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FEATURES OF THE COURSE AND OUTCOME OF PREGNANCY IN WOMEN WITH COVID-19

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Abstract

Having appeared in China, the new coronavirus SARS-CoV-2 has spread rapidly around the world. Pregnant women are patients with risk factors for the development of severe/complicated course of acute respiratory viral infection and influenza, but currently only a small number of studies have been published that highlight the features of the course of COVID-19, a disease caused by the new coronavirus SARS-CoV-2, in pregnant women and newborns.

The purpose of this article is retrospective analysis of the course of pregnancy and childbirth in women with COVID-19.

The research method is retrospective analysis of the medical record of 128 pregnant and parturient women who were treated in the department of infectious disease from October 2021 to February 2022 at the premises of the Regional Perinatal Center in Taldykurgan City (Republic of Kazakhstan). Retrospective analysis also included 65 newborn histories from mothers who had experienced COVID-19.

COVID-19 disease can worsen the course of pregnancy by causing respiratory distress syndrome which can lead to premature birth and miscarriage. Currently, there is no reliable evidence of intrauterine transmission of COVID-19 from mother to fetus through the placenta, as well as transmission of the virus from mother to child through breast milk.

Keywords: *COVID-19, pregnancy, childbirth, respiratory distress syndrome.*

Introduction

The outbreak and spread of a new coronavirus disease since 2019 (COVID-19), which leads to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues at the present time, and therefore there remains an increased interest in studying the role of a new coronavirus infection in the emergence of a pandemic among the population. In many countries, the current dynamics of morbidity resembles the events that took place in China after the discovery of COVID-19. Since the history of the disease is short, there is still small amount of data on the clinical course of SARS-CoV-2 infection, as well as on the possible risks of complications in infected pregnant women and newborns from infected mothers.

Coronaviruses are a family of RNA-containing viruses belonging to the Nidovirales suborder and including 40 species grouped into 2 suborders. Until December 2019, the coronavirus family consisted of six species pathogenic to humans, among

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which were the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle

East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 is the seventh human pathogenic species which was added to this group in 2019 by WHO and entitled as 2019-nCoV, and then renamed in 2020 by the International Committee on Taxonomy of Viruses to SARS-CoV-2 [*David S et al., 2016*]. The remaining four endemic species out of seven pathogenic to humans (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) also have clinical significance causing upper respiratory airway diseases manifested by mild clinical symptoms of the common cold. These species cause approximately 10% of seasonal respiratory diseases caused by non-influenza [*Shchelkanov M et al., 2016; Lvov D et al., 2020*].

SARS-CoV and MERS-CoV which cause very serious symptoms and respiratory diseases associated with a high mortality rate (about 10-30%) have so far been limited to one outbreak in 2002-2003 (SARS-CoV) and 2014 (MERS-CoV) and were mainly of regional significance [*Chan J et al., 2020*].

Coronaviruses are single-stranded RNAs, unsegmented, shrouded in viruses that cause diseases of varying severity – from the common cold to diseases with a possible fatal outcome. The term "coronavirus" comes from the Latin word corona, which means "crown" or "halo"; the name is due to the appearance of coronavirus virions viewed using electron microscopy, in which viral particles have a crown-like fringe, usually called spikes [*Stovba L et al., 2015*].

In its structure, SARS-CoV-2 contains four key proteins: nucleocapsid protein, spike protein, small membrane protein and membrane glycoprotein [*Yu C et al., 2020*]. Angiotensin converting enzyme 2, located on the cells of the alveolar epithelium of types I and II, is the main receptor of SARS-CoV-2, through which the infection enters the body, causing respiratory symptoms and, ultimately, acute respiratory syndrome. Such a receptor is also found in the intestine, although in small quantities, which can cause the development of diarrhea and vomiting. Protein S is necessary for the virus to fuse with the host cell through the receptor-binding domain. This protein includes two subunits – S1 and S2; S1 determines cellular tropism, and S2 mediates the fusion of the virus with the cell membrane. After membrane fusion, viral RNA is released into the cytoplasm, and viral replication begins. Newly formed viral particles fuse with the plasma membrane through virion-containing vesicles to release the virus [*Hui D et al. 2014; Yu C et al., 2020; Gorenkov D et al., 2020*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

It should be noted that during the development of atypical pneumonia, ACE 2 is also used as a receptor for cell entry, however, the receptor binding capacity of pneumonia with SARS-CoV-2 is 10-20 times higher than that of atypical pneumonia, and the number of cases of such pneumonia exceeded the number of infections with atypical pneumonia during the outbreak in China in 2002-2003, which indicates higher transmission rates [*Donnelly C et al., 2016; Yu C et al., 2020; Gorenkov D et al., 2020*].

In addition, men tend to have higher levels of ACE 2 than women, and Asians show higher levels of ACE 2 expression in alveolar cells than Caucasians and African Americans, which suggests that Asian men are most susceptible to this infection. Transmission of SARS-CoV-2 is mainly carried out by airborne transmission from person to person during coughing or sneezing, as well as in close contact with an infected person or objects on which these drops could settle [*Shamsheva O et al., 2020*].

After contact with an infected COVID-19 that spreads the virus, the average incubation period of the disease is about 5 days, varying from 1 to 14 days. Clinically, SARS-CoV-2 infection can be asymptomatic or with severe respiratory failure. In most cases, the clinical performance is like that of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). The most common symptoms are fever, cough, and a feeling of congestion in the chest. Confirmation of the presence of infection requires laboratory diagnostics to detect SARS-CoV-2 RNA by Polymerase chain reaction (PCR) [*Donnelly C et al., 2016; Shamsheva O et al., 2020*].

Immunosuppression and other physiological changes during pregnancy cause high susceptibility to respiratory pathogens and severe pneumonia in pregnant women, which can lead to hospitalization in intensive care units and artificial respira-

tion. Hormone levels and immune competence show significant fluctuations throughout pregnancy. Pregnancy in the first trimester is more at risk due to adaptive changes in response to fetal antigens, however, with the gradual adjustment of the mother's immune and endocrine systems, processes stabilize in late pregnancy.

The initial stages of pregnancy are crucial in the development of fetal organs, and the immune system is especially sensitive at this stage, which significantly affects the course of the infectious process. Experience with previous respiratory virus epidemics may offer some insights regarding the susceptibility of COVID-19 and the frequency of complications during pregnancy. As for other coronaviruses, the SARS epidemic in 2002-2003 caused 8,442 cases and 916 deaths, and studies have shown that clinical results during this epidemic were worse in pregnant women than in non-pregnant women [*Alfaraj S et al., 2019; Zhu H et al., 2020*].

In addition, there has been an increase in preterm births and abortions, which are also associated with SARS-CoV infections. Approximately 50% of pregnant women suffering from SARS needed intensive care, and about 33% needed artificial respiration. The mortality rate of pregnant women during the SARS epidemic reached 25%. Taking into account the MERS epidemic, which has led to a much larger number of confirmed cases and deaths, it can be argued that MERS in its course progresses much faster to the development of respiratory failure and leads to higher mortality rates than SARS [*Stovba L et al., 2014*].

However, there was no evidence of vertical transmission of infection from mother to fetus. Based on this evidence, there is no doubt that SARS-CoV and MERS-CoV infections are associated with high rates of complications among pregnant women. Even though the COVID-19 pandemic continues, data on the course of the disease in pregnant women are limited. Recent reports indicate that the clinical characteristics of the course of the disease detected in pregnant women with confirmed SARS-CoV-2 infection are like those in non-pregnant women with COVID-19 pneumonia [*Nikiforov V et al., 2020*].

Also, no evidence of vertical transmission of SARS-CoV-2 at the end of pregnancy has been obtained so far. A joint study conducted by WHO and Chinese doctors examined 147 pregnant women in China (65 confirmed cases of COVID-19 and 82 suspected), 8% of whom had severe symptoms, 1% had a critical course of the disease. It was concluded that pregnant women with COVID-19 did not have a higher risk of developing severe symptoms, therefore, there may be many pregnant women with an asymptomatic course of the disease.

There was also one case of infection of a newborn infected with SARS-CoV-2, which was confirmed 36 hours after birth, but there is no exact data whether this was due to vertical transmission of infection from mother to child [*Zhang L et al., 2020*]. Currently, there is a small amount of data on the possible risk of vertical transmission of infection from mother to fetus. The risk of transmission of SARS-CoV-2 was considered in a study recently published in The Lancet, devoted to the study of the incidence of Wuhan residents. To do this, immediately after birth, samples of amniotic fluid, umbilical cord blood and throat swabs were taken from newborns, the results of the study were negative. Milk samples taken during this study immediately after the first appearance of milk in the postpartum period were also unremarkable [*Chen H et al., 2020; Chen S et al.,2020*].

In one of the case studies, the placentas of three pregnant women with confirmed SARS-CoV-2 infection were examined. None of the newborns were diagnosed with the infection. Histopathological correlates for infection in placentas were not found [*Rasmussen S et al., 2019; Chen H et al., 2020*].

Thus, at this time, based on the very low number of reported pregnancies in women with confirmed COVID-19, as well as experience gained during the SARS-CoV epidemic, it is not possible to speak of intrauterine transmission of SARS-CoV-2 infection. To date, there are no studies on severe COVID-19 and obstetric complications during the first trimester of pregnancy, so there is not enough information to judge the potential impact of infection on the course of pregnancy in the initial stages. As for other coronaviruses, the SARS-CoV and MERS epidemics did not show a correlation with the incidence of malformations [*Ng W et al., 2006; Shchelkanov M et al., 2015*].

In addition, data from the current epidemic should be considered for the management of COVID-19 infections during pregnancy since the clinical course of this disease and the response to treatment are determined to be different from previous outbreaks of other types of coronaviruses.

Further research is needed to understand the

pathogenesis and epidemiology of SARS-CoV-2 during pregnancy, including aspects such as the time of infection of the mother, gestational age, the influence of concomitant pathology factors and the frequency of adverse outcomes; however, preliminary observations of pregnant women infected with SARS-CoV-2 allow us to make an optimistic prognosis regarding the clinical course.

It is important to consider that the COVID-19 pandemic has caused psychological stress and anxiety among the general population, including pregnant women. Several concerns have been raised regarding potential infection during pregnancy, including the presence of family members in quarantine near pregnant women; potential infection with SARS-CoV-2 during physician visit; the potential need for early delivery by caesarean section; the constant use of disinfectants containing alcohol, which can have toxic effects; the development of potential postpartum complications, for example, during breastfeeding or caring for newborns [*Di Renzo D et al., 2020*].

Therefore, it is necessary to follow infection control measures and conduct diagnostic testing in all pregnant women with suspected COVID-19. Currently, when managing pregnancy in infected women, it is advisable to observe the following measures: with a mild severity of the disease for up to 12 weeks, prolongation of pregnancy is possible, since there is no evidence of negative effect of SARS-CoV-2 on the fetus [*Shifman E et al., 2020*]; with a severe and moderate course of the disease for up to 12 weeks, termination of pregnancy is possible after the destruction of the infectious agent; if a woman is against termination, it is necessary to conduct a study of chorionic villi to assess the presence or absence of chromosomal abnormalities in the fetus [*Shamsheva O et al., 2020*].

Treatment that is considered appropriate for non-pregnant patients should also be used in case of infection of pregnant women, provided there are no clear contraindications for available therapy; in case of suspicion of the presence of infection in pregnant women requires the adoption of isolation measures at an early stage of the development of the disease and diagnostic studies to confirm or refute the disease [*Poon L et al., 2020*]; it is necessary to monitor the condition of the fetus; to exclude placental insufficiency with the development of intrauterine growth retardation, regular cardiotocography studies should be conducted with the measurement of fetal size, as well as doplerometry and amniotic fluid [*Baibarina E et al., 2017*].

Regarding the mode of delivery of infected pregnant women, no recommendations can be made at this time due to the small number of cases. Now, it is considered unlikely that infection of a child can occur during passage through the maternal passages, which means that the choice of the method and time of delivery should be strictly individual, based on the clinical condition of the woman and the fetus, as well as the gestational age [*Shifman E et al., 2020; Liang H, Acharya G, 2020*].

Material and methods

A retrospective analysis of the medical history of 128 pregnant and parturient women, 65 histories of newborns treated in the infectious diseases department from October 2021 to February 2022 at the premises of the Regional Perinatal Center, Taldykurgan City (Republic of Kazakhstan) was performed. Retrospective analysis also included 65 newborn histories from mothers who had experienced COVID-19. Patients were with or without PCR-confirmed COVID-19, with severe clinical symptoms and signs of COVID-19 pneumonia, identified by computed tomography.

The age of the patients ranged from 17 to 41 years, the average age of which was 27.79±5.547 years. The gestation period at the time of diagnosis of COVID-19 varied from 6 to 40 weeks of pregnancy, in 5 (3.9%) women in the early stages of pregnancy, in 123 (96.1%) – for a period of more than 24 weeks. Bed-day in the hospital averaged 6.4±3.132 days. Body mass index in 36 (28.1%) women was 18-25; in 53 (41.4%) – 25-30 and in 39 (30.5%) – 30 and above.

Results

The disease was asymptomatic in 8 (6.25%) women. Symptoms of COVID-19 at the time of diagnosis were registered in 120 (93.75%), the most frequent patients were: general weakness in 110, (85.9%) pregnant women; distress in 105, (82.03%); cough in 86(67.1%); shortness of breath in 70 (54.68%); temperature in 68 (53.1%); loss of appetite in 58 (45.3%); a feeling of shortness of breath in 55 (42.9%) and retrosternal pain in 53 (41.4%). Symptoms such as lack of taste, sense of smell, sore throat, headache, nasal congestion, and diarrhea were reported in less than 17% of women (Fig. 1)

The severity of COVID-19 disease was mild in 68 (52.6%) women, moderate in 40 (31.5%), severe in 19 (14.7%) and extremely severe in 1 (1.2%) pa-

tient. In a critical case, multiple organ failure syndrome was noted, including acute respiratory distress syndrome, the patient required mechanical ventilation, including extracorporeal membrane oxygenation, treatment was carried out in intensive care units, the outcome was an improvement in the condition and discharge of the patient with prolonged pregnancy from the hospital.

Laboratory confirmation of COVID-19 using PCR method was performed in all 128 pregnant women, of whom PCR-positive was detected in 96 (75%) In patients, PCR was negative in 32 (25%) women. Samples for PCR diagnostics were collected by sampling smears from the nasopharynx. Computed tomography of the chest was performed in all 128 patients, out of this number of cases, typical bilateral signs of lung damage according to chest computed tomography were detected in 104 (81.3%) women, unilateral – in 6 (4.6%) patients. Chronic bronchitis was noted in 11 (8.6%) women, and in 7 (5.5%) women, according to the results of chest CT, no pathological changes were detected.

The increase in laboratory parameters in pregnant women was as follows: the level of D-dimer in 29 (22.4%) cases, C-reactive protein in 25 (19.1%), ferritin in 16 (12.2%), aspartate aminotransferase in 45 (57.6%), alanine aminotransferase in 28 (35.7%), leukocytosis in 27 (34.7%) and acceleration of erythrocyte sedimentation rate in 69 (88.2%) cases, as well as a decrease in laboratory parameters as: lymphocytopenia – in 56 (43.8%), thrombocytopenia in 35 (27.1%) cases and anemia 93 (72.8%) cases (Fig. 2).

Childbirth against the background of COVID-19 infection occurred in 58 (45.3%) women, pregnancy was prolonged in 65 (50.8%) women, medical abortion was performed in 4 (3.1%) patients, spontaneous abortion occurred in 1 (0.8%) patient. Among 58 deliveries, caesarean section was performed in 34 (58.6%) and 24 (41.4%) delivered vaginally.

There were 57 (87.7%) mature infants and 8 (12.3%) premature infants. According to the weight category, newborns were distributed as follows: from 1000-1500 *g* – 1 (1.53%), from 1500-2500 *g* – 3 (4.6%), from 2500 *g* and higher – 61 (93.8%).

All newborns according to the Management of childbirth protocol dated 2019 were evaluated on the Apgar scale and distributed as follows: 3/4 points were assigned to 1 (1.53%) child, 4/5 points – 3 (4.6%), 6/7 points – 6 (9.2%), 7/8 points – 3 (4.6%), 7/9 points – 3 (4.6%), 8/9 points – 7 (10.7%), 9/10 points – 41 (63.1%), 10/10 points – 1 (1.53%) were assigned to one newborn. Of the newborns – 6 (9%) were transferred to the department of anesthesiology, resuscitation, and intensive care of newborns, due to the severity of the condition of them with respiratory distress syndrome – 5 (7.5%)

According to the history of 58 newborns, the condition of newborns on the Apgar scale from 0 to 10 points, 3-4b – 2 (3.8%), 4-5b – 2 (3.8%), 5-6b – 3 (5.8%), 6-7b – 7 (11.5%), 7-8b – 3 (5.8%), 8-9b – 7 (13.4%), 9-10b – 34 (61.5%) newborns.

In total, 8 (13.4%) newborns were admitted to the intensive care unit, 10 (17.3%) were diagnosed with respiratory distress syndrome, 2 (3.4%) had neonatal pneumonia, of which 2 cases were fatal. One early neonatal death was due to complications associated with prematurity after a caesarean section at 27 weeks due to antepartum hemorrhage.

All newborns were tested PCR for COVID-19; the results were negative. No vertical transmission pathway has been identified.

Figure 1. *Symptoms at the time of diagnosis*

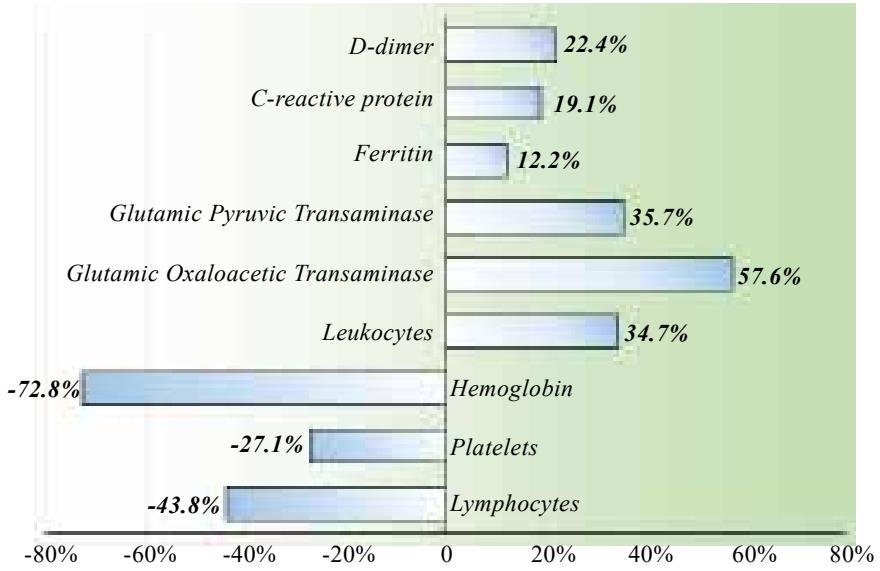

Figure 2. *Changes in laboratory tests*

Discussion

According to the literature, the initial stages of pregnancy are crucial in the development of fetal organs, and the immune system is especially sensitive at this stage, which significantly affects the course of the infectious process. In our observations, in 5 (3.9%) of 128 women, COVID-19 infection was diagnosed in the early stages of pregnancy, and due to the severe course of the disease, 4 (3.1%) patients underwent medical abortion and spontaneous miscarriage occurred in 1 (0.8%) patient. Recent reports indicate that the clinical characteristics of the course of the disease detected in pregnant women with confirmed SARS-CoV-2 infection are like to those in non-pregnant women with COVID-19 pneumonia [*Nikiforov V et al., 2020*]. In our observations, the incidence of the severity of COVID-19 disease was also mild in 68 (52.6%) women, moderate in 40 (31.5%), severe in 19 (14.7%) and extremely severe in 1 (1.2%) patient, which confirms the literature data.

Further evidence suggests that the most common symptoms are fever, cough, and a feeling of congestion in the chest [*Donnelly C et al., 2019; Shamsheva O, 2020*]. In our observations, the following were frequent: general weakness in 110 (85.9%) pregnant women; distress in 105 (82.03%); cough in 86 (67.1%); shortness of breath in 70 (54.68%); fever in 68 (53.1%); lack of appetite in58 (45.3%); feeling of shortness of breath in 55 (42.9%) and retrosternal pain in 53 (41.4%).

According to the WHO definition of preterm birth before 37 weeks of pregnancy and an estimated preterm birth rate of 10% [*WHO, 2018*], the rates of preterm birth in pregnant women affected by COVID-19 seem to correspond to those in the general population. Regarding the mode of delivery of infected pregnant women, no recommendations can be made at this time due to the small number of cases. In this regard, our observations noted an increase in the frequency of caesarean sections of 58.3%, which was associated with the general condition of the pregnant woman due to COVID infection.

The latest epidemiological data on the peculiarities of the course of COVID-19 infection during pregnancy indicate that there is no increased risk for the mother and fetus. Current data indicate that there is no connection between vertical transmission of infection and fetal malformations. In our study, a PCR positive test was detected in one child (1.53%).

The tactics of medical examination of pregnant women should be individualized based on obstetric indications and the state of health of the mother/fetus.

Conclusion

At present, pre-conceptional preparation of women is of great importance to identify and treat extragenital pathologies that can affect the course of pregnancy and complications from COVID-19 infection. The course of pregnancy and its outcomes in patients with COVID-19 infection require a comprehensive, thorough, further study and expert analysis of clinical material.

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