PREMATURE OVARIAN FAILURE

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ABSTRACT

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. At the same time, endocrinopathies and premature ovarian failure can also be considered in the paradigm of psychosomatic disorders of ovarian function, due to the high prevalence of anxiety and depressive disorders in this cohort of patients. 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 and international databases in Russian and English. Free access to the full text of articles was a priority. The selection of sources was prioritized from 2020 to 2022. However, given the insufficient knowledge of the chosen topic, the selection of sources dates back to 1985.

INTRODUCTION

POI is a disease in which ovarian function ceases in women under 40 years of age, which is accompanied by an increase in the level of gonadotropins, a decrease in estrogen levels and ultimately leads to amenorrhea, infertility and long-term health consequences: early development of cardiovascular diseases, osteoporosis, decreased cognitive function and overall life expectancy. To make a diagnosis, it is necessary to register an increase in FSH of more than 25 IU/L twice with a difference of a month; a decrease in the number of antral follicles by ultrasound, as well as the level of anti-Mullerian hormone and estradiol can be detected [59]. The prevalence of this pathology averages 3.5% in the population, while in developing countries it is slightly higher than in developed countries - 5.1%. This is probably due to worse socio-economic

conditions, individual and public health, and difficult access to preventive health services or information [60]. The main causes of POI are genetic abnormalities, autoimmune processes, severe infections, iatrogenic factors (surgery, radiation/chemotherapy), familial forms of the disease and idiopathic causes [59]. Among the genetic factors, the most common are chromosomal pathologies (fragile X syndrome), gonadal dysgenesis, and Shereshevsky–Turner syndrome. However, in some cases, abnormal epigenetic changes are found in patients with POF. The latter include DNA methylation, noncoding RNA expression, and histone modifications. These processes perform a regulatory function in relation to gene expression and serve as one of the key factors influencing the ovarian microenvironment and follicular development, while their abnormalities impair oocyte maturation [61]. Autoimmune pathology as a cause of POF accounts for 10.5% of the total number of cases of ovarian failure and includes autoimmune endocrine (adrenal insufficiency, Hashimoto‘s thyroiditis and type 1 diabetes mellitus) and non-endocrine disorders (Sjögren’s syndrome, rheumatoid arthritis, systemic lupus erythematosus, inflammatory disease intestines, multiple sclerosis, myasthenia gravis) [59]. However, in more than 50% of cases, the etiology of the disease is unknown even after a thorough examination - this is a spontaneous or idiopathic form of this nosology. Is it possible that psychopathological disorders in this case will be the triggering factor for early depletion of the ovarian reserve, and POI is a classic psychosomatic disease that occurs in the presence of a genetic predisposition or abnormal epigenetic changes in a woman? It is known that among patients with POI there is a high risk of depressive and anxiety disorders. According to a meta-analysis, which included 1316 participants, the odds ratio (OR) for depression was 3.33, 95% confidence interval (CI) = 2.31–4.81, p Mental disorders in women with early depletion of ovarian reserve often remain undiagnosed. Patients usually come for infertility and problems with the menstrual cycle, ignoring mental problems. Unfortunately, sometimes doctors tend not to recognize the significance of the psychosomatic problems of this cohort of patients, which leads to the fact that a third of them are missed by the diagnosis of anxiety or depressive disorders of moderate or severe severity. Psychopathological disorders can, among other things, affect fertility and the results of infertility treatment. J. Ventura et al. found a positive correlation between mental status and ovarian function in patients with POI [63]. The psychosocial impact of this nosology can also affect male partners, which leads to an inadequate perception of the disease in their wives. K. Chu et al. analyzed indicators of anxiety, depression and marital relationships in 52 men in the study group (POG) and 52 participants in the control group [64]. Men from group 1 experienced increased levels of anxiety and depression, and were also less satisfied with their marital relationships in some aspects compared to the control group. Many

partners did not have reliable information about their companions' illness, which may be the result of insufficient counseling from doctors. Moreover, their level of understanding of the disease correlated with anxiety (r = -0.64; p) Thus, the patient may experience additional psycho-emotional stress in marriage, which will aggravate the disturbances in her mental state. It is not indicated whether the spouses of patients with POI were in an anxious-depressive state before marriage; perhaps the reason is the distorted choice of the women themselves in a state of mental exhaustion. The exact etiology of anxiety and depressive disorders in patients with POI is still unknown. It is likely that mechanisms of neuroendocrine regulation in the hypothalamic-pituitary-ovarian axis, cytokines and psychosocial stress are involved here. Excessive release of FSH.and a decrease in estrogen levels directly affect the synthesis, metabolism and receptor activity in the neurotransmitter system: 5-hydroxytryptamine, dopamine and norepinephrine, which ultimately increases the risk of developing depressive and anxiety disorders in menopausal women [65]. A similar process may also occur in patients with POI. Another mechanism for the pathogenesis of psychopathological disorders may be associated with the level of transforming growth factor-β and interferon gamma. They were found to be associated with the development of early depletion of ovarian reserve and depressive disorders, which can be explained by immune disorders and activation of the inflammatory response system [66]. Another important cause of affective pathology is psychosocial stress, which is directly related to the infertility of patients. In women with infertility, mood disorders are significantly more often detected, and in patients with POI, the situation is aggravated by the fact that the manifestation of premature cessation of ovarian function can occur at a very young age, when the patient did not even think about her reproductive plans, which leads to even greater levels of stress, aggravated by the public stigmatization of infertility [67, 68]. We should not forget that psychopathological disorders can initiate the development of amenorrhea and worsen ovarian function, as discussed above (FGA). Chronic negative emotions activate the hypothalamic-pituitary-adrenal axis, leading to the secretion of large amounts of cortisol, which suppresses the pulsatile rhythm of GnRH release [69]. In addition, mental stress induces the synthesis of β-endorphin in the hypothalamus and pituitary gland, indirectly affecting the release of gonadotropins, and those, in turn, on ovarian function, which can lead to the development of POI. Therefore, there is no clear answer to the question whether psychopathological disorders are a premorbid background for the idiopathic ("psychogenic") form of POI or accompany the onset of estrogen deficiency.

CONCLUSION

Psychosocial stress has many adverse health consequences. Assessing the negative effect of prolonged psychogenicity is problematic, since there are no objective

criteria. In women, phenotypic markers of chronic stress include menstrual irregularities, amenorrhea, or infertility. Rare polymorphisms that control the development and/or function of GnRH neurons may contribute to the adaptability of the reproductive axis to stress factors. FHA is a classic psychosomatic disease, when a somatic illness is provoked (caused) by mental pathology, personality disorders or psychogenic factors. At the same time, concomitant depressive and anxiety disorders, often diagnosed in patients with PCOS and POI, can act as a trigger factor in the manifestation of endocrinopathy, which makes it possible to classify these diseases as psychosomatic. Therefore, an interdisciplinary team of gynecologist and psychiatrist will be able to improve an individual therapeutic approach based on targeted therapy and provide reproductive rehabilitation for patients with various forms of amenorrhea.

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