FEATURES OF THE COURSE OF COVID-19 IN WOMEN WITH HYPERPROLACTINEMIA

Halyna Semenyna PhD in Medicine, Professor, Professor of the Department of Obstetrics and Gynecology
Danylo Halytsky Lviv Medical University, Ukraine

Tetiana Fartushok PhD in Medicine, Associate Professor, Associate Professor of the Department of Obstetrics and Gynecology
Danylo Halytsky Lviv Medical University, Ukraine

Anastasiia Perfun Student of Faculty of Medicine
Danylo Halytsky Lviv Medical University, Ukraine

Anna Saliuk Student of Faculty of Medicine
Danylo Halytsky Lviv Medical University, Ukraine

Summary. The 2019 coronavirus pandemic is a major stressful event. In turn, stressful situations are triggers for the exacerbation of existing and activation of new diseases caused by a violation of the immune response in the human body and the development of inflammatory diseases. A stressful state causes the release of stress-mediated hormones, which in turn contributes to an increase in the level of PRL. Obviously, it is a closed circle. Therefore, the questions become relevant: 1. Can stress against the background of Covid-19 really cause an increase in the level of PRL? 2. Can Covid-19 worsen the course of an already existing HP? Purpose: to conduct an analysis of available medical research on the peculiarities of the course of Covid-19 in women with HP, highlighting research on this topic in order to systematize new views on the diagnosis and treatment of Covid-19 against the background of already existing HP. Materials and methods. 10 articles from 2018 to 2022 with the keywords prolactin, hyperprolactinemia and Covid-19 were analyzed. Research results and their discussion. A review and analysis of a closed cohort study in which 30 men and 15 women participated and passed the Trier social stress test showed that PRL levels were significantly increased in response to a stressor [10], which could be the Covid-19 pandemic. In SARS-CoV-2, the defined receptor binding domain of the viral membrane protein uses angiotensin-converting enzyme 2 (ACE2) as a receptor for virus-host membrane fusion [2]. ACE2 regulates the activity of dopamine decarboxylase (DDC), which is responsible for the synthesis of dopamine and serotonin. Thus, SARS-CoV-2 disrupts the biosynthesis of dopamine, which leads to an increase in the level of PRL. With Covid-19, the expression of TLR4 and NF-κB is activated and increases the induction release of pro-inflammatory cytokines with the development of ALI, ARDS and cytokines with MOF. Conclusions Based on the studies described above, it can be concluded that Covid-19 inhibits the synthesis of dopamine and thus increases the level of prolactin. Also, prolactin can...
Exhibit both immunostimulating and immunosuppressive, as well as pro-inflammatory and anti-inflammatory effects. Treatment with agonists of dopamine receptors can lead to deepening of depression in Covid-19. Treatment of hyperprolactinemia should be carried out with caution, because in critically ill patients who require personal support, the use of amine derivatives with DRA can cause additional vasospasm and, as a result, a rapid increase in blood pressure.

**Keywords:** hyperprolactinemia, Covid-19, prolactin, cytokine, reproductive axis

**Introduction.** The syndrome of hyperprolactinemia (HP) includes a number of diseases or pathological conditions associated with an increase in the blood serum level of prolactin (PRL).

Human PRL is a polypeptide chain consisting of 199 amino acid residues. Approximately 16% of the amino acid residues of PRL have homology with the structure of the somatotropin hormone molecule. Research in recent years has established that PRL, except for the pituitary gland, is secreted in almost all tissues of the body [7]. PRL receptors have also been identified in all tissues, which indicates that PRL, in addition to hormonal, also exhibits paracrine or autocrine effects and performs the role of a cytokine [4].

Recent studies have shown that PRL can modulate the reproductive axis by affecting a certain population of hypothalamic neurons that express the Kiss1 gene [11]. The Kiss1 gene encodes neuropeptides known as kisspeptins. Kisspeptin1 reduces the secretion of GnRHI by hypothalamic neurons, which leads to a decrease in LH and FSH secretion and a loss of ovarian stimulation, which can lead to infertility, since PRL also reduces the sensitivity of LH and FSH receptors in the gonads [12].

The biological action of PRL is diverse. Based on the localization of PRL receptors and data on the effect on metabolism, all effects of PRL in the body are divided into 7 categories: effects on reproduction and lactation, on water-salt exchange, on morphogenesis and growth, on metabolism, on behavioral reactions, on immunoregulation, on the ectoderm and skin [1]. The relationship between PRL and the immune system has been revealed, since PRL receptors for various cytokines (interleukin-2 (IL-2), IL-3, IL-4, IL-5, IL-6, IL-7, granulocyte colony-stimulating factor, granulocytic macrophage colony-stimulating factor [6].

In this context, the course of the disease due to COVID-19 in patients with HP deserves special attention.

Corona virus disease 2019 (Covid-19) is an infectious disease caused by a positive single-stranded RNA virus (SARS-CoV-2), characterized by severe respiratory damage and a hyperimmune response [7].

The 2019 coronavirus pandemic is a major stressful event. In turn, stressful situations are triggers for the exacerbation of existing and activation of new diseases caused by a violation of the immune response in the human body and the development of inflammatory diseases [9].

A stressful state causes the release of stress-mediated hormones, which in turn contributes to an increase in the level of PRL. Obviously, it is a closed circle. Therefore, the questions become relevant: 1. Can stress against the background of Covid-19 really cause an increase in the level of PRL? 2. Can Sovid-19 worsen the course of an already existing HP?
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Purpose: to conduct an analysis of available medical research on the peculiarities of the course of Covid-19 in women with HP, highlighting research on this topic in order to systematize new views on the diagnosis and treatment of Covid-19 against the background of already existing HP.

Materials and methods. 10 articles from 2018 to 2022 with the keywords prolactin, hyperprolactinemia and Covid-19 were analyzed.

Research results and their discussion. A review and analysis of a closed cohort study in which 30 men and 15 women participated and passed the Trier social stress test showed that PRL levels were significantly increased in response to a stressor [10], which could be the Covid-19 pandemic [7]. There are certain indications that the magnitude of the response in women is greater, depends on the level of estradiol and requires further study [10].

In SARS-CoV-2, the defined receptor binding domain of the viral membrane protein uses angiotensin-converting enzyme 2 (ACE2) as a receptor for virus-host membrane fusion [2]. ACE2 regulates the activity of dopamine decarboxylase (DDC), which is responsible for the synthesis of dopamine and serotonin. Thus, SARS-CoV-2 disrupts the biosynthesis of dopamine, which leads to an increase in the level of PRL (Fig. 1).

![Fig.1. Mechanism of hyperprolactinemia in Covid-19: prolactin (PRL) increases angiotensin II (AngII), IL-1β, IL-6 and arginine vasopressin (AVP) with a decrease in dopa decarboxylase (DDC) followed by an increase in PRL.](https://link.springer.com/article/10.1007/s11010-022-04381-9#:~:text=High%20PRL%20serum%20level%20is%20increased,PRL%20serum%20level%20is%20increased)

PRL can have an inflammatory or anti-inflammatory effect depending on the underlying pathological condition. The anti-inflammatory effect occurs due to the weakening of the expression of TLR4 and NF-κB, followed by a decrease in the release of pro-inflammatory cytokines. In turn, with Covid-19, the expression of TLR4 and NF-κB is activated and increases the induction release of pro-inflammatory cytokines with the development of ALI, ARDS and cytokines with MOF (Fig. 2) [7].

PRL can have an immunostimulating effect or an immunosuppressive effect under certain conditions in higher doses. The immunostimulating effect of PRL is manifested in the stimulation of B and T cells (humoral immunity), NK cells, neutrophils, macrophages (innate immunity)[4].
Fig 2. Prolactin (PRL) and severity of Covid-19: SARS-CoV-2 induces activation of pro-inflammatory cytokines, toll-like receptor 4 (TLR4) and mitogen-activated protein kinase (MAPK) with suppression of thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and calcitonin gene-related peptide (CGRP), leading to activation of PRL release, which in turn stimulates inflammatory protein-1α (MIP-1α) and interferon protein 10 (IP-10) with inhibition regulatory T cells (Treg), leading to hyperinflammation and severity of Covid-19.

The figure is taken from the study “The crucial role of prolactin-lactogenic hormone in Covid-19” Hayder M. Al-Kuraishy, Ali I. Al-Gareeb, Monica Butnariu & Gaber El-Saber Batiha Published: 11 February 2022 https://link.springer.com/article/10.1007/s11010-022-04381-9#:~:text=High%20PRL%20serum%20level%20is%20increased

Recent studies have shown that the progression of macrophages to the condition M 1 is accompanied by a greater increase in the basal expression of the PRL gene (Fig. 3).

Fig. 3. qRT-PCR of PRL gene expression after 24-hour treatment with norepinephrine or adrenaline in naive M 0 (A), inflammatory M 1 (B) and anti-inflammatory M 2 (C) monocytic macrophages.

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Although M1 and M2 macrophages showed similar fold changes in PRL gene expression when exposed to hypertension, the overall expression in the M1 population was much higher because the fold expression was compared to an already elevated basal level of PRL [4].

Patients with pre-existing HP may continue dopamine receptor agonist (DRA) therapy during the pandemic and during acute mild to moderate COVID-19 disease. In patients with HP, PRL should not be measured to assess disease control during acute illness.

It is worth noting that patients on DRA therapy who develop COVID-19 are at risk of drug interactions. The antiretroviral agents lopinavir/ritonavir, currently used to treat COVID-19 in some parts of the world, may inhibit CYP3A4 enzymes and may increase plasma bromocriptine levels [5]. However, the clinical significance of higher bromocriptine plasma levels has not been determined. Cabergoline is less affected by such enzyme modulations, since only a small part of it is metabolized through the cytochrome P450 system [6]. In critically ill patients with COVID-19 who require pressor support due to septic shock, the use of amine derivatives (norepinephrine, epinephrine, dobutamine, dopamine) DRA may cause additional vasospasm and a rapid increase in blood pressure due to pharmacological synergism [11]. Thus, careful monitoring and temporary suspension of DRA use in severe form of COVID-19 is necessary. Chloroquine is not known to interact adversely with DRA. In fact, it has been shown to induce cell apoptosis in pituitary tumors when used in combination with cabergoline in animal studies [8]. However, these beneficial effects are unlikely to be observed during short exposure [2].

Patients receiving long-term DRA treatment have an increased risk of depression, which is already high during the Covid-19 pandemic [3].

Prospects for further scientific research. Creation and implementation of new approaches to the prevention, diagnosis and treatment of patients with hyperprolactinemia and Covid-19.

Conclusions
1. In modern conditions, Covid-19 serves as a stress factor for the population, and prolactin, in turn, tends to increase against the background of stress, which can potentially lead to hyperprolactinemia.
2. Based on the studies described above, it can be concluded that Covid-19 inhibits the synthesis of dopamine and thus increases the level of prolactin. Also, prolactin can exhibit both immunostimulating and immunosuppressive, as well as pro-inflammatory and anti-inflammatory effects.
3. Treatment with agonists of dopamine receptors can lead to deepening of depression in Covid-19.
4. Treatment of hyperprolactinemia should be carried out with caution, because in critically ill patients who require personal support, the use of amine derivatives with DRA can cause additional vasospasm and, as a result, a rapid increase in blood pressure.

References:


