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Hypogonadotropic hypogonadism in women

Hipogonadyzm hipogonadotropowy u kobiet

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Abstract

This article presents the role of the hypothalamus in reproduction, the definition of hypogonadotropic hypogonadism (HH), and the causes of acquired and syndromic HH and idiopathic HH (IHH). The authors present a short review of major causes of acquired HH, but most of the causes of IHH will not be discussed because they do not fall within the scope of the article. More attention is devoted to idiopathic HH, especially the genetic basis of IHH. Also presented in the article are clinical criteria of CHARGE syndrome. Later, the article discusses the clinical presentation, establishing the diagnosis, and management of IHH. The article ends with a brief overview of nutritional hypothalamic dysfunction and athletic amenorrhea. **(Pol J Endocrinol 2011; 62 (6): 560–567)**

Key words: *hypogonadotropic hypogonadism, gonadotropin-releasing hormone (GnRH), Kallmann syndrome*

Streszczenie

Artykuł przedstawia rolę podwzgórza w reprodukcji, definicję hipogonadyzmu hipogonadotropowego (HH), przyczyny nabytego i systemowego HH oraz idiopatycznego HH. Autorzy prezentują krótki przegląd najważniejszych przyczyn nabytego HH, ale większość nie została omówiona, ponieważ nie wchodzą w zakres tego artykułu. Więcej uwagi poświęcono idiopatycznemu HH, szczególnie jego genetycznym podstawom. Przedstawiono kliniczne kryteria zespołu CHARGE. Omówiono również kliniczne objawy, ustalanie rozpoznania oraz postępowanie w IHH. Artykuł kończy się krótkim przeglądem żywieniowych zaburzeń podwzgórza i braku miesiączki u młodocianych stosujących intensywny trening fizyczny. **(Endokrynol Pol 2011; 62 (6): 560–567)**

Słowa kluczowe: *hipogonadyzm hipogonadotropowy, gonadoliberyna (GnRH), zespół Kallmanna*

Introduction

During the last decade, the rapidly expanding fields of molecular biology and genetics have allowed us to better understand the clinical symptoms of endocrine disorders, including menstrual cycle disturbances at reproductive age.

The role of the hypothalamus in reproduction

Hypothalamic nuclei secrete gonadotropin-releasing hormone (GnRH), which is the primary regulator of reproductive function. The pulsatile nature of hypothalamic GnRH release determines episodic pituitary secretion. The periodicity and amplitude of the pulsatile rhythm of GnRH/gonadotropin secretion are crucial in the entire reproductive axis. The fact that GnRH plays a critical role in the feedback regulation of gonadotropin secretion has been known for many years. But the neural mechanism of its action remains unclear. Intensive investigations over the past seven years strongly suggest that sex steroid feedback regulation of GnRH cells is predominantly exerted via kisspeptin cells, although many other cell types in the brain also play a role [1].

GnRH acts as a primary stimulus for gonadotropin release. An optimal frequency of GnRH pulsatile stimulation of the gonadotropes is essential to maintain appropriate plasma levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH). The circulating gonadotropins decline when the frequency of GnRH pulses is too low, and also when GnRH stimulation is too frequent or continuous. Different GnRH pulse frequencies have been found to participate in the regulation of LH β and FSH β gene expression. Interestingly, an increase in GnRH pulse frequency favours LH β gene expression, while a decrease favours FSH β gene expression [2]. In addition to GnRH, regulation of the activin/follistatin/inhibin feedback loop is thought to be important for differential LHβ and FSHβ synthesis. The main roles which gonadotropins play are the regulation and control of sex differentiation and gonadal function, namely gametogenesis and steroidogenesis. Hypogo-

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nadotropic hypogonadism occurs when GnRH neurons are damaged.

Definition of hypogonadotropic hypogonadism

Hypogonadotropic hypogonadism (HH) is characterised by absent or decreased function of the female ovaries. It can be defined by inappropriately low serum concentrations of LH and FSH, which is an effect of GnRH deficiency. HH is most frequently acquired and caused by a number of pathological processes, but it can also occur as part of various congenital syndromes. Genetic causes of central hypogonadism have been identified. Idiopathic or isolated HH (IHH) was then used to indicate cases in which secondary causes of HH had been excluded.

Acquired and syndromic causes of HH

Acquired and syndromic causes of HH include the following: CNS or pituitary tumours, infiltrative diseases, infection, brain/pituitary radiation, pituitary apoplexy, head trauma, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy), functional deficiency resulting from chronic systemic illness, eating disorders, hypothyroidism, hyperprolactinemia, diabetes mellitus, and Cushing's disease.

Hypogonadotropic hypogonadism may be present in hypothyroidism. Pituitary sensitivity to GnRH may be reduced in hypothyroid children. In hypothyroid women, pituitary responsiveness to LHRH is not altered but chronic elevation of basal gonadotropins may partially explain the anovulation [3]. Hypothyroidism in women is less frequently associated with menstrual disturbance, but menstrual irregularities tend to be more frequent in severe hypothyroidism [4]. Some women with diagnosed hypothyroidism have associated hyperprolactinemia.

Hyperprolactinemia may cause hypogonadism. Overt hypogonadism occurs when prolactin (PRL) is significantly increased. GnRH release is suppressed, resulting in low gonadotropin levels. LH pulse frequency is decreased, while LH response to GnRH is normal or increased [5]. The normalisation of PRL is associated with recovering LH pulse frequency and correcting hypogonadism.

Mass lesions in the hypothalamus can also affect the secretion of GnRH, disrupt the hypothalamic–hypophyseal portal circulation and cause hypogonadotropic hypogonadism. Such cases usually cause other pituitary hormone abnormalities as well. Examples of tumours that cause HH are craniopharyngiomas and germ cell tumours. Craniopharyngiomas are rare epithelial tumours arising from remnants of the craniopharyngeal duct that occur with an annual incidence of 0.13 cases per 100,000 person–years. They are histologically benign lesions, usually cystic or mixed (84% to 99%). Craniopharyngiomas almost always have a suprasellar component and are rarely purely intrasellar. The endocrine, visual, and neuropsychological morbidities associated with craniopharyngiomas are significant. The frequency of individual hormone deficits varies significantly across studies (88% to 100% for growth hormone, 80% to 95% for FSH and LH, 55% to 88% for adrenocorticotropic hormone, 39% to 95% for thyroid-stimulating hormone, and 25% to 86% for antidiuretic hormone). Potentially more disabling are the consequences of hypothalamic damage that occurs so commonly in patients with craniopharyngiomas [6]. Germ cell tumours are believed to result from malignant transformation and abnormal migration of primordial germ cells. Germ cell tumours occur most commonly in the pineal region (50%) and in the anterior hypothalamus (30%); these tumours can cause hypopituitarism.

Infiltrating diseases which cause hypothalamic dysfunction include sarcoidosis, Langerhans cell histiocytosis, haemochromatosis, leukaemia, lymphoma and Wegener's granulomatosis. Central infiltrating disease is often the presenting feature of the other associated hormonal abnormalities. In this article, we present a short review of the major causes of acquired HH, but most of the above causes of HH will not be discussed because they do not fall within the scope of the article.

Idiopathic HH

Idiopathic hypogonadotropic hypogonadism (IHH), also called isolated GnRH deficiency, is characterised by a failure of initiation of puberty due to insufficient gonadotropin release, thus resulting in the failure to develop secondary sexual characteristics and a mature reproductive system. Currently known genetic defects account for about 30% of all IHH cases. When embryonic migration of GnRH neurons from the nasal placode to their final destination in the hypothalamus is disrupted, the resulting phenotype is Kallmann syndrome (KS), which is clinically characterised by hypogonadotropic hypogonadism and anosmia. Normosmic idiopathic hypogonadotropic hypogonadism (nIHH) distinguished from Kallmann syndrome has been observed. Both chromosomal abnormalities and single gene mutations have been identified in patients with IHH and KS [6].The prevalence of cytogenetic abnormalities is unknown in IHH/KS patients unless they have additional features suggesting a contiguous gene deletion syndrome that may be detectable by karyotyping.

Family members with the same genotype may display a range of features of the GnRH neurons that successfully completed their embryonic journey to the hypothalamus. The prevalence of IHH has been estimated at between 1 in 4,000 and 1 in 10,000 males. It is reported to be between two and five times less frequent in females [7]. The paradigm of this division is to define Kallmann syndrome as a form generally combined with anosmia. There is substantial variation in clinical expression of the same genetic defect in families of patients with complete anosmia and hypogonadotropic hypogonadism to less severe hypogonadotropic hypogonadism manifesting as delayed puberty.

Genetic basis for IHH

The genetic causes of Kallmann syndrome and nIHH are summarised in Table I. Some genes (FGFR1, FGF8, PROKR2, PROK2, CHD7) have been associated with both Kallmann syndrome and nIHH.

Kallmann syndrome 1, caused by mutation in the KAL1 gene, is inherited in an X-linked manner. Deletion of KAL1 is an extremely rare cause of this syndrome. The KAL1 gene encodes an extracellular glycoprotein called anosmin-1, which is an adhesion molecule responsible for the migration of GnRH neurons and formation of the olfactory bulb in the foetal period. This syndrome has not been described in women so far.

Kallmann syndromes 2 and 6 are caused by mutations of the FGFR1 (fibroblast growth factor receptor) and FGF8 (fibroblast growth factor 8) genes. FGFR1 requires heparin sulphate proteoglycans as co-receptors, and anosmin-1. Loss of FGFR1 function has been confirmed as producing reproductive abnormalities ranging from severe autosomal dominant Kallmann syndrome through autosomal dominant, fully penetrant nIHH, to delayed puberty.

Approximately 10% of patients with Kallmann syndrome have been found to have loss of function mutations in FGFR1. FGF8 mutation patients exhibited vari-

Table I. *Genetic defects causing idiopathic hypogonadotropic hypogonadism (IHH). Modified by [28]*
Tabela I. *Uszkodzenie genetyczne powodujące idiopatyczny hipogonadyzm hipogonadotropowy. Zmodyfikowane przez [28]*

Gene	Year linked to human HH	Syndrome name	Phenotypes	Inheritance	Comment
KAL1	1991	Kallmann syndrome 1	KS	X-linked R	70% synkinesia 30% unilateral renal agenesis
FGFR1	2003	Kallmann syndrome 2	KS nIHH	DA (AR) oligogenic	30% Cleft lip/palate common
NELF		KSIHH	Digenic monogenic		
PROKR2	2006	Kallmann syndrome 3	KS nIHH	AR AD oligogenic	Weak reported association with epilepsy, sleep disorder, synkinesia, fibrous dysplasia, obesity
PROK2	2006	Kallmann syndrome 4	KS nIHH	AR AD oligogenic	
CHD7	2004	Kallmann syndrome 5	CHARGE syn KS	AD	Deafness and semicircular canal hypoplasia common
FGF8	2008	Kallmann syndrome 6	KS nIHH	AD (AR) oligogenic	Cleft lip/palate relatively common
GNRHR	1997		nIHH	AR oligogenic	No accessory features
GNRH1	2009		nIHH	AR AD?	No accessory features
KISS1R	2003		nIHH	AR	No accessory features
TAC3	2009		nIHH	AR	Only 2 patients described to date, both with mild learning disability
TACR3	2009		nIHH	AR	No accessory features
LEP	1997		IHH	AR	Obesity
LEPR	1998		IHH	AR	Obesity
NROB1	1994		IHH	XLR	Adrenal hypoplasia congenital
PCSK1			IHH	AR	Obesity

KS — Kallmann syndrome; nIHH — normosmic isolated hypogonadotropic hypogonadism; AD — autosomal dominant; AR — autosomal recessive; XLR — X-linked recessive

Table II *Clinical criteria of CHARGE Syndrome by [10]*

Tabela II. *Kryteria kliniczne zespołu CHARGE. Na podstawie [10]*

Major criteria
Coloboma of the iris, retina, choroid or disc (75–90%)
Microphthalmia
Choanal atresia (35–65%)
Ear abnormalities (> 95%): — external ear (lop or cup shaped) — middle ear (ossicular malformations — chronic serous otitis media) — inner ear (cochlear defects) — mixed deafness (60–90%)
Cranial nerve dysfunction: — unilateral or bilateral facial palsy — sensorineural deafness — swallowing problems
Minor criteria
Hypoplastic genitalia: — micropenis and cryptorchidism (80%) — hypoplastic labia (30–40%)
HH (65–85%)
Developmental delay: — delayed motor milestones — language delay — learning disability of varying degree
Cardiovascular malformations: — conotruncal defect, e.g. Fallot's tetralogy — AV canal defects — aortic valve or arch defects
Growth deficiency: — short stature — GH deficiency Orofacial cleft (15–20%) Tracheoesophageal fistula Characteristic facies
Inclusion rule
4 majors OR 3 majors + 3 minors

HH — hypogonadotropic hypogonadism; GH — growth hormone

ous degrees of olfactory function and GnRH function. In addition, cleft palate is found in up to 30% of patients, while cartilage abnormalities in either ear or nose, and some digital anomalies, have been reported [8].

Nasal embryonic LHRH factor (NELF) may play a pivotal role in GnRH neuron migration, puberty and reproduction. A NELF gene mutation and an FGFR1 mutation have been reported in a family which together produced KS, but not NELF by itself [9].

Kallmann syndromes 3 and 4 are caused by mutations in the PROKR2 (prokineticin receptor 2) and PROK2 (prokineticin 2) genes. Prokineticin 2 is an 81-amino acid peptide, which together with its receptor has been recognised as a strong candidate for failed development of the olfactory bulb and migration of GnRH neurons. These syndromes were found in 9% of Kallmann syndrome patients, most of them being heterozygous; however, homozygous and compound heterozygous mutations have also been described. Patients with PROK2 or PROKR2 mutations have considerable phenotypic variability ranging from Kallmann syndrome to nIHH. A variety of accompanying clinical features, including fibrous dysplasia, synkinesia, and epilepsy, have been reported in patients with PROK2 or PROKR2 mutations.

Kallmann syndrome 5 is caused by a mutation of the CHD7 gene, which encodes a chromatin-remodelling factor (chromodomain helicase DNA-binding protein 7) and is defective in CHARGE syndrome. Some patients also have IHH and hyposmia. On the basis of the hypothesis that Kallmann syndrome and nIHH may be a milder allelic variant of CHARGE syndrome, patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome. The term 'CHARGE syndrome' is used to describe a pattern of birth defects in children with coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital anomaly and ear abnormality. The prevalence of CHARGE syndrome is approximately 1 in 10,000, and more than 400 patients have now been reported [10]. The clinical criteria of CHARGE syndrome are summarised in Table II. GnRH1 and GnRHR gene defects cause nIHH. To date, many familial and some sporadic cases of GnRHR gene mutation have been reported. On the basis of a large series, GnRHR mutations have been suggested to account for about 40–50% of familial nIHH, and around 17% of sporadic nIHH. In most early reports, the GnRHR defects consisted of point mutations leading to amino acid substitutions.

Rarer mutations lead to frame-shifts or premature stop codons, resulting in a truncated protein, but no true GnRHR1 deletions have so far been described [11]. The most consistent characteristic of patients with GnRHR mutation is their pituitary resistance to pulsatile GnRH administration when the phenotype is severe. Pregnancy has been obtained after pulsatile administration of GnRH. In addition, isolated cases of nIHH have presented with pregnancy after the administration of clomiphene citrate [7]. The differentiated clinical expression of GnRHR mutation results in partial loss of the GnRHR function, and in one case this was attributed to interaction with a mutation in FGFR1, which produces different phenotypes [2].

Recently, defects in the GNRH1 gene itself have been reported for the first time. Chan et al. [3] reported a homozygous mutation in a male patient with severe nIHH. This single basepair deletion produces a frame shift that is predicted to disrupt the GnRH decapep-

tide. These authors also identified a rare heterozygous GnRH1 sequence variant in four patients with nIHH. Simultaneously, Bouligand et al. [11] presented isolated familial nIHH and GnRH1 mutation. The case reports concerned two of four children of non-consanguineous parents who were found to have nIHH. Both brother and sister showed characteristics of severe nIHH, and simultaneously they had a blunted response to GnRH bolus administration (100 μg intravenously).

A mutation in the G-protein-coupled receptor GPR 54 was described in 2003 [14]. GPR 54 had previously been shown to be the receptor for a small peptide derived from the KISS1 gene (leading to its redesignation as KISS1R). Before this discovery, some cases of familial nIHH had been identified as resulting from defects of the short arm of chromosome 19 [15]. Two genetic studies, one performed in the USA and the other in France, demonstrated that nIHH may be due to inactivation of KISS1R [16]. KISS1R mutations are a rare cause of nIHH. Individuals with nIHH have been shown to have severely reduced LH pulse amplitude, but approximately normal pulse frequency. Successful pregnancy has been reported after specific stimulation of ovulation [17].

Topaloglu et al. [18] reported four human pedigrees with severe congenital gonadotropin deficiency and pubertal failure in which all affected individuals were homozygous for loss of function mutation in TAC3 (encoding neurokinin B) or its receptor TACR3 (encoding neurokinin B receptor). Gianetti et al. [20] presented phenotypic information concerning seven females with coding sequence variants in TACR3/TAC3. None of the females had spontaneous thelarche, and five of them demonstrated evidence for reversibility of their hypogonadism after discontinuation of therapy. Neurokinin B, a member of the substance P related tachykinin family, is known to be highly expressed in hypothalamic neurons, especially in the actuate nucleus, and is co-expressed there with kisspeptin. Neurokinin B exerts an influence on reproductive function, and its importance in sustaining the integrity of the hypothalamic-pituitary-gonadal axis is expected to be elucidated over the next few years.

Clinical presentation

Kallmann syndrome may be suspected in a prepubertal patient with anosmia, especially when there is already a positive family history. Usually, however, a clear picture of the disorder is revealed in adolescence. Rarely, individuals have normal sexual maturation and develop IHH in adulthood. The majority of girls can be suspected of IHH when pubertal development is incomplete or absent after the age of 13. Primary amenorrhea occurs in approximately 90% of cases of IHH. Girls before puberty have normal stature, but the pubertal growth spurt does not occur. Stature retardation is very rare, but in contrast the absence of long-bone epiphyseal closure explains these patients' frequent eunuchoid aspect and relative tallness. To distinguish nIHH from constitutional late puberty can be difficult when these reversible forms occur before 20 years of age.

Adult females have little or no breast development, although in some patients it may be almost normal. Since adrenal maturation proceeds normally, the low levels of androgen production in the adrenal glands may allow normal onset of pubic hair growth (adrenarche) and therefore the pubic hair may be absent, sparse, or even normal. Partial forms are frequent in women, while a very mild form occurs in only a minority of women. This form of IHH can be revealed by isolated chronic anovulation, whereas oestradiol secretion is adequate for endometrial development, and can be shown by onset of bleeding after progestin administration, as well as by oligomenorrhea. These attenuated forms have also been described as having conceived spontaneously.

Retarded bone maturation, osteopenia and osteoporosis are frequent when the gonadotropin deficiency is discovered in adulthood [17].

Establishing the diagnosis

The diagnosis of IHH is established by the presence of both suggestive clinical findings and laboratory findings consistent with hypogonadotropic hypogonadism, and the absence of secondary causes of hypothalamic hypogonadism. The first step of the diagnostic procedure is a detailed physical examination with the assessment of the development of secondary sexual characteristics, and checking family history. Then it is necessary to perform a semiquantitative assessment of olfaction to detect hyposmia. Examination of the outer ear and hearing is also useful to rule out mild CHARGE syndrome. In women without anosmia or hyposmia or identified genetic anomalies, the diagnostic procedure should exclude eating disorders, excessive physical activity, and chronic underlying conditions. Body mass index and body fat should also be calculated. Laboratory tests should be limited to assessing the levels of LH, FSH, PRL and oestradiol. Plasma LH, FSH and oestradiol concentrations are often low in women, sometimes being near the detection limit. In very mild form, which occurs in only a minority of women, nIHH can be revealed by isolated chronic anovulation, whereas oestradiol secretion is almost normal. The test with intravenous administration of 100 μg GnRH provides no extra diagnostic information relative to baseline go-

nadotropin levels, but its outcome reflects the severity of the gonadotropin deficiency.

Layendecker et al. [20] divided gonadotropin deficiency into three degrees of severity on the basis of tests with the administration of progesterone, clomiphene citrate and GnRH. Patients having degree 3a or 3b have a chance of recovery of menstruation and fertility, but for patients with degree 3c, the only chance of becoming pregnant is after treatment with gonadotropins. The diagnostic procedures should also exclude hyperprolactinemia, global anterior pituitary insufficiency and an associated endocrine disorder that may be part of syndromic forms of IHH.

Magnetic resonance imaging (MRI) of the brain and olfactory bulbs is useful in IHH. MRI can rule out expansive, infiltrative, or malformative disorders, and can also be useful to analyse the olfactory bulbs. Renal ultrasound examination should be made in Kallmann syndrome, as it can reveal renal malformation or agenesis. Pelvic sonography, which is now a routine part of gynaecological examination, should always be performed to determine the size of the uterus, endometrial thickness and ovary development. In adult women, especially those with osteoporotic risk factors, such as glucocorticoid treatment and smoking, one should consider measuring bone mineral density.

Management

Treatment options for IHH include sex steroids, gonadotropins, and pulsatile GnRH administration. The choice of therapy is determined by the goal of treatment. The majority of young women have a lack of development of the secondary sexual characteristics, and they should be treated with oestrogens, initially with low doses (1 mg/oestradiol *p.o.*). After approximately six months, when breast development has been optimised, replacement doses of oestradiol and progestagens should be implemented. In women with nIHH who wish to become pregnant, pulsatile GnRH stimulation can be used. Intravenous pulsatile administration of GnRH mimics normal cycle dynamics with the resulting ovulation of a single follicle [21]. This therapy offers a clear advantage over treatment with exogenous gonadotropins, which involves higher rates of both multiple gestation and ovarian hyperstimulation syndrome. For either approach, however, the rate of conception is approximately 30% per ovulation cycle [7]. Recently, in nIHH women, in order to stimulate ovulation, recombinant FSH has commonly been used. Its use provides a low risk of hyperstimulation syndrome. But in cases of severe form of IHH at a concentration of LH in the blood below 1.2 mIU/ml, it is necessary to add to the therapy recombinant hCG, or a preparation containing FSH and LH, or recombinant LH, since FSH administration itself does not lead to luteinisation of granulosa cells. It is also recommended to follow it with administration of progesterone to maintain corpus luteum function. This therapeutic regimen is assessed to give 70% of pregnancies with the application of six cycles of treatment, but it increases the risk of ovarian hyperstimulation syndrome and the development of multiple pregnancies.

Nutritional hypothalamic dysfunction

Adaptation of a woman's body to starvation leads to menstrual and fertility disorders. A number of reproductive disorders appear to be related to dieting and the desire for leanness. Adolescent girls who present with eating disorders before menarche have not only lost weight but are also stunted in growth [22]. Girls first begin to develop a preoccupation with dieting for weight loss and to describe feelings and behaviour associated with dieting around the time of menarche. This concern is accentuated by the rapid increase in height, weight, and body fat that occurs just before menarche, but it is also related to a window of vulnerability to socio-cultural influences that focus on body image and weight.

Most eating disorders first develop in adolescence, with 90% of eating disorders present before the age of 25 [22]. In healthy adult women, a short-term calorie restriction diet (800–1,100 kcal/per day) does not change the menstrual rhythm. When dietary restriction persists for more than one cycle, it is followed by weight loss and suppression of ovulation. Moderate dietary restriction and weight loss in normal cyclic women are associated with a reduction of oestradiol levels in the face of almost normal LH levels, a consequence of which is functional hypothalamic amenorrhea (FHA). Severe starvation in healthy women for two and half weeks induces a reversal of LH pulses to prepubertal patterns [6]. Women with FHA have reduced central GnRH drive, resulting in low FSH and LH levels, which causes anovulation.

The most serious eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating disorder, are classified as psychiatric illnesses, and therefore will not be discussed here.

Athletic amenorrhea

The physiological and psychosocial health benefits of exercise have been widely promoted by society, but we should not forget that intense exercise can cause adverse health effects. First described in 1997, the female athletic triad is a syndrome that includes disordered eating, amenorrhea and osteoporosis. Athletic amenorrhea has

been described in women involved in long-distance running, rowing, skiing, high-performance gymnastics, volleyball, judo and ballet. It has been found that the disorder may affect not only professional sportswomen, but also women practicing recreational exercises. Intense recreational exercises cause one in three of these women to develop ovulatory dysfunction. Female athletes are characterised by changes in metabolism in the form of intermittent or chronic imbalance due to increased energy expenditure or caloric intake. Another factor negatively affecting hypothalamic function is stress associated with competition and performance. Under normal conditions, after acute stress or energy demand passes, hormonal equilibrium is restored. In contrast, chronic stress can result in alteration of hormone secretion, and in particular it may damage hypothalamic secretory function. The important role played by energy imbalance and psychological factors in the pathogenesis of athletic amenorrhea should be stressed [23].

Risk factors of athletic amenorrhea are: age below 17 years, psychological factors and food restrictions. But the mechanism most likely to initiate development of the disorder is a disparity between the calorie intake and energy expenditure. FHA is estimated to affect up to 5% of women of reproductive age and is the underlying cause of 35% of women seeking evaluation for secondary amenorrhea.

This disorder of energy balance reduces the activity of the hypothalamic centres responsible for the secretion of GnRH. Reduction of central drive GnRH results in low FSH and LH levels, which causes anovulation. In FHA women, the disruption of GnRH drive is also connected to activation of the hypothalamic-pituitary-adrenal (HPA) axis, and suppression of the hypothalamic-pituitary-thyroidal (HPT) axis. Changing functions of the two axes are due to the need to mobilise energy in response to stress. Other peripheral metabolic factors such as ghrelin, insulin, leptin and peptide YY also play a role in communicating energy status to the brain areas that modulate metabolism. Gut peptides and adipocytokines also appear to be altered in exercising women with FHA, and have been hypothesised to be involved in the etiology of this disorder. Ghrelin is produced by cells in the stomach and appears to be a signal of disordered eating independent of weight or body fat, such that elevated ghrelin may result in continuing suppression of the hypothalamic–pituitary–ovarian axis with amenorrhea despite normal body fat and leptin levels. Eating disorders are also characterised by elevations in corticotropin-releasing hormone and cortisol, along with loss of the normal circadian rhythm of cortisol. Neuropeptide Y is produced by nuclei in the hypothalamus and appears to have both stimulatory and inhibitory effects on GnRH secretion in response to leptin [24]. A critical leptin level threshold is suggested to be necessary for regular menses. Additionally, in FHA, elevated night-time serum growth hormone levels and lower 24 h prolactin levels have been observed [25].

A prospective study by Rauh et al. [26] showed that high school female athletes with disordered eating and oligomenorrhea/amenorrhea have a reduced BMD (bone mineral density). A BMD level below the expected range for age was associated with musculoskeletal injury. The authors conclude that BMD levels should be closely monitored in adolescent female athletes.

Eating disorders and athletic amenorrhea treatment

Appropriate intervention depends on determining which behaviour needs to be modified. Attention should be concentrated on the promotion of psychosocial harmony, restoring ovulation and menstrual cyclicity. Methods that are considered useful include a combination of cognitive behaviour therapy with relaxation techniques coupled with adequate caloric intake. One should avoid extensive workups for physical causes when women have a clear fear of fatness, drive for thinness, preoccupation with weight, binging and purging, or compulsive exercise suggesting an eating disorder. The implementation of hormonal therapy to regularise menstrual cycles is not indicated when the patient is underweight, dieting despite a normal weight range, or compulsively exercising. It is advisable to prescribe 1,500 mg calcium citrate/400 units vitamin D per day in divided doses. Before the plan of ovulation stimulation in order to become pregnant, a healthy weight should be established. The patient should also be educated about the effect of underweight on ovulation and risks of eating disorders for pregnancy and offspring [22].

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