Review Article

The effects of weight loss-related amenorrhea on women's health and the therapeutic approaches: a narrative review

Ling Chen[1,2#], Ye Lu[1#^], Yi-Fan Zhou[1#], Yang Wang[1], Hai-Feng Zhan[1,3], Yu-Ting Zhao[1], Yu-Lu Wang[1], Fei-Fei Zhang[1], Hang Chen[1], Xin Li[1^]

[1]Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China; [2]Department of Gynecology, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China; [3]Department of Gynecology, Shanghai Jing'an Central Hospital of Fudan University, Shanghai, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xin Li. Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai 200011, China. Email: lxsure@fudan.edu.cn.

Background and Objective: Weight loss-related amenorrhea is defined as the reversible functional inhibition of the hypothalamic-pituitary-ovarian (HPO) axis associated with weight loss or low body weight, which occurs mostly in adolescents and women of reproductive age. The specific pathological mechanisms of this disease have not yet been elucidated, and the optimal evidence-based guidelines for its clinical assessment and management are limited. This review summarizes its adverse effects on female health, and the individualized, emerging, and multidisciplinary therapeutic approaches used to treat it.

Methods: We searched the PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) databases for Chinese and English literature on functional hypothalamic amenorrhea (FHA), and retrieved original articles (on basic and clinical research) and reviews published up to December 2022.

Key Content and Findings: We reviewed the findings on the unfavorable effects of weight loss-related amenorrhea with a focus on reproduction, the skeletal and cardiovascular system, other endocrine effects, and mental health. Lifestyle changes and hormonal replacement have been shown to alleviate the underlying causes and lead to the recovery of menstruation. However, the efficacy of treatments is affected by many factors, such as psychological stress and heterogeneity.

Conclusions: Weight loss-related amenorrhea, which is an important type of FHA, is manifested by anovulation and hypoestrogenism, and has both short- and long-term adverse effects on women's overall health. It is difficult to alleviate its underlying causes. Individualized treatments need to be optimized and emerging or multidisciplinary therapeutic approaches need to be explored that aim to recover normal menstruation and ovulation, eliminate the undesirable effects of prolonged hypoestrogenism and alleviate psychological disorders.

Keywords: Weight loss; functional hypothalamic amenorrhea (FHA); female health; hormonal replacement; emerging treatment

Submitted Nov 24, 2022. Accepted for publication Jan 07, 2023. Published online Jan 31, 2023.
doi: 10.21037/atm-22-6366
View this article at: https://dx.doi.org/10.21037/atm-22-6366

^ ORCID: Ye Lu, 0000-0002-2252-3860; Xin Li, 0000-0002-6530-0894.

Introduction

Functional hypothalamic amenorrhea (FHA) is a condition characterized by the absence of menses due to the suppression of the hypothalamic-pituitary-ovarian (HPO) axis without any detectable structural lesions. There are 3 types of FHA: weight loss-related, stress-related, and exercise-related amenorrhea (1). It is difficult to define each type exactly, as they are sometimes overlapped and coexistent under complex interaction, but weight loss is a common and identifiable characteristic in most cases.

Weight loss-related amenorrhea is defined as the cessation of menstrual periods for >6 months following a short-term weight loss >10–15% of the standard body mass, and mainly occurs in adolescents and women of reproductive ages (2). Extensive research has shown that energy balance is closely linked to the reproductive system (3). A threshold of low energy availability can disturb the pulsatile release of the gonadotropin-releasing hormone (GnRH) from the hypothalamus, which can suppress the activity of the HPO axis to various degrees (4). As the suppression increases, normal folliculogenesis, ovulation, and estrogen production cannot be fully maintained due to decreases in and persistent low levels of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Thus, a luteal phase defect, anovulation, oligomenorrhea, and amenorrhea, gradually develop (5,6). Chronic energy deficiency causes variabilities in the degree of weight loss and decreased body fat (7). Adipose tissue and adipokines have been proven to have critical roles in reproduction (8). The specific mechanism that how adipose and adipokines effect reproduction indirectly or directly has not yet been fully elucidated. An energy deficient state, hypoestrogenism, and other abnormal endocrinological and metabolic activities not only impair female reproductive function, but also affect critical physiological functions of other tissues and organs. Amenorrhea with oligo/anovulation can cause infertility, but the prolonged effects of persistent hypoestrogenism are not limited to reproduction. It could impact peak bone mass acquisition among premenopausal women, subsequently leading to osteopenia, osteoporosis and even stress fracture. And the cognitive function, emotion and mood could be affected. Besides, due to loss of protective effects on vascular function, the risks of cardiovascular diseases (CVDs) may increase.

This review focuses on the short- and long-term health consequences of weight loss-related amenorrhea, summarizes current first-line treatment options and explores the emerging or multidisciplinary therapeutic approaches. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6366/rc).

Methods

The PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) databases were browsed for articles on FHA and weight loss published up to December 2022 using the following search terms: "weight loss AND functional hypothalamic amenorrhea AND (consequence OR influence)", and "weight loss AND functional hypothalamic amenorrhea AND (treatment OR therapy OR management)". The retrieved articles were reviewed and analyzed. The search strategy is summarized in *Table 1*.

Results

Epidemiology

According to the American Society of Reproductive Medicine, FHA results in 20–35% of secondary amenorrhea cases, and approximately 3% of primary amenorrhea cases (9). FHA occurs in women with anorexia nervosa or other eating disorders, and up to approximately 60% of high-performing athletes (10,11). We conjecture that the increasing morbidity of weight loss-related amenorrhea patients is correlated with the development of material condition and spiritual civilization. When enough food is available and people do not need to store energy for survival, they begin to seek spiritual satisfaction, a healthier lifestyle, and a slimmer body. When women are exposed to incorrect evaluations of body and weight through social media, and their schools and families. Despite normal weight and body mass index (BMI), they may limit their calorie intake and/or engage in excessive exercise to lose weight and keep their weight greatly below the normal limit. And no-indication use and misuse of weight-loss pills could cause marked weight loss in short term, inducing the inhibition of HPO axis activity, menstrual irregularity and amenorrhea. The risk of FHA caused by weight loss increases progressively as a result of the following 4 nutritional behaviors (12): (I) dieting for aesthetic reasons; (II) dieting for neurotic concerns related to diet and body weight; (III) an anorectic reaction; and (IV) anorexia nervosa. Today, the morbidity

Table 1 Search strategy summary

Item	Specification
Date of search	23/11/2021 to 1/12/2022
Databases and other sources searched	PubMed; Web of Science; CNKI
Search terms used	"Weight loss AND functional hypothalamic amenorrhea AND (consequence OR influence)", and "weight loss AND functional hypothalamic amenorrhea AND (treatment OR therapy OR management)"
Timeframe	Up to December 2022
Inclusion criteria	Published Chinese and English original articles and reviews of basic and clinical research focused on FHA
Selection process	Ling Chen and Ye Lu searched the databases independently

CNKI, Chinese National Knowledge Infrastructure; FHA, functional hypothalamic amenorrhea.

of FHA patients continues to increase, especially among adolescents and young women in developing countries, such as China (13).

Etiology

The link between energy balance and reproduction has been recognized for a long time. In 1984, Frisch proposed that a minimum body weight for height and body fat percentage were necessary for menarche and the maintenance of ovulatory menstruation in women (14,15). However, the critical weight/body fat hypothesis was subsequently contradicted by unfavorable observations that athletes with low body fat regularly menstruate (16), and the threshold of body weight or fat is difficult to determine because of individual differences. In 2003, Loucks reported a relationship between energy availability and LH pulsatile secretion, and conjectured that the failure to provide sufficient metabolic fuels to meet the energy requirements of the physiological activities causes an alteration in hypothalamic function that disrupts the GnRH pulse generator, which he referred to as low energy availability (4).

Psychological disorders and psychiatric morbidities are common in FHA patients, and are also significant causes of FHA (17). Stress is another strong inhibitor of reproductive function. Psychosocial stressors, including externally imposed stressors, mood disorders, negative attitudes, and psychiatric morbidities, activate the hypothalamic-pituitary-adrenal (HPA) axis, boost corticotrophin-releasing hormone (CRH) and cortisol secretory, and subsequently inhibit GnRH secretion (18).

More and more evidence is being gathered that suggests that there is a balance between energy metabolism and reproduction. When energy expenditure exceeds dietary energy intake, a negative energy balance in macro- and micronutrients occurs, and this imbalance can disrupt the neuroendocrine axis, contributing to the development and maintenance of FHA (19,20). Researchers have shown that other hypothalamic-pituitary axis hormones, adipokines, and appetite-regulating hormones are involved in female reproduction and the nutrition system (21-23). These factors, including leptin, galanin, galanin-like peptide (GALP), alpha-melanocyte-stimulating hormone (aMSH), neuropeptide Y (NPY), oxytocin, ghrelin, and insulin, interact with each other, maintain the balance of the reproduction and nutritional state (24), and together play an important role in the pathophysiology of weight loss-related amenorrhea. In particular, leptin is considered a promising and effective therapeutic strategy for FHA (25,26).

Leptin is mainly produced by white adipose tissues, and acts as a permissive factor in pubertal maturation and reproduction development (27). It is involved in several physiological processes, such as the regulation of body weight and total fat storage, both of which can reflect the energy balance (28). It protects individuals from the risks of being too thin or too obese, and is a critical factor linking nutritional and hormonal signals and reproductive status (29).

The nutritional balance is a key factor involved in the onset of puberty (30). An appropriate body weight and fat mass are conducive to sexual maturation, menstruation, and pregnancy. The signal of leptin pulses was initially considered a positive mediator of puberty, and animal studies (31,32) have shown that its nocturnal timing and amplitude may stimulate the growth hormone (GH)-insulin growth factor 1 (IGF-1) and hypothalamic pituitary gonads

(HPG) axis. Leptin bridges the regulation of the fat mass with reproduction by linking peripheral metabolism to central neuroendocrine activity (33). Women who suffered persistent anovulation and amenorrhea present with lower leptin levels than normal-menstruating women (34), and the cyclicity secretion of leptin is synchronized with LH and estradiol, which indicates that gonadotropin level and the development of ovarian follicles may be associated with the leptin produced by adipose tissue.

According to pioneering studies (35,36), the mechanism of the permissive action of leptin in the hypothalamus involves Kisspeptin, agouti-related peptide (AgRP), and GnRH neurons (37). Leptin stimulates gonadotropes to enhance the translation of LH and FSH proteins. However, recent research has shown that leptin has a biphasic effect on ovarian cells, and an optimal range of leptin exists, which can amplify the effects of FSH or LH on follicular and oocyte maturation (38). Thus, during short- and long-term fasting and weight loss, the plasma level of leptin decreases along with energy deprivation, metabolism and hormonal changes, which in turn impairs female reproduction, and amenorrhea may occur (39). In animal studies, it has been reported that leptin administration in infertile, restricted feeding rats improved the ovulatory process and reversed the adverse effects of negative energy balance on menstruation (40). It has also been proven that leptin administration restores the pulsatile secretion of GnRH and ovulation in patients with hypothalamic amenorrhea (41).

The mechanisms underlying the pathophysiology of FHA are elusive. In addition to leptin, kisspeptin, NPY, ghrelin, CRH, β-endorphin, and allopregnanolone have complex interactions and act together to affect reproduction (42). Moreover, research has shown that a negative energy balance can also affect other neuromodulator signaling systems (43). These disturbances, including the activation of the HPA axis and the impairment of the hypothalamic-pituitary-thyroid axis, could affect the HPO axis and reproduction.

Health consequences

Regardless of the specific triggers and mechanisms, the complicated and prolonged state of anovulation, hypoestrogenism, and other endocrine and metabolic abnormalities due to FHA may impair entire homeostasis and have both short- and long-term adverse effects on women's health.

Amenorrhea

As stated above, the suppression of the HPO axis leads to the reduction of pulsatile GnRH secretion, which impairs pulsatile secretory mode of LH and FSH, consequently resulting in hypoestrogenism and anovulation. Hypoestrogenism and a lack of cyclical fluctuations of estradiol and progesterone lead to the absence of regular menstruation. Endometrium persistently remains in the early proliferative phase. It is typically characterized by amenorrhea. It has become more and more common in pubescent females with primary amenorrhea and post-pubescent females with secondary amenorrhea, especially in adolescents and young women of reproductive ages (44,45).

Amenorrhea can continue for several months or even several years, and being different to other eumenorrheic women can make young women feel uncomfortable and depressed. Oligo and amenorrhea were the main complaints of the patients who presented to the gynecological endocrine department at hospitals.

Secondary sexual characteristics

The activation of the HPO axis results in the development of secondary sexual characteristics and the maturation of the reproductive system. The inhibition of the HPO, especially prolonged hypoestrogenism, affects reproductive health. Delayed menarche and the underdevelopment of secondary sex characteristics are common manifestations in girls affected by this disease during puberty. When lasting into adulthood, it can lead to atrophic changes in sexual hormone-affected organs among adult women such as the shrunken breasts and urogenital mucosa (46). Given the above-mentioned influences, the sexual dysfunction caused by hypoestrogenic condition, such as dyspareunia and a low libido, has become a major issue. Women with FHA have more sexuality problems than their healthy counterparts (47).

Infertility

Anovulation is a basic feature of weight loss-related amenorrhea. Patients with this condition find it difficult to become pregnant spontaneously (48), and while these patients may unexpectedly fall pregnant due to irregular ovulation, the state of undernutrition and negative energy balance cannot support the whole process of physiological pregnancy, which may lead to preterm labor, miscarriage, and the premature rupture of membranes.

It is well established that infertility is one of the most serious impairments of reproductive function. The BMI

and body fat, which reflect the energy availability of an individual, appear to send a signal to the hypothalamus that the energy reserves are adequate to sustain pregnancy and lactation. Conversely, *nutritional* status also triggers a self-protection mechanism to inhibit the reproductive function when the body is in a negative energy balance (49).

Weight loss-related amenorrhea is an underestimated clinical problem not only in terms of its morbidity but also in terms of its effects on fertility. Restrictive diet and/or excessive exercise behaviors for aesthetic reasons are prevalent among adolescents, and the symptoms of irregular menses or amenorrhea can be easily neglected, which may cause infertility in adult women. For young women of reproductive age, the reproduction function is important, as infertility not only effects the women themselves but their families, society, and the nation.

Bone loss

Estrogens are the critical determinants that ensure normal bone metabolism in women (50). The action of estrogens can be shown in two roles: stimulating production of osteoprotegerin (OPG) and inhibiting receptor activator of nuclear factor-κB ligand (RANKL) which could adjust the balance of bone remodeling process (51). The minimal effective action concentration of serum estradiol ranges from 40 to 50 pg/mL (52). According to the literature and clinical practice, serum estradiol levels are usually below 20 pg/mL among patients with FHA (53). Women who suffer from hypoestrogenism for a long time present with diminished bone mineral density (BMD), are more likely to develop osteopenia and osteoporosis (54), and are at risk of pathological fractures (55). For patients with eating disorders, in addition to hypoestrogenism, restrictive diet or nutrition deprivation (low calcium and vitamin D3 intake), and other hormonal adaptions [low IGF-1, testosterone, dehydroepiandrosterone (DHEA), fibroblast growth factor 21 (FGF-21], leptin, and elevated cortisol] have a negative effect on bone health (42).

According to the International Society for Clinical Densitometry, amenorrhea-related hypoestrogenism that lasts 6 months could be considered to perform a densitometry of the spinal column (56). The female athlete triad is defined as low energy availability, FHA, and osteoporosis. In these women, the risk of a stress fracture is 2.4–4.9 times higher than healthy women with same age, and the risk of fracture persists throughout their lifespans (50). Low energy availability is the starting point of the female athlete triad and leads to a decrease in estrogen concentration and BMD (50).

For adolescents with a long history of amenorrhea, a lower peak bone mass could occur in this critical pubertal period, which places them at greater risk of osteopenia, osteoporosis, and fractures later in life. Thus, patients who are in puberty, of reproductive age, or in the perimenopausal period need more attention than eumenorrheic women and need to receive timely and suitable treatments.

CVD

Recently, data have indicated that the mortality rate of CVD is low in premenopausal women but high in both postmenopausal women and men in the United States (57). Estrogen exerts a positive, protective effect on the cardiovascular system. For the vascular endothelium, estrogen mediates anti-inflammation, decreases oxidative stress, increases endothelial-cell growth, and inhibits smooth muscle cell proliferation (46). Conversely, long periods of hypoestrogenism can lead to CVD, which is common in postmenopausal women. This correlation could be explained by the following CVD processes: endothelial dysfunction, the reduced bioactivity of nitric oxide, autonomic nervous function perturbation, the hyperactivity of the rennin-angiotensin system, and altered lipid profile. There is limited evidence about the adverse effects of hypoestrogenism on the cardiovascular system of young women. Thus, the effects on the cardiovascular system in young women with hypothalamic amenorrhea require further investigation (58).

Mental disorders

A woman's mood is affected by the cyclical fluctuations of menstruation, particularly serum estrogen levels (59). Hypoestrogenism in young women with FHA is strongly related to the activity changes of various neuropeptides, neurotransmitters, and neurosteroids in the brain. For example, the fluctuation of serotonin, dopamine, and allopregnanolone can modulate mood in amenorrhoeic women (60). Thus, these women who suffered FHA are more likely to suffer from mental disorders. Psychiatric disorders and mood disorders, especially anxiety disorders, depression, and eating disorders, were observed in those patients with anorexia nervosa who were likely to have more dysfunctional attitudes (as demonstrated by higher levels of control, perfectionism, rigidity of ideas, incorrect cognition and being overly concerned about the judgements of others) (17). Amenorrheic women have greater difficulty coping with stressful and negative events from daily life and

show more interpersonal dependence than eumenorrheic women (18).

Treatment

Weight loss-related amenorrhea is a condition that involves the reversible inhibition of the normal function and activity of the HPO axis. We suggest lifestyle change combined with hormonal replacement. The former includes increasing calorie intake and decreasing exercising expenditure is aimed to restore adequate energy availability. But when we found it difficult to correct disordered eating attitudes and compulsive exercising behaviors, it would be considered to assist psychotherapy to treat these coexistent mental disorders. After a positive energy balance is restored, body weight and fat mass subsequently increase, and most patients resume menses. If patients expect to be pregnant but under prolonged amenorrhea and anovulation, we may suggest that application of Pulsatile GnRH therapy help induce ovulation and conceive.

Weight, BMI and body fat percent are effective predictive factors for the resumption of menses (61). Thus, the most effective treatments tend to aim at alleviating the underlying cause. As a combination of factors are often involved in its pathophysiology, including sustained low weight, excessive exercise, poor nutritional intake, and stress, a multidisciplinary treatment approach is needed and more novel therapies need to be developed (62,63).

Treatment of underlying causes

The treatment of chronic menstrual disorders, anovulation, secondary amenorrhea, and infertility resulting from hypothalamic disorders should first aim to alleviate the primary causes. To restore the optimal body fat percentage and BMI, several approaches could be considered, such as modifying lifestyle and dysfunctional attitudes related to high levels of control, perfectionism, and body image, increasing nutrition absorption, reducing physical exercise intensity, and decreasing psycho-emotional strains and chronic stressors. The underlying causes for each person may differ. Thus, both psychological and nutritional interventions require multidisciplinary therapeutic approaches.

It has been proposed that psychosocial and metabolic stressors contribute to FHA and they may affect HPO axis synergistically. Lifestyle changes, such as increasing caloric intake and reducing physical exercises, and cognitive behavioral therapy (CBT) aimed at alleviating psychological stressors, are commonly used non-pharmacological treatment strategies for improving reproductive function and hormonal and energy metabolic status, but not bone health (25). Some observations and clinical trials have indicated that diet interventions that increase the caloric intake for overtraining female athletes with FHA could ameliorate their reproductive function (64,65). Both CBT and hypnotherapy, which are common psychotherapies in clinical practice, can result in follicular growth and ovulation (66). Usually, menses resumes spontaneously as a result of life style modification or environmental changes, but the time at which menses will recover and the threshold of energy availability, body weight, and fat percent are still uncertain and vary from person to person (61). Weight loss-related amenorrhea can be recurrent and refractory if the underlying causes persist or recur.

Hormonal replacement therapy

For patients who do not recover menses after 6–12 months of non-pharmacological therapy, or for those who decline behavioral or psychological treatment, individualized hormonal replacement therapy should be included in therapeutic protocols to prevent long-term complications (62). Research has shown that the administration of a physiologic or small-dose of estrogen exerts positive therapeutic effects. For example, Li *et al.* observed that small-dose estrogen replacement therapy restored ovulation in patients with weight loss-related amenorrhea within an average of 24.1±13.6 months (67). The recovery of pulsatile GnRH secretion with normal frequency and altitude is the critical mechanism for rebuilding ovulation. Other studies have shown that estrogen administration improves the function of the HPO axis, BMD, eating attitudes, and body shape perceptions (68-71).

Cyclic estrogen-progesterone treatment can maintain menstruation and secondary sexual characteristics, promote spontaneous ovulation, and reduce the risk of long-term consequences, such as bone loss. The estrogen dose is important. An optimal dose should be chosen to ensure the attainment of the effective serum estrogen level while minimizing the side effects. Some researches recommend that low-dose contraceptives should be used in sexually active patients suffering from FHA (72). Combined oral contraceptives (COCs) provide higher concentrations of estrogen and progesterone than necessary for hormone therapy and could theoretically suppress the FSH, thereby exacerbating anovulation, which is completely opposite to our purpose of rebuilding ovulation function. Thus,

we are of the view that COCs are not the best choice for the hormonal replacement of FHA. Further, COCs may suppress the IGF-1, which is an important bone trophic hormone. A recent study found that young females who begin to use COCs shortly after menarche may experience detrimental skeletal effects (73).

Treatment of infertility

Most patients can recover menses and ovulation after restoration of energy availability and body fat and weight. When it comes to fertility needs, good nutritional status and an optimal body weight are important conditions that need to be achieved, but it may still be difficult for some women to resume ovulation. Ovulation induction with application of some drugs, such as clomiphene citrate, exogenous gonadotropins, or pulsatile GnRH therapy should be considered (74). A reduced or blunt response to clomiphene does not necessarily present a bad prognosis in terms of menses or fertility in teenagers with FHA (75), because weight loss-related amenorrhea, one kind of FHA, is in hypoestrogenism. Thus, Hypoestrogenic status is unlikely to respond to clomiphene citrate, an anti-estrogen drug.

Pulsatile GnRH therapy is an efficient and practical treatment for ovulation induction in FHA patients (76). The pulsatile administration of GnRH via an infusion pump stimulates the production of the FSH and LH, which increases the estradiol, leads to the development of the growth follicles, and results in ovulation. The intravenous (IV) route and subcutaneous route can be adopted. The pulse interval is 60 to 90 minutes, and the optimal physiological dose of intravascular (IV) administration to mimic the normal pulsatile release of GnRH is 75 ng/kg (77). In clinical practice, a threshold dose of GnRH that reliably induces ovulation has been set pulsatile GnRH therapy triggers normal feedback mechanisms and produces normal concentrations of serum FSH and LH, which can result in single dominant follicle maturation and ovulation in most cycles. Thus, it has been reported that ovulation rates of 90% and pregnancy rates of 80% or higher in women treated with pulsatile GnRH therapy. The rates of multiple gestation and the risk of ovarian hyperstimulation syndrome are extremely low (78). A smaller infusion device has been introduced, making this kind of therapy more convenient and promising.

A study reported a successful pregnancy after the application of pulsatile GnRH therapy in hypothalamic amenorrhea, and ovulation resulted in 10 pregnancies among 7 FHA patients (and 2 pregnancies in 3 FHA patients) (79). Mattle *et al.* observed 120 women with FHA, and found that all the patients ovulated during the first cycle of pulsatile GnRH therapy, as indicated by the pre-ovulatory LH surge and subsequent increase in progestin that reached levels typical to those of a normal luteal phase (80).

Gonadotrophin therapy is widely used to treat infertility caused by anovulation in clinical practice. When pulsatile GnRH therapy is unavailable, gonadotrophin therapy, which includes both LH and FSH therapy, as women do not respond to FSH therapy alone, should be initiated. Gonadotropins were introduced into clinical practice in 1961, human menopausal gonadotropins (HMG) is an ovulation induction drug extracted from the urine of postmenopausal women, in which the ratio of LH to FSH bioactivity is 1:1. Tsutsumi *et al.* reported on a patient with hypothalamic amenorrhea due to weight loss who became pregnant following the administration of HMG and human chorionic gonadotropins (81). If a patient who suffered FHA or had been recovered from it for some time now becomes pregnant, she may require special pregnancy monitoring due to their increased risk of miscarriage and preterm labor (82). However, after pregnancy terminates, patients may still remain amenorrhoeic and anovulation due to prolonged weight loss, energy deficiency or some other complicated psychological factors, so it's difficult to be pregnant spontaneously again.

Psychotherapy

Psychiatric disorders and mood disorders (e.g., anxiety disorders, depression, eating disorders, and obsessive-compulsive disorders) are more common in FHA women than eumenorrheic women. Behavioral and psychological interventions, such as CBT and family-based therapy, have been shown to reverse amenorrhea (66). Pharmacotherapy may be considered to treat psychiatric morbidities when behavioral therapy is ineffective (83). Faced with some special cases of severe or refractory psychiatric disorders, gynecologists should consult with psychiatrists on treatments. Thus, multidisciplinary and emerging therapeutic approaches that focus on both the physical and mental conditions of patients are needed.

Experimental or emerging treatment

Leptin is an adipokine hormone secreted in proportion to fat mass; thus, a state of hyperleptinemia may be observed in weight loss-related amenorrhea patients. As an important mediator, leptin affects reproduction in acute or chronic energy deficient patients by regulating the HPO axis,

ovarian function, and the activin-follistatin system (38,84). Research has proven that recombinant leptin as a potential therapy in FHA, as it has been proven to be effective in increasing estradiol and progesterone levels (85), restoring menstruation, and improving bone metabolism (86).

Kisspeptin is a key regulator of hypothalamic GnRH neurons and is essential for reproductive health (87). A study has shown that a kisspeptin receptor (KISS1R) agonist and kisspeptin-54 potently stimulate the function of the HPG axis (88). However, more studies need to be conducted to determine the safety and efficacy of these experimental treatments. Additionally, more cooperative multidisciplinary research (including in the areas of psychiatry and neurology) is needed to explore emerging treatments.

Conclusions

Weight loss-related amenorrhea is an important and common type of FHA with suppressive but reversible HPO axis's function, and there is no effective treatment could induce recovery of spontaneous ovulation as soon as we diagnose it. It is likely a chronic disease. Besides its prominent symptom (i.e., amenorrhea), some important long-term consequences (e.g., infertility) and other negative effects of hypoestrogenism (e.g., bone loss and CVDs), especially in young women, also need to be recognized timely and properly. While the underlying causes need to be distinguished and judged clearly and carefully, and then we could adopt an individualized therapeutic protocol. However, the appropriate and effective therapies are still under debate and investigation.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6366/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6366/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Fontana R, Della Torre S. The Deep Correlation between Energy Metabolism and Reproduction: A View on the Effects of Nutrition for Women Fertility. Nutrients 2016;8:87.
2. Xu CJ, Hua KQ, Li XT, et al. Practice of obstetrics & gynecology. 4th edition. Beijing: People's Medical Publishing House; 2018:1158.
3. Morrison AE, Fleming S, Levy MJ. A review of the pathophysiology of functional hypothalamic amenorrhoea in women subject to psychological stress, disordered eating, excessive exercise or a combination of these factors. Clin Endocrinol (Oxf) 2021;95:229-38.
4. Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab 2003;88:297-311.
5. Williams NI, Leidy HJ, Hill BR, et al. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. Am J Physiol Endocrinol Metab 2015;308:E29-39.
6. Koltun KJ, De Souza MJ, Scheid JL, et al. Energy Availability Is Associated With Luteinizing Hormone Pulse Frequency and Induction of Luteal Phase Defects. J Clin Endocrinol Metab 2020;105:185-93.
7. Melin AK, Heikura IA, Tenforde A, et al. Energy Availability in Athletics: Health, Performance, and Physique. Int J Sport Nutr Exerc Metab 2019;29:152-64.
8. Mathew H, Castracane VD, Mantzoros C. Adipose tissue and reproductive health. Metabolism 2018;86:18-32.
9. Current evaluation of amenorrhea. Fertil Steril 2006;86:S148-55.
10. Ma SY, Zhu M. Research Progress on Functional

Hypothalamic Amenorrhea. Journal of International Reproductive Health/Family Planning 2020;39:67-70.
11. Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. Lancet Diabetes Endocrinol 2014;2:581-92.
12. De Souza MJ, Hontscharuk R, Olmsted M, et al. Drive for thinness score is a proxy indicator of energy deficiency in exercising women. Appetite 2007;48:359-67.
13. Mei L, Chen J. Surveys on the prevalence of eating disorders in mainland China. Journal of Clinical Psychiatry 2021;31:80-1.
14. Frisch RE. Body fat, menarche, fitness and fertility. Hum Reprod 1987;2:521-33.
15. Frisch RE. Body fat, puberty and fertility. Biol Rev Camb Philos Soc 1984;59:161-88.
16. Sanborn CF, Albrecht BH, Wagner WW Jr. Athletic amenorrhea: lack of association with body fat. Med Sci Sports Exerc 1987;19:207-12.
17. Bomba M, Corbetta F, Bonini L, et al. Psychopathological traits of adolescents with functional hypothalamic amenorrhea: a comparison with anorexia nervosa. Eat Weight Disord 2014;19:41-8.
18. Valsamakis G, Chrousos G, Mastorakos G. Stress, female reproduction and pregnancy. Psychoneuroendocrinology 2019;100:48-57.
19. Diamanti A, Ubertini GM, Basso MS, et al. Amenorrhea and weight loss: not only anorexia nervosa. Eur J Obstet Gynecol Reprod Biol 2012;161:111-2.
20. Schneider JE. Energy balance and reproduction. Physiol Behav 2004;81:289-317.
21. Bo S, Fadda M, Fedele D, et al. A Critical Review on the Role of Food and Nutrition in the Energy Balance. Nutrients 2020;12:1161.
22. Pinilla L, Fernández-Fernández R, Roa J, et al. Selective role of neuropeptide Y receptor subtype Y2 in the control of gonadotropin secretion in the rat. Am J Physiol Endocrinol Metab 2007;293:E1385-92.
23. Scheid JL, De Souza MJ, Hill BR, et al. Decreased luteinizing hormone pulse frequency is associated with elevated 24-hour ghrelin after calorie restriction and exercise in premenopausal women. Am J Physiol Endocrinol Metab 2013;304:E109-16.
24. Evans JJ, Anderson GM. Balancing ovulation and anovulation: integration of the reproductive and energy balance axes by neuropeptides. Hum Reprod Update 2012;18:313-32.
25. Kyriakidis M, Caetano L, Anastasiadou N, et al. Functional hypothalamic amenorrhoea: leptin treatment, dietary intervention and counselling as alternatives to traditional practice - systematic review. Eur J Obstet Gynecol Reprod Biol 2016;198:131-7.
26. Dardeno TA, Chou SH, Moon HS, et al. Leptin in human physiology and therapeutics. Front Neuroendocrinol 2010;31:377-93.
27. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995;1:1155-61.
28. Smith GD, Jackson LM, Foster DL. Leptin regulation of reproductive function and fertility. Theriogenology 2002;57:73-86.
29. Zhang Y, Chua S Jr. Leptin Function and Regulation. Compr Physiol 2017;8:351-69.
30. Elias CF. Leptin action in pubertal development: recent advances and unanswered questions. Trends Endocrinol Metab 2012;23:9-15.
31. Chehab FF, Lim ME, Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. Nat Genet 1996;12:318-20.
32. Chehab FF, Mounzih K, Lu R, et al. Early onset of reproductive function in normal female mice treated with leptin. Science 1997;275:88-90.
33. Chehab FF. 20 years of leptin: leptin and reproduction: past milestones, present undertakings, and future endeavors. J Endocrinol 2014;223:T37-48.
34. Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: facts and expectations. Metabolism 2015;64:146-56.
35. Baver SB, Hope K, Guyot S, et al. Leptin modulates the intrinsic excitability of AgRP/NPY neurons in the arcuate nucleus of the hypothalamus. J Neurosci 2014;34:5486-96.
36. Gonçalves GH, Li W, Garcia AV, et al. Hypothalamic agouti-related peptide neurons and the central melanocortin system are crucial mediators of leptin's antidiabetic actions. Cell Rep 2014;7:1093-103.
37. Chen X, Xiao Z, Cai Y, et al. Hypothalamic mechanisms of obesity-associated disturbance of hypothalamic-pituitary-ovarian axis. Trends Endocrinol Metab 2022;33:206-17.
38. Childs GV, Odle AK, MacNicol MC, et al. The Importance of Leptin to Reproduction. Endocrinology 2021;162:bqaa204.
39. Park HK, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 2015;64:24-34.
40. Roman EA, Ricci AG, Faletti AG. Leptin enhances ovulation and attenuates the effects produced by food restriction. Mol Cell Endocrinol 2005;242:33-41.

41. Chou SH, Chamberland JP, Liu X, et al. Leptin is an effective treatment for hypothalamic amenorrhea. Proc Natl Acad Sci U S A 2011;108:6585-90.
42. Roberts RE, Farahani L, Webber L, et al. Current understanding of hypothalamic amenorrhoea. Ther Adv Endocrinol Metab 2020;11:2042018820945854.
43. Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol 2017;13:174-86.
44. Kimmel MC, Ferguson EH, Zerwas S, et al. Obstetric and gynecologic problems associated with eating disorders. Int J Eat Disord 2016;49:260-75.
45. Maïmoun L, Georgopoulos NA, Sultan C. Endocrine disorders in adolescent and young female athletes: impact on growth, menstrual cycles, and bone mass acquisition. J Clin Endocrinol Metab 2014;99:4037-50.
46. Shufelt CL, Torbati T, Dutra E. Hypothalamic Amenorrhea and the Long-Term Health Consequences. Semin Reprod Med 2017;35:256-62.
47. Dundon CM, Rellini AH, Tonani S, et al. Mood disorders and sexual functioning in women with functional hypothalamic amenorrhea. Fertil Steril 2010;94:2239-43.
48. Juul A, Hagen CP, Aksglaede L, et al. Endocrine evaluation of reproductive function in girls during infancy, childhood and adolescence. Endocr Dev 2012;22:24-39.
49. Nutrition Working Group, O'Connor DL, Blake J, et al. Canadian Consensus on Female Nutrition: Adolescence, Reproduction, Menopause, and Beyond. J Obstet Gynaecol Can 2016;38:508-554.e18. Erratum in: J Obstet Gynaecol Can. 2018 Feb;40(2):268.
50. Nose-Ogura S, Harada M, Hiraike O, et al. Management of the female athlete triad. J Obstet Gynaecol Res 2018;44:1007-14.
51. Chou SH, Mantzoros C. Bone metabolism in anorexia nervosa and hypothalamic amenorrhea. Metabolism 2018;80:91-104.
52. Crandall CJ, Tseng CH, Karlamangla AS, et al. Serum sex steroid levels and longitudinal changes in bone density in relation to the final menstrual period. J Clin Endocrinol Metab 2013;98:E654-63.
53. Shen ZQ, Xu JJ, Lin JF. Resumption of menstruation and pituitary response to gonadotropin-releasing hormone in functional hypothalamic amenorrhea subjects undertaking estrogen replacement therapy. J Endocrinol Invest 2013;36:812-5.
54. Lambrinoudaki I, Papadimitriou D. Pathophysiology of bone loss in the female athlete. Ann N Y Acad Sci 2010;1205:45-50.
55. Pepper M, Akuthota V, McCarty EC. The pathophysiology of stress fractures. Clin Sports Med 2006;25:1-16, vii.
56. Crabtree NJ, Arabi A, Bachrach LK, et al. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom 2014;17:225-42.
57. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018;137:e67-e492.
58. Ouyang P, Michos ED, Karas RH. Hormone replacement therapy and the cardiovascular system lessons learned and unanswered questions. J Am Coll Cardiol 2006;47:1741-53.
59. Wan L, Huang RJ, Luo ZH, et al. Reproduction-Associated Hormones and Adult Hippocampal Neurogenesis. Neural Plast 2021;2021:3651735.
60. Kormos V, Gaszner B. Role of neuropeptides in anxiety, stress, and depression: from animals to humans. Neuropeptides 2013;47:401-19.
61. Pape J, Herbison AE, Leeners B. Recovery of menses after functional hypothalamic amenorrhoea: if, when and why. Hum Reprod Update 2021;27:130-53.
62. Gordon CM, Ackerman KE, Berga SL, et al. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017;102:1413-39.
63. Sophie Gibson ME, Fleming N, Zuijdwijk C, et al. Where Have the Periods Gone? The Evaluation and Management of Functional Hypothalamic Amenorrhea. J Clin Res Pediatr Endocrinol 2020;12:18-27.
64. Mallinson RJ, Williams NI, Olmsted MP, et al. A case report of recovery of menstrual function following a nutritional intervention in two exercising women with amenorrhea of varying duration. J Int Soc Sports Nutr 2013;10:34.
65. De Souza MJ, Mallinson RJ, Strock NCA, et al. Randomised controlled trial of the effects of increased energy intake on menstrual recovery in exercising women with menstrual disturbances: the 'REFUEL' study. Hum Reprod 2021;36:2285-97.
66. Michopoulos V, Mancini F, Loucks TL, et al. Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: a randomized, controlled trial. Fertil Steril 2013;99:2084-91.e1.
67. Li X, Xue XH, Xu JJ, et al. Effect of small dosage of estrogen on ovulation functional recovery of patients

with weight-loss related amenorrhea. Chinese Journal of Clinical Medicine 2016;23:477-9.
68. Ackerman KE, Singhal V, Baskaran C, et al. Oestrogen replacement improves bone mineral density in oligo-amenorrhoeic athletes: a randomised clinical trial. Br J Sports Med 2019;53:229-36.
69. Genazzani AD, Podfigurna-Stopa A, Czyzyk A, et al. Short-term estriol administration modulates hypothalamo-pituitary function in patients with functional hypothalamic amenorrhea (FHA). Gynecol Endocrinol 2016;32:253-7.
70. Genazzani AD, Meczekalski B, Podfigurna-Stopa A, et al. Estriol administration modulates luteinizing hormone secretion in women with functional hypothalamic amenorrhea. Fertil Steril 2012;97:483-8.
71. Misra M, Katzman DK, Estella NM, et al. Impact of physiologic estrogen replacement on anxiety symptoms, body shape perception, and eating attitudes in adolescent girls with anorexia nervosa: data from a randomized controlled trial. J Clin Psychiatry 2013;74:e765-71.
72. Sowinska-Przepiera E, Andrysiak-Mamos E, Jarzabek-Bielecka G, et al. Functional hypothalamic amenorrhoea – diagnostic challenges, monitoring, and treatment. Endokrynol Pol 2015;66:252-60.
73. Almstedt HC, Cook MM, Bramble LF, et al. Oral contraceptive use, bone mineral density, and bone turnover markers over 12 months in college-aged females. J Bone Miner Metab 2020;38:544-54.
74. Martin KA, Hall JE, Adams JM, et al. Comparison of exogenous gonadotropins and pulsatile gonadotropin-releasing hormone for induction of ovulation in hypogonadotropic amenorrhea. J Clin Endocrinol Metab 1993;77:125-9.
75. Devoto E, Aravena L. Favorable reproductive and menstrual evolution in adult women, who presented in the adolescence, menstrual disturbances by hypothalamic dysfunction and lack of response to clomiphene. Rev Med Chil 2002;130:745-52.
76. Germain N, Fauconnier A, Klein JP, et al. Pulsatile gonadotropin-releasing hormone therapy in persistent amenorrheic weight-recovered anorexia nervosa patients. Fertil Steril 2017;107:502-9.
77. Martin K, Santoro N, Hall J, et al. Clinical review 15: Management of ovulatory disorders with pulsatile gonadotropin-releasing hormone. J Clin Endocrinol Metab 1990;71:1081A-G.
78. White DM, Hardy K, Lovelock S, et al. Low-dose gonadotropin induction of ovulation in anovulatory women: still needed in the age of IVF. Reproduction 2018;156:F1-F10.
79. Christou F, Pitteloud N, Gomez F. The induction of ovulation by pulsatile administration of GnRH: an appropriate method in hypothalamic amenorrhea. Gynecol Endocrinol 2017;33:598-601.
80. Mattle V, Bilgyicildirim A, Hadziomerovic D, et al. Polycystic ovarian disease unmasked by pulsatile GnRH therapy in a subgroup of women with hypothalamic amenorrhea. Fertil Steril 2008;89:404-9.
81. Tsutsumi R, Fujimoto A, Osuga Y, et al. Successful pregnancy following low-dose hCG administration in addition to hMG in a patient with hypothalamic amenorrhea due to weight loss. Gynecol Endocrinol 2012;28:460-2.
82. Easter A, Treasure J, Micali N. Fertility and prenatal attitudes towards pregnancy in women with eating disorders: results from the Avon Longitudinal Study of Parents and Children. BJOG 2011;118:1491-8.
83. Bulik CM, Berkman ND, Brownley KA, et al. Anorexia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007;40:310-20.
84. Perakakis N, Upadhyay J, Ghaly W, et al. Regulation of the activins-follistatins-inhibins axis by energy status: Impact on reproductive function. Metabolism 2018;85:240-9.
85. Welt CK, Chan JL, Bullen J, et al. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med 2004;351:987-97.
86. Foo JP, Polyzos SA, Anastasilakis AD, et al. The effect of leptin replacement on parathyroid hormone, RANKL-osteoprotegerin axis, and Wnt inhibitors in young women with hypothalamic amenorrhea. J Clin Endocrinol Metab 2014;99:E2252-8.
87. Abbara A, Eng PC, Phylactou M, et al. Kisspeptin receptor agonist has therapeutic potential for female reproductive disorders. J Clin Invest 2020;130:6739-53.
88. Jayasena CN, Nijher GM, Chaudhri OB, et al. Subcutaneous injection of kisspeptin-54 acutely stimulates gonadotropin secretion in women with hypothalamic amenorrhea, but chronic administration causes tachyphylaxis. J Clin Endocrinol Metab 2009;94:4315-23.

(English Language Editor: L. Huleatt)

Cite this article as: Chen L, Lu Y, Zhou YF, Wang Y, Zhan HF, Zhao YT, Wang YL, Zhang FF, Chen H, Li X. The effects of weight loss-related amenorrhea on women's health and the therapeutic approaches: a narrative review. Ann Transl Med 2023;11(2):132. doi: 10.21037/atm-22-6366