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THE CLINICAL COURSE OF COVID-19 IN PREGNANCY, THE IMPORTANCE OF PHYSIOLOGICAL CONDITIONS IN PREGNANCY AND GENETIC FACTORS IN THE DEVELOPMENT OF THE DISEASE (Literature analysis)

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Abstract
Studies shows that pregnant women are slightly more likely to get infected with Covid-19 and have a more severe disease than women in other contingents. The main reason for this is the weakening of immune system with the physiological changes observed in the body of a pregnant woman. In addition, it has been confirmed in many literatures that the role of genetic factors in the development and aggravation of Covid-19 infection is high. All of these conditions increase the risk of contracting Covid-19 during pregnancy, increasing the likelihood of the disease worsening and developing complications, as a result, the risk to the life of the mother and child increases.

Keywords: Hypoxia, polymorphism, hypervolemia, sepsis, coagulopathy, acidosis-acid-base imbalance.

Introduction

Covid-19 is a disease of viral etiology with the development of acute respiratory syndrome of human. While most people with COVID-19 have a mild or moderate illness, about 14% of patients require inpatient treatment and oxygen support. In 5% of cases, intensive care treatment is necessary. In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiple organ failure, including acute renal failure, and myocardial damage.

There are 4 different severity levels of Covid-19 in pregnancy:

1. At a mild level: the disease shows the main symptoms of Covid-19 (cough, fever, loss of appetite and loss of sense of smell) without symptoms of pneumonia and hypoxia.
2. Moderately severe: pregnant women have clinical signs of pneumonia (fever, cough, difficulty breathing), but no signs of severe pneumonia, including SpO2 ≥ 90%. Diagnosis can be made based on clinical signs, but instrumental methods such as X-ray, CT, and ultrasound of the chest can help to diagnose and identify or exclude complications.

3. Severe: clinical signs of pneumonia (fever, cough, painful or frequent breathing) and respiratory rate ≥ 30 breaths/min, SpO2 <90%. Clinical symptoms indicate the degree of the disease, but it is necessary to use additional diagnostic methods, which help to identify complications.

4. Critical situation. Acute respiratory distress syndrome (ARDS) is progressive. The condition develops within 1 week after the onset of clinical pathology (pneumonia) or after the exacerbation of previously existing respiratory symptoms.

Chest examination (x-ray, CT or lung ultrasound) shows the extent of lung damage. When pulmonary infiltrates occur: respiratory failure with heart failure or hypervolemia, an objective assessment (for example, echocardiography) is required to exclude a hydrostatic cause for infiltrates, edema.

The breakdown of oxygen is as follows:

• Mild : 200 mm Hg. Art. <PaO2/FiO2a ≤ 300 mmHg Art. (with PEEP or CPAP ≥ 5 cm H2O).

• Average : 100 mm Hg. Art. < PaO2/FiO2 ≤ 200 mmHg Art. (with PEEP ≥ 5 cm H2O).

• Severe : PaO2/FiO2 ≤ 100 mmHg. Art. (with PEEP ≥ 5 cm H2O).

In some cases, patients may develop sepsis. Sepsis during pregnancy: childbirth or the postpartum period: is a life-threatening acute multiorgan failure (organ dysfunction) caused by the body's uncontrolled response to a suspected or confirmed infection. Signs of organ dysfunction include: altered mental status, difficulty breathing or rapid breathing, hypoxia, decreased urine output, tachycardia, decreased pulse, low blood pressure, skin rash, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, and high blood lactate levels or hyperbilirubinemia.

In pregnant women, Covid-19 has been found to be somewhat more severe than women in other contingents. Professor Aris Papageorgiou said that when a pregnant woman is infected with Covid-19, the risk of infection increases. Physiological changes in the body of a pregnant woman are mainly caused by weakening of the immune system. It turns out that pregnant women infected with Covid-19 have a worse pregnancy and coronavirus infection. These two conditions complicate each other and increase the risk of maternal mortality.

A number of physiological changes are also observed in the respiratory system during pregnancy: hyperventilation occurs in 50-65% of pregnant women, the minute volume of breathing increases 1.3-1.4 times.

Due to the high oxygen demand of the fetus, the placenta and the increased energy expenditure of the woman during pregnancy and childbirth: oxygen consumption during pregnancy increases continuously, by 30-40% at the end of pregnancy, and by

150% of the initial value during labor. -250% more. These loads increase the activity of the lungs and cardiovascular system.

In the second half of pregnancy, when the fetus grows, the pressure of the uterus on the diaphragm increases, as a result of which the mother's breathing becomes shallow. If a viral infection of the lungs is added to this natural process, the risk of oxygen deficiency increases dramatically. At the same time, pregnancy in women infected with Covid-19 ends in premature birth, as a result of which various complications, such as underdeveloped lungs and vision impairment, were observed in newborns. Some studies have shown that infection with Covid-19 during pregnancy can also lead to spontaneous abortion, premature birth and fetal growth restriction.

Physiological changes in the body of a pregnant woman increase susceptibility to lung infections and increase the clinical manifestations of the disease. Specifically, suppression of cytotoxic T cells, a 4:1 predominance of type 2 T-helpers over type 1 T-helpers, which leads to decreased secretion of interleukin-2, tumor necrosis factor β, and interferon-γ. The activity of natural killer cells also decreases.

Changes in the immune system play a major role in the development of infectious diseases during pregnancy, because pregnancy is a unique immunological state. The mother's immune system faces major challenges during pregnancy: establishing and maintaining tolerance to the allogeneic fetus, while maintaining its ability to protect against microbes. The normal continuation of pregnancy relies on a well-tuned immune adaptation at the systemic and local levels. Recently, Aghaeepour and colleagues proposed a precise timing of immunological events in peripheral blood occurring during full-term pregnancy, termed the "immunity clock." They found that pregnancy induced a robust and progressive increase in endogenous STAT5αb signaling in multiple T-cell subsets, including CD25 + FoxP3 + T reg cells, naive and memory CD4 + and CD8 + T cells, and gd T cells . During pregnancy, the mother's immune system is well prepared to protect against the attack of foreign pathogens. Innate immune cells such as NK cells and monocytes respond more strongly to viral challenges, while some adaptive immune responses decline during pregnancy, e.g. The number of T and B cells decreased. In addition, during pregnancy, the upper respiratory tract is saturated with estrogen and progesterone, as a result, the mucous membranes swell slightly, and the limited expansion of the lungs makes the pregnant woman susceptible to pathogens of the respiratory tract. For this reason, a pregnant woman may be more susceptible to some infectious diseases and may have a slightly more severe illness.

Changes in blood coagulation in pregnant women infected with Covid-19 are more difficult to interpret because they are similar to physiological changes caused by

pregnancy. In pregnancy, most of the coagulation factors (fibrinogen, VII, VIII, IX and X factors) increase, physiological anticoagulants decrease (resistance to protein C activation and decrease in protein S level), and fibrinolytic activity is observed. All this is aimed at maintaining placental perfusion and preventing pathological bleeding during childbirth. During pregnancy, the fibrinogen concentration and D-dimer level increase, the number of platelets may decrease, while the activated thromboplastin time and prothrombin time decrease significantly. COVID-19 causes additional coagulation changes. Their intensity may depend on the severity of the disease. Hypercoagulation increases the risk of thromboembolic complications.

Thromboembolism during pregnancy happens with 2-5 per 1000 births. Thromboembolism develops against the background of physiological hypercoagulation under the influence of additional risk factors. International guidelines have defined risk factors for thromboembolism and low molecular weight heparins for prevention, as well as tactics for treatment of complications. All women with four or more risk factors (except thrombophilia) should be given prophylactic low-molecular-weight heparin during pregnancy until delivery.

The development of pneumonia also plays a role in the increased risk of venous thrombosis: in this case, the increase in the inflammatory process, a long stay in bed complicates the disease. The presence of pneumonia in pregnant women infected with COVID-19 puts this pregnant woman at high risk for the development of thromboembolism.

Along with physiological changes during pregnancy, there is a role of a number of features in the genotype of the organism in the development of Covid-19 infection.

Recent literature shows that in severe cases, the infection of COVID-19 is associated with a cytokine storm, which is characterized by plasma interleukins 2 (IL-2), IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and tumor necrosis factor (TNF-α) are associated with mutations. Based on the data that pregnant women in the first and third trimester are in a pro-inflammatory state, the cytokine storm induced by SARS-CoV-2 may induce a more severe inflammatory state in these women. Furthermore, maternal inflammation as a result of viral infection during pregnancy can affect several aspects of fetal brain development and subsequently lead to changes in a wide range of neuronal dysfunctions and behavioral phenotypes in the postnatal period.

Genetic studies have shown that maternal immune activation increases maternal IL-17α levels, leading to an autism spectrum-like phenotype and brain development abnormalities in the offspring. Other studies have also shown an association between

poor pregnancy outcomes, maternal comorbidities, and systemic cytokine concentrations in women, including TNF-α, IFN-γ, and IL-10. An abnormal increase of TNF-α in the peripheral blood of the mother can hinder the early development of the embryo.

In particular, more attention should be paid to pregnant women in the first and second trimester. Although there is no evidence that there is a possibility of vertical transmission from mothers to babies, the infection can affect the developing fetus.

It is known that the study of genetic predisposition is becoming one of the important issues in modern medicine. It helps to identify not only the main causes of individual differences in patients, but also the pathogenesis of many diseases. A better understanding of genetic predisposition may provide better directions for the prevention and treatment of related diseases, which is especially important for individual prevention and treatment. Genetic factors are the basis of the body's reactivity, which includes protective immunity, functional states of the nervous and endocrine systems, nutritional status, psychological factors, age, gender and all other factors, which is called general genetic predisposition. The COVID-19 virus is a new infectious pathogen that can cause severe disease in human, and we still do not have a complete understanding of it. Information about its origin and development remains limited.

Also, with the emergence of the new 2019-nCoV coronavirus, researchers around the world began to look for the possible pathogenesis of the disease. The renin-angiotensin system (RAT) and angiotensin-converting enzymes have attracted much attention as possible pathways involved in the pathogenesis of 2019-nCoV. The ACE2 gene encodes angiotensin-converting enzyme-2, which has been shown to be a receptor for SARS-coronavirus (SARS-CoV) and human respiratory coronavirus NL63. Recent studies suggest that ACE2 may be a specific receptor for the novel coronavirus 2019-nCoV/SARS-CoV-2.

Research is also underway to investigate APOE gene haplotypes and their role in the spread and course of the infection caused by COVID-19. This study includes the study of polymorphisms of the ACE gene, genes of the basic histocomposition complex, and the APOE gene. As a result of the study, all people can calculate the integral risk of contracting the COVID-19 virus.

Currently, there is no doubt that individual genetic characteristics of a person are an important risk factor for the development of various diseases. The role of genetic polymorphism in the occurrence and development of acute infectious diseases is understudied, as investigations have only investigated a range of candidate genes and are mainly limited to cytokine genes . However, the general stability of organs depends

on several other genes. Therefore, further studies should be aimed at identifying all possible gene alleles.

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