adrenal etiologies (136). Some experts consider an elevated free testosterone level (measuring both total and free testosterone using a gold standard assay) the most useful indicator of PCOS

Table 2. Common Causes of Anovulation and Accompanying Laboratory Patterns

	LH (IU/L)	FSH (IU/L)	LH/FSH	E2 (pg/mL)	P4 (ng/mL)	AMH (ng/mL)	PRL (ng/mL)	TSH (μU/mL)	T4 (μg/dL)	DHEA-S (μg/dL)	17OHP (ng/dL)	T (ng/dL)
Functional hypothalamic anovulation	<10	<10	~1	<50	<1	>1	Low nl	Low nl	Low nl	nl	nl	Low nl
Ovarian insufficiency menopause	>15	>15	FSH > LH	<50	<1	<0.5	nl	nl or ↑	nl or ↓	nl	nl	Low nl
PCOS	<15	<10	LH > FSH	<50	<1	nl or ↑	High nl	nl	nl	High nl	nl	High nl or slight↑
Nonclassical CAH	<15	<10	LH > FSH	<50	≤1	nl	nl	nl	nl	High nl	↑	↑
Hyperprolactinemia	<10	<10	LH < FSH	<50	<1	nl	↑	nl or ↑	nl	nl or slight ↑	nl	nl

Abbreviations: 17OHP, 17-hydroxyprogesterone; nl, normal; P4, progesterone; PRL, prolactin; T, testosterone.

(137). However, defining an absolute level that is diagnostic of PCOS or other causes of hyperandrogenism is difficult; familiarity with local assays is paramount (138). Levels of adrenal androgens tend to be higher in normal-weight compared with overweight women with PCOS (139). A serum AMH concentration is an indicator of ovarian reserve (140, 141) and can be an additional helpful assessment measure in women with PCOS (142). In FHA, gonadotropins will be lower than expected for PCOS. Similarly, in a patient with primary ovarian insufficiency, the diagnosis could be delayed because hypothalamic amenorrhea attenuates gonadotropin secretion.

If the patient has signs of virilization and/or substantial elevations in DHEA-S and/or testosterone (free or total), an 8 AM 17-hydroxyprogesterone level can serve as an initial screen for nonclassic CAH, although a high-dose ACTH stimulation test may be necessary to confirm the diagnosis. Clinicians should also consider this type of morning testing in patients at risk based on ethnicity or family history (143). High DHEA-S levels in concentrations that far exceed the normal range (*e.g.,* DHEA-S >600 μg/dL) might indicate an adrenal tumor (144). Some patients with poorly differentiated adrenal tumors may have higher circulating levels of DHEA than DHEA-S (145).

If clinicians suspect Cushing syndrome, a 24-hour urinary free cortisol, late-night salivary cortisol, or a 1-mg overnight dexamethasone suppression test are reasonable screening tests. If hypercortisolism is present, clinicians should obtain one additional positive test to confirm the diagnosis (146). When the cause of FHA is stress, the increase in cortisol secretion is less than that seen with Cushing syndrome, and the circadian pattern (although amplified) is preserved (5). Thus, increases in cortisol concentrations compared with controls are greatest overnight and in the early morning hours, but are typically still within the normal range. Studies have variably reported an increase in basal (147) or pulsatile (14) cortisol secretion in patients with FHA compared with controls, depending on the method researchers used to assess cortisol secretory dynamics. Rarely, secondary adrenal insufficiency presents as fatigue and anovulation, and it may require an ACTH stimulation test for diagnosis. Acromegaly may present with amenorrhea or irregular menstrual cycles, along with an elevation in growth hormone, insulin-like growth factor (IGF)-I, and (occasionally) prolactin concentrations (148). Poorly controlled diabetes may present as oligomenorrhea or amenorrhea from reduced GnRH drive and is diagnosed with an elevated hemoglobin A1C level (149).

IGF-I, a nutrition-dependent factor that stimulates osteoblast function and bone formation, can be another useful factor to measure, especially in cases of FHA with a low bone mass (150, 151). In those patients with overlapping FHA and anorexia nervosa, there may be relative GH resistance—a pattern that is common in the setting of malnutrition, associated with metabolic bone alterations, and that shows improvement with nutritional rehabilitation (152). Similarly, studies have shown low DHEA-S levels in adolescents and young women with FHA in the setting of anorexia nervosa, despite the presence of hypercortisolemia and adequate ACTH (153–155). The actions of DHEA may be mediated through IGF-I (156). Thus, this hormonal deficiency may further mediate low concentrations of IGF-I.

2.5 After excluding pregnancy, we suggest administering a progestin challenge in patients with FHA to induce withdrawal bleeding (as an indication of chronic estrogen exposure) and ensure the integrity of the outflow tract. (2|⊕⊕⊕○)

Evidence

Absence of withdrawal bleeding after a course of progestin may indicate outflow tract obstruction or low endometrial estrogen exposure (157, 158). The response to a progestin challenge can provide additional information about a patient's estrogen status, especially in

those cases in which there is overlay between FHA and PCOS. Options include medroxyprogesterone acetate (5 to 10 mg/d for 5 to 10 days), norethindrone acetate (5 mg/d for 5 to 10 days), or micronized progesterone (200 to 300 mg/d for 10 days).

Remarks

Progestins are not well tolerated by some patients. Therefore, some clinicians may start with a shorter, 5-day course and repeat in a few weeks if there is no withdrawal bleed. Follow-up with a pelvic ultrasound may be necessary if the patient does not have a withdrawal bleed and is useful in determining endometrial thickness and Müllerian tract integrity. The latter may require confirmation with MRI.

2.6 We recommend a brain MRI (with pituitary cuts and contrast) in adolescents or women with presumed FHA and a history of severe or persistent headaches; persistent vomiting that is not self-induced; change in vision, thirst, or urination not attributable to other causes; lateralizing neurologic signs; and clinical signs and/or laboratory results that suggest pituitary hormone deficiency or excess. (1l⊕⊕⊕◯)

Evidence

In the absence of the clinical features listed above, there are limited studies to inform the need for obtaining a pituitary MRI, and the number of cases where MRI provides valuable additional information is small. However, if there are no clear indications or other explanations for the amenorrhea (such as anorexia nervosa or history of excessive exercise, weight loss, or an eating disorder), clinicians should consider ordering a brain MRI. Empty sella syndrome can also be present as an underlying diagnosis (159). Of note, starvation-induced patterns of thyroid function tests can resemble central hypothyroidism in patients with eating disorders (65, 70). A history of significant head trauma should raise suspicions of pituitary stalk damage and associated pituitary hormone deficiencies.

2.7 We suggest that clinicians obtain a baseline BMD measurement by DXA from any adolescent or woman with 6 or more months of amenorrhea, and that clinicians obtain it earlier in those patients with a history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility. (2l⊕⊕⊕◯)

Evidence

The goal of bone densitometry is to identify individuals at risk for skeletal fragility, determine the magnitude of compromised bone mass in patients with established bone fragility, and guide and monitor treatment (160). Clinicians should more attentively monitor nutritional intake and a patient's skeletal status if a baseline BMD *Z*-score is −2.0 or less at any skeletal site (160). For athletes involved in weight-bearing sports, the American College of Sports Medicine recommends increased surveillance when the BMD *Z*-score is −1.0 or less, considering that an athlete should have a higher than average BMD from ongoing continuous skeletal loading (45). Although current scanners typically generate both *Z*-scores and T-scores, clinicians should only consider a BMD *Z*-score in adolescents or premenopausal women. The *Z*-score compares the BMD measure to age-, sex-, and often race- or ethnicity-matched controls. DXA is the most commonly used densitometric technique for adolescents and adults throughout the world because of its speed, precision, safety, low cost, and widespread availability. Studies have used total body BMD measurements to assess many chronic conditions, including eating disorders (*e.g.*, anorexia nervosa) (44, 150, 161), as low bone density measures of the total body predict fracture risk and also provide an assessment of body composition (160). However, the spine (a trabecular-rich site) is the most common site of low bone density in adolescents and young women with amenorrhea and also predicts fracture risk; it is therefore an important site to monitor (150, 162–166). In older adolescents (above age 15 years) and women with FHA, measuring hip bone density affords additional information about weight-bearing cortical bone and can be useful to monitor bone density longitudinally (160). Two studies have noted deficits in bone geometry and strength at the hip in older adolescents with anorexia nervosa (156, 167), and another study noted deficits in adolescent and young adult athletes (168). Therefore, hip BMD measures can provide important information in the older adolescent or young woman. After 6 months of amenorrhea, clinicians should consider a baseline DXA evaluation in any adolescent or woman with FHA (45, 53, 64, 65).

Restrictive eating disorders, such as anorexia nervosa, represent the extreme end of the spectrum of energy availability. Affected patients exhibit skeletal losses and/or lack of bone accretion (50, 52, 169–172) and are known to be at high risk for fracture (173, 174) compared with normal-weight peers. Although we know that weight-bearing exercise is beneficial for healthy youth, with beneficial effects on bone accrual and peak bone mass (175, 176), we can see a lack of skeletal gains and even frank bone loss in both female athletes with eating disorders and low weight and female athletes with normal-weight amenorrhea during adolescence (163, 165, 166, 169, 171, 177). In addition to deficits in areal bone density (as assessed by DXA), studies have reported deficits in volumetric bone density, abnormal bone

microarchitecture, and lower strength estimates in patients with eating disorders (167, 174, 178, 179) and in adolescent and young adult amenorrheic athletes (165, 166, 180).

Young women with eating disorders are known to be at a sevenfold higher risk of fracture (181), and stress fractures are a recurrent problem among female athletes with amenorrhea (45, 50, 182). Recent work has indicated that athletes with eating disorders or other evidence of compromised energy availability should meet established weight goals and other clinic criteria before continue exercising, and these athletes may need to modify their training and competition (51, 182). Recent sports consensus groups, including the Female Athlete Triad Coalition and International Olympic Committee, recommend that athletes undergo screening for components of the triad and potentially meet certain energy availability requirements before continuing to exercise (53, 64).

Fractures are much more common in athletes with distorted eating patterns than in those with normal dietary habits (54). A low-energy state leads to low bone formation and low bone turnover rates, whereas postpubertal hypogonadism favors a resorptive state. Low bone turnover impairs the normal mechanisms that repair bone microdamage and injuries due to overuse, leading to a higher risk for fracture. Adolescents with anorexia nervosa are characterized by reduced bone turnover (183), whereas young adult women with the condition have an uncoupling of bone turnover (43, 150). The uncoupling of bone turnover is seen even in short-term starvation in normal exercising women (184); this pattern of uncoupling is unique to nutritional deprivation (55–57). Researchers also reported the uncoupling of bone turnover markers in exercise-associated amenorrhea, with the most significant effects on bone mass occurring in women who were both energy deficient and estrogen deficient (185) or had multiple risk factors (186). One study showed that a combination of risk factors, including a high exercise load (>12 h/wk), participation in a low-weight sport (*e.g.,* gymnastics, long distance running, figure skating), and dietary restraint was associated with a 46% incidence of bone stress injury (51). When the energy status of exercising women is adequate, there appears to be no perturbation of bone formation, regardless of estrogen status (53, 185). These studies present compelling evidence that the bone loss of anorexia nervosa and exercise-associated amenorrhea is not analogous to the bone loss seen with ovarian insufficiency or castration, which represent a pure form of hypogonadism with isolated estrogen deficiency but without hypercortisolemia and other endocrine alterations. Bone accretion can be adversely affected by elevated cortisol, reduced T3 and T4, reduced E2, and alterations in other hormones that result in a catabolic metabolic state.

2.8 In cases of primary amenorrhea, we suggest evaluating Müllerian tract anomalies (congenital or acquired). Diagnostic options include physical examination, progestin challenge test, abdominal or transvaginal ultrasound, and/or MRI, depending on the context and patient preferences. (2l⊕⊕⊕◯)

Evidence

Defining reproductive tract anatomies is always the first step in excluding anatomic causes of amenorrhea, and it is especially important in primary amenorrhea (Table 1) (65). Outflow tract anomalies often present as primary amenorrhea and require both a physical examination (which is critical in the identification of an imperforate hymen) and imaging with pelvic ultrasound or MRI to exclude and/or define anatomic anomalies.

Remarks

In some women with FHA, clinicians may consider a hysterosalpingogram, sonohysterogram, or saline infusion sonogram or hysteroscopy to establish acquired gynecologic tract abnormalities. Asherman syndrome from intrauterine synechiae, adhesions, or unintended endometrial ablation may present as secondary amenorrhea. A history of a postpartum dilation and curettage or pelvic infection may raise suspicion of endometrial injury. Irregular and erratic bleeding may be due to intrauterine polyps or intramural fibroids rather than functional hypothalamic hypogonadism.

2.9 In patients with FHA and underlying PCOS, we suggest:

- a baseline BMD measurement by DXA in those with 6 or more months of amenorrhea and earlier in those with history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility (2/⊕⊕◯◯); and
- clinical monitoring for hyperresponse in those treated with exogenous gonadotropins for infertility. (2l⊕⊕◯◯)

Evidence

PCOS is a common endocrine diagnosis among premenopausal women, which can manifest as oligomenorrhea or amenorrhea, and FHA can conceal the diagnosis of PCOS. In some adolescents and women, overzealous dieting masks PCOS symptoms. Normoandrogenic, oligomenorrheic women with PCO morphology and FHA and an elevated AMH level are at high risk for hyperandrogenic PCOS when hypothalamic function

normalizes (187). Clinicians should pay close attention to concerns about weight and appearance (including signs of hyperandrogenism) in the patient's history. One study compared the hormonal/clinical profiles and markers of bone health among women with FHA to women with suspected FHA and underlying PCOS (188). Compared with women with FHA, women with FHA and underlying PCOS had higher BMI, BMD, LH and testosterone concentrations, and incidence of hyperandrogenism; they also exhibited increased hyperandrogenism and irregular menses with weight gain. Recovered FHA patients with underlying PCOS may never resume regular menses and may develop other phenotypic characteristics of PCOS. However, they seem to be at similar risk for developing osteopenia and osteoporosis, based on World Health Organization criteria (188). These patients are also hyperresponsive to exogenous gonadotropins when treated for infertility and need to be monitored carefully (189–192).

Remarks

FHA and PCOS may coexist, and as patients recover from FHA, manifestations of PCOS may emerge, including irregular menses.

3.0 Treatment of functional hypothalamic amenorrhea and concomitant medical conditions

3.1 We recommend that clinicians evaluate patients for inpatient treatment who have FHA and severe bradycardia, hypotension, orthostasis, and/or electrolyte imbalance. (1|⊕⊕⊕◯)

Evidence

Adolescents and young women who exhibit a severe energy deficit (as in a restrictive eating disorder) can ultimately develop hemodynamic instability, exhibiting hypotension, bradycardia, and orthostasis. International experts have developed guidelines to address criteria for an inpatient medical admission (193). Careful monitoring of the very low weight patient is warranted, as the mortality rate associated with eating disorders, and especially anorexia nervosa, is high (193–195).

3.2 In adolescents and women with FHA, we recommend correcting the energy imbalance to improve HPO axis function; this often requires behavioral change. Options for improving energy balance include increased caloric consumption, and/or improved nutrition, and/or decreased exercise activity. This often requires weight gain. (1|⊕⊕⊕◯)

Remarks

Clinicians often need to refer patients to a dietitian or nutritionist to provide individualized dietary instructions.

Evidence

It is well established that low energy availability from decreased energy intake and/or high-energy exercise expenditure leads to HPO disruption, as reflected in menstrual dysfunction, LH pulsatility disruption, and changes in other hormone levels (17, 74, 109, 112). Energy availability is dietary energy intake minus exercise energy expenditure, normalized to fat free mass. This concept encompasses the amount of energy remaining for other bodily functions after exercise training (45). Weight gain through refeeding and improved energy availability in amenorrheic patients with anorexia nervosa correlated with the resumption of menses (196). Increased energy availability through diet or diet and exercise modification in dancers and athletes with FHA also improved menstrual function (85, 86, 197, 198). First ovulation may occur before resumption of the first menstrual period, and sexually active young women need to be especially cognizant of this fact.

Because FHA often includes a combination of etiologic factors, including stress, low weight, excessive exercise, and poor nutrition, a multidisciplinary approach is ideal. The approach should include dietary evaluation and counseling (through work with a registered dietitian to optimize calories and intake of vitamin D, calcium, and other nutrients), as well as psychological support for treating stress and enhancing behavioral change (through work with a psychotherapist, licensed social worker, psychologist, or psychiatrist) (45, 53, 64).

Some think that physiological adaption to inadequate caloric intake is an etiologic factor for metabolic changes and ensuing reproductive dysfunction. Multiple physiologic changes occur, but are reversible. The reversal of these with weight gain or a decrease in exercise may point to precipitating factors, although few studies have examined the precise weight gain needed for the resumption of HPO function. Amenorrhea may persist for some time after the reversal of precipitating factors. One study suggested that the weight gain needed for the restoration of menses was 2.0 kg higher than the weight at which menses stopped (199). At least 6 to 12 months of weight stabilization may be required for the resumption of menses. In some cases, regular menses may never resume after weight stabilization, emphasizing the importance of psychological factors and stress. In-depth nutritional studies of women with FHA have suggested nutritional aberrations or an incipient eating disorder (33, 34, 41, 42, 50, 129, 199, 200).

3.3 In adolescents and women with FHA, we suggest psychological support, such as CBT. (2|⊕⊕◯◯)

Evidence

Women with FHA have been found to exhibit more dysfunctional attitudes, have greater difficulty in coping with daily stresses, and tend to have more interpersonal dependence than do eumenorrheic women. They also more often have a history of psychiatric disorders and primary mood disorders than do eumenorrheic women (20, 21). A study of 16 women with FHA (normal body weight and no reported psychiatric conditions, eating disorders, or excessive exercise) randomized eight subjects to CBT and eight to observation for 20 weeks. Most of the CBT-treated group (six of eight) achieved ovulatory recovery compared with only in one of eight in the observation group (25). The CBT group also had improvements in cortisol, leptin, and TSH (24). CBT not only restores ovarian function, it also alters metabolic function. The long-term impact of CBT on the acute and chronic health sequelae of FHA remains to be shown. However, in most studies that tested the use of CBT for psychosomatic conditions, the effect size accrued across time as subjects incorporated the lessons into daily living. Effects of other forms of psychotherapy, including dialectical behavior therapy and family-based treatment (among others), have not been well described in FHA and thus merit investigation.

3.4 We suggest against patients with FHA using OCPs for the sole purpose of regaining menses or improving BMD. (2l⊕⊕○○)

3.5 In patients with FHA using OCPs for contraception, we suggest educating patients regarding the fact that OCPs may mask the return of spontaneous menses and that bone loss may continue, particularly if patients maintain an energy deficit. (2l⊕⊕○○)

Evidence

OCPs provide a progestin and various doses and types of estrogen (typically ethinyl E2) in a daily pill. Patients use OCPs to prevent pregnancy and treat dysmenorrhea, menorrhagia, hyperandrogenism, and acne, among other conditions. OCP treatment is not intended for the resumption of normal menses with normal endogenous hormonal fluctuations, as OCP formulations modulate endogenous hormone levels and suppress ovarian function even in women who report previously normal cycles (201–203). Clinicians often prescribe OCPs for women and adolescents with FHA, but most studies have shown limited to no benefit of this intervention on BMD. Several studies have shown a lack of a protective effect of oral contraceptives on bone (172, 204).

The Endocrine Society conducted a recent systematic review of studies that evaluated the impact of oral hormonal therapy on BMD in FHA. The review included nine studies reported in 10 publications (six had a control arm and three were before/after single cohort studies) (172, 205–213). The studies reported mean BMD changes, but not *Z*-scores, T-scores, or the incidence of fractures. In a pooled data analysis, the lumbar, femoral neck, trochanteric region, Ward's triangle, and total body BMD demonstrated clinically insignificant changes over a median of 12 months. The lack of clear benefit is likely related to the persistence of neuroendocrine concomitants, including hypercortisolism and decreased thyroid levels. The findings are consistent with the concept that FHA is more than an isolated disruption of the HPO axis. There are no published prospective studies of fracture risk with OCP treatment in FHA.

3.6 We suggest short-term use of transdermal E2 therapy with cyclic oral progestin (not oral contraceptives or ethinyl E2) in adolescents and women who have not had return of menses after a reasonable trial of nutritional, psychological, and/or modified exercise intervention. (2l⊕○○○)

Evidence

One study has examined combined therapy with transdermal estrogen and oral progesterone in adolescents with anorexia nervosa. The study randomized 96 female adolescents with a bone age ≥15 years to receive 100 μg of 17β-E2 transdermally with cyclic progesterone orally (medroxyprogesterone 2.5 mg daily for 10 days each month) or placebo patches and cyclic placebo pills for 18 months. At 6, 12, and 18 months, there were significant increases in lumbar BMD in the treatment vs placebo groups; these increases approximated bone accrual rates in normal-weight healthy controls. There were also significant improvements in hip BMD at 18 months in the treatment vs placebo groups. That same study titrated incremental low-dose oral ethinyl E2 over the 18 months in those girls with a bone age of <15 years (3.75 μg daily from 0 to 6 months, 7.5 μg from 6 to 12 months, and 11.25 μg from 12 to 18 months) to mimic pubertal estrogen increases (vs placebo) (214). Transdermal estrogen likely has a more positive effect on BMD than OCPs because it does not affect IGF-I secretion, a bone-trophic hormone that OCPs downregulate (162, 215–217). In contrast, a 2-year study of ballet dancers showed no effect of daily oral estrogen (conjugated estrogens 0.625 mg) plus medroxyprogesterone acetate (10 mg for 10 days/month) therapy vs placebo on BMD (172). Another study examined combined antiresorptive/anabolic therapy [50 mg DHEA plus oral ethinyl E2 (20 μg)/levonorgestrel ([100 μg)] in older adolescents and young women with eating disorders (218). The study reported that bone loss was arrested at the hip, spine, and

whole body in the treatment group, whereas there were progressive skeletal losses during 18 months in subjects randomized to placebo. None of these studies assessed fracture outcomes following study-related interventions. The optimal type of estrogen and optimal estrogen replacement dose for bone and other tissues deserves further study.

Remarks

Clinicians may consider estrogen replacement if reasonable attempts to modify nutritional, psychological, and exercise-related variables are not successful in establishing menses. Bone outcomes may be compromised even after 6 to 12 months of amenorrhea, and thus clinicians may consider short-term hormone replacement therapy after 6 to 12 months of nutritional, psychological, and exercise-related interventions in those with low bone density and/or evidence of skeletal fragility. Of note, bone health may not be protected with E2 replacement therapy if nutritional factors/energy deficit continue.

3.7 We suggest against using bisphosphonates, denosumab, testosterone, and leptin to improve BMD in adolescents and women with FHA. (2|⊕⊕◯◯)

Evidence

The systematic review commissioned by the Endocrine Society did not identify published studies that have evaluated the use of bisphosphonates to prevent bone loss in patients with FHA. Four studies have evaluated their use in premenopausal women with anorexia nervosa and associated amenorrhea. The studies reported small but significant increases in BMD in both adolescents and adults [up to 4.9% at the lumbar spine at 9 months in adults, and increases at the femoral neck (but not the spine) in adolescents] (219–222). However, the studies were small, used different bisphosphonate formulations and protocols, and no study examined efficacy and safety in patients with FHA (outside of an eating disorder).

Importantly, note that bisphosphonates are incorporated into bone and retained for years in the human skeleton. Animal models have demonstrated risks to fetuses of mothers receiving bisphosphonates. Thus, there are concerns that even prepregnancy administration of bisphosphonates may result in drug mobilization from the maternal skeleton during pregnancy, with transplacental passage that can result in the potential for fetal teratogenicity. A review of available published cases of human exposure to bisphosphonates before or during pregnancy (51 cases) did not identify any skeletal or other fetal anomalies (223). However, we need to carefully balance the theoretical risks with potential treatment benefits.

Denosumab is a human monoclonal antibody directed against receptor activator of nuclear factor-κB ligand, which limits bone resorption by inhibiting osteoclast maturation. It has not been tested in premenopausal women. However, inadvertent fetal exposure is a theoretical risk in reproductive age women who use denosumab, as a study in nonhuman primates reported transplacental transfer and potential for teratogenicity (224). In postmenopausal women with osteoporosis, denosumab use has resulted in decreased fracture risk and improved BMD compared with placebo (225). We need studies in premenopausal women, specifically those with FHA.

In a small study, subcutaneous recombinant human leptin (n = 8) or no treatment (n = 6) was given for 2 to 3 months to women with FHA secondary to increased exercise and/or low weight. All had stable weight (within 15% of ideal body weight for 6 months or more prior to enrollment). Those on treatment had increased mean LH levels and pulse frequency after 2 weeks and improved follicular development, ovarian volume, and E2 levels by 3 months. Three patients had an ovulatory menstrual cycle and two others had preovulatory follicular development and withdrawal bleeding during treatment. Recombinant leptin significantly increased levels of free T3, free T4, IGF-I, IGF-binding protein-3, bone alkaline phosphatase, and osteocalcin, but did not increase levels of cortisol, corticotropin, or urinary N-terminal telopeptides. Unfortunately, the study reported subjective reductions in appetite and significant decreases in weight and fat mass in the treatment group, which has called into question the use of leptin in this patient group (226). The controls had no significant changes in LH pulsatility, body weight, ovarian variables, or other hormone levels (226).

A follow-up study in women with exercise-associated FHA found that seven of 10 women recovered menses after a 9-month treatment period with metreleptin (a synthetic analog of leptin) vs only two of the nine women who received placebo. Researchers noted weight loss and decreased body fat and therefore made adjustments to metreleptin dosages. Despite these adjustments, women receiving metreleptin had a reduction in body fat mass. The study did not find BMD differences between treatment groups, although bone mineral content increased in the treatment group (227). In a study extension, after a 3-month washout period, six subjects chose to continue on open-label metreleptin treatment for another 12 months. Metreleptin significantly increased BMD and bone mineral content at the lumbar spine (range, 2.2% to 10.8% and 1.4% to 6.5% from baseline, respectively) in the four subjects who completed the entire 2-year intervention. Changes in hormonal and metabolic

parameters and bone markers were moderate during the first year of treatment, but metreleptin further increased IGF-I and decreased cortisol and bone resorption markers (serum C-terminal telopeptides) during the second year (228). However, because of the small numbers studied and the serious weight loss side effect, we need more exploration before recommending metreleptin as an FHA treatment.

3.8 In rare adult FHA cases, we suggest that short-term use of rPTH is an option in the setting of delayed fracture healing and very low BMD. (2l⊕○○○)

Evidence

Small studies of parathyroid hormone in adult premenopausal women with idiopathic osteoporosis and premenopausal women with anorexia nervosa have reported short-term improvements in BMD, but there has been no long-term follow-up. In a randomized controlled trial of adults with anorexia nervosa randomized to rPTH or placebo for 6 months, spine BMD increased significantly more with teriparatide (posteroanterior spine, 6.0% ± 1.4%; lateral spine, 10.5% ± 2.5%) compared with placebo (posteroanterior spine, 0.2% ± 0.7%, $P < 0.01$; lateral spine, −0.6% ± 1.0%; $P < 0.01$) (229).

A recent systematic review of the role of rPTH in human fracture healing included 16 case reports/case series; two randomized, prospective, double-blind placebo-controlled trials; and one retrospective subgroup analysis. Although there were differences noted in type of fracture, time since fracture prior to initiating rPTH, age of patients, duration of treatment, and other discrepancies, this review suggests there may be a role for rPTH to improve fracture healing in selected patients (230). There are no published studies on effects of rPTH treatment and fracture risk reduction in premenopausal women. There is a black box warning on teriparatide describing an increased incidence of osteosarcoma in rats [these rats received a 3- to 60-fold greater systemic exposure than did humans, who receive (typically) a 20-μg daily dose for up to 2 years]. There have been no reported cases of osteosarcoma after teriparatide therapy in humans. However, we need more studies in the FHA population.

3.9 In patients with FHA wishing to conceive, after a complete fertility work-up, we suggest:

- treatment with pulsatile GnRH as a first line, followed by gonadatropin therapy and induction of ovulation when GnRH is not available (2l⊕○○○);
- cautious use of gonadotropin therapy (2l⊕○○○);
- a trial of treatment with clomiphene citrate for ovulation induction if a woman has a sufficient endogenous estrogen level (2l⊕○○○);
- against the use of kisspeptin and leptin for treating infertility (2l⊕○○○); and
- given that there is only a single, small study suggesting efficacy, but minimal potential for harm, clinicians can consider a trial of CBT in women with FHA who wish to conceive, as this treatment has the potential to restore ovulatory cycles and fertility without the need for medical intervention. (2l⊕⊕○○)

Evidence

In most patients, exogenous GnRH or exogenous gonadotropin would likely be efficacious for inducing ovulation and pregnancy in women with FHA. Because GnRH allows pituitary–ovarian feedback mechanisms to remain intact, pulsatile GnRH is widely accepted as an ideal treatment of FHA that leads to a more physiologic ovulatory menstrual cycles with monofollicular development and minimal (if any) increase in multiple pregnancy (231, 232). However, GnRH is currently unavailable in the United States.

Large case series favor the use of GnRH. Leyendecker *et al.* (233) administered pulsatile GnRH treatments in 359 cycles in 73 patients and reported pregnancy rates of 29% per cycle in women with no other infertility factors present. Filicori *et al.* (234) reported on the outcomes of 600 cycles of pulsatile GnRH administration. Of the 600, approximately half were in women with hypogonadotropism. Overall ovulatory rates were 75%, but were highest in the primary hypogonadotropic amenorrhea subgroups. Per cycle conception rates were 23% in ovulatory cycles. Only 3.8% of these cycles resulted in multiple pregnancy.

Martin *et al.* (235) compared pulsatile GnRH (41 women; 118 cycles) to gonadotropins (30 women; 111 cycles). Although not a randomized trial, the cumulative incidence of conception after six cycles of GnRH treatment was 96% compared with 72% with exogenous gonadotropin. The study observed three or more follicles in 16.6% of the gonadotropin cycles vs in 5.4% of the GnRH cycles and multiple gestations in 14.8% of gonadotropin cycles compared with 8.3% of GnRH cycles, a difference that was not statistically significant. The gonadotropin preparation Martin *et al.* used was human menopausal gonadotropin, which contains both FSH and LH activity. Women with FHA may require both LH and FSH activity for an optimal gonadotropin response. Schoot *et al.* (236) found inadequate E2 responses in seven women treated with recombinant FSH without LH activity who had hypophysectomy, isolated gonadotropin deficiency, or Kallmann syndrome. The researchers suggested that LH activity was essential in

individuals without endogenous LH. Although overall safety considerations favor GnRH treatment of women with FHA, as mentioned above, GnRH therapy is not currently available in the United States.

There are no randomized clinical trials that have evaluated the use of clomiphene citrate for treating infertility in women with FHA. Most case series do not favor its use, as we do not expect that women with FHA would be able to respond successfully to opening the estrogen negative feedback loop. One case series of eight women with FHA suggested that a prolonged clomiphene protocol might be more successful than the 5-day regimen typically used in clinical practice (237). Djurovic *et al.* (238) reported that a 10-day course of clomiphene citrate induced menses in nine out of 17 women who had recovered normal body weight, but not menstrual function, after an anorexia nervosa diagnosis. All 17 had significant increases in LH and E2 levels. Clinicians have induced ovulation in women with PCOS using the aromatase inhibitor letrozole (239), but studies have not tested its efficacy in FHA or overlapping FHA/PCOS.

Researchers have investigated kisspeptin as a possible modality for restoring LH pulsatility and gonadal function in women with FHA. Jayasena *et al.* (240) administered kisspeptin-54 via constant infusion for 10 hours at variable doses to five women with FHA and demonstrated an increase in LH pulsatility in all women without evidence of desensitization. This dosing regimen may prove more effective than the twice daily and twice weekly subcutaneous injections previously studied (241, 242). We need more research on therapeutic uses of kisspeptin, which is not yet clinically available.

As discussed previously, one small 20-week study of normal-weight women with FHA randomized to CBT vs observation showed that CBT not only leads to recovery of ovulation, but also improves metabolic function (24, 25). However, further research is needed to understand the long-term effect of this therapy on health outcomes in adolescents and women with FHA.

3.10 We suggest that clinicians should only induce ovulation in women with FHA that have a BMI of at least 18.5 kg/m^2 and only after attempts to normalize energy balance, due to the increased risk for fetal loss, small-for-gestational-age babies, preterm labor, and delivery by Cesarean section for extreme low weight. (2l⊕⊕◯◯)

Evidence

A BMI of 18.5 kg/m^2 is the weight threshold under which we consider an adult woman very underweight and possibly malnourished. Therefore, we also considered this weight the minimal threshold that a woman needs to optimize her chances for fertility, and higher would be better. There are data suggesting that an extremely low BMI is associated with a higher risk for adverse pregnancy outcomes (59). A case control study associated a BMI of <20 kg/m^2 with a fourfold higher likelihood of preterm labor (odds ratio, 3.96; 95% confidence interval, 2.61 – 7.09) after adjusting for other known factors (243). Undernutrition is also associated with lower birth weight (3233 g compared with 3516 g for normal controls) (244). Limited data suggest fetal loss as a possible consequence of FHA, particularly in those patients with eating disorders. Because ovulation induction is often successful, it should be noted that these complications might ensue. Women with anorexia nervosa are also at risk for preterm labor and delivery by Cesarean section (58–60). Therefore, clinicians should limit ovulation induction to women of satisfactory body weight (59).

Future Directions

It is possible that prolonged exercise-induced amenorrhea has adverse cardiovascular consequences (245). In a study of 68 women athletes, 24 with amenorrhea and 44 with regular cycles, the women with amenorrhea had significantly higher serum concentrations of total cholesterol [210 vs 186 mg/dL (5.47 vs 4.84 mmol/L)], triglycerides [68 vs 55 mg/dL (0.75 vs 0.61 mmol/L)], low-density lipoprotein cholesterol [121 vs 108 mg/dL (3.2 vs 2.8 mmol/L)], and high-density lipoprotein cholesterol [75 vs 66 mg/dL (1.95 vs 1.73 mmol/L)].

Studies have also noted impaired endothelial function and increased vascular resistance (246–248). Whether the cardiovascular consequences of these differences are clinically important or whether the increased serum high-density lipoprotein cholesterol concentration is protective is not known. There is also evidence of increased visceral fat (a known risk factor for cardiovascular disease) in women nutritionally rehabilitated from anorexia nervosa (249) and evidence that estrogen levels are inversely related to abdominal fat. Women with FHA had more central fat than did healthy controls (250). Preclinical primate evidence suggests that stress-associated hypoestrogenism causes a precocious acceleration of coronary artery atherosclerosis. Studies found a similar effect across all individuals following oophorectomy, which eliminates the "protection" typically observed in non-stressed animals (40, 251, 252).

Other evidence that FHA may be associated with adverse cardiovascular consequences comes from the Women's Ischemia Syndrome Evaluation, an angiographic study in premenopausal women. Those with angiographic evidence of coronary disease were more likely to have a serum E2 of <50 pg/mL and low gonadotropins of LH <10 IU/L and FSH <10 IU/L when

compared with women with normal coronaries. The diagnosis of FHA by this definition remains an independent predictor of coronary disease, even after adjustment for other risk factors such as diabetes. However, this criterion for FHA is broad, with no recognition given to menstrual history, and we often see E2 levels <50 pg/mL in normal women during the follicular phase of the cycle (253).

In women with hypothalamic hypogonadism, clinicians can get an estimation of ovarian reserve using AMH measurements, because gonadotropins will be falsely low (140). An antral follicle count can also provide a reliable estimate. In a patient with primary ovarian insufficiency, the diagnosis could be delayed because of FHA-attenuated gonadotropin secretion.

It should be recognized that adolescents and young women with type 1 diabetes mellitus represent a group at high risk for the development of disordered eating behaviors and purging (*e.g.,* vomiting, hyperexercise, and insulin omission) (254, 255). Future studies should identify strategies that lead to the prevention of energy deficit situations in this population. Data indicate that HPO dysfunction is also common in these patients, although the underlying mechanisms beyond hypothalamic disturbances are not entirely clear (256).

Research has yet to determine the acute and chronic consequences of ovulation induction and pregnancy in the face of elevated cortisol, low T3 and T4, and the other neuroendocrine concomitants associated with FHA, but available data suggest reason for concern (257), and the risks include preterm labor and neurodevelopmental disorders, such as autism spectrum disorder and cardiovascular disease.

Another area of concern is the impact of prolonged hypogonadism on cognitive status and anxiety and mood symptoms. However, implications of FHA in these areas are currently unclear. Recent studies have reported that physiologic estrogen administration improves anxiety outcomes in adolescents with anorexia nervosa (258).

We need more research into the treatment of amenorrhea and low BMD in FHA, with careful consideration of the effects on weight and body composition and the need for appropriate dosing adjustments, and we need more research regarding the impact of FHA on other body systems and neural function. Risk factors for the development and persistence of FHA include conditions that chronically activate the HPA axis. These risk factors include: greater energy expenditure than intake, as with excessive exercise and/or nutritional restriction; unrealistic expectations of self and others; and attitudes that increase reactivity to common and uncommon stressors, including perfectionism, high need for social approval, and conditional love (19–21). Exercise *per se* can be considered as a stress situation (259), and stressors are likely synergistic rather than additive (22).

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