A Comprehensive Review of the Management of Pregnant Women with COVID-19: Useful Information for Obstetricians

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Abstract: Due to the physiological changes of the cardiovascular system and respiratory system in pregnancy, pregnant women are vulnerable to pathogen infection and severe pneumonia. With the increasing incidence of COVID-19 pneumonia, its influence on pregnant women and neonates has attracted more attention. In this review, we collected all relevant articles published in English from September 1, 2019 to June 10, 2021, regarding the epidemiology, clinical presentations, chemical examinations, imaging findings, the timing of delivery and delivery mode, maternal and neonatal complications, medication, and vertical transmission of COVID-19 in pregnancy. It has been reported that compared with non-pregnant females, pregnant women with COVID-19 are more likely to develop into severe type. In particular, the risk of entering the intensive care unit and endotracheal intubation was higher. Chest computed tomography and blood routine examination are useful for the diagnosis of COVID-19 in a short period of time. COVID-19 pneumonia is not an independent indication for terminating the pregnancy, and it is not contraindicated for vaginal delivery. Compared to normal pregnant females, patients with COVID-19 showed an elevated susceptibility of preterm delivery. Multidisciplinary consultation was suggested in the treatment policy of COVID-19 in pregnancy. Currently, there is no evaluation on the safety, efficacy, and immunity of the approved vaccines for mothers and infants. In human placental tissues, the COVID-19 virus has been found by different detection methods. The mechanism by which the virus enters the placental tissue is unclear, which may be related to placental inflammation. The long-term prognosis of pregnant women with COVID-19 remains unclear and requires further detailed investigation.

Keywords: pregnant, COVID-19, SARS-CoV-2, neonate, vertical transmission

Introduction

The novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gradually spread in many countries. Up to June 15, 2021, there were 116,665 cases of COVID-19 in China. Among these patients, 5306 deaths (4.5%) were identified. In the world, 175,987,176 individuals have been infected with COVID-19, and 3,811,561 people died of this disease as of June 15, 2021, according to the statistics of the World Health Organization (WHO).

Gene sequencing found that COVID-19 belonged to the subgenus Sarbecovirus.[1] The diameter of SARS-CoV-2 is approximately 50–200 nm with a single-chain RNA genome.[2] In terms of genome composition, the similarity of

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COVID-19 with severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS) is 80%[3] and 50%,[1] respectively. COVID-19 can be highly contagious through air foam from the respiratory tract, aerosols in confined spaces, and close contact, and it can be transmitted from one person to another.[4] The clinical manifestations of the disease vary from mild to severe. A large study of 44,672 patients showed that 81% of the cases were mild (mild symptoms), 14% (imaging examination indicates that over half of the lungs are involved within 1–2 days) were severe, and the remaining 5% were critical (multiple organ dysfunction or need tracheal intubation).[5] The general mortality rate of COVID-19 was 2.3%.[5] Although most patients are mild, for those with high-risk factors, many patients need to enter the intensive care unit (ICU) for treatment and may die.[6]

At a time when COVID-19 is rapidly spreading, obstetricians should be aware of the clinical manifestations, principles of management, and prognosis of the disease during pregnancy and postpartum. Hence, the purpose of this review was to collect updated reports regarding the epidemiology, clinical presentations, chemical examinations, imaging findings, timing of delivery and delivery mode, maternal and neonatal complications, medication, and vertical transmission of COVID-19 in pregnancy.

Data Collection

Two independent researchers searched the articles in PUBMED with the following medical subject headings (MeSHs): "COVID-19", "SARS-CoV-2", "pregnant", "neonate", or "vertical transmission". All articles were published in English from September 1, 2019 to June 10, 2021.

Physiological and Immunological Changes in Pregnancy

Due to the physiological changes of the cardiovascular system and respiratory system in pregnancy, pregnant women are vulnerable to pathogen infection and severe pneumonia. Pregnant women have increased heart rate, more blood volume, decreased lung volume, elevated diaphragm, increased oxygen consumption, and edematous respiratory tract mucosa. Changes in lung volume and vasodilation result in airway edema and elevated respiratory secretions. Therefore, pregnant women have poor tolerance for hypoxia.[7] Besides, pregnant women show specific immune status that can tolerate the semi-allogeneic fetus.[8] Due to the effect of suppressive T cells, pregnant women have transient immunosuppression, so they are more susceptible to virus infection.[9,10] Furthermore, changes in cell-regulated immunity make pregnant women more vulnerable to intracellular pathogens, including viruses.[11] Dysfunction of elements such as cytokines and the complement system caused by viruses also have adverse effects on the growth of the neonatal brain.[12] In patients with COVID-19 infection, T helper (Th) 17 immunity was found to be significantly increased, resulting in the release of numerous inflammatory cytokines.[13,14] Fetuses born from infected pregnant women may be in an inflammatory state promoted by placental sample or systemic immune response from their mothers. The Treg/Th17 immune balance is very important for normal pregnancy.[15,16] If Treg cells decrease and Th17 cells increase, it may cause recurrent pregnancy loss, preeclampsia and preterm birth.[13,17–19] Accordingly, it can be concluded that the immune inflammatory reaction of COVID-19 infection may lead to many obstetrical complications, resulting in short- and long-term adverse maternal and fetal outcomes.

SARS and Pregnancy

SARS infection during pregnancy may cause many pregnancy complications, such as spontaneous abortion, fetal growth restriction, and premature delivery, and pregnant women with SARS had worse consequences compared with non-pregnant women.[20–23] During the SARS epidemic in 2002–2003, 12 pregnant women were infected with SARS in a report.[20] Seven women were infected in the first trimester, and four of them (57%) had a spontaneous abortion. Among the five pregnant women who were infected in the second and third trimester, 2 cases (40%) had fetal growth restriction, 4 cases (80%) had premature delivery (1 baby was born naturally, 3 cases had induced labor due to severe complications of mothers). In total, three of the twelve died.[20] Furthermore, some studies have found that there was SARS virus in peritoneal fluid of 28 cases of pregnant women during cesarean section through the detection of Reverse Transcription-Polymerase Chain Reaction (RT-PCR),[24] which suggested that obstetricians should shorten the operation time and reduce the chance of contact between neonate and maternal blood or body fluid during cesarean section. It was gratifying to note that during the SARS epidemic, there were no reports of neonatal vertical

infection with SARS-CoV.[21,24–26] However, breastfeeding was not recommended for pregnant women with SARS to avoid potential neonatal infection.

MERS and Pregnancy

MERS is another coronavirus that can lead to severe pneumonia. The first case occurred in Saudi Arabia in 2012, subsequently, the disease gradually spread to 27 countries.[27] There are few reports of MERS in pregnant women. In a review including 11 pregnancies with MERS, 10 (91%) had poor pregnancy outcomes, 6 newborns (55%) needed to be admitted to the neonatal intensive care unit (NICU),[6] and 3 (27%) maternal deaths were recorded.[28] Due to severe respiratory failure of mothers, two newborns were born prematurely.[28] During the outbreak of MERS in Jordan in 2012, there was a stillbirth in a pregnant woman with five months of gestation due to MERS infection.[29] In Korea, a pregnant female was infected with MERS in the third trimester.[30] Although she had vaginal bleeding and premature rupture of membranes, she successfully delivered a live fetus by cesarean section at full-term and recovered completely.[30] No antibody (IgG, IgM, or IgA) was found in the blood of the newborn, indicating that there was no proof of vertical transmission of MERS from mother to infant,[30] which was consistent with other reports.[21]

Clinical Manifestations of COVID-19 in Pregnancy

When COVID-19 pneumonia attacks, fever and cough are the common symptoms, other symptoms, such as myalgia, shortness of breath, discomfort, diarrhea, sore throat, can also appear, but not common.[31,32] It was worth noting that 56% of pregnant females with COVID-19 infection might have normal body temperature and atypical clinical manifestations.[33] Farida Elshafeey et al[34] assessed 385 pregnant women with COVID-19 infection with data collected from 33 studies and concluded that patients with mild disease accounted for the largest proportion, followed by those with severe disease and then those in critical condition, with the percentages of 95.6%, 3.6%, and 0.8%, respectively. Seventeen women were sent to ICU, 6 women received mechanical ventilation, and 1 woman died.[34] Studies have shown that pregnancy regulates the immune system, and HCG and progesterone inhibit Th1 pro-inflammatory pathway by reducing tumor necrosis factor-α (TNF-α).[35] We hypothesized that this regulation

of the immune system might prevent pregnant women from cytokine storm syndrome and lower morbidity and mortality. This could interpret the relatively optimistic outcomes of 385 women in 33 reports.[34] A report from France included 617 pregnant women with COVID-19.[36] Among these patients, 35 of them (5.7%; 95% CI 4.0–7.8) belonged to the severe group, and one pregnant woman died (0.2%).[36] A newborn died of premature birth.[36] The incidence of preterm birth was related to the severity of the maternal condition.[36] Since COVID-19 may lead to severe and fatal respiratory distress, pregnant females with primary diseases may benefit from the lockdown policy.[36] Furthermore, a study from the UK included 1148 pregnant women with SARS-CoV-2, 63% of the patients had symptoms.[37] Compared with pregnant women without SARS-CoV-2, Black, Asian and other ethnic minorities were more likely to suffer from this virus.[37] Pregnant women with symptoms had a higher possibility of entering the ICU for treatment (aOR 57.67, (7.80–426.70)), but the risk of adverse prognosis was relatively low.[37] The rate of cesarean section and neonatal NICU admission were elevated regardless of symptom condition.[37] According to this report, most pregnant women infected with SARS-CoV-2 did not have serious complications.[37] Another large sample report included 4005 pregnant women with suspected or confirmed COVID-19 infection from the UK and the United States.[38] Patients with SARS-CoV-2 had a higher incidence of premature delivery compared with normal pregnant women in the same period.[38] The prevalence of stillbirth, small for gestational age (SGA), and early neonatal death was comparable to that of normal pregnant women.[38] Although the probability of maternal death was low, it was higher than the expected data in the UK and the United States.[38] The reason may be related to the lack of awareness of asymptomatic patients.[38] These data provide strong evidence supporting the prevention of COVID-19 infection during pregnancy, especially the increased incidence of premature birth and maternal death, which further clarify the necessity of vaccination for pregnant women and females planning pregnancy.[38]

A meta-analysis including 192 studies reported that compared with females who are not pregnant, pregnant women are less likely to have symptoms after COVID-19 infection.[39] However, pregnant women had a higher risk to receive ICU treatment (OR: 2.13, 1.53–2.95; I^2 = 71.2%), endotracheal intubation (OR: 2.59, 2.28–2.94; I^2 = 0%), and extracorporeal membrane oxygenation (ECMO) (OR: 2.02, 1.22–3.34; I^2 = 0%).[39] In this report, 0.02% of

pregnant women with COVID-19 died for various reasons.[39] Another meta-analysis included 24 studies involving 1100 pregnant women.[40] The incidence of pneumonia was 89%.[40] 8% of the patients were admitted to the ICU.[40] Three stillbirths occurred and five pregnant women died.[40] The cesarean section rate for these pregnant women was 85%, although most of them had no clear indication for cesarean section.[40] Besides, a systematic review collected 13 studies including 462 pregnant women with COVID-19.[41] Maternal ICU occupancy rate was 3%, 1.4% of the patients were critically ill, no maternal deaths were demonstrated, and the incidence of preterm birth was 20.1%.[41] Only one of the 313 newborns died.[41] Another systematic review analyzed 24 studies, including 324 pregnant women with COVID-19.[42] The incidence of severe cases was 0–14% among different reports.[42] Almost all of the patients had positive pulmonary imaging findings.[42] The cesarean section rate was 78% among these patients, and 4 pregnant women had miscarriages.[42]

It has been reported that some factors, such as obesity, diabetes, hypertension, primary maternal diseases, and advanced age, are related to severe COVID-19 in pregnant women in China, the United States, France, and the UK.[36,37,39,43–46] A number of high risk factors of preeclampsia are consistent with those of severe COVID-19.[46] Some patients with severe COVID-19 showed similar symptoms to preeclampsia, but there was no significant change in the markers related to preeclampsia (fms-like tyrosine kinase-1 and placental growth factor), indicating that COVID-19 could induce systemic inflammation similar to preeclampsia, but COVID-19 was not caused by poor placentation.[47,48] It should be noted that COVID-19 may aggravate the hypercoagulable state of pregnant women, resulting in lower fetal vascular perfusion and excessive placental fibrin deposition.[49,50]

Pregnant women with COVID-19 may be asymptomatic during pregnancy, but diagnosed after delivery. The hormone level of pregnant women in postpartum had a significant change, and the steroid hormone dropped sharply.[51] The immune cells (hemophagocytes, natural killer (NK) cells, dendritic cells (DCs), and T cells) in postpartum also altered significantly, compared with the late pregnancy.[52] These hormonal and immunological changes may lead to the susceptibility of SARS-CoV-2 infection in postpartum. However, the mortality rate was not increased.[53–56] In the future, we need to closely follow up pregnant women with COVID-19 after delivery to collect more valuable data. These experimental results are conducive to the formulation of compatible health care policies, and may help obstetricians to make appropriate treatments during the epidemic period.

Psychological Distress During COVID-19 Pandemic

During the COVID-19 epidemic, many pregnant women showed depression and anxiety.[57,58] Pregnant women with depression and anxiety were more likely to suffer from insomnia.[59] The content of cortisol in plasma and amniotic fluid increased significantly among pregnant women with anxiety.[60] Depression and anxiety in pregnancy may lead to preeclampsia, gestational diabetes, premature delivery, low birth weight, and postpartum depression.[60,61] Previous reports have also shown that perinatal depression and anxiety may also cause abortion, neonatal asphyxia, and fetal brain dysfunction.[62–64] Children born to females with increased stress may also have mental developmental disorders.[65] These short-term and long-term adverse effects of COVID-19 infection on pregnant women and fetuses deserve physicians' concern.

Diagnosis and Imaging of COVID-19 in Pregnancy

There were some abnormal laboratory indicators in pregnant women with COVID-19, such as increased C-reactive protein (6/9), elevated alanine aminotransferase (ALT) and aspartate aminotransferase (3/9),[46] and lymphopenia (5/9).[31] In one study, 118 pregnant women with COVID-19 were collected in Wuhan.[66] Among them, 84 (71%) were positive by PCR assay, and 34 (29%) were diagnosed as lung computed tomography (CT) lesions.[66] It is relatively difficult to diagnose COVID-19 for pregnant women due to physiological leukocytosis and elevated neutrophil ratio during pregnancy. In COVID-19 patients, eosinopenia occurred in the early stage of fever, and the decrease of eosinophils was significant.[67] Lymphopenia was considered to be of great significance in the diagnosis of COVID-19,[31] but rarely occurred in pregnant women.[68] Therefore, eosinopenia may be used as one of the early diagnostic indicators. It has been discovered that glucocorticoids may cause eosinopenia,[69] which can be inferred that COVID-19 could affect the release of endogenous glucocorticoids in vivo.

With the help of RT-PCR, lung CT can be used to diagnose COVID-19, showing the sensitivity of 97%,

specificity of 25%, positive predictive value of 65%, and negative predictive value of 83%.[70] Since lung CT has a vital role in the diagnosis of COVID-19 in pregnant women, and the risk is relatively small, it is suggested that pregnant women should take lung CT examination after signing the consent form. During the process of the CT examination, the abdomen can be shielded, and the examination time should be reduced to lower the radiation exposure of the fetus. Laboratory tests such as RT-PCR need a certain amount of time, but maternal delivery is impending. For patients with atypical or mild symptoms, rapid lung CT test and blood routine examination are more useful for the diagnosis of COVID-19 in a short period of time. Early diagnosis is helpful to protect other normal pregnant women and medical workers.

The Timing of Delivery and Delivery Mode of Pregnant Women with COVID-19

According to the specialists' suggestions from the Chinese Medical Association (CMA),[71] COVID-19 pneumonia is not a strong indication for terminating a pregnancy, and the time of ending pregnancy needs to be determined according to the specific condition of each patient. The main considerations are maternal physical condition, gestational weeks, and the intrauterine situation of the fetus. If the maternal condition is stable, the timing of delivery depends on the gestational weeks. If the type of COVID-19 pneumonia is severe or critical (according to the edition reported),[72] earlier delivery should be considered even though the gestational age is very small. Many studies have shown that the conditions of severe or critical patients could be significantly improved after the termination of pregnancy.[72]

As for the mode of delivery, cesarean section was conducted in most of the reports, and fetal distress was the main reason for the surgery.[31,33,73] However, there were still some cases of vaginal delivery, with good pregnancy results.[31,33] Most guidelines and expert recommendations pointed out that COVID-19 pneumonia is not contraindicated for vaginal delivery.[74,75] Clinically, if a puerpera needs to have a cesarean section, it is better to be done by a qualified obstetrician to reduce the possibility of complications and shorten the operation time. In the process of cesarean section, doctors need to pay attention to reduce the bleeding to maintain hemodynamic stability and decrease the cardiopulmonary burden caused by blood transfusion. In the process of delivery, related

samples (including amniotic fluid, umbilical cord blood, placenta, vaginal secretions, and neonatal throat swabs) should be sent to test the SARS-COV-2 virus, to determine whether vertical transmission occurred.

Anesthesia During Cesarean Section for Pregnant Women with COVID-19

Epidural or general anesthesia can be applied in cesarean section for pregnant women with COVID-19.[23] Most anesthesiologists prefer epidural anesthesia since it can avoid infection caused by endotracheal intubation, as well as avoid the respiratory depression and decline of neonatal muscle tension caused by general anesthesia. If the complication of COVID-19 occurs, such as kidney failure or disseminated intravascular coagulation, invasive monitoring should be considered, including central venous catheterization.[76] It is essential to perform anesthesia by skillful anesthesiologists to reduce the duration of operation and needless contact with the virus. In the process of endotracheal intubation, anesthesiologists must use intact personal protective equipment (PPE) to avoid infection.

Maternal and Neonatal Complications Among Pregnant Women with COVID-19

COVID-19 did not seem to elevate the incidence of preeclampsia.[31] Compared with COVID-19 patients without preeclampsia, the prognosis for patients with preeclampsia was not worse.[31] For pregnant women with COVID-19, the incidences of premature rupture of membranes and spontaneous miscarriage did not increase compared with normal pregnant women in early reports.[31] However, Allotey et al reported that the rate of premature birth in pregnant women with COVID-19 was 6%.[39] Similarly, compared to normal pregnant females, patients with COVID-19 showed a higher risk for preterm delivery (OR: 1.47, 95% CI: 1.14–1.91; I^2 =18.6%).[39] Recently, Dubey et al conducted a meta-analysis and revealed that 27% of pregnant women with COVID-19 showed adverse pregnancy outcomes, including preterm delivery, fetal vascular hypo-perfusion, and premature rupture of fetal membranes.[77] The cesarean section rate of patients with COVID-19 was significantly increased (67.2–94%), and the rate of vaginal delivery was just 6–32.8%.[78–82]

Ten percent of newborns with mothers with COVID-19 showed fetal growth restriction.[83] Yoon et al[81] made

a systematic analysis of the prognosis of 201 neonates whose mothers were COVID-19 positive. Between 36–48 hours after birth, 2.4% (4/167) of newborns were tested to be positive for COVID-19.[81] The four COVID-19 positive newborns were all delivered by cesarean section with typical pneumonia imaging on chest X-ray.[81] One week later, the four RT-PCR results of nasopharyngeal were negative, and they all recovered well.[81] It has been reported that the neonatal survival rate was about 65% in pregnant women who were treated with ECMO for different reasons.[84] Up to now, in public data related to COVID-19, most pregnant women gave birth within 2 weeks of onset. It is not clear whether COVID-19 pneumonia affects fetal development in the subsequent pregnancy. Studies about perinatal complications were summarized in Table 1.

Table 1 Included Studies About Perinatal Complications

Studies	Research Type	Number of Mothers/ Neonates	Maternal Outcomes	Neonatal Outcomes
Chen et al[31]	Retrospective study	9/9	No pregnant women developed pneumonia. No patients died.	Nine newborns survived without asphyxia.
Elshafeey et al[34]	Systematic review	385/256	17 pregnant females had ICU admission. One female died.	There were two cases of intrauterine fetal death, and one neonate died.
Kayem et al[36]	Retrospective study	617/NA	The incidence of preterm birth was between 10.6–79.3%. One pregnant woman died.	One neonate died.
Vousden et al[37]	Prospective study	1148/NA	Symptomatic patients were more likely to have ICU admission, but the overall incidence of adverse outcomes was low.	The admission of NICU increased regardless of symptom condition.
Allotey et al[39]	Systematic review and meta-analysis	67,271/9466	Compared with non-pregnant females, pregnant women with COVID-19 were more likely to have preterm delivery, ICU admission and maternal death.	The neonates were more likely to enter NICU compared with those born from non-pregnant females.
Dubey et al[77]	Systematic review and meta-analysis	790/548	The proportions of cesarean section, premature delivery, low birth weight, and adverse pregnancy complications were considered as 72%, 23%, 7%, and 27%.	One newborn died.
Yan et al[80]	Retrospective study	116/100	6.9% of the patients had severe pneumonia. There was no maternal death, and the incidence of preterm birth was 21.2%.	One newborn died.
Yoon et al[81]	Systematic review	223/201	The incidence of preterm birth was 25.9%.	The incidences of small for gestational age and low birth weight were 8.3% and 15.6%.
Di et al[40]	Systematic review and meta-analysis	1100/444	89% of the patients developed pneumonia, 8% received ICU treatment, and 5 pregnant women died.	The NICU occupancy rate associated with infection was 2%, and 3 newborns died.
Huntley et al[41]	Systematic review	538/313	Maternal ICU admission occurred in 3.0% of cases. No maternal deaths were reported. The preterm birth rate was 20.1%.	One neonate died.
Juan et al[42]	Systematic review	324/221	Four pregnant women experienced spontaneous abortion.	Eight newborns showed low birth weight. About one third of newborns were admitted to NICU. One newborn had asphyxia and one newborn died.

Abbreviations: ICU, intensive care unit; NICU, neonatal intensive care unit; NA, non-analyzed.

Medication of Pregnant Women with COVID-19

The fundamental treatment policies of COVID-19 in pregnancy are as follows: immediate segregation, detection for SARS-CoV-2, oxygen inhalation, reduction of excessive liquid input, fetal intrauterine observation, timely auxiliary ventilation if the respiratory failure occurs, choosing the appropriate mode of delivery, and multidisciplinary collaboration. Anticoagulants are often used to prevent thrombosis during cardiopulmonary bypass; however, placental hemorrhage may occur during this process. The establishment of ECMO needs multidisciplinary consultations, which is suggested to be carried out in a tertiary hospital.

There is an interaction between the surface glycoprotein of SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) of epithelium in the patient's respiratory tract. The appearance of ACE2 in alveolar type 2 cells is the main lung characteristic. The combination between the virus and ACE2 may lead to hypertension in patients with COVID-19 pneumonia,[85] which is easily misdiagnosed as preeclampsia for pregnant women. Besides, if the result of D-dimer in a non-pregnant patient with COVID-19 was more than 1 mg/mL, the mortality was high.[86] Nevertheless, the levels of D-dimer are difficult to explain since these values are frequently elevated during pregnancy, and according to the traditional thresholds, only 84%, 33%, and 1% of women in the early, middle, and late stages of pregnancy have normal D-dimer values.[76] Corticosteroids are not recommended for patients with mild or atypical symptoms, unless the pregnant woman is likely to give birth before 34 weeks.[87] It has been reported that the incidence of thrombosis in ICU patients with COVID-19 is increased.[88] Combined with the hypercoagulable state in the maternal body, it is strongly recommended to give anticoagulant drugs at therapeutic doses for severe pregnant women with COVID-19.

The latest data has discussed the efficacy of remdesivir and chloroquine in the treatment of COVID-19.[89] At present, researchers in the United States and China are in full swing to carry out phase three experiments to evaluate the effect of remdesivir on COVID-19. Since the randomized controlled trials did not include pregnant women, it is not recommended to use remdesivir outside of an experimental setting.[90] Chloroquine phosphate was mainly applied in the treatment of malaria, and it has the abilities of antivirus and immunomodulation. It can promote cell fusion through increasing intracellular pH value and interfering with glycosylation of cell receptors of the SARS virus in cell lines, thus blocking COVID-19 infection.[89] Chloroquine and its products of metabolism can pass through the placenta. However, it can be securely applied in different stages of pregnancy without harmful effects on mothers and neonates.[19] Pharmacokinetic reports showed that the concentration of chloroquine in plasma of pregnant woman was obviously reduced due to the extensive infiltration all through the body,[91] resulting in the necessity of the increase of dosage for pregnant women with COVID-19 (about 500 mg two times a day).[92] It should be noted that too much chloroquine can cause low blood pressure, which is a burden for pregnant women with supine hypotension syndrome already. In addition, pregnant women should be fully aware of the possibility of impaired fetal growth affected by the use of alpha interferon in the first trimester. Due to the complex clinical condition of COVID-19 in pregnancy, a multidisciplinary team is necessary to evaluate and treat patients individually and carefully. Concerned specialists include obstetricians, infectious physicians, respiratory doctors, cardiologists, pediatricians, anesthesiologists, and ICU physicians.

Many guidelines recommend to provide COVID-19 vaccines for pregnant women.[93] However, there is no evaluation on the safety, efficacy, and immunity of the approved vaccines for mothers and infants. At present, the widely used COVID-19 mRNA vaccines are not live vaccines, and there is no adjuvant. The benefits of vaccines in pregnant women are obvious.[94] According to the results, the vaccine can protect the general population from laboratory confirmed infection and mild symptomatic COVID-19 infection 7–14 days after injection with an effective rate of 94–95%.[95] Moreover, in other vaccine studies, the protection rate of pregnant women and non-pregnant women is close.[96,97] Therefore, the vaccine may have a similar effective function for pregnant women.[98] The IgG produced by the vaccine may be transmitted to neonates through breastfeeding, which has a certain protective effect on their children.[99] Obstetricians need to pay close attention to the experimental results of vaccines for pregnant women.

A recent meta-analysis included 1239 pregnant women infected with COVID-19 from 66 studies.[100] The authors found that among moderate-risk patients, the percentage of receiving oxygen inhalation, antibiotics, antiviral drugs and plasma therapy in Asia was significantly higher than that in the United States and Europe.[100] The reason for the

high application of antibiotics in Asia may be related to the local diagnosis and treatment guidelines.[101] In addition, doctors may be worried about the co-infection of bacteria and fungi, as well as potential iatrogenic infection, and it is difficult to distinguish viral from bacterial infection in a short time.[102] According to their results,[100] the application of antibiotics in the United States and Europe was also very common. In a report from the United States, more than 96% of patients with COVID-19 had no bacterial infection, so antibiotics might be unnecessary.[103] Some reports have also shown that antiviral therapy has no obvious benefits.[104,105] For moderate-risk and severe patients with COVID-19, oxygen sustain may increase ICU occupancy and the incidence of preterm birth.[100] Immunosuppressants may cause serious adverse consequences, thus, the condition needs to be carefully evaluated before its application.[106]

Polycystic Ovary Syndrome (PCOS) and COVID-19

PCOS refers to the symptoms and signs of androgen overmuch and ovulation disorder after excluding other causes.[107] The mechanism of COVID-19 aggravation caused by androgen excess may be related to transmembrane protease serine 2 (TMPRSS2), which is a receptor required for COVID-19 infection.[108] Besides, androgens may promote infection through immune regulation.[109] Compared with normal women, PCOS patients have a 28% increased risk of COVID-19 infection.[110] Furtherover, the symptoms of PCOS patients after infection were more obvious compared with infected women with normal androgen.[111] These results suggest that doctors should strengthen the monitoring of women with PCOS during the epidemic. In addition to obesity, PCOS patients often have low-level inflammation, decreased vitamin D and imbalance of intestinal flora.[112] These factors are the reasons why PCOS patients are prone to severe types of COVID-19 infection.[113] The animal experiment suggested that infected mice with PCOS had cardiac, renal and gastrointestinal abnormalities.[114] Therefore, physicians should pay attention to the changes of these organ functions in order to avoid these patients turning into severe cases. Metformin could be used to treat COVID-19, since it can change the ACE-2 receptor through activated protein kinase (AMPK) pathway, then, the virus can not enter the host.[115] It should be noted that metformin may cause lactic acid accumulation in patients with

dehydration or renal dysfunction among PCOS patients with COVID-19.[116]

Pregnant Patients with Underlying Comorbidities

A meta-analysis showed that pregnant women were more likely to develop into the severe cases if they were older than 35 years old, with hypertension, diabetes or body mass index (BMI) greater than 30.[39] Gestational diabetes mellitus and obesity are the most common comorbidities, and the mortality of these patients was increased by three times compared with normal pregnancies.[117] Obese pregnant females with COVID-19 may have thrombotic diseases, therefore, anticoagulant therapy can be considered for this population.[118] For infected pregnant women with comorbidities, they should be admitted to the specific hospital in time, with closely monitor for both mothers and fetuses, and multidisciplinary consultation and treatments were extremely essential.[119] Moreover, more information about patients needs to be collected in order to identify pregnant women who may turn into severe types.

Vertical Transmission and Breastfeeding for Pregnant Women with COVID-19

According to the existed reports from China, the virus has not been found in the vaginal mucosa, umbilical cord blood, amniotic fluid, or throat swabs of newborns (Table 2).[31] Pathological reports showed that there were no infectious or inflammatory changes in the placentas from pregnant patients with COVID-19 in some studies.[120] One neonate developed COVID-19 infection 36 hours after delivery.[121] Nevertheless, the results of the nucleic acid examination in umbilical cord blood and placenta were both negative for COVID-19, so vertical infection was not confirmed.[121] Two newborns were born with positive PCR results through nasopharyngeal swabs, but there was no evidence of positive culture in the placenta or other tissues, so they were considered as possible cases.[122,123] PCR positive results have been found in amniotic fluid[124] and umbilical cord blood[125] before rupture of fetal membranes during cesarean section in case reports. In other studies, viral specific IgM[126] and IgG antibodies[127] have been found to be elevated in blood of neonates after birth. However, all the throat swabs and blood samples showed negative RT-PCR results. In subsequent literature, the scholars did not consider the

Table 2 Included Studies About Vertical Transmission

Studies	Number of Tested Neonates	Neonatal Throat Swab Viral RNA	Cord Blood Viral RNA	Amniotic Fluid Viral RNA	Placenta Viral RNA	Breast Milk Viral RNA	Increased IgM (≥10 AU/mL)	Increased IgG (≥10 AU/mL)	Neonatal Blood Viral RNA
Chen et al[31]	6	–	–	–	NA	–	NA	NA	NA
Yu et al[121]	3	+	–	NA	–	NA	NA	NA	NA
Kirtsman et al[122]	1	+	NA	NA	NA	NA	NA	NA	+
Alzamora et al[123]	1	+	NA	NA	NA	NA	–	–	–
Zamaniyan et al[124]	1	+	–	+	NA	NA	NA	NA	NA
Fenizia et al[125]	31	+	+	NA	+	+	NA	NA	NA
Dong et al[126]	1	–	NA	NA	NA	NA	+	+	NA
Zeng et al[127]	6	–	NA	NA	NA	NA	+	+	–
Hosier et al[129]	1	NA	+	NA	+	NA	NA	NA	NA
Baud et al[130]	1	–	–	–	+	NA	NA	NA	–
Penfield et al[131]	11	–	NA	NA	+	NA	NA	NA	NA
Hecht et al[132]	19	NA	NA	NA	+	NA	NA	NA	NA
Menter et al[133]	5	–	–	–	+	–	NA	NA	NA
Vivanti et al[138]	1	+	NA	+	+	NA	NA	NA	+

Abbreviation: NA, non-analysed.

presence of IgM to be any evidence of vertical infection, since there are many technical issues in the detection of IgM antibody.[128]
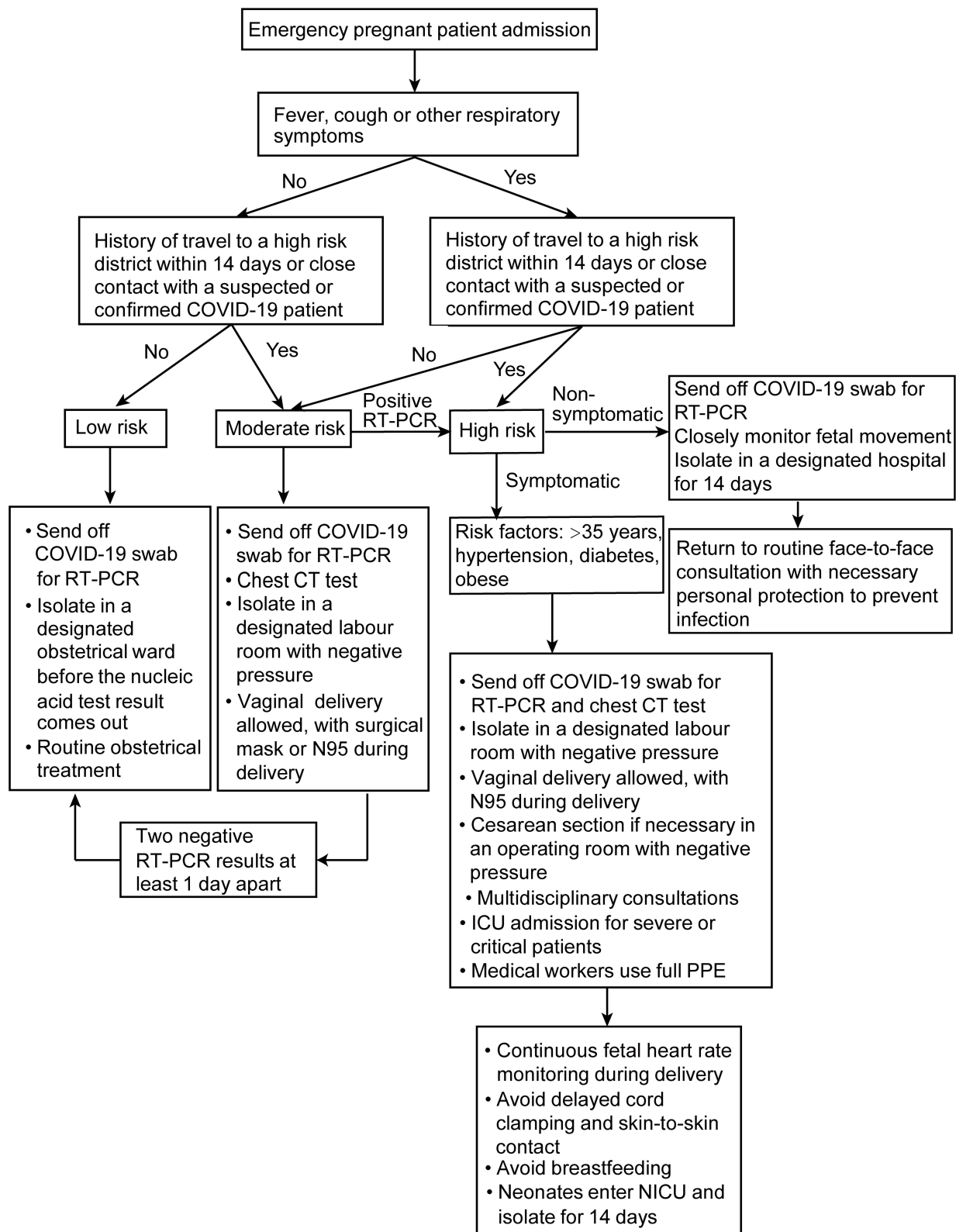
Two cases were reported at 19 and 22 weeks of pregnancy, COVID-19 viruses were detected in both placentas, and the two fetuses died.[129,130] These cases demonstrated the placental invasion of COVID-19, highlighting the seriousness of this virus among pregnant women. The possibility of virus contamination during delivery, sampling, or testing was low because samples from other tissues were all negative. No other cause of fetal death was found. In human placental tissues, the COVID-19 virus has been found by other detection methods, including PCR,[131] positive strand RNA in situ hybridization,[132,133] immunohistochemistry,[134] and electron microscopy.[135] In a systematic review involving 38 studies and 936 subjects, the authors analyzed the infection situation of newborns with positive COVID-19 mothers within 48 hours after birth, and they found that the rate of vertical transmission was 3.2% (95% CI 2.2–4.3%).[78] Up to now, the negative sense RNA representing virus replication has not been detected. The mechanism by which the virus enters the placental tissue is unclear, which may be related to placental inflammation. Further research is needed to determine whether the virus can pass through the placenta barrier.

We should be aware of the impact of viral load on the vertical transmission. Some assays have shown that more viral load of some viruses improves the possibility of vertical transmission;[136,137] however, it is not clear whether SARS-CoV-2 has the same features. A study has shown that the incidence of vertical infection was related to the severity of the maternal condition.[131] In a recent article from Alexandre et al,[138] they confirmed a case of transplacental transmission of COVID-19 infection in late pregnancy with neonatal nervous system abnormalities, which may be related to the high viral load in the placenta.

Based on the common view of Chinese experts, if the mother of the newborn is suspected or diagnosed with COVID-19, the infants should be isolated for two weeks. Our hospital is not a designated delivery center for suspected or confirmed COVID-19 patients; however, since it is a tertiary hospital, we have developed a workflow for emergency admission of pregnant women during the epidemic of COVID-19 pneumonia (Figure 1). One study found the SARS-CoV-2 virus in breast milk,[139] however, most of the other studies did not find the virus in breast milk,[31] so breastfeeding is not forbidden for suspected or confirmed patients with COVID-19.

ACE2 is a receptor of SARS-CoV-2 for human beings. The relationship between ACE2 and SARS-CoV-2 at the maternal-fetal interface is controversial. Dong et al[126] found a temporary up-regulation and elevated response of ACE2 in the placenta and generative organs of pregnant rats. However, Zeng et al[127] found that the expression of ACE2 was very low at the maternal fetal interface in the

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                    ┌─────────────────────────────────┐
                    │ Emergency pregnant patient      │
                    │ admission                       │
                    └─────────────────────────────────┘
                                    │
                    ┌─────────────────────────────────┐
                    │ Fever, cough or other respiratory│
                    │ symptoms                        │
                    └─────────────────────────────────┘
                      No                        Yes
```

Figure 1 Admission workflow of emergency pregnant patients during the epidemic of COVID-19 pneumonia in our hospital.
Abbreviations: COVID-19, novel coronavirus disease; RT-PCR, Reverse Transcription-Polymerase Chain Reaction; CT, Computed Tomography; ICU, intensive care unit; PPE, personal protective equipment; NICU, neonatal intensive care unit.

Boxes in flowchart:

- History of travel to a high risk district within 14 days or close contact with a suspected or confirmed COVID-19 patient — No / Yes
- History of travel to a high risk district within 14 days or close contact with a suspected or confirmed COVID-19 patient — No / Yes

- Low risk
- Moderate risk — Positive RT-PCR
- High risk — Non-symptomatic / Symptomatic

Send off COVID-19 swab for RT-PCR
Closely monitor fetal movement
Isolate in a designated hospital for 14 days

Return to routine face-to-face consultation with necessary personal protection to prevent infection

Low risk:
- Send off COVID-19 swab for RT-PCR
- Isolate in a designated obstetrical ward before the nucleic acid test result comes out
- Routine obstetrical treatment

Moderate risk:
- Send off COVID-19 swab for RT-PCR
- Chest CT test
- Isolate in a designated labour room with negative pressure
- Vaginal delivery allowed, with surgical mask or N95 during delivery

Two negative RT-PCR results at least 1 day apart

Risk factors: >35 years, hypertension, diabetes, obese

- Send off COVID-19 swab for RT-PCR and chest CT test
- Isolate in a designated labour room with negative pressure
- Vaginal delivery allowed, with N95 during delivery
- Cesarean section if necessary in an operating room with negative pressure
- Multidisciplinary consultations
- ICU admission for severe or critical patients
- Medical workers use full PPE

- Continuous fetal heart rate monitoring during delivery
- Avoid delayed cord clamping and skin-to-skin contact
- Avoid breastfeeding
- Neonates enter NICU and isolate for 14 days

first trimester, indicating that the placenta was not susceptible to SARS-CoV-2. This may be explained by the absence of TMPRSS2 in the placenta. The role of TMPRSS2 is to assist the SARS-CoV-2 virus in entering cells, but this is just a hypothesis.[108,128] The possible mechanism of vertical transmission of SARS-CoV-2 in pregnant women is shown in Figure 2. Besides, COVID-19 may have some other receptors in the placenta that need further study, including CD147, NRP1, and Cathepsine L-like cysteine protease proteases (CTLS).[140–142] Regarding the studies that were included in this review, there is a possibility of underestimating the problem. On the contrary, the type of publications may increase the real vulnerability of pregnant women and mothers to infection and to the disease as a consequence of the tendency to publish severe cases.

Conclusions

In a word, pregnant women infected with COVID-19 may develop into severe respiratory distress and perinatal death. Compared with non-pregnant females, pregnant women may have a higher probability of ICU admission and endotracheal intubation. The long-term prognosis is still uncertain and requires investigations in detail. Vaccines can significantly reduce the incidence of severe diseases. At present, there is no report of obvious side effects of vaccines. Therefore, pregnant and lactating women should be suggested to receive vaccination. All factors should be inspected for the benefit/risk assessment. Steroids, zinc/magnesium and plasma treatment have been employed among pregnant women with COVID-19.[100] By reducing unnecessary treatments, such as antibiotics and immunosuppressive drugs, risk stratification and detailed evaluation can promote the prognosis of mothers and infants. Symptomatic patients should be treated differently than non-symptomatic patients since the former may progress to the severe type of COVID-19. Pregnant women with related comorbidities should be given priority to the measurement of vaccinal effectiveness and security. Weight and specific comorbidities can
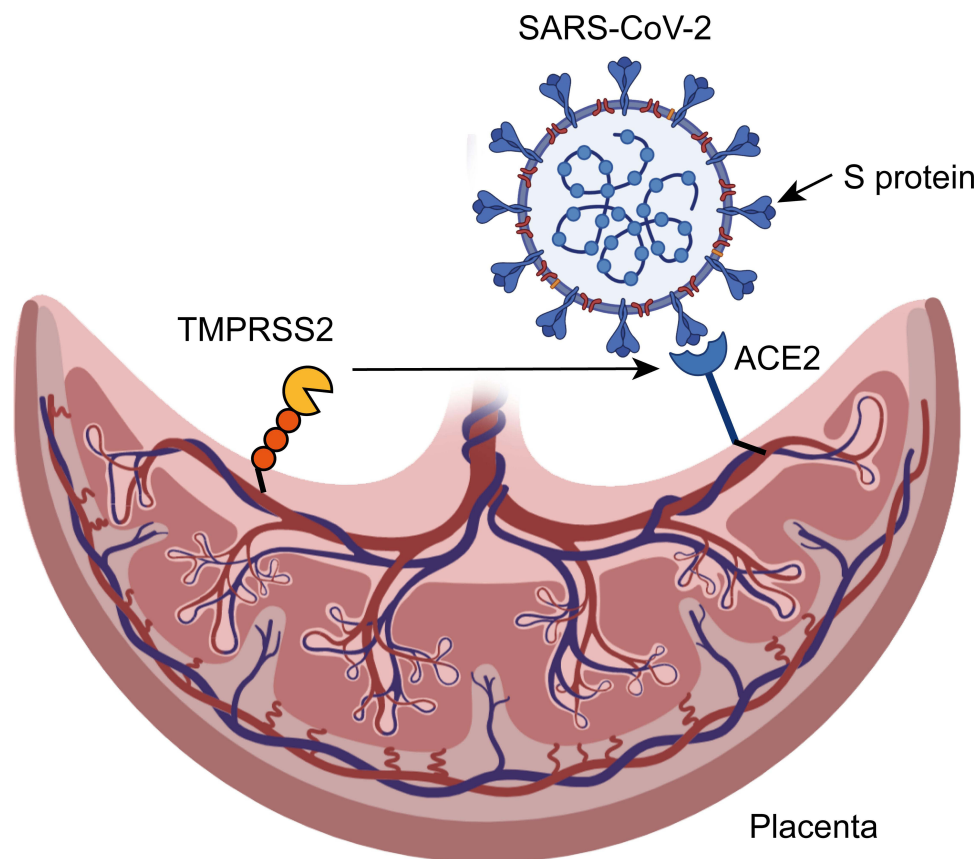
Figure 2 The possible mechanism of vertical transmission of SARS-CoV-2 in pregnant women.
Notes: In infection process, SARS-CoV-2 combines with angiotensin-converting enzyme 2 (ACE2) through sharp S protein on the surface of the virus. Afterwards, transmembrane protease serine 2 (TMPRSS2) helps the S protein of SARS-CoV-2 to enter the cell and cause infection.

be controlled before pregnancy to reduce the risk of infection in pregnancy. Pregnant women with hypertension, diabetes, obesity, and ethnic minorities should be hospitalized in time regardless of illness seriousness. As the pneumonia progresses day by day, obstetricians should be aware of the characteristics of this pneumonia in pregnant women, strengthen routine monitoring of COVID-19, identify asymptomatic pregnant women as early as possible, and properly treat pregnant women infected with COVID-19, to avoid adverse pregnancy outcomes.

Funding

Disclosure

The authors report no conflicts of interest in this work.

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