

Management of SARS-CoV-2 infection in pregnancy

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ABSTRACT

The SARS-CoV-2 infection, which originated from a market in Wuhan, China, spread rapidly, so on March 11, 2020, the WHO decreed that the outbreak became a pandemic. Over 90% of people infected with SARS-CoV-2 are either asymptomatic or have mild symptoms. However, there are cases that develop severe forms of the disease, from acute respiratory distress syndrome to septic shock with multiorgan failure and exitus. However, reports of pregnant women diagnosed with Covid-19 are low.

Changes in the maternal organism in pregnancy, including immunity, respiratory system and hypercoagulability, but also various comorbidities, could be a risk factor for pregnant women to develop complications associated with COVID-19, with increased morbidity and mortality compared to the general population.

The effects of SARS-CoV-2 infection on pregnancy are not sufficiently understood, nor are the effects of pregnancy on disease progression. Although the existence of the virus has been shown in biological samples such as the placenta, umbilical cord, or amniotic fluid, the maternal and fetal effects of the virus are not well known.

Recent studies confirm the possibility of intrauterine maternal-fetal transmission of the virus, but also of specific antibodies. The possibility of infection by breastfeeding is not yet sufficiently investigated.

We looked for data on the treatment and prophylaxis of SARS-CoV-2 infection during pregnancy, as well as on the choice of the optimal birth pathway in these women.

The aim of this paper was to conduct a systematic review of the literature on pregnancy and birth management in patients infected with SARS-CoV-2 that could lead to an improvement in the quality of their medical care.

Keywords: SARS-CoV-2 and pregnancy, COVID-19 and pregnancy, vertical transmission of SARS-CoV-2, perinatal infection with SARS-CoV-2

INTRODUCTION

The SARS-CoV-2 infection, which left China, spread rapidly and became a pandemic. The evolution of the disease both in pregnant women and in the general population is very heterogeneous, from asymptomatic or mild forms to death. Common symptoms include fever, headache, cough, fatigue, loss of taste and smell, and respiratory symptoms (1).

The effects of SARS-CoV-2 infection on pregnancy are not sufficiently understood, nor are the effects of pregnancy on disease progression (2,3).

Preliminary effects of diseases with other coronaviruses (SARS and MERS) have suggested that pregnant women are more likely to have severe manifestations of the disease, morbidity and mortality compared to the general population (4-6). Moreover, some studies have shown an increased risk of developing critical forms of the disease in advanced stages of pregnancy (7,8).

The mother's body undergoes a series of changes during pregnancy that make it able to ensure the growth and development of the fetus. These changes affect the main devices and systems, but also the

main metabolisms. These include changes in the immune response, respiratory system and clotting.

Pregnancy is a specific immune condition that requires the development of tolerance to the allogeneic fetus, while maintaining the ability to protect against infection (9,10). Pregnancy is associated with significant changes in the areas of innate, cellular and adaptive immune responses (11). These changes create an increased susceptibility to infections (12). Beyond the symptoms of the disease, these infections increase the risk of complications in the mother and newborn (e.g., premature birth, restriction of intrauterine growth and miscarriage) (13). COVID-19 can alter the immune responses to the maternal-fetal interface and thus affect the well-being of mothers and girls (14).

Pregnant women are more likely to develop infections caused by respiratory pathogens and are more likely to have a severe course of the disease due to their immunosuppressive status and physiological changes during pregnancy. The diaphragm is ascended, and the base of the thorax is flared, there is a diffuse congestion of the mucous membrane of the airways and an increased demand for oxygen, pregnant women being more vulnerable to hypoxia (15). Hyperventilation causes pregnant women to inhale more air at the same time (16).

Coagulation factors change differently during pregnancy, labor and birth. Increased coagulation factors (fibrinogen, factors VII, VIII, IX and X) and decreased fibrinolytic activity during pregnancy are protective physiological reactions that allow their increased use at the time of delivery. Because pregnancy is a physiological prothrombotic condition, pregnant women may be at increased risk of developing coagulopathic and/or thromboembolic complications associated with COVID-19 (17).

Existing data suggest that pregnant women may experience severe symptoms that include hypoxia, altered blood pressure, electrolyte disturbances, and placental hypoperfusion, which can cause fetal distress, premature labor, or miscarriage, respiratory distress, thrombocytopenia, and even abnormal liver function. death in newborns (18-20).

Recent studies confirm the possibility of maternal-fetal intrauterine transmission by positive genetic tests and the presence of IgM in newborns immediately after birth. At present, the probability of transmission through breast milk is inconclusive (21).

The aim of this paper was to identify in the literature new data on pregnancy and birth management in patients infected with SARS-CoV-2.

We searched in electronic databases (PubMed, Google Scholar) articles and clinical studies published since the onset of the COVID-19 pandemic, related to: prophylaxis of SARS-CoV-2 infection, methods of diagnosis and treatment of infection in pregnancy, symptoms, perinatal transmission, maternal-fetal consequences of infection, optimal route of birth. We selected the materials that went through the peer review procedure.

PROPHYLAXIS OF SARS-COV-2 INFECTION

The usual practice of managing emergent infections in a pandemic is prevention through social mechanisms and vaccination. The World Health Organization (WHO) has recommended wearing facial masks and social distancing in order to reduce the transmission of the disease. Proper hand and surface washing and hygiene are also recommended, using soap and water and/or alcohol-based sanitizers (22).

Another WHO directive is the rapid expansion of in vitro diagnostic tests to allow mass screening and testing of high-risk groups, followed by the application of measures to isolate those infected as well as contacts (23). There are two types of tests available for COVID-19: viral tests that reflect current infection and antibody tests that detect established seroconversion to previous or ongoing infection (24).

The biomedical industry has tried to quickly find effective drugs and vaccines for the treatment and prevention of COVID-19 (25,26).

There are currently 3 types of vaccines on the market: mRNA vaccine, viral vector vaccine, subunit protein vaccine. None of these vaccines can cause COVID-19, as they do not contain the virus (antigen), but instructions for the production of antigens (SARS-CoV-2 proteins) that stimulate the body's immune system to produce specific antibodies (27,28).

Manufacturing companies (Pfizer, Moderna, Astra Zeneca) reported a vaccine efficacy of over 90%. Vaccines are well tolerated in all populations without serious safety issues. Minor side effects included fatigue, headache, muscle aches, headache, fever and chills, or pain, itching or bruising at the injection site (29).

The lack of data on any COVID-19 vaccine in pregnant women raises many questions and concerns

about how best to approach the administration of the vaccine during pregnancy (30). Vaccines are immunogenic, and patients may experience body aches, fever, and headaches for a few days after vaccination. These acceptable and non-life-threatening side effects should be recognized and taken into account when assessing mothers, understanding that these side effects may lead to further assessments for pregnancy-related morbidities, including sepsis and preeclampsia, which may occur with similar symptoms (31). The fetal impact of COVID-19 vaccination is unknown and the potential for fetal risk must be recognized. Pregnant women should be given the opportunity, together with their doctor, to weigh the potential risk of severe maternal illness against the unknown risk of exposure of the fetus in order to decide whether or not to accept the vaccine (32).

We do not yet know how long the protection gained by recovered patients will last. This point is of interest because often the duration of protection after healing corresponds somewhat to the duration of protection afforded by the vaccine (33).

Maternal vaccination, which stimulates the maternal IgG response, can provide protection to the newborn. Maternal specific SARS-CoV-2 IgG antibodies are transferred to newborns, especially when the mother has high IgG levels. If the mother responds to vaccinations against SARS-CoV-2, antibodies appear to cross the placenta, potentially protecting both the mother and the newborn from future infection. It is not known how protective these IgG antibodies from the mother to the newborn are and how long the protection lasts (34).

DIAGNOSIS OF SARS-COV-2 INFECTION IN PREGNANT WOMEN

The current pandemic due to SARS-CoV-2 has called for the rapid expansion of diagnostic tests to allow mass screening and testing of high-risk groups. To meet the exponential demand in testing, there has been an accelerated development of nucleic acid amplification tests, direct viral antigen tests, and laboratory serological tests (35,36). The main concern is the high false-negative rate probably due to low viral titers (37).

The data suggest that seroconversion after exposure to SARS-CoV-2 is very similar to that after other acute viral infections, with IgG levels starting to increase as IgM levels reach a plateau. Rapid serological

tests (POC immunoassays) have also been designed for the rapid detection of SARS-CoV-2, IgG and IgM antibodies (38).

Pregnant women must be examined, as must the general population, before maternity leave (39). Screening procedures should be performed to confirm the diagnosis of SARS-CoV-2 infection by performing a real-time analysis of the reverse transcription polymerase chain reaction (RT-PCR) (40). According to WHO recommendations, detection of SARS-CoV-2 virus can be performed using nasopharyngeal and oropharyngeal swabs in outpatients, sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with severe disease (41). RT-PCR tests performed on rectal stools, urine and plasma were less sensitive to virus detection (42). The difference in sensitivity between different types of smears may depend on the degree of disease progression (43). However, some studies indicate that the risk of obtaining false-negative results for COVID-19 is approximately 30-40% (44). If the SARS-CoV-2 nucleic acid is not detected in two consecutive tests performed at least 24 hours apart, the result may be considered negative (45).

Pregnant women are tested for IgM and IgG antibodies against SARS-CoV-2 using serum or plasma from peripheral blood, and newborns from umbilical cord blood plasma. IgM and IgG antibody levels are correlated with the number of days elapsed since the onset of COVID-19 symptoms (46).

The response of IgG antibodies in symptomatic pregnant women is significantly higher than in asymptomatic pregnant women. In pregnant women, IgM and IgG levels peak at 15 days and 30 days, respectively, from the onset of COVID-19 symptoms. A certain level of maternal IgG may be needed to transfer a sufficient level of antibodies to the newborn. Passive immunity in the form of IgG has been demonstrated in a large number of newborns, and serology levels in mothers have been correlated with serology levels in newborns. Maternal antibody levels and oxygen supplementation may predict antibody levels in newborns (47).

The diagnosis of COVID-19 also includes X-rays and computed tomography (CT) of the chest. Previous data have shown that the lowest dose of radiation exposure for fetal side effects is usually 50 ~ 200 mGy, so these investigations can be performed in pregnancy (48). Pulmonary imaging using ultrasound can also be performed in pregnant women (49). As

they cannot clearly differentiate SARS-CoV-2 infection from other respiratory diseases, the results of each imaging examination (CT, X-ray and ultrasound) should be interpreted carefully (50).

Pregnant women should be examined for the most common symptoms reported in SARS-CoV-2 infection: fever, cough, dyspnoea, anosmia, ageusia, gastrointestinal disorders, fatigue, myalgia, or close contact with a confirmed case of COVID-19 (51). Due to the high risk of developing asymptomatic infections, the WHO recommends monitoring all pregnant women who are in contact with a person with SARS-CoV-2 (52).

Laboratory results in pregnant women with SARS-CoV-2 show leukopenia, or lymphopenia, increased C-reactive protein, increased procalcitonin, increased alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST), dimer D and lactate dehydrogenase (53,54).

The impairment of coagulation is highlighted by a prolonged activated partial thromboplastin time (APTT). Hemolysis is indicated by a decrease in hemoglobin and an increase in lactate dehydrogenase (55).

TREATMENT OF SARS-COV-2 INFECTION IN PREGNANCY

There is currently no specific medication for COVID-19. So an emergency method for the pandemic was to administer existing preparations. Medication should be selected for both maternal and fetal safety (56).

Due to the presence of the fetus, many antiviral drugs are banned during pregnancy because of their proven teratogenicity, such as ribavirin (57).

Antivirals (remdesivir, lopinavir/ritonavir, Oseltamivir, arbidol) slightly reduce the risk of death in patients with COVID-19, but not during hospitalization (58).

Preparations such as chloroquine, hydroxychloroquine, included in the category of antimalarials, are considered in the treatment of COVID-19 in pregnant women. They may be combined with an antibiotic, such as azithromycin, or a cephalosporin if a bacterial infection is suspected (59).

The positive interaction of ivermectin with viral protein targets is recommended in the treatment of COVID-19 (60).

Studies in animals and humans have shown that interferon (I-IFN) has antiviral effects on various cell models. In view of this evidence, I-IFN is used in the treatment of COVID-19 (61).

For the inhibition of hyperactive inflammatory responses in COVID-19, metformin, glitazone and atorvastatin are commonly used drugs (62). They can reduce immunopathology and improve the immune response, reducing the severity of lung damage and mortality in patients with COVID-19. Metformin could significantly reduce maternal and neonatal adverse outcomes, such as gestational hypertension, hypoglycaemia and the need for neonatal intensive care, as a safe and effective complementary therapy for insulin in women with gestational diabetes (63). Statins have an anti-inflammatory role in influenza and other diseases that cause lung damage. Metformin and statins can be used as an adjunct to cyclosporine, lobinavir/ritonavir, interferon-1b, monoclonal antibodies and antiviral peptides targeting SARS-CoV-2, thereby reducing the use of antiviral drugs and reducing side effects (64).

Corticosteroids can be administered during pregnancy. There is limited information on the effects of dexamethasone on the postpartum period and breastfeeding, so the use of methylprednisolone is recommended, but if the woman is not breast-feeding, she may use dexamethasone (65).

Plasma containing anti-SARS CoV-2 antibodies, collected from people recovered after COVID-19, are collected using apheresis devices and stored in blood banks and administered to patients with COVID-19 to reduce the need for intensive care and rates of mortality. Convalescent plasma appears to be a safe and probably effective treatment for patients with critical illness with COVID-19 (66).

Pregnancy increases the risk of thrombosis, which is why the use of anticoagulant prophylaxis is recommended in patients with COVID-19. The decision on the initiation and duration of prophylactic anticoagulant therapy should depend on the severity of the disease, the time remaining until birth, the prothrombotic risk associated with pregnancy-associated comorbidities. Unfractionated heparin, low molecular weight heparin and warfarin are recommended, which can also be used during breast-feeding (67).

Respiratory rate and oxygen saturation should be monitored in pregnant women infected with SARS-CoV-2. Oxygen saturation must be maintained above 94% (68) by nasal cannula, intubation, me-

chanical ventilation or oxygenation of the extracorporeal membranes, depending on the severity of the disease.

SARS-COV-2 INFECTION AND CESAREAN SECTION

Maternal SARS-CoV-2 infection is not in itself an indication to shorten gestation or cesarean section. They are indicated for pregnant women infected with COVID-19 in case of severe or critical symptoms (pneumonia, aggravated dyspnea, acute respiratory failure, multiorgan damage). Postoperative pulmonary complications after obstetric surgery occurred in 49% of patients with SARS-CoV-2 infection (69). For this reason, caesarean section should be performed only in justified cases, especially since there is no direct evidence that it would reduce the risk of transmission of the infection from mother to fetus.

It is recommended that the birth be performed in a negative pressure isolation room and that newborns with SARS-CoV-2 positive mothers be admitted to an isolated room with negative pressure (70).

All newborns with SARS-CoV-2 infected mothers should be tested for COVID-19, whether or not they show signs of infection. Newborns should be tested by an RT-PCR test of nasopharyngeal, oropharyngeal or nasal swabs within 24 hours of birth. If the result is negative or inconclusive, the test should be repeated every 48 hours. In places with limited testing capabilities, priority is given to symptomatic infants and those exposed to SARS-CoV-2 (71).

Any pregnant woman suspected of COVID-19 should be treated as infected until a test result is obtained. Although separating the newborn from the mother reduces the risk of infection, this can lead to excessive stress as well as discontinuation of breastfeeding. Infants born to women diagnosed with COVID-19 at birth are treated as possibly infected. The risk of infection of the newborn from the mother does not exist if at least 10 days have passed since the first symptoms, or 20 days after the critical evolution of the disease (72). Separation is necessary for newborns in the high-risk group and when the mother is too ill to care for the baby. Isolation of the infected mother is not necessary when the infant is infected with SARS-CoV-2. The risk of infecting the newborn from the mother is low when following the hygiene instructions (mask and hand washing) (73).

EVOLUTION AND COMPLICATIONS OF SARS-COV-2 INFECTION IN MOTHER AND FETUS

The risk of SARS-CoV-2 infection and the development of severe symptoms of COVID-19 increase with age and prevalence of comorbidities, for example, diabetes and chronic hypertension, asthma, hypothyroidism, autoimmune diseases, obesity (74). It seems that race can also influence the appearance and severity of the disease. In fact, pregnant women may have an increased risk of developing severe symptoms of COVID-19 compared to the general population, moreover, they more often required mechanical ventilation in intensive care units (75).

However, the asymptomatic evolution of the disease in pregnant women is estimated at up to 90%. However, the risk of death was similar to that of the general population. In symptomatic COVID-19 pregnant women, miscarriages, premature births, or intrauterine growth restrictions are more common (76).

In pregnant women infected with SARS-CoV-2 who presented to the emergency room with vaginal bleeding and uterine contractions, but without fever, lymphocytopenia, high levels of C-reactive protein and ferritin were detected, and immediately after birth, the mother developed severe respiratory symptoms and multi-organ lesions that can even lead to the death of the newborn shortly after birth, or in case of infection require rapid respiratory support (77).

The main symptoms of COVID-19 in pregnant women are similar to those seen in the general population. They will be managed depending on the mild form (fever, cough, anosmia, gastrointestinal disorders), moderate (tachypnea, hypoxia, abnormal chest imaging) or severe (respiratory failure, shock). Acute worsening of symptoms or their occurrence in the perinatal or postpartum period in asymptomatic or mild women is frequently reported in the literature (78).

Coagulopathy and thromboembolism are both elevated in pregnancies affected by COVID-19. Their identification is of particular importance in the recognition of patients with increased mortality (79).

An increasing number of patients with neurological symptoms have been reported. These manifestations can range from mild and common symptoms, such as anosmia or ageusia, to severe and uncommon ones, such as a stroke. The symptoms of extrapulmonary disease could be explained by endothelial lesions of the brain caused by the virus (80).

Preliminary studies on complicated pregnancies with SARS-CoV-2 infection have suggested a low rate of care in intensive care units and maternal and neonatal death, comparable to the general population (81).

Newborns from infected mothers had more frequent respiratory distress compared to those born to healthy mothers. These newborns are more likely to have low birth weight and may have a lower APGAR score. The risk of fetal complications increases if mothers suffered infections in the first trimester of pregnancy (82). Perinatal infection with SARS-CoV-2 can cause fetal distress, premature labor, respiratory distress, thrombocytopenia with abnormal liver function, gastrointestinal bleeding, necrotizing enteritis, and even neonatal death (83). However, the vast majority of newborns in mothers infected with SARS-CoV-2 are asymptomatic.

VERTICAL TRANSMISSION OF THE INFECTION

Current studies indicate that the probability of vertical SARS-CoV-2 transmission from mother to newborn varies from 3% to 8% (84). The positive diagnosis of the newborn is most often made from a nasopharyngeal swab in the RT-PCR test, collected at a maximum of 36 hours after birth, less often from blood samples from the umbilical cord, placenta and breast milk. If the viral load is high enough, a positive result can be obtained, but cases have been reported in which although the mother was asymptomatic, or with a negative RT-PCR test, the fetus, born prematurely, developed specific symptoms and was diagnosed positively (85). It should be noted that in the antibody tests the mothers were positive and the maternal placenta showed chronic intervillitis, with the presence of macrophages (86). The symptoms of SARS-CoV-2 infection in a newborn should not appear immediately after birth, but in the following days. There are studies that have reported the presence of SARS-CoV-2 in the placenta, umbilical cord and decidua, so it can be concluded that SARS-CoV-2 can penetrate the placental tissues, cause an inflammatory reaction and be transmitted to the fetus (87). Furthermore, in the case of intrauterine viral transmission from mother to child, attention should be paid to the IgM level for SARS-CoV-2 and the cytokine IL-6 and IL-10 in newborn serum, even if the nasopharyngeal swab is tested negative (88). IgG an-

tibodies, not IgM, can be transmitted to the fetus via the placenta. Therefore, elevated levels of IgM antibodies suggest that the newborn may have been infected during pregnancy (89).

The results of many studies on the transmission of SARS-CoV-2 from mother to child are inconclusive. However, they indicate the possibility of maternal-fetal transmission, although it is rare.

A newborn is usually infected by the mother or other caregiver with COVID-19 airborne. Therefore, further research is needed on the mother-to-child transmission of the virus.

Breast-feeding

Breast milk is the basic diet necessary for the good development and health of infants, the WHO recommending exclusively breastfeeding newborns in the first 6 months of life (90). Infected mothers must adhere to proper hygiene (mask is easy to disinfect hands and surfaces frequently) (91).

Most available studies confirm that SARS-CoV-2 cannot be transmitted to infants via breast milk (92,93). However, there are studies that have shown SARS-CoV-2 in milk samples (94).

WHO recommends that mothers with confirmed or suspected COVID-19 infection breastfeed their infants. Whether the mother or child has been diagnosed or suspected of COVID-19, the mother and child should be allowed to sit together in a room so as not to promote postnatal depression.

CONCLUSIONS

In the context of the coronavirus pandemic, it is essential that pregnant women are not ignored. They are more likely to develop infections caused by respiratory pathogens and are more likely to have a severe course of the disease due to the immunosuppressive condition and physiological changes during pregnancy. The risk of SARS-CoV-2 infection and the development of severe COVID-19 symptoms increase with age and prevalence of comorbidities.

Acute worsening of symptoms or their appearance in the perinatal or postpartum period has been found in asymptomatic or mild women. However, a low maternal and neonatal death rate has been reported, comparable to the general population, and the vast majority of newborns from mothers infected with SARS-CoV-2 are asymptomatic.

Current studies indicate the possibility of maternal-fetal transmission of the virus. Although there are studies that have shown the presence of SARS-CoV-2 in milk samples, the WHO recommends breastfeeding.

Although we do not have enough data on vaccination against COVID-19 in pregnant women, immunization of the mother, which stimulates its IgG response, could provide protection for the newborn.

Conflict of interest: none declared

Financial support: none declared

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