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COVID-19, neutrophil extracellular traps and vascular complications in obstetric practice

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Abstract: An issue of the novel coronavirus infection spreading is currently in the first place among others in the list of the international medical community. Due to lack of information, conflicting research findings, multicomponent effect of the virus on the body host, as well as various consequences that the virus triggers in the body, now every medical specialty does study the viral attack pathogenesis. Recent months showed that vascular complications are the most severe in the Coronavirus Disease 2019 (COVID-19) and are the main cause of death in the patients. The mechanisms of vascular complications are complex and affect both the hemostatic system and immune responses, "inflammatory storm", disorders of the renin-angiotensin-aldosterone system, endotheliopathy, etc.

Due to the leading role of vascular complications in the viral infection pathogenesis, several groups of patients are at extra risk, including pregnant women, patients with a burdened obstetric history, with hereditary thrombophilia and antiphospholipid syndrome, and patients after *in vitro* fertilization (IVF). In this category of pregnant women, use of low-molecular-weight heparins (LMWH) is particularly important for both prevention of vascular and obstetric complications, and for pathogenetic therapy of COVID-19.

Keywords: COVID-19; extracellular neutrophil traps; neutrophil extracellular traps (NETs); thrombophilia; vascular complications.

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Introduction

We live in an extraordinary time when intensive care units around the world are overloaded with patients with severe Coronavirus Disease 2019 (COVID-19). Viral pneumonia has been a major public health problem for many years. Most patients who had severe viral pneumonia develop complications in the form of acute respiratory distress syndrome (ARDS), which is characterized by alveolar capillary damage, edema, parenchymal hemorrhage, microvascular pulmonary thrombosis (MT), and a cytokine storm.

Novel coronavirus infection

In December 2019, a series of unexplained cases of pneumonia appeared in Wuhan, Hubei. Clinical manifestations indicated viral pneumonia. Sequencing of samples received showed a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting disease was named COVID-19. Coronaviruses are a type of single-stranded RNA viruses with a positive chain, which diameter is 80~120 nm [1]. There are several types of viruses-α, β, δ, γ. COVID-19 belongs to the genus β with a capsule on the surface of which there is a crown-like protein spike [2]. Clinical manifestations of the novel

coronavirus infection include fever, cough, chest pain, fatigue, myalgia, diarrhea, nausea, and vomiting. Severe cases can quickly progress to an ARDS, metabolic acidosis, septic shock, coagulopathy, and multiple organ failure.

On March 11, 2020 the World Health Organization (WHO) declared global pandemic of COVID-19. SARS-CoV-2 is characterized by a long incubation period, high infectivity, and multiple transmission routes. Genome analysis showed 86.9% similarity of the nucleotide sequences of the COVID-19 genome with the SARS-CoV virus gene.

Possible mechanisms of pathogenesis of vascular complications in patients with COVID-19 infection

(1) Disorders of the renin-angiotensin system: Previously, it was shown that the virus can bind to the human membrane-bound angiotensin-converting enzyme 2 (ACE2) for further penetration into a cell. ACE2 is an important component of the renin-angiotensin system [3]. Renin hydrolyzes angiotensinogen to angiotensin I (Ang I), which is then converted to angiotensin II (Ang II) by ACE [4]. Ang II leads to vasoconstriction, raises blood pressure, and remodels blood vessels by binding to the angiotensin type II receptor 1 (AT1R). ACE2 can affect Ang I, leading to angiotensin synthesis. Angiotensin synthesis can occur via ACE2 dependent or independent pathways, or ACE2 can directly hydrolyze Ang II to angiotensin. Angiotensin, binding to receptors, triggers vasodilation, oxidative stress, suppresses cell proliferation, and protects the vascular endothelium against damage. These two systems balance each other. ACE2 is expressed by epithelial cells of the alveoli and is a site of the virus invasion, which further leads to pulmonary damage and development of pulmonary failure caused by the viral infection [5]. Observations showed that plasma Ang II levels are well above in patients with COVID-19 infection. The COVID-19 virus seems to bind to ACE2 receptor, which leads to an excessive Ang II release and vasoconstriction, thus increasing the heart load, eventually leading to cardiomyocyte hypertrophy and elevated blood pressure.

(2) Invasion of the virus into the lung tissue immediately triggers the inflammation processes. Invasion of the virus into cardiomyocytes leads to edema, degeneration and necrosis of cardiomyocytes. Meanwhile, cell lysis leads to a release of pro-inflammatory cytokines such as interleukins (IL) 1–6, endothelial adhesion factor, tumor necrosis factor-α (TNF-α), granulocyte colony stimulating factor, interferon, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1α [6]. The accumulation of cytokines, as well as attraction of inflammatory cells from the blood stream to the site of damage, lead to development of an "inflammatory storm", stimulating excessive activation of the body's immune response, increasing damage or apoptosis of myocardial cells, thus reducing stability of atherosclerotic plaques of the coronary arteries. By violating an integrity of the atherosclerotic plaque on the vessel wall, the virus contributes to progression of atherosclerosis and additional thrombosis. All this contributes to an increased risk of exacerbations of cardiovascular diseases [4, 6, 7].

(3) The lung damage caused by COVID-19 leads to hypoxia, reduced oxygen partial pressure, and tissue oxygen saturation, to accumulation of oxygen free radicals, lactic acid, and other metabolites. These circulating substances inevitably damage the myocardium. Hypoxia results in heart activity increase and heart failure gradually develops. In addition, hypoxia is one of the factors that trigger an inflammatory response and increase a build-up of the "inflammatory storm" [6, 7]. An oxidative stress is one of the causes of endotheliopathy, and therefore-of hypercoagulation and thrombosis.

(4) The first response to the viral invasion is an activation of immune and inflammatory responses. The impact of pathogens on tissues and organs is a complex process. At the same time, there is an emotional attitude to the disease, manifested by anxiety, fear etc., which also makes the stress more intense. The stress results in a release of large quantities of catecholamines. High concentrations of catecholamines have a toxic effect on the myocardium, they can lead to impaired microcirculation, vascular spasm, arrhythmia, and sudden death [6, 7].

Typical signs of severe course of COVID-19:

(1) Sudden deterioration of the course of the disease approximately one to two weeks after the disease onset.

(2) Very low level of lymphocytes, especially natural killer cells (NK) in the peripheral blood [8]. Severe immune system dysfunction, manifested by an atrophy of the spleen [9, 10] and lymph nodes [9], along with a decrease in the number of lymphocytes in the lymphoid organs; in the spleen there is a significant cell degeneration, focal hemorrhagic necrosis,

macrophage proliferation and phagocytosis of macrophages. Similar lymph node atrophy processes. In the severe form of COVID-19, despite lymphopenia, there is an activation of lymphocytes. In one study subgroups of lymphocytes and cytokines of 123 patients were analyzed, all of whom had lymphopenia [11]. Percentage of CD8+ T-cells decrease was 28.43 and 61.9% in the mild and severe group, respectively, while a decrease in NK cells was 34.31 and 47.62%, respectively. In addition, serum levels of IL-6 in the severe group were significantly higher than in the mild group [12]. Expression of HLA-DR in CD4+ and CD8+ cells, and concentration of CD4+ CCR4+ CCR6 + Th17 cells also increased, and an increase in the expression of cytotoxic perforin and granolysin in CD8 + T cells was also found [12].

(3) Thrombocytopenia. In patients with COVID-19, thrombocytopenia mechanism is probably multifactorial. It was suggested that a combination of the viral infection and an artificial ventilation leads to endothelial damage, triggering platelet activation, aggregation, and thrombosis in the lungs, in which significant platelet consumption occurs [13]. Moreover, since the lung can be a site of release of platelets from mature megakaryocytes, severe pneumonia can lead to impaired platelet defragmentation. Coronaviruses can also directly infect elements of the bone marrow, leading to abnormal hematopoiesis, or trigger an autoimmune response against blood cells [14].

(4) Cytokine storm. In patients with coronavirus pneumonia, accompanied by rapid viral replication, abundant tissue infiltration with inflammation and cytokine storm leads to acute lung damage, ARDS, and death [7, 15, 16]. Cytokine storm is observed in most patients with severe COVID-19 and is manifested by excessive and uncontrolled release of pro-inflammatory cytokines. Accumulated data showed that some patients with severe COVID-19 have an increased profile of such cytokines as IL-1B, IL-1RA, IL-7, IL-8, IL-6, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ), granulocyte-colony-stimulating factor (G-CSF), interferon-γ-induced protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1-α (MIP1A), platelet growth factor (PGF), TNF-α, vascular endothelial growth factor (VEGF) [17, 18].

(5) Hypercoagulation and multiple organ failure. In the majority of severe patients with COVID-19 in intensive care units, there is a constant increase in the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and high levels of IL-6, TNF-α, IL-1β, IL-8, IL-2R, thrombocytopenia, etc., due to ARDS, hypercoagulation and disseminated intravascular coagulation (DIC) [19].

(6) Another pronounced clinical sign in the patients with severe COVID-19 is endothelial damage. Many patients in critical condition have vasculitis-like manifestations and even gangrene of the extremities. Post-mortem examination showed hyperemia and swelling of the blood vessels of the alveolar septum, with moderate infiltration of monocytes and lymphocytes [20, 21]. Small vessels showed wall thickening, lumen stenosis, hemorrhages in the surrounding tissues. In some cases, there were hyaline thrombi in the microvasculature [22].

Factors, contributing to thrombus formation

Neutrophil extracellular traps

Main mechanism of vascular damage can be associated with direct damage to endothelial cells by a virus, as well as with massive activation of neutrophils during a cytokine storm and massive release of NETs and uncontrolled development of pathological processes of thromboinflammation [23].

NETs are extrusions of intracellular DNA and attached histones that provide destruction of bacteria [24]. The role of NETs is increasingly recognized as important factor of the respiratory diseases' pathogenesis. NETs consist of intracellular material that neutrophils organize in the cytoplasm, and then release when activated (netosis). Together, they capture and destroy many genera of microbes, including bacteria, fungi, viruses, and protozoa, limiting infection, especially where phagocytosis is not possible [25]. At first, NETs formation was thought to be a terminal event for neutrophils; however, it is now clear that some neutrophils survive this process by becoming non-nuclear and can cause ongoing tissue damage. It is currently known that NETs are directly cytotoxic to the epithelium and endothelium of the lungs [24].

Although much attention is currently being paid to hyperactivation of immune system as a part of pathogenesis of severe COVID-19, the etiological factors that contribute to development of severe complications are not yet fully clear. Earlier studies have shown that extracellular neutrophil traps may significantly contribute to virus-associated pathology [26]. NETs produced in large quantities in the conditions of a new viral infection contribute to

development of alveolitis, endothelial damage and trigger intravascular coagulation; these events eventually lead to pathological manifestations of ARDS [27]. Previous studies in patients with viral pneumonia have shown that excessive activation of neutrophils with production of NETs contribute to acute damage to lung tissue, microthrombosis, hemorrhages and lung failure [28].

Histones are the main protein components of extracellular neutrophil traps and are known to have cytotoxic effects. Mice infected with the flu virus had a high accumulation of extracellular histones with widespread pulmonary microvascular thrombosis (MT). Histones released during NETs synthesis induce cell damage and are detected in the structure of blood clots along with platelets in the lungs of infected mice. The nasal discharge of the flu-infected patients also showed an increased accumulation of extracellular histones, which is indicative of possible clinical significance of NETs in the lung damage. Administration of antihistone antibodies leads to a noticeable reduction in lung pathology in mice with severe flu. Histones are important chromatin structures in an intact cell [29]. Histones interact with membrane phospholipids and enhance intracellular transfer of calcium ions, which triggers cytotoxic reactions [30]. H2A, H2B and H4 histones have the highest cytotoxicity against the endothelium and epithelium [30]. H4, H3, and H2B histones can increase platelet aggregation [29]. Chromatin networks in NETs destroy the alveolar-capillary barrier, leading to epithelial damage, epithelial damage, vessel integrity damage, and hemorrhage [31]. Despite the known protective properties of NETs against capture and inactivation of viruses and bacteria, there are no such effects in cases of viral pneumonia.

It was shown that NETs are critical for promoting inflammatory process in poor pregnancy outcomes [32]. Pregnancy itself is associated with a slightly pro-inflammatory state with increased neutrophils activation contributing NETs formation. Preeclampsia, recurrent pregnancy losses appear to be a result of not only high prothrombotic state but excessive inflammatory neutrophils activity which promotes increased NETs. Histological examination performed on placentas from preeclamptic women, including a case of a woman with catastrophic antiphospholipid syndrome revealed an excessive deposit of neutrophils/NETs with inflammatory histological characteristics [33].

CD40L ligand

A degree of pulmonary capillary thrombosis, platelet activation and aggregation, and endothelial damage is associated with the severity of the inflammation in patients with viral pneumonia [34]. Among various inflammatory mediators that contribute to development of thrombosis, the CD40L ligand is active in enhancing platelet aggregation [35]. CD40L is widely expressed by the platelets and white blood cells [29]. Soluble CD40L, a product of CD40L cleavage, is a strong inducer of platelet aggregation and induces B-cell proliferation and modulation of immune responses [36]. It has been reported that 95% of circulating sCD40L is secreted by platelets, suggesting that histone-platelet interaction may be crucial in the development of thrombosis.

Antiphospholipid antibodies and genetic thrombophilia

Interestingly, some patients were found to have high titer of antiphospholipid antibodies, including anti-cardiolipin antibodies and β_2-glycoprotein 1 (β_2-GP1) antibodies, which was accompanied by severe thrombosis [37].

Clinical observations have shown that almost 20% of patients with COVID-19 have coagulopathy, including almost all severe patients [38]. Studies have shown that hypercoagulation in patients with COVID-19 may be associated with increased cytokine levels. In addition, studies have shown that in patients with COVID-19, D-dimer levels were significantly elevated [38]. Research by Ning Tang et al. showed higher levels of D-dimer in severe patients [39]. According to the recommendations of the International Society on Thrombosis and Hemostasis (ISTH) it is necessary to determine D-dimer level, prothrombin time (PT), and platelet count in all patients with COVID-19 infection [40].

Estimates of thrombotic conditions per 100,000 people in Denmark, Korea, Hong Kong, Sweden, and the United States showed that the most common vascular complication is a heart attack. The second cause is stroke, and the third is venous thrombosis [41]. According to the results of studies in the European community, venous thrombosis accounts for a combined 12% of deaths in the population [42]. It is more than acquired immune deficiency syndrome (AIDS), breast cancer, and traffic deaths combined.

In this regard, it is worth mentioning patients with inherited forms of thrombophilia (factor V Leiden mutation, prothrombin gene mutation, protein C, S, antithrombin deficiency) as previously confirmed and non-manifest thrombophilia, which manifestation can occur due to a contact with the viral infection.

Genetic thrombophilia and antiphospholipid syndrome, as well as hyperhomocysteinemia, which turn into thrombosis in older age, in young women are manifested

by recurrent pregnancy losses, miscarriages, undeveloped pregnancies, stillbirths, severe pregnancy complications such as preeclampsia, premature detachment of the normally located placenta, and HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome. Patients with a burdened obstetric history and COVID-19 have higher risk of obstetric and vascular complications (Table 1).

COVID-19 and pregnancy

Pregnant women are more susceptible to coronavirus infection due to changes in the body, primarily in the respiratory and immune systems [43]. At the same time, the available data are not indicative of a more severe course of COVID-19 in pregnant women compared to the general population. The results of a recent meta-analysis of 19 studies evaluating pregnancy complications and outcomes in patients with various coronavirus infections have shown that pregnancy with COVID-19 is associated with higher rates of miscarriage, preterm birth, preeclampsia, cesarean section, and perinatal death [44]. Meta-analysis by Juan et al. which included 324 pregnant women with COVID-19 were studied and no significant differences in frequency of obstetric complications were found. But the authors note the necessity of the future more in-depth study of the impact of virus on the pregnancy and fetus [45].

A group at high risk of developing severe forms of COVID-19 includes pregnant women with somatic diseases: chronic lung diseases, including moderate and severe asthma; diseases of the cardiovascular system, hypertension; diabetes; immunosuppression, including treatment of cancer; obesity; chronic kidney and liver disease. It is still unknown whether a pregnant woman with COVID-19 can transmit the virus to her baby during pregnancy or childbirth. Hitherto, the virus has not been detected in samples of amniotic fluid, placenta and breast milk [46]. Almost all reports indicate that there is no vertical transmission of the virus, further research is needed on the effects of COVID-19 on the course of pregnancy and the body of both the mother and the fetus [40]. Documented neonatal cases of COVID-19 infection have been attributed to close contact with a sick mother or other carriers. We must not forget that new data is accumulated every day, and information is constantly updated.

For the diagnosis of pregnant COVID-19 pneumonia, computed tomography (CT) can be used. CT of the chest can be the primary method for identifying cases of COVID-19; it provides a low dose to the fetus and can be reasonably used during pregnancy [47]. Magnetic resonance imaging can be performed at any stage of pregnancy without contrast for the differential diagnosis of lung damage [48]. Echocardiography is recommended for pregnant women, women in labor and women in childbirth with signs of respiratory failure. The cardiovascular system is frequently

Table 1: Risk groups for vascular and obstetric complications among pregnant women with COVID-19.

Risk factor	Characteristics
Thrombosis in personal and family history	
Pregnant women with thrombophilia	–Genetic thrombophilia (Leiden V mutation, prothrombin, antithrombin III deficiency, protein C and S) –Hyperhomocysteinemia –Antiphospholipid syndrome –Thrombotic microangiopathy
Complicated obstetric history	–Preeclampsia –Fetal growth restriction –Recurrent pregnancy loss –Postpartum hemorrhage –Preliminary detachment of normally located placenta. –HELLP syndrome –Postpartum inflammatory processes
Pregnancy in the IVF program	
Multiple gestation	
Pregnancy in patients with	–Obesity, diabetes, polycystic ovary syndrome in anamnesis –Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, etc.) –Chronic liver and kidney diseases –Heart diseases, cardiovascular diseases, hypertension, sickle cell anemia

affected in COVID-19 and this has evoked interest in the possibility of peripartum cardiomyopathy, which is often diagnosed in women with preeclampsia [49]. Juusela et al. described in their article two cases of cardiomyopathy in pregnant women against the background of COVID-19 infection and comorbidities (cardiac diseases) and other risk factors (obesity, ethnicity, age and others) [49]. Authors recommend the necessity of performing an echocardiogram for evaluating of cardiomyopathy in pregnant women with COVID-19.

Another article by Pierce-Williams et al. pointed to the absence of cardiomyopathy in 64 pregnant hospitalized women with severe and critically ill COVID-19 cases. There was one case of maternal cardiac arrest and were no cases of maternal death or cardiomyopathy, no stillbirths or neonatal deaths, or cases of vertical transmission [50].

The indications to admit to the hospital pregnant women with COVID-19 are the moderate and severe forms of the disease. With a mild form of the disease, pregnant women can get treatment at home under the doctor's control, the woman's monitoring should be provided without compromising the safety of her family. In mild to moderate forms of the disease, therapy consists of maintaining the right balance of electrolytes and fluid, symptomatic treatment, and surveillance [51]. Antipyretic drugs should be prescribed at temperatures above 38.0–38.5 °C. However, if there is a poor tolerance of fever, headaches with increased blood pressure and severe tachycardia (especially in the presence of ischemic changes or rhythm disturbances), antipyretic drugs should be used at lower temperatures. Paracetamol is the antipyretic drug of first choice in pregnant women, before and after delivery: it should be prescribed at a dosage of 500–1000 mg up to four times a day (no more than 4 g per day). Saline solution (isotonic, and in case of congestion-hypertonic) is the topical treatment of rhinitis, pharyngitis, in case of nasal congestion and/or nasal discharge. In the case of poor effect, nasal decongestants may be indicated. With poor relief or according to severity of symptoms, various solutions with antiseptic effect can be used. It is necessary to rule out the presence of a bacterial infection (blood culture, microscopic examination of an average portion of urine or a sample of urine obtained through a catheter; urine culture) and to prescribe the appropriate antibiotics in case of a secondary bacterial infection. In the second and third trimesters of pregnancy, in the postpartum and after an abortion it is possible to use mucolytic agents as mesh nebulizer and bronchodilators. During pregnancy (all trimesters), in the postpartum and post abortion periods, salbutamol can also be used with a mesh nebulizer as a bronchodilator.

Supportive treatment with hydration and oxygen therapy is necessary for the severe forms of the disease, which needs intensive care. The patient should be kept in an isolated room with negative pressure in the intensive care unit, the patients should be kept on the left side preferably, and managed by a multidisciplinary team (obstetricians, anesthesiologists, reanimation staff, therapists or pulmonologists, neonatologists, infectious disease specialists, clinical pharmacologists). If there are suspected or confirmed secondary bacterial infections, antibiotic treatment in combination with antiviral drugs should be started immediately [52]. Several aspects determine obstetric strategy: the severity of the patient's condition, the condition of the fetus, and the gestational age. In case of a mild COVID-19 up to 12 weeks of gestation, due to an unproven negative effect on the fetus, pregnancy can be followed up to the full term. The main indication for abortion in the early stages is the severity of the disease with no effect of the therapy. In severe cases of the disease manifested up to 12 weeks of gestation due to the high risk of perinatal complications associated with both the indirect effect of a viral infection (hyperthermia) and the potential embryotoxic effect of drugs, pregnancy termination during or after treatment of the infection is an option. If the patient does not intend to terminate pregnancy, chorionic villus sampling before 12–14 weeks or amniocentesis at 16 weeks of gestation may be offered in order to detect fetal chromosomal abnormalities [53].

The presence of COVID-19 infection is not an indication for delivery except in cases requiring improvement of blood oxygenation. For cases of suspected or confirmed COVID-19, delivery should take place in an isolated room with negative pressure [54]. In the case of the development of spontaneous labor at the height of the disease (pneumonia), delivery is preferably carried out through vaginal delivery under continuous monitoring of the condition of the mother and fetus (there is a reported increased risk of fetal distress during labor). In the second stage of labor, in order to prevent the development of respiratory and cardiovascular insufficiency, the pushing should be avoided. If we need to accelerate the delivery process in case of fetal distress, or uterine dysfunction or if woman's conditions worsen, it is suggested to use vacuum extraction or obstetric forceps. An emergency caesarean delivery is indicated (or termination of pregnancy, the depends from the gestational age and viability of the fetus) when the pregnant woman is facing an increase in respiratory failure, septic shock, acute organ failure or there is fetal distress. Caesarean delivery should ideally be performed in an operating room with negative pressure. In cases requiring early delivery in a critically ill patient, FIGO (2020) experts

call for caution regarding the antenatal use of corticosteroids for the prevention of fetal respiratory distress syndrome, as the high doses used in this case can lead to the worsening of the condition of a woman [54]. The decision on antenatal use of corticosteroids should be made in agreement with infection diseases specialists, obstetricians, and pediatricians.

Caesarean delivery is performed according to standard obstetric indications. However, if hypoxia is difficult to eliminate during mechanical ventilation or there is a progressive respiratory failure and/ or alveolar pulmonary edema, and there is also a refractory septic shock, in the interests of the mother and fetus an emergency abdominal delivery (caesarean section) with all necessary measures for the prevention of coagulopathic and hypotonic obstetric bleeding should be performed.

It is recommended that with any method of delivery in women in labor with COVID19, to use the lowest effective doses of uterotonics for prophylactic and therapeutic purposes. It is advised to avoid prostaglandins for the prevention and treatment of postpartum hemorrhages since they can cause bronchospasm and increase shortness of breath. With increasing respiratory failure amid severe preeclampsia with COVID-19, it is recommended to avoid magnesium therapy [55]. In pregnant women and puerperas with COVID-19 with a serious or extremely serious condition, it is recommended not to use non-steroidal anti-inflammatory drugs [56]. In pregnant women and puerperas with COVID-19, it is recommended not to use narcotic analgesics for routine analgesia, due to the high risk of developing respiratory depression. In pregnant women with COVID-19, it is recommended to use conduction methods of analgesia (transverse abdominal plane block or quadratus lumborum block). It is recommended in the postpartum (postoperative) period that women with COVID-19 should be prescribed low molecular weight heparin (LMWH) in the absence of contraindications [40].

Special group are patients after *in vitro* fertilization (IVF) [57]. Recent studies have shown that the patients after embryo transfer in the stimulation cycle have an eight-fold increased incidence of venous thromboembolism (VTE) in the first trimester (HR 8.69, 96% CI 3.83 to 19.71) compared to spontaneous pregnancies. Frequency of VTE in the patients after cryopreservation did not increase in the first trimester. The reason is probably a significant hormonal load in the stimulation cycle, supplemented by hypercoagulation due to pregnancy, especially in patients with risk factors [57].

Making an effective vaccine against COVID-19, a new and not fully understood virus, is a very complicated task. Since the severe course of the disease is mediated not only by the virus itself, but also by host factors, treatment with antiviral drugs does not always effectively control mortality rates [58–61]. The use of antiviral drugs is also limited by side effects and rapid development of resistance [61, 62].

Data about the prevalence and severity of COVID-19 among pregnant women and whether symptoms differ among pregnant and nonpregnant women are limited. Based on what we know pregnant women with pre-existing comorbidities might be at increased risk for severe COVID illness. Therefore, it is much more important to study the pathogenesis of severe viral infection and turn our focus toward prevention of development of severe complications using pathogenetic therapy [63, 64]. Additional data are needed to evaluate these observed elevated risks. Given that fact that pregnancy itself is a hypercoagulable state, pregnant women infected with SARS-COV-2 is even more hypercoagulable and have an increased risk of maternal VTE [40]. During pregnancy, these changes in the hemostatic system may be aggravated by an inflammatory reaction of COVID-19 contributing to the development of venous thromboembolic complications. All pregnant women admitted with confirmed or suspected COVID-19 should receive prophylactic LMWH, unless birth is expected within 12 h. When there is a suspicion of a VTE complication therapeutic dose thromboprophylaxis should be used. For women with severe complications of COVID-19, the appropriate dosing regimen of LMWH should be discussed in a multidisciplinary team [65]. It is recommended in the postpartum (postoperative) period that women with COVID-19 should be prescribed LMWH in the absence of contraindications.

In recent years many studies have shown that LMWH has various non-anticoagulant properties [66], including anti-inflammatory properties by reducing the release and biological activity of IL-6 [67]. Von Willebrand factor (vWF) is a mediator between the endothelium and platelets, promoting their adhesion. Previous studies have shown that vWF levels increase and platelet levels decrease [64] in SARS-CoV-2 patients, thus activating the coagulation cascade. At the same time, studies have shown that LMWH is hardly inactivated by platelet factor 4 (PF4) [68, 69], and has a strong affinity with vWF, which can interfere with the interaction between vWF and platelets and reduce platelet aggregation and consumption. Numerous studies have shown that LMWH can reduce a release of IL-6 in the body by regulating the levels of antithrombin or activated protein C in plasma, as well as inhibit an expression of nuclear factor κB (NF-κB) [70]. In addition, the study by Mummery et al. [66] demonstrated that LMWH can bind to IL-6, competitively reducing the binding of IL-6 to soluble IL-6 receptor (sIL-6R) and soluble gp 130 (sgp130) [70] and block signal transmission, thereby inhibiting the biological activity of IL-6.

Conclusions

Vascular complications are a leading cause of death in patients with severe COVID-19. In this regard, it is extremely important to identify risk groups, including among pregnant women, to carry out adequate laboratory monitoring and use drugs that have pathogenetically justified therapeutic effects.

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