Nutritional, Physical, and Psychological Stress and Functional Amenorrhea

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Abstract

The lack of regular, cyclic menstruation in reproductive-aged women in whom there is no organic or anatomic cause is called functional hypothalamic amenorrhea (FHA). The cause of this malfunction in the hypothalamic-pituitary-ovarian axis is generally attributed to psychological, physical, or nutritional stress, and the underlying deficit is the suppression of gonadotropin-releasing hormone release by the hypothalamus. The diagnosis of FHA is reached by the exclusion of all other factors and conditions that could cause amenorrhea. FHA, by definition, is a chronic condition and can have serious health consequences if not treated. Since the underlying causes of the FHA are thought to be either low energy availability or dysfunctional attitudes and behaviors that result in stimulation of the hypothalamic-pituitary-adrenal axis and/or suppression of thyroid function, cognitive behavioral therapy and hypnotherapy are the best potential approaches for ameliorating this condition. Finally, increasing food intake and reducing stressful activities can be very effective in restoring menstruation.

Keywords

Functional hypothalamic amenorrhea • Psychological stress • Cortisol • CRH • Endogenous opioids • Leptin

6.1 Learning Objectives

After completing this chapter, you should have an understanding of:

- The definition of functional hypothalamic amenorrhea (FHA)
- The causes of FHA
- The importance of seeking medical attention for this condition
- The long-term consequences of chronic low estrogen levels

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6.2 Introduction

FHA is the absence of menstrual cycles for more than 6 months without any anatomic or pathologic cause for the condition. The term "functional" indicates that the lack of menstrual cycles is due to improper functioning of the hypothalamic-pituitary-ovarian axis rather than due to an anatomic (organic) problem. The diagnosis of women of FHA requires the exclusion of all other possible metabolic, neurological, or organic causes for the absence of menstruation such as prolactin-secreting pituitary adenomas, thyroid dysfunction, and polycystic ovarian syndrome (PCOS) [1]. The underlying deficit in FHA is suppressed gonadotropin-releasing hormone (GnRH) release from the hypothalamus resulting in low gonadotropin (LH and FSH) and estrogen levels. When estrogen levels are low, the endometrium of the uterus does not develop and periodic menstruation is absent.

6.3 Research Findings

6.3.1 Potential Causes of FHA

Since primitive times, a common belief among women has been that regular menstrual bleeding is a sign of mental health and that emotional trauma results in disrupted menstruation [2]. Hans Selye [3] was the first to recognize that mental stress was among those changes in the environment that disturbed the sexual cycle in females. Refeinstein [4] was also among the first to link disrupted menstrual cycles with "overt or latent psychological disturbances." He recognized that psychogenic or functional amenorrhea was a problem associated with the brain even before it was accepted that reproductive function (i.e., release of LH and FSH) was governed by the hypothalamus (GnRH release). Recent studies suggest that FHA is triggered by a variety of stressors, including energy deprivation induced by dieting, excessive exercise, and psychosocial distress. Women experience one or all three factors at the same time, which results in the suppression of the GnRH drive [1, 5, 6]. Evidence of hypercortisolemia in amenorrheic women provides the link for the relationship between stress and FHA [7]. For instance, amenorrheic women were observed to have elevated cortisol levels while sleeping compared to healthy controls [8]. Women cope with and respond to these stressors differently, which makes it difficult to establish a threshold at which psychogenic stress interferes with the normal menstrual cycle [9, 10].

Low energy availability due to dieting coupled with excessive exercise suppresses the reproductive system in both women and nonhuman primates. When female rhesus monkeys were kept on a constant diet and increased their energy expenditure by increasing the time they exercised each day, all of the animals eventually became amenorrheic [11]. Menstrual cycles were re-established when additional calories were provided during a treatment period of constant training intensity and volume [12]. One study in women with FHA found that 46 and 39 % of amenorrheic participants were anorexic and bulimic, respectively [13]. When these amenorrheic women were compared to matched controls, calorie intake over a 24-h recall was not significantly different between groups; however, calories expended per day during high-intensity aerobic exercise were considerably greater in amenorrheic women. The greater energy expenditure coupled with the anorexic and bulimic behaviors of the amenorrheic group suggests that they had lower energy availability compared to their normal healthy counterparts. These women also experienced other endocrine alterations associated with FHA such as reduced leptin, thyroxine, and triiodothyronine levels [13]. It is the availability of energy not the stress of exercising that reduces both LH secretion [14, 15] and diurnal rhythm of leptin [16]. Together, these studies in women and nonhuman primates convincingly demonstrate that reproductive cycles are dependent on adequate energy availability and are quickly disrupted when energy is limited.

An acute psychological stressor can also inhibit gonadotropin secretion from the pituitary [17, 18], which may cause FHA. In nonhuman primates, ACTH and cortisol were elevated and

LH levels were decreased when the animals were moved from the home cage to a restraining chair. Within a few hours after returning to their cages, pulsatile LH secretion resumed and stress hormone levels returned to normal. These data are consistent with the general notion of how stress inhibits reproductive function (i.e., by suppressing the release of GnRH from the hypothalamus and, subsequently, the function of the pituitary and ovary). Some psychological stressors experienced by women and which have been associated with FHA are performance pressure, intellectual pursuits, aiming for perfection, traumatic experiences (e.g., sexual molestation), problems with social approval, having unrealistic goals, negative attitude towards eating, and other negative attributions [5, 6, 19].

6.3.2 Neuroendocrinology and Pathophysiology of FHA

Nutritional, physical, and psychological stressors affect the neuroendocrine control of the reproductive axis, which leads to the suppression of GnRH and, in turn, FHA. Specifically, neuropeptides such as corticotropin-releasing hormone (CRH), vasopressin, β-endorphin, leptin, ghrelin, allopregnanolone, and neuropeptide Y all may play a role in the pathophysiology of FHA. CRH and vasopressin are released by the paraventricular nucleus of the hypothalamus and can inhibit GnRH release. CRH causes the release of ACTH from the pituitary which then stimulates cortisol secretion by the adrenal. In vitro [20, 21] and in vivo [22] studies have shown that the release of GnRH can also be directly inhibited by CRH through its direct connections with GnRH neurons in the hypothalamus [23].

Cortisol is also coupled with a progesterone metabolite, allopregnanolone, in women with FHA as well as in healthy controls. However, women with FHA experience a blunted allopregnanolone response to CRH [24]. CRH stimulates the production of β-endorphin, an opioid peptide, and circulating levels of this peptide increase during intense exercise. In vitro studies have shown that β-endorphin inhibits GnRH release [25]. When β-endorphin release was blocked by naxolone, an opioid antagonist, GnRH levels increased [17, 26]. β-endorphin can also directly inhibit LH release [7]. These findings suggest that β-endorphin mediates the action of CRH in suppressing GnRH [27].

In women with FHA, leptin (a protein produced by fat and implicated in reproductive function) levels are lower than in normal healthy women and the normal diurnal rhythm in leptin levels is also absent [7, 28]. Low leptin levels are typical in amenorrheic women with low body fat, and leptin levels increase as body fat increases in women with FHA [29]. Leptin levels increase significantly with every 1 kg increase in weight and are associated with the return of pulsatile LH release. Moreover, hypoleptinemia may increase cortisol levels through activating the adrenergic pathway and CRH release [7]. Low leptin levels stimulate the release of neuropeptide Y in the hypothalamus. Neuropeptide Y stimulates GnRH production (if estradiol concentrations are high) as well as increased pulsatile LH release. However, in women with FHA, estradiol levels are low (<20 pg/ml) [19], and basal levels of neuropeptide Y are lower compared to healthy women [7]. Another hormone from the gut, ghrelin, opposes leptin function. Ghrelin inhibits GnRH secretion and is elevated in women with FHA, especially if these women have disrupted eating habits [30].

Other peptides such as orexin A and kisspeptin that control GnRH release [7] have not been studied in women with FHA.

6.4 Contemporary Understanding of the Issues

6.4.1 Possible Genetic Contribution to FHA

FHA is a condition that is similar to isolated hypogonadotropic hypogonadism and may have a genetic component as well [31]. Both conditions refer to the amenorrhea due to the suppression of GnRH; however, hypogonadotropic hypogonadism has a genetic basis. Mutations in

genes for fibroblast growth factor receptor, prokineticin receptor 2, GnRH receptor, and KAL-1 are among those found in the hypogonadotropic hypogonadism and are also found in some women with FHA. These genes are known to be loss-of-function mutants; for instance, expression of prokineticin receptor 2 on the cell surface and its signaling activity were significantly less in women with FHA than in healthy controls [31]. Furthermore, these genetic defects, particularly in the fibroblast growth factor receptor and prokineticin receptor 2, may contribute to the negative eating habits of women with FHA, as they alter eating behavior in animal models [32, 33]. Finally, the mutant GnRH receptor, KAL-1, and prokineticin receptor 2 are involved in the processes that lead to suppressed GnRH, altered LH activity, and absence of menstruation.

6.4.2 Psychiatric Contribution to FHA

Psychiatric histories of women with FHA have also been compared with amenorrheic (from organic causes) and eumenorrheic controls [34]. Women with FHA had more dysfunctional attitudes, did not cope as well with ordinary stresses, and showed more interpersonal dependence than did eumenorrheic women. These women also more often had a history of psychiatric mood disorders, particularly depression and anxiety, than did women with normal cycles [35]. Depression was also linked to sexual function problems experienced by women with FHA [35]. These psychiatric disorders are associated with elevation in hypothalamic-pituitary-adrenal axis activity. When combined with performance anxiety and dietary restriction, these disorders may contribute to significant endocrine dysfunction and result in FHA.

6.4.3 Medical Problems Associated with FHA

Significant weight loss may occur in women with FHA because of dieting and/or excessive exercise; however, not all women with this condition are underweight. Weight loss-induced amenorrhea significantly lowers bone mineral density such that women with FHA have osteopenia [36–39]. Indeed, an inverse relationship exists between the length of amenorrhea (in months) and bone mineral density [37, 39]. Low bone mineral density may affect cardiovascular factors as well. Bone mineral density is inversely correlated with total cholesterol, apolipoprotein A, and very-low-density lipoprotein levels [40]. Endothelial dysfunction, which increases the risk for atherosclerosis, may also occur in women with FHA [41]. Amenorrheic female athletes, who participate in high-intensity training and strict dieting, can develop a serious condition called the female athlete triad (discussed in Chap. 5).

6.4.4 Diagnosis of FHA

The diagnosis of FHA has gained a firmer basis over the past few years. A thorough review of the medical history, including exercise and eating habits (e.g., binging or purging), must be conducted to identify the specific nutritional, physical, and psychological stressors that are present. The physical examination must exclude all other possible medical reasons that would cause amenorrhea such as PCOS, adrenal hyperplasia, presence of an adrenal-secreting tumor, adnexal mass, an imperforated hymen, and Mullerian duct anomaly (i.e., absence of uterus) [1]. Signs of hirsutism, acne, male pattern baldness, clitoromegaly, voice changes, and vomiting (i.e., gingival abrasions, loss of dental enamel, parotid swelling) must also be examined [1]. Thus, levels of beta subunit of chorionic gonadotropin, thyrotropin, thyroxine, prolactin, follicle-stimulating hormone, free testosterone, and dehydroepiandrosterone sulfate must all be analyzed [1]. Magnetic resonance images of the brain may also be used to determine conditions that might contribute to FHA [1].

The long-term negative health consequences of FHA include increased risk of cardiovascular disease (e.g., coronary artery disease), osteoporosis, increased risk for fractures,

depression, dementia, and other psychiatric conditions [39, 42, 43]. Both pharmacologic and non-pharmacologic therapies have been suggested for treatment of FHA.

6.4.5 Potential Interventions in Women with FHA

Several forms of estrogen administration have been investigated, including estriol and 17-ß estradiol [36, 44]. In general, estrogen treatment increases plasma levels of LH and bone mineral density; however, bone mineral density does not return to levels observed in healthy women [36, 44]. Naltrexone cloridate, an opioid antagonist, administered at 50 mg/day for 3–6 months resulted in marked increases in estrogen and restoration of menses in some women [45]. Recently, leptin administration has also been shown to increase LH levels and pulse frequency as well as increase estradiol levels, number of dominant follicles, ovarian volume, follicular diameter, free triiodothyronine levels, free thyroxine levels, insulin-like growth factor 1 levels, insulin-like growth factor-binding protein 3, bone alkaline phosphatase, and osteocalcin and even restored menstruation in some women [46]. Although these pharmacologic therapies have provided positive results, scientists argue that drug use does not address the underlying causes of FHA [42]. Merely increasing food intake and decreasing exercise load are highly effective in increasing bone mineral density and restoring menstruation [43, 47]. However, non-pharmacologic treatment has its limitations. Regular menstrual periods may not return until after 1 year of increased food intake and decreased exercise [47], while pharmacologic treatments restore menstruation within 3–6 months [45]. Furthermore, no specific threshold for weight or percent body fat has been established for the restoration of menses [1]. Finally, the practicality of non-pharmacologic approaches is questionable, especially in serious athletes who maintain a strict diet [1]. Psychological approaches to reduce stress such as cognitive behavioral therapy [48] and hypnotherapy [49] are highly effective, and recovery of ovarian function and restoration of menses occurred in as high as 87.5 % of the women with FHA [48, 49].

6.5 Future Directions

Prolonged FHA increases the risk for potentially fatal outcomes. Future directions include the possible use of CRH antagonists to treat women with FHA. Some speculate that women with FHA experience blunted ACTH and cortisol response to CRH due to the reduced expression and sensitivity of CRH receptors [7]. Treatment with CRH antagonists may reduce cortisol levels and allow the return of pulsatile GnRH secretion. Moreover, women with FHA should increase food intake and reduce exercise load. The active guidance of a primary care physician, nutritionist, and psychotherapist may help these women recover and restore menstruation more successfully [1].

6.6 Concluding Remarks

The lack of regular, cyclic menstruation in reproductive-aged women in whom there is no organic or anatomic cause is called FHA. The cause of this malfunction in the hypothalamic-pituitary-ovarian axis is generally attributed to psychological, physical, or nutritional stress. The diagnosis of FHA is reached by the exclusion of all other factors and conditions that could cause amenorrhea. FHA, by definition, is a chronic condition, and thus it can have serious health consequences if not treated. Since the underlying causes of the FHA are thought to be dysfunctional attitudes and behaviors that result in stimulation of the hypothalamic-pituitary-adrenal axis and/or suppression of the thyroid function, cognitive behavioral therapy and hypnotherapy are the best potential approaches for ameliorating this condition [42]. Finally, increasing food intake and reducing stressful activities can be very effective in restoring menstruation.

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