FUNCTIONAL HYPOTHALAMIC AMENORRHEA

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ANNOTATION. *The article presents data on the relationship between the pathogenetic mechanisms of development of menstrual cycle disorders of functional and organic origin and mental disorders from the point of view of the psychosomatic concept. According to the latter, functional disorders of the menstrual cycle are considered psychosomatic, in which gynecological pathology develops as a result of psychopathological disorders. A striking example of such a disease is functional hypothalamic amenorrhea. This review highlights the importance of interdisciplinary collaboration between gynecologist and psychiatrist for the most effective reproductive rehabilitation of patients with amenorrhea. The literature search was carried out in domestic (eLibrary, CyberLeninka.ru) and international (PubMed, Cochrane Library) databases in Russian and English. Free access to the full text of articles was a priority. The selection of sources was prioritized for the period from 2022 to 2024. However, given the insufficient knowledge of the chosen topic, the selection of sources dates back to 1997.*

Introduction. FHA is a disease that often occurs in patients due to weight loss, excessive physical exertion, and psycho-emotional stress. Suppression of reproductive function during periods of "stress" is a natural fundamental survival process and a way to protect a woman's health in order to prevent pregnancy [5, 6]. The American College of Sports Medicine has even identified a separate term, the "female athlete triad," which includes amenorrhea, eating disorders, and low bone mineral density [7]. At the first stage of the disease, with a long delay in menstruation, normal levels of gonadotropins can be found in the hormonal profile of patients: luteinizing hormone (LH) and follicle-stimulating hormones (FSH), however, with continued exposure to the stress factor, inhibition of the hypothalamic-pituitary-ovarian axis leads to a decrease in the release of gonadotropin-releasing hormone -hormone (GnRH) and,

accordingly, to low levels of LH, FSH and estradiol. Decreased LH pulsatility and low estradiol levels subsequently lead to anovulation and cessation of menstruation. Considering that FHA is a secondary form of amenorrhea for which there is no structural or organic cause, the term “functional” emphasizes that this condition can be reversed once the cause is identified and eliminated [8] The psychopathological characteristics of patients with FHA are extremely important in relation to the development, progression and general prognosis of the disease [9]. Patients suffering from functional amenorrhea have significantly higher rates of depression and anxiety compared to the control group, more often exhibit dysfunctional attitudes, such as neurotic perfectionism with increased vulnerability to the opinions of other people, report an internal feeling of insecurity and the need to control the slightest changes in life, It is much more difficult for them to adapt to the daily events of everyday life compared to women without menstrual dysfunction [10, 11]. Patients with FHA are also characterized by various sexual disorders, which manifest themselves in the form of decreased sexual desire, arousal disorder, inadequate hydration of the mucous membranes during sexual intercourse, and dyspareunia [12]. In clinical studies, estrogen therapy reduced the severity of anxiety in girls with anorexia nervosa and prevented its worsening with weight gain compared with participants receiving placebo, which confirms the important role of estrogen as regulatory hormones in the functioning of neurotransmitters and neurotransmitters responsible for women’s emotions and mood. [13]. An adequate level of estrogen is also necessary for the full implementation of cognitive function. Estrogen deficiency negatively affected verbal memory and executive control (a term used to refer to the control of motor function and cognitive actions aimed at achieving specific goals) in oligo-amenorrheic athletes compared to regularly menstrual athletes and women. those who do not engage in sports [14]. Cognitive impairments, which were recorded during the manifestation of FHA in adolescents and adult women, were successfully resolved by restoring the natural rhythm of menstruation or by prescribing hormone replacement therapy with sex steroids [15]. Estrogens affect many areas of the brain: the hypothalamus, cerebellum, nigrostriatal and mesolimbic systems, amygdala, hippocampus, cerebral cortex and brain stem [13]. Malfunctions in the functioning of the neurotransmitters serotonin, acetylcholine, dopamine, norepinephrine during estrogen deficiency can be aggravated against the background of hypercortisolemia, which develops with FHA as a response of the hypothalamic-pituitary-adrenal system to stress. Estrogen deficiency and excess cortisol, acting synergistically, form the organic basis for neuropsychiatric and neurocognitive disorders in patients with amenorrhea. The autonomic nervous system in patients with FHA, in turn, triggers inadequate autonomic reactions (excessive increase in heart rate, systolic and diastolic blood pressure) in response to

the action of a “psychological stimulus”, i.e. the perception of stress at the physical level with functional hypoestrogenism will differ significantly from the reactions of healthy women, and the level of cortisol directly correlates with the severity of anxiety, depressive disorders and eating disorders [16]. And although stress factors that can lead to FHA have been studied for a long time, at the moment it is not possible to predict an individual reaction to them, or the same severe events do not always cause similar pathological reactions, which indicates a genetic predisposition to menstrual dysfunction, and stress plays a possible role the role of the trigger [17]. Clinical studies have documented significant variability in the occurrence of menstrual irregularities following strenuous exercise. In female athletes, the frequency of FHA ranges from 6 to 43%, while in women who play amateur sports and maintain a similar training regimen as professionals, the frequency of pathology is significantly higher, and only 14% of women maintain regular menstrual cycles [18, 19]. The variability of the reaction of the hypothalamic-pituitary-ovarian axis was confirmed in experimental models (macaques): the severity of ovulatory dysfunction depended on the degree of stress exposure [20]. Immunohistochemical analysis of hypothalamic sections from stress-resistant and stress-sensitive monkeys revealed a higher density of GnRH-secreting neurons and a lower density of their fibers in the median eminence in stress-sensitive animals, suggesting differences in the neural mechanisms involved in the synthesis, transport and release of releasing hormone. -hormone depending on stress resistance [21]. These studies show that variability in genes that control the development and function of GnRH neurons may contribute to the adaptation of the reproductive axis to stressful conditions. This hypothesis is supported by recent studies that revealed a higher frequency of rare variants in genes associated with idiopathic hypogonadotropic hypogonadism in patients with FHA compared with women with regular menstruation [22]. The similar clinical picture of these two pathological processes is likely due to mutations in the genes responsible for the development of congenital hypogonadism, which lead to a functional deficiency in GnRH secretion, characteristic of FHA, in contrast to hereditary pathology, in which there is no or no pulsatile secretion of releasing hormone its adequate effect on the pituitary gland [23]. In addition to genetic variants and polymorphisms, there are epigenetic mechanisms that regulate the functioning of the hypothalamic-pituitary-ovarian axis and, therefore, are involved in the development of FHA, forming an individual predisposition to anovulation as a result of a stressful event, or represent biological markers of the stress response that are transmitted as acquired habitual response to past significant events [24]. A search is underway for genes responsible for an individual’s response to stress and predisposition to anxiety disorders. Specific polymorphisms (e.g., rs16147 and rs3214187) in neuropeptide Y, which acts as a regulator of energy balance and

antagonizes the anxiogenic effect of corticotropin-releasing hormone, have been associated with resistance or sensitivity to stress factors [25]. Neuropeptide Y controls the concentration of GnRH by inducing its release in the presence of adequate levels of estradiol: during hypoestrogenism it suppresses the release of releasing hormone, and during amenorrhea the basal level of this peptide decreases sharply [26]. Thus, this peptide likely acts as a link between the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal axis, and variants in its gene may influence the sensitivity of the reproductive axis to stress. Neuroplasticity plays an important role in susceptibility to stress-related disorders. According to the neurotrophic hypothesis, affective disorders may be associated with changes in structural plasticity and cellular resistance, in which brain-derived neurotrophic factor (BDNF) plays a key role. The latter is actively expressed in the hippocampus and is involved in neurogenesis, neuroplasticity, neuronal survival and differentiation. M. Miranda et al. found elevated serum BDNF levels during stress exposure and mood disorders [27]. Although its role in the development of FHA is not completely clear, significantly lower plasma concentrations of this factor were reported in patients compared with healthy women, which may indicate a contribution of BDNF to the altered stress response in amenorrhea [28]. . This hypothesis may become the basis for the analysis of common variants of the BDNF gene, which would explain the anxiogenic phenotype of patients with FHA. An increasing number of studies describe the mechanisms of influence on the reproductive axis of the hypothalamus-pituitary-ovary through the kisspeptin system, which includes the family of hypothalamic neuropeptides encoded by the KISS1 gene in humans [29]. Inactivation of KISS1 and its receptor encoded by KISS1R leads to delayed puberty and congenital hypogonadotropic hypogonadism [30], and conversely, activating variants of KISS1R and KISS1 caused central precocious puberty [31]. Patients with FHA and PH ≤3 IU/L were found to have lower kisspeptin levels compared to control group participants with PH >3 IU/L (1.7 ng/ml and 2.6 ng/ml, respectively) [32]. . These and many other studies formed the basis of the hypothesis about the potential beneficial effect of using kisspeptin preparations to restore reproductive function in women [33]. The first use of this exogenous neuropeptide in patients with FHA was described in the work of S. Jayasena et al. (2009) [34].

Conclusion. The relationship between psychological stress and FHA is bidirectional, as stress suppresses the hypothalamic-pituitary-ovarian axis, and conversely, low estrogen levels greatly affect psychological functioning, leading to a vicious cycle. Therefore, it becomes critically important not only to prescribe adequate hormone replacement therapy with sex steroids, but also to influence the psychopathological part of the disease, including psychoeducational strategies

(informing the patient about the characteristics of her disease), primarily from the gynecologist, and from the psychiatrist-psychotherapist - selection psycho-pharmaco-therapeutic drugs for the treatment of anxiety, depressive disorders and psychotherapy to correct pathological cognitive and behavioral distortions. The effect from them will be maximum only with a combination of all of the listed methods.

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