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Clinical and Immunological Features of Coronavirus Infection in Pregnant Women

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Abstract: In addition to the changes that occur in the immune system during pregnancy, there are also systemic physiological changes in the vascular bed, in particular, an increase in maternal blood volume, an increase in heart rate, stroke volume and, as a result, an increase in cardiac output by 30-50%, a decrease in vascular resistance; in the respiratory system - a decrease in functional residual capacity and a decrease in chest excursion. Pregnancy is a hypercoagulable state with increased thrombin production and increased intravascular inflammation. All of these factors suggest that pregnant women are more vulnerable to COVID-19 infection than the general population.

Keywords: pregnancy, COVID-19, immunological changes.

Introduction. Coronaviruses are viruses that cause diseases in humans and animals. They got their name due to the outer villous shell resembling a solar corona. Recently, WHO experts reported a new manifestation of infection — redness of the eyes caused by viral conjunctivitis. The symptom occurs when the mucous membrane of the eye comes into contact with an aerosol containing particles of the pathogen SARS-CoV-2. Conjunctival hyperemia occurs in 1-3% of patients among all infected with coronavirus. Despite the large number of cases, doctors still find it difficult to determine the typical clinical picture. Perhaps this is due to a mutation of the virus, which was recently reported by scientists from a clinic in Houston. They found the D614G mutation, which increases the virulence of the pathogen and helps it “hide” from the human immune system. It is with changes in the genome that doctors associate the onset of the second wave of coronavirus in the city. Physiological changes in the immune, cardiovascular and respiratory systems during pregnancy suggest that pregnant women are particularly vulnerable to the effects of pathogenic infectious agents and the development of severe infection, which, in turn, can lead to higher morbidity and mortality of the mother and fetus.

Analysis. Pregnant women with pneumonia are more likely to have premature births, premature babies with low body weight are born, and the frequency of cesarean section is higher. In addition, during pregnancy, the predisposition to the development of hypertension and gestational diabetes mellitus increases, which are currently recognized risk factors for the development of severe acute respiratory syndrome caused by coronaviruses, including SARS-CoV-2. Let's turn to the physiological immunological changes in the body of a pregnant woman. They are characterized by the following:

An increase in the level of circulating progesterone. Progesterone is a steroid hormone with immunomodulatory properties. Progesterone also enhances lung recovery after damage caused by the influenza virus, which makes its high levels during pregnancy potentially useful for recovery from viral lung diseases. However, in an experiment in mice with influenza A infection after treatment with progesterone or progestin, levonorgestrel, there was a decrease in the level of virus-specific antibodies, as well as a decrease in the content of virus-specific CD8+ T cells. Repeated infection of mice with influenza A led to a more severe course of the disease. Further research is important to understand the role of pregnancy-related changes in the levels of progesterone, estrogens, androgens and other hormones that may contribute to immunoregulation in response to COVID-19 infection [2].

In the absence of pregnancy, the inflammation caused by the penetration of the virus attracts T cells (mainly Th1 CD4+), which can clear infected cells and prevent further spread and replication of the virus. Further, the virus is blocked by neutralizing antibodies, and macrophages purify neutralized viruses and apoptotic cells by phagocytosis. During pregnancy, there is a shift in the population of CD4+ T cells (with a predominance of Th2), which can lead to a change in the clearance of infected cells in the immune response to viral infections [2].

During pregnancy, the number of circulating natural killer cells decreases, which, in turn, probably reduces the body's ability to clear viruses. However, at the moment it is unclear whether this decrease in circulating killer cells has any clinical consequences in COVID-19 [2].

During pregnancy, changes occur in the immune system, including they relate to Toll-like receptors. Toll-like receptors (TLR) are a class of cellular receptors with a single transmembrane fragment that recognize the conservative structures of microorganisms and activate the cellular immune response. They play a key role in the formation of innate immunity. COVID-19 infection causes apoptosis of host cells and the release of a number of endogenous DAMPs ligands (molecules that are released in response to cell damage), providing a rapid cell response, further enhancing the inflammatory response.

W. Guan et al. the first to describe a cohort of patients (41 people) with laboratory-confirmed pneumonia caused by COVID-19. They described epidemiological, clinical, laboratory and radiological characteristics, as well as treatment and outcomes in these patients. According to the authors, pregnant women are also susceptible to infection and to the development of severe pneumonia, as well as the general population, there is no increase in the risk of infection or a more severe course of the infectious process in pregnant women. There is no evidence of possible vertical transmission of COVID-19 infection from mother to child. Subsequent studies with larger samples showed similar results [3, 4].

J. Segars et al. We analyzed 79 publications in PubMed and Embase on the impact of new and previous coronavirus infections on human reproduction, in particular on male and female gametes, as well as on pregnancy. The binding of coronavirus to cells includes the S1 domain of the S protein with receptors present in reproductive tissues, including angiotensin converting enzyme 2 (ACE-2), CD26, ezrin and cyclophilins. Severe acute respiratory syndrome coronavirus — SARS-CoV-1 can cause severe orchitis, leading to the destruction of germ cells in men. Reports indicate a decrease in sperm concentration and motility within 72-90 days after infection with a new coronavirus infection — COVID-19 [5]. This is also confirmed by the data of Russian scientists: changes in the morphology of spermatozoa, an increase in the number of white blood cells in the ejaculate and a decrease in testosterone levels in patients who have undergone a new coronavirus infection were noted [6]. Gonadotropin-dependent expression of ACE-2 has been detected in human ovaries, but it is unclear whether SARS-CoV-2 has an adverse effect on female gametogenesis. Evidence suggests that COVID-19 infection is accompanied by a lower maternal mortality rate than SARS or Middle East respiratory syndrome, but some reports suggest that infected women with an asymptomatic course of the disease may develop respiratory symptoms after childbirth. COVID-19 infection during pregnancy is more often associated with premature birth. There are reports of postpartum neonatal transmission of infection from mother to child [5]. According to published data in the Cochrane Library on

12.01.21, which were presented at the XV International Congress on Reproductive Medicine (19.01.21—21.01.21), the following perinatal outcomes were noted worldwide: 43,107 cases in total (8414 cases among them in the third trimester), pneumonia developed in 3758 cases, transfer to the intensive care unit — 1673 patients, maternal mortality — 733 cases, delivery — 16,749 women (by caesarean section — 6331). 16,394 children were born. Pneumonia of newborns was noted in 47 cases, fetal distress — in 102 cases; hospitalization in the neonatal intensive care unit — 1621 cases, stillbirth — 124 cases, neonatal mortality — 97 cases. A total of 716 deliveries were carried out in patients aged 18-40 years, 727 live children (17 twin births) were born at a period of 22 to 42 weeks, 293 (41%) patients out of 716 patients underwent cesarean section. 4 (0.6%) newborns were born at 22-27 weeks gestation, 21 (2.9%) newborns — at 28-31 weeks, 71 (9.8%) newborns — at 32-36 weeks, 631 (86.7%) newborns — at 37 weeks or more. Operative delivery was performed in 293 (41%) patients. Before the pandemic, the rate of operative delivery did not exceed 30%. The main clinical symptoms in pregnant women at admission were fever, cough, shortness of breath, muscle pain, loss of sense of smell, taste and appetite, weakness and fatigue, dyspeptic symptoms. Laboratory diagnostics were: detection of SARS-CoV-2 RNA using nucleic acid amplification methods (polymerase chain reaction — PCR), detection of class M and class G immunoglobulins to SARS-CoV-2 (enzyme immunoassay, immunochemiluminescence analysis), determination of the level of D-dimer, prothrombin time and fibrinogen, C-reactive protein, procalcitonin, ferritin. The methods of instrumental diagnostics were: pulse oximetry with measurement of blood oxygen saturation, computed tomography of the lungs (CT), ultrasound examination of the lungs and pleural cavities, overview radiography of the lungs. Asymptomatic carriage was detected in 30% of patients, mild and moderate course — in 55-80% of patients, severe course — in 10-15% of patients, extremely severe course — in 3-5% of patients. At CT, pneumonia was detected in 89.6%, and mainly bilateral pneumonia of mild or moderate severity. In laboratory parameters, leukopenia, lymphopenia, thrombocytopenia, increased ESR, lactate dehydrogenase, ferritin, C-reactive protein, interleukin-6, fibrinogen and D-dimer were noted. According to the authors, the most important place in understanding the pathogenesis of the disease is given to the hyperimmune response and increased thrombosis.

Features of the course of COVID-19 disease during pregnancy.

Testing in non-pregnant women most often occurs when they show symptoms or have been in contact with infected people, while pregnant women are often tested for COVID-19 when seeking medical help for pregnancy or reasons unrelated to the COVID-19 outbreak. A systematic review of 28 studies involving 11,432 patients showed that one in 10 pregnant or maternity women admitted to the hospital tested positive for COVID-19. Of these, 75% were asymptomatic carriers, and one of 20 asymptomatic pregnant women tested positive for COVID-19. As in the general population, the predominant symptoms of COVID-19 in pregnant women were hyperthermia, cough, shortness of breath and lymphopenia [7]. Compared with non-pregnant women of reproductive age, pregnant or recently pregnant women with COVID-19 reported myalgia less frequently [7]. A French cohort study showed that the presence of gastrointestinal symptoms was associated with a more severe course of the disease [8]. The clinical symptoms of infection, as a rule, did not differ depending on the gestational age [9]. A recent study showed an increased risk of severe diseases and artificial lung ventilation (ventilator) in pregnant women compared with non-pregnant women, adjusted for age, race and concomitant diseases [15]. In addition, COVID-19 is associated with the development of cardiomyopathy in 7-33% of the general population [16, 17]. Data on COVID-19 cardiomyopathy during pregnancy are limited, as this complication manifested itself in only two pregnant patients [18]. Due to the lack of data, it is not clear whether the risk of developing COVID-19-related cardiomyopathy in pregnant women is increased compared to the general population. The differential diagnosis of COVID-19 symptoms during pregnancy is complex and includes preeclampsia, cardiomyopathy, pleural or pericardial effusion, gestational rhinitis, physiological dyspnea and manifestations of other viral-bacterial pneumonia. Many conditions associated with an increase in body temperature, cough or shortness of breath can provoke early termination of pregnancy, including leading to preeclampsia and pulmonary

embolism [7]. The frequency of hospitalization in intensive care increases with increasing gestation, and in one study it was reported that more than 90% of pregnant patients need intensive care in the third trimester [11]. The data indicate that 40% of pregnant women who died from COVID-19 were obese, diabetic, or the mother's age was 40 or more. Complications of the severe course of the disease include the need for invasive ventilator or extracorporeal membrane oxygenation, premature birth and COVID-related cardiomyopathy [15]. Late maternal age, high body mass index, pre-existing arterial hypertension and diabetes mellitus (DM) were associated with severe COVID-19, and the presence of extragenital diseases was an unfavorable prognostic marker for ventilators [7, 9-11]. These indicators were closely correlated with the risk of near-miss or neonatal death [11]. Other studies also demonstrate severe outcomes in pregnant women with COVID-19. While the estimated mortality rates of pregnant women with COVID-19 are 0.6-2%, which is comparable to the general population, patients with critical illness account for the vast majority of deaths secondary to COVID-19 [7, 11].

Complications and outcomes of pregnancy on the background of COVID-19

One of the large cohort studies included 242 COVID-19-positive pregnant women and 248 newborns from these mothers who were observed during the third trimester of pregnancy and one month after delivery [11]. The results of this study showed a higher incidence of cesarean section and premature birth in hospitalized patients with COVID-19 symptoms [11]. It was noted that preterm labor occurred in about a third of pregnant women with COVID-19, of which 40.0% were early and early (from 24.0 to 33.6 weeks of pregnancy) and 60.0% were late preterm labor (from 34.0 to 36.6 weeks of pregnancy). Spontaneous miscarriage is more common in patients who became ill in the first trimester, compared with the second trimester, with a frequency of 16.1% and more than 3.5%, respectively [24-27]. Somewhat more often during pregnancy, fetal growth retardation, placental insufficiency with morphologically confirmed changes in the placenta in the form of uteroplacental vascular malperfusion, interventricular inflammation and thrombosis of the interventricular vessels of the fetus are detected in patients with a new coronavirus infection [10]. The data obtained confirm the results of the following studies reporting histopathological studies of 14 placentas of patients with clinically mild COVID-19, who found occlusive fibrin deposition and non-occlusive thrombi with placental hypoperfusion in all samples [11, 28].

The frequency of spontaneous preterm labor does not increase in comparison with the general population, and cesarean section was the main method of delivery in all cases of preterm labor [7]. Accordingly, most complications in newborns born to mothers diagnosed with COVID-19 are the result of prematurity, not COVID-19 infection. Infants with mothers whose disease was detected closer to delivery were more likely to have a severe course than those whose mothers tested positive two or more weeks before delivery [10]. In a recent cohort study, almost a tenth of newborns from mothers with positive COVID-19 were tested for antibodies in the first month of life. Stillbirths and neonatal mortality do not increase in comparison with the general population. None of them tested positive for COVID-19. The results obtained are consistent with the findings of another study, in which there were no cases of pneumonia or lower respiratory tract diseases in newborns under the age of 6-8 weeks born to COVID-positive mothers. Several cases of mild symptoms have been reported in newborns diagnosed with COVID-19 at birth or shortly after. The most common manifestations of COVID-19 in newborns are fever, pneumonia, cyanosis, respiratory distress. Most of these children showed moderate symptoms, and the outcome was favorable. It was found that most of the complications were associated with prematurity and sepsis, and not with SARS-CoV-2. Evidence of transmission of SARS-CoV-19 through breast milk is limited, and current guidelines recommend that mothers positive for COVID-19 continue breastfeeding.

Conclusion. COVID-19 is a potentially fatal infection, but data on its course in pregnant women are limited today. The heterogeneity of the information obtained is most likely due to the diversity of the studied populations of people, survey methods and, as a consequence, the results obtained. Existing different approaches to the treatment of pregnant women with COVID-19 make it difficult to analyze the course of infection, the development of specific and non-specific complications during pregnancy, and approaches to delivery. Pregnant patients with a mild form of infection and the absence of

concomitant diseases, obstetric complications should be delivered naturally in due time and can be safely discharged home. Women in the third trimester of pregnancy, especially with obesity, diabetes, chronic arterial hypertension, have the highest risk of a critical course of the disease, complicated pregnancy, in such conditions, the tactics of early delivery are discussed collectively. Of course, this topic is interesting, insufficiently covered in the literature, and has prospects for further study.

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