PREMATURE OVARIAN INSUFFICIENCY DUE COVID-19: WHAT MECHANISM PLAYS A ROLE?

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Abstract. *Today, premature ovarian failure (POF) is one of the most difficult problems of women's health. Relevance. As the main cause of infertility, a decrease in the quality of life of women with POI is a problem that needs special attention. After a confirmed diagnosis, there are currently no methods to restore ovarian function and fertility. The spread of the COVID-19 virus and pandemic-related quarantine measures have led to women's mental health and menstrual irregularities, up to and including amenorrhea. Therefore, it is important to identify risk factors for the development of POI at an earlier stage. Purpose. To evaluate the plasma concentration of KISS1 and BDNF in patients with POI that developed after coronavirus infection. Conclusion. We can say that kisspeptin and BDNF play an important role not only in women's reproductive health, but also in their mental state. Stress due to the coronavirus pandemic, reducing the level of KISS1 and BDNF in the blood can lead to the development of premature ovarian failure. This observation brings important potential insight into the pathogenesis of POI.*

Keywords: *premature ovarian insufficiency, COVID-19, stress, anxiety, depression, KISS1, BDNF.*

Premature ovarian failure (POF) is the cessation of ovarian function before the age of 40 years. This is due to hypoestrogenism and loss of residual follicles, leading to menstrual irregularities, infertility, and reduced health-related quality of life. The European Society for Human Reproduction and Embryology (ESHRE) suggests the following diagnostic criteria: amenorrhea or oligomenorrhea for at least four months and elevated follicle-stimulating hormone (FSH) > 25 IU/L [14].

In 1942, F.Albright first published the concept of "premature ovarian failure" - a disease that occurs with amenorrhea, low estradiol levels and high levels of FSH [8;10]. But in the 80s of the XX century, 2 concepts appeared: "resistant ovarian syndrome" - a condition when spontaneous restoration of ovulation occurs and "depleted ovary syndrome" - a condition in which ovarian function ceases irreversibly [21]. L. Nelson proposed to return the concept of "premature ovarian failure", as this characterizes this disease more accurately [19].

The prevalence of POI according to various studies ranges from 1 to 3.7% of the female population [2;3;6;11]. The prevalence of POI varies with age and is 1:10,000 in women aged 18–25 years, 1:1,000 in women aged 25–30 years, and 1:100 in the age range of 35–40 years. Epidemiological studies have shown differences in the incidence of POI depending on ethnicity, and it is highest in Caucasian, African American and Hispanic women [7]. According to Khaydarova F.A., Fakhrutdinova S.S. (2019), the incidence of POI in Uzbekistan is 2.5%. The average age of women with POI is 31.4±0.5 years [20].

Premature ovarian failure (POF), which causes the onset of early menopause, is characterized by accelerated loss of follicles in the fertile period and premature cessation of ovarian function [5;16;17]. This process has consequences for the entire female body, including

because, in addition to physical changes, it is also characterized by psychological disorders (psychosocial discomfort), which together significantly reduces the quality of life of women with early menopause [5; 16; 18]. The etiopathogenesis of the disease in most cases remains unclear. However, genetic abnormalities, metabolic disorders, autoimmune, iatrogenic procedures, infections or environmental factors are considered to be the main causes of the syndrome. However, only 10% of POI cases could be explained by the known causes mentioned above. Among them, genetic etiology is of great concern. Thus, the study of unknown potential risk factors for the development of POI is important.

During the COVID-19 pandemicThe virus itself, as well as the measures taken to reduce its spread, have seriously affected the lives of the world's population. The pandemic has significantly affected the mental health of many people in the population, leading to loneliness, social isolation, financial stress, as well as anxiety and fear of contracting the virus and uncertainty about the future. It is known that periods of stress and psychological distress can affect women's reproductive health. Stressors can affect the hypothalamic-pituitary-gonadal (HPG) axis and can alter the neuromodulator cascade that governs the regulation of gonadotropin-releasing hormone (GnRH) [15]. It has been proven that dysmenorrhea is associated with high levels of stress and emotional instability [1]. But exactly what mechanism develops a violation of the reproductive system after stress and COVID-19 remains unclear. In recent years, attention has been paid to the role of kisspeptin and BDNF.

The discovery of kisspeptin made it possible to take a fresh look at the mechanisms of suppression of the reproductive system due to stress. Recent studies have demonstrated that the suppressive effects of psychosocial stress on the hypothalamus and pituitary gland are mediated by cortisol, which binds to type II glucocorticoid receptors located on the KND neurons of the arcuate nucleus. Impaired secretion of dynorphin and neurokinin B by KND neurons leads to inhibition of kisspeptin synthesis. These changes can suppress the activity of GnRH neurons and inhibit the pulsatile secretion of gonadotropins [4]. Some studies have shown that BDNF expression disorders may be associated with the development of POF. The association between BDNF and follicular function and depletion has been shown in many studies [13]. The release of LH by the paracrine pathway stimulates follicular production of BDNF in granulosa cells, including the NTKR2.T1 receptor. This mechanism, together with the stimulation of the KISS1R receptor by kisspeptin, ensures the survival of oocytes and further development [13]. Czyzyk et. al. found lower plasma levels of BDNF in patients with overt POI (FSH > 40 IU/L). Dorfman et al. [12] also showed that in mice with the removed NTRK2 or KISS1R receptor, oocyte decay occurred and, as a result, oocyte cell death. This process caused POI in mice. There is also a positive correlation between the number of mature oocytes and the concentration of follicular fluid BDNF [13]. Gaytan et al. [9], causing abnormal signaling between kisspeptin and the BDNF signaling pathway, caused a progressive loss of all classes of follicles in the ovary, leading to premature menopause. The secretion of gonadotropins initially remained, but then increased, mimicking the hormonal profile of POI. Our study raises the question of whether impaired synthesis and reduced levels of KISS1 and BDNF in post-COVID women may affect ovarian function (POI development).

Materials and research methods. In the period from January 2021 to July 2022 on the basis of the Republican Specialized Medical Center for Endocrinology named after acad. Y.Kh. Turakulova in the department of the "Consultative Polyclinic" examined women 112 women. The

patients were divided into 3 groups. The main group included 52 women (mean age 31.05 ± 1.78 years) who had COVID-19 and had menstrual irregularities that arose after the illness. In comparison group were 28 women (mean age 34.28±2.56 years) with confirmed diagnosis of POI. The control group consisted of 32 healthy women (mean age 28.68±2.1 years, with a regular menstrual cycle, confirmed by the results of hormonal and ultrasound examinations. The DASS-21 questionnaire was conducted, which gives 3 indicators: the degree of stress, depression and anxiety. Laboratory examination of all patients included an assessment of the level of FSH, AMH, KISS1, BDNF in the blood, ultrasound examination.

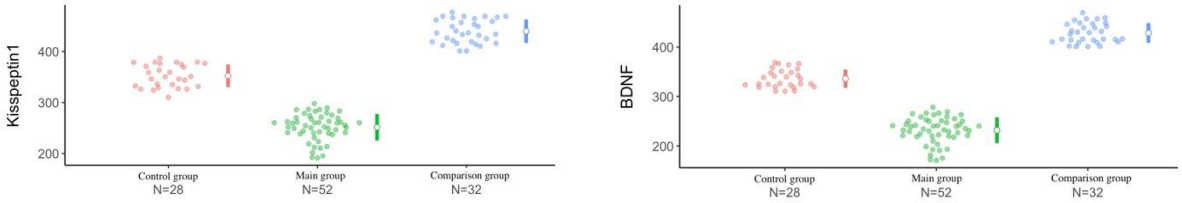
Research results. Blood levels of kisspeptin (HUMAN KISS1) and BDNF (HUMAN BDNF) were determined using an enzyme immunoassay kit ELISA KIT in the laboratory of RSNPMC Endocrinology. Statistical analysis was carried out using Minitab 14. In the main group, blood sampling was performed on any day against the background of amenorrhea, and in the control group, the examination was carried out in the follicular phase (on the 3-5th day of MC).

Table 1.

Clinical and laboratory data of examination of women of the main and control groups.

Indicators	Main group n=52	Control group n=32	Comparison group n=28
Age	31±1.78	28.6±2.1	34.28±2.56
DASS-21: Stress (score)	29.90±0.79	9.65±0.64	12.07±0.64
DASS-21: Anxiety (score)	17.44±0.54	5.31±0.47	6.32±0.43
DASS-21: Depression (score)	23.42±0.71	6.09±0.57	11.92±0.61
FSH (mIU/ml)	79.61±11.89	6.3±0.78	70.82±12.85
KISS1 (pg/ml)	251.69±7.27	439.90±8.32	352.50±8.61
BDNF (pg/ml)	231.82±7.3	428.59±7.22	336.15±7.12

In the POI group, the level of kisspeptin was lower (251.69±7.27 pg/ml, $p<0.05$) than in healthy women (439.90±8.32 pg/ml, $p<0.05$) and in comparison group (352.50±8.61pg/ml, $p<0.05$). The BDNF concentration was also lower in the first group (231.82±7.3pg/ml, $p<0.05$) than in healthy women (428.59±7.22 pg/ml, $p<0.05$) and in comparison group (336.15±7.12 pg/ml, $p<0.05$).



Picture 1. Comparison of serum levels of kisspeptin and BDNF in patients with POI due to COVID-19, comparison and control groups.

Blood levels of KISS1 and BDNF are negatively correlated with stress severity. The level of kisspeptin and BDNF depended on the severity of stress and anxiety (against the background of a previous coronavirus infection). By questionnaire "DASS-21" the level of stress, anxiety and depression in points were higher in the main group (in women with POI who had COVID-19), than in other 2 groups. This showed that stress, anxiety and depression lead to deficiency of KISS1 and BDNF, and this in turn leads to dysregulation of the HTH axis leading to the development of POI.

Conclusion. The study of the features of the stress response of the reproductive system, as the basics of the formation of persistent endocrine disorders, as well as the continued search for effective methods for correcting stress-dependent menstrual disorders remain highly relevant. Thus, the pathogenesis of premature ovarian failure in women of reproductive age after coronavirus infection and stress remains not fully understood. The presented data of the study show the relationship of kisspeptin and neurotrophic brain factor with the secretion of GnRH by the hypothalamus, the production of gonadotropins by the pituitary gland and steroidogenesis in the ovaries suggest the importance of these hypothalamic markers in the pathogenesis of POI caused by stress and COVID. In this regard, it is very important to study the relationship between KISS1 and BDNF in women of reproductive age. With the results obtained, we hoped to open a new area of research into the action of KISS1 and BDNF in the pathogenesis of premature ovarian failure.

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