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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Clinical and genetic aspects of menopausal hormone therapy — a modern paradigm. What changed COVID-19 pandemic?

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Abstract. In the modern paradigm of public health protection, much attention is paid to the health of women in peri- and postmenopause, and a personalized approach prevails. It is generally recognized that the pathogenetic therapy of menopausal disorders is hormone therapy. But the COVID-19 pandemic has made its own adjustments to the routine strategy of choosing menopausal hormone therapy (MHT). The purpose of this review was to analyze studies on the dependence of the effectiveness of MHT on clinical and genetic aspects in the context of the ongoing COVID-19 pandemic. The review highlights the main risks of MHT for thromboembolic diseases and coagulation complications characteristic of COVID-19, discusses genetic predispositions that aggravate the course of the post-COVID period, as well as the effectiveness of estrogens in protecting the vascular endothelium and increasing the number of CD4+ T cells, providing an adequate immune response when infected with SARS-CoV-2. Numerous studies show that the complications characteristic of the severe course of COVID-19 are multifactorial in nature and cannot be unambiguously explained only by genetic predisposition. However, with the development of personalized medicine, special attention should be paid to the study of genetic aspects that can equally contribute to the occurrence of menopausal disorders in healthy women and aggravate the course of the post-pregnancy period. The data presented allow us to conclude that in the context of the ongoing COVID-19 pandemic at the population level, MHT can bring significant benefits to women during menopause due to the beneficial effect of estrogens on vascular walls. Additional study of the relationship between the course of the postcovid period in MHT users and polymorphisms of candidate genes that determine the risks of thrombotic complications and metabolic consequences is required.

Key words: COVID-19, postcovid syndrome, menopausal hormone therapy, gene polymorphism, PAI-1, ITGB 3, MTHFR, VEGF, Vitamin D

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Introduction

Increasing the life expectancy of Russians entails a whole range of practically significant problems of organizing medical care for middle-aged women. Disorders related to aging require special attention, among which diseases associated with a deficiency / imbalance of sex hormones occupy a leading position [1—4].

Conditions associated with physiological age-related hypogonadism can be of a very diverse nature and manifest themselves with varying degrees of severity. Most often, the progressive deficiency of sex hormones is associated with the appearance and progression of cardiovascular, metabolic, urogenital and sexual disorders, as well as the development of immunodeficiency states [1—3]. The "gold" standard of treatment and prevention of such diseases and disorders is menopausal hormone therapy (MHT) [2, 3, 5].

The ongoing discussions about its safety have good reasons. On the one hand, a review of numerous data shows that MHT increases the risks of thromboembolic diseases and hypercoagulation-related complications characteristic of COVID-19, including iatrogenic [6—8]. On the other hand, estrogens have been proven to protect the vascular endothelium, since their expression increases the synthesis of endothelial NO synthase, an enzyme involved in the formation of a powerful vasodilating factor nitric oxide (NO). In addition, estradiol increases the number of CD 4+ T cells, providing an adequate immune response when infected with SARS-CoV-2 [4, 8].

Noteworthy are the results of the analysis of electronic medical records of a large international cohort of patients with COVID-19 (n=68,466), which examined the effects of systemic MHT on mortality rates. The odds ratios and Kaplan-Mayer survival curves were measured, cohorts of 37,086 women with COVID-19 at reproductive age (15—49 years) and peri- and postmenopausal (>50 years) were compared. The results obtained confirmed that the use of systemic MHT reduces the risk of mortality from COVID-19 among women over 50 years of age by almost half [9].

Over time, it becomes obvious that under equal conditions of sex hormone deficiency in postmenopausal women as such, and in those who have had a coronavirus infection, complications may occur, different in nature and severity: from asymptomatic course to pronounced disorders, especially from the cardiovascular system and the coagulation system [6, 7, 10]. Therefore, the approach to the management of such patients cannot be generalizing, but should be of an individual nature, considering race, ethnicity, initial state of health, social risk factors, as well as hereditary history. With the development of personalized medicine, special attention should be paid to the study of genetic aspects that can equally contribute to the occurrence of menopausal disorders in healthy women and aggravate the course of the post-ovarian period, contributing to the development of complications [10—12].

Clinical and genetic aspects of MHT and thrombotic complications of COVID-19

According to the modern paradigm, infection caused by the coronavirus SARS-CoV-2 (COVID-19) can occur in a variety of ways: from asymptomatic viral transmission to clinically significant severe forms, including complications in the post-ovoid period. The severe course of COVID-19 is associated with a violation of the regulation of the immune system, accompanied by an excessive release of inflammatory cytokines, which creates a hyperinflammatory reaction and activates the procoagulant medium [7].

Their specificity is very variable: from venous thromboembolism to the development of DIC syndrome. In particular, due to this variability, the safety aspect of the use of anticoagulants in preventive or therapeutic dosages is relevant. In addition, the question arises: why do only some patients with severe COVID-19 develop thrombosis, despite the proven hypercoagulation component of the pathogenesis of the disease? Accumulated experience shows that an important element to be taken into account is the pre-existing individual thrombophilic profile predisposing to thrombotic complications during SARS-CoV-2 infection. These include race, ethnicity, as well as a number of hereditary genetic factors [11, 13, 14].

When studying genetic risk factors, it was shown that the polymorphism of the plasminogen activator inhibitor-1 (PAI-1) 4G/5G gene is associated with osteonecrosis after COVID-19 mediated by thrombosis. The gene encoding plasminogen activation inhibitor 1 (PAI-1) is a component of the fibrinolytic blood system and plays an important role in fibrin stabilization, vascular remodeling, and cell migration. PAI-1 binds to the tissue activator of plasminogen and inhibits the activity of plasminogen, which reduces fibrinolysis [12].

The results of other studies demonstrate that polymorphism of the ITGB3 gene is also an independent risk factor for severe COVID-19. So, in one of the studies, 16 polymorphisms of genes responsible for prothrombotic and cardiovascular complications, including COVID-19, were studied. It was found that polymorphism of the ITGB3 PIA2 gene was independently associated with a higher risk of severe COVID-19, while single-nucleotide polymorphism in the β-Fbg gene was detected in a homozygous mutated form only in a cohort of severe COVID-19 patients. The ITGB3 and ITGA2B genes encode subunits of the platelet integrin glycoprotein complex IIb/IIIa (GPIIb/IIIa), which is responsible for platelet adhesion and activation. The ITGB3 PIA1/A2 polymorphism is the result of a single amino acid substitution (leucine → proline) in residue 33 in the β-chain gene GPIIb/IIIa, which leads to isoforms PIA1 or PIA2. This changes the structural conformation of its β3 subunit, transferring the latter to a fully active state, which determines the increased reactivity of platelets and their ability to adhere, naturally increasing thrombogenicity [10].

In addition, suggest the participation of polymorphism of the C677T methylenetetrahydrofolate reductase (MTHFR) gene in the formation of prerequisites for the morbidity and severity of COVID-19 [15]. MTHFR is an intracellular enzyme that participates in the conversion of homocysteine to methionine in the presence of pyridoxine and cyancobalamin cofactors, as well as folic acid substrate. It is known that a high level of homocysteine in plasma significantly increases the frequency of damage to both small and large vessels [16]. Hyperhomocysteinemia has neurotoxic, neuroinflammatory, neurodegenerative, proatherogenic, prothrombotic and prooxidant effects. Recent data indicate the role of homocysteine as a risk factor for thromboembolism, given its effect on platelet reactivity. Thus, there is a high degree of correlation between mutations of the MTHFR gene, morbidity and mortality from COVID-19 [15—22].

According to some authors, one of the most significant indicators associated with the severe course of COVID-19 and helping to calculate the prognosis of the disease is a high level of VEGF-D [23, 24].

The VEGF gene encodes vascular endothelial growth factor (VEGF), which stimulates vasculogenesis and angiogenesis in both normal tissues and tumors. The results show that VEGF polymorphisms rs699947, rs1570360 and rs3025039 can affect the predisposition to coronary heart disease. In addition, VEGF polymorphism rs699947 and rs2010963 can serve as

genetic markers of collateral circulation disorders after myocardial ischemia [26, 27].

There is also evidence that the cytokine storm that occurs during COVID-19 promotes inflammation in brain tissues and subsequently causes neurological manifestations. Vascular growth factor (VEGF), which is widespread in the brain, probably plays a crucial role in this inflammation, promoting the attraction of inflammatory cells and regulating the level of angiopoietins II (Ang II). Thus, VEGF is considered a promising therapeutic target for suppressing inflammation in SARS-CoV-2 infection with neurological symptoms [28].

However, other studies show that the use of VEGF inhibitors, for example, in oncological diseases, is associated with the risk of hypertensive complications, which are caused, among other things, by endothelial dysfunction, an imbalance between nitric oxide, oxidative stress, endothelin signaling and prostaglandins [29].

The role of vitamin (hormone) D in the development of various menopausal disorders, including in the postcovid period, deserves special attention.

As is known, vitamin D enters the human body in two forms: in the form of ergocalciferol with plant foods and in the form of cholecalciferol with animal foods. Cholecalciferol is also synthesized in the skin under the influence of ultraviolet radiation. In the future, its metabolism occurs in the liver, where, under the influence of the enzyme 25-hydroxylase, cholecalciferol is converted into the prohormone D –, or calcidiol. It is this relatively stable molecule (25(OH)D) used for laboratory assessment of vitamin D levels. Further, in the kidneys, under the influence of the enzyme 1α-hydroxylase, calcidiol turns into its active metabolite calcitriol -, 1,25(OH)2D or "hormone D". The boom in studies of the hormonal activity of calcitriol became possible after the discovery of specific intracellular and nuclear receptors for vitamin D (VDR).

Binding 1.25(OH)2D with VDR can regulate hundreds of different genes. VDR are active in almost all tissues, including colon, mammary gland, lungs, ovaries, endometrium, bones, kidneys, parathyroid gland, pancreatic B cells, monocytes, T lymphocytes, melanocytes, keratinocytes, and others, including tumor cells [30, 31]. Some studies have studied various types of VDR polymorphism and their correlations with various malignant diseases in terms of ethnicity [32].

Vitamin D plays an important role in bone metabolism and is important for the prevention of multifactorial pathological conditions, including osteoporosis (OP) [33, 34]. Polymorphism of the VDR gene can affect individual predisposition to OP and reaction to vitamin D supplements. The association of polymorphisms VDR rs7975232, rs1544410, rs731236 and rs11568820 with a predisposition to OP has been revealed, which can be taken into account for an individual assessment of the risk of fractures and the development of personal recommendations for optimizing vitamin D supplementation, especially in postmenopausal women [35, 36].

In addition, polymorphisms of the VDR gene and their manifestations may differ in different ethnic groups. Thus, the VDR FokI genotype is associated with an increased risk of osteoporosis in Asian women, but not in Caucasian women. In order to draw exhaustive and correct conclusions, further prospective studies with a large number of participants around the world are needed to study the relationship between VDR FokI polymorphism and OP [37]. However, the same polymorphism is associated with an increased risk of cancer of the female reproductive organs. Vitamin D and VDR play a protective role in gynecological cancers. Vitamin D deficiency is detected in ovarian, cervical and vulvar cancers. VDR expression increases in endometrial, ovarian, cervical and vulvar cancers [38].

Some studies show that the replenishment of vitamin D deficiency in the same doses in healthy people has a differentiated effect on the results, which also suggested different variants of mutations of the VDR gene. Vitamin D deficiency is a risk factor for autoimmune diseases, which is also associated with the consequences of COVID-19 [39, 40]. However, some patients develop autoimmune diseases, while others do not, which may also be due to certain genetic determinants, including mutations of the VDR gene [41].

Vitamin D deficiency is directly associated with a high risk of cardiovascular diseases. It is known that VDR activation induces an increase in nitric

oxide (NO) in endothelial cells, and enhances the angiogenic properties of endothelial progenitor cells [42]. In addition, vitamin D can regulate the activity of immune cells by suppressing the release of pro-inflammatory cytokines and increasing the release of anti-inflammatory cytokines, thereby playing a role in protecting blood vessels [43—45]. At the same time, vitamin D is an important regulator of the renin-angiotensin-aldosterone system. Vitamin D deficiency can "turn on" the activation of the renin gene, which leads to an increase in angiotensin II levels, and this, in turn, can lead to hypertension and hypertrophy of the ventricles of the heart. In addition, an increase in the level of angiotensin II may lead to an increase in the production of reactive oxygen species (ROS) and activation of G-proteins, such as Rho A, which threatens the inhibition of pathways necessary for intracellular glucose transport, and, consequently, prerequisites for the development of insulin resistance and the start of the mechanisms of pathogenesis of metabolic syndrome [46—50].

Finally, vitamin D is associated with an atherogenic lipid profile, which includes an increase in serum LDL levels and a decrease in HDL levels. In connection with VDR, calcitriol suppresses the formation of foam cells, reduces the absorption of cholesterol by macrophages and causes LDL autophagy [51]. As a result, vitamin D can lower blood pressure and have anti-inflammatory, antiproliferative, antihypertrophic, antifibrotic, antidiabetic and antithrombotic effects, beneficially modulating classical risk factors for cardiovascular events. At the same time, it was revealed that the polymorphism of VDR FokI (rs2228570) is significantly associated with the development of cardiovascular diseases [52—54].

Vitamin D is an important regulator of the immune system and has an anti-infective and immunomodulatory effect. Recent studies have shown a link between the risk of developing pneumonia in COVID-19 and vitamin D deficiency. The primary point of these studies was to identify the alleged interaction between polymorphisms of vitamin D receptor genes and SARS-CoV-2 infection. There were significant differences ($p < 0.005$) in the frequency of genotypes for polymorphic loci FokI and TaqI between infected SARS-CoV-2 patients and the control group [55, 56].

Conclusion

Thus, the main complications leading to the severe course of COVID-19 are multifactorial, including those related to genotypes, and cannot be unambiguously explained only by the studied genetic risk factors, which once again confirms the complexity of the pathophysiology of COVID-19. However, there is no doubt that the combination of a number of alleles of the coagulation system genes and the immune response aggravate the course of COVID-19 and postcovid syndrome in people with age-related hypogonadism. This is especially important to consider in women taking MHT [8].

According to the modern paradigm, the focus of attention is primarily on the consequences of the transferred COVID-19. New sections have been added to the ICD-10, including codes U09.9 — condition after COVID-19, U08 — personal history of COVID-19, code U08.9 is recommended to be used to register "an earlier episode of confirmed or probable COVID-19, which affects the state of human health, and the person is no longer sick with COVID-19 [57, 58]. Summarizing all the above, it is logical to assume that MHT can bring significant benefits to peri- and postmenopausal women in the context of the ongoing COVID-19 pandemic, due to the beneficial effect of estrogens on vascular walls. However, the situation requires additional study in the context of studying the relationship of polymorphisms of candidate genes that determine the personal risks of thrombotic complications and metabolic consequences, with the correction of the dosage regimen, considering contraindications to MHT and justifying the need to enrich the diet with drugs or supplements of folic acid, vitamin D, pyridoxine and cyanocobalamin.

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Клинико-генетические аспекты менопаузальной гормональной терапии — современная парадигма. Что изменила пандемия COVID-19?

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Аннотация. В современной парадигме охраны здоровья населения здоровью женщин в пери- и постменопаузе уделяется большое внимание, причем господствует персонифицированный подход. Общепризнанно, что патогенетической терапией менопаузальных расстройств является гормональная терапия. Но пандемия COVID-19 внесла свои коррективы в рутинную стратегию выбора менопаузальной гормональной терапии (МГТ). Целью данного обзора являлся анализ исследований зависимости эффективности МГТ от клинико-генетических аспектов в условиях продолжающейся

пандемии COVID-19. В обзоре выделяются основные риски МГТ тромбоэмболических заболеваний и коагуляционных осложнений, характерных для COVID-19, обсуждаются генетические предрасположенности, отягчающие течение постковидного периода, а также эффективность эстрогеныов, защищающих эндотелий сосудов и увеличивающих количество CD4+ Т-клеток, обеспечивая адекватный иммунный ответ при инфицировании SARS-CoV-2. Многочисленные исследования показывают, что осложнения, характерные для тяжелого течения COVID-19, носят многофакторный характер и не могут быть однозначно объяснены только генетической предрасположенностью. Однако, с развитием персонализированной медицины, особого внимания заслуживает исследование генетических аспектов, которые могут в равной мере способствовать возникновению менопаузальных расстройств у здоровых женщин и отягощать течение постковидного периода. Приведенные данные позволяют сделать вывод, что в условиях продолжающейся пандемии COVID-19 на популяционном уровне МГТ может принести существенную выгоду женщинам в период климактерия за счет благоприятного влияния эстрогенов на стенки сосудов. Требуется дополнительное изучение взаимосвязи течения постковидного периода у пользовательниц МГТ и полиморфизмов генов-кандидатов, определяющих риски тромботических осложнений и метаболических последствий.

Ключевые слова: COVID-19, постковидный синдром, менопаузальная гормональная терапия, полиморфизм генов, PAI-1, ITGB 3, MTHFR, VEGF, витамин D

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