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Recommendations for the Diagnosis and Treatment of Maternal SARS-CoV-2 Infection

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread worldwide and threatened human's health. With the passing of time, the epidemiology of coronavirus disease 2019 evolves and the knowledge of SARS-CoV-2 infection accumulates. To further improve the scientific and standardized diagnosis and treatment of maternal SARS-CoV-2 infection in China, the Chinese Society of Perinatal Medicine of Chinese Medical Association commissioned leading experts to develop the Recommendations for the Diagnosis and Treatment of Maternal SARS-CoV-2 Infection under the guidance of the Maternal and Child Health Department of the National Health Commission. This recommendations includes the epidemiology, diagnosis, management, maternal care, medication treatment, care of birth and newborns, and psychological support associated with maternal SARS-CoV-2 infection. It is hoped that the recommendations will effectively help the clinical management of maternal SARS-CoV-2 infection.

Keywords: COVID-19; Diagnosis; SARS-CoV-2 ; Newborns; Pregnancy; Recommendation; Treatment

To improve the scientific basis and standardize the diagnosis and treatment of maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, under the guidance of the Maternal and Child Health Department (MCH Department) of the National Health Commission (NHC), Chinese Society of Perinatal Medicine of Chinese Medical Association commissioned leading experts to develop the recommendations hereunder. These recommendations are based on the NHC's *Diagnosis and Treatment Protocol for COVID-19 (Edition 10 for Trial)* and take into consideration the characteristics of pregnant women and newborns as vulnerable groups, as well as diagnosis and treatment experiences from home and abroad.

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Epidemiology and prognosis

As the entire population is generally susceptible to infection with SARS-CoV-2, [1] the incidence of maternal SARS-CoV-2 infection is not significantly increased compared with that of the general population.[2] However, pregnancy may exacerbate the clinical course of SARS-CoV-2 infection and therefore result in pregnant women presenting with severe disease.[3,4]

The incidence of spontaneous abortion or birth defects has not been elevated during the global coronavirus disease 2019 (COVID-19) pandemic.[5] However, fever and hypoxemia in maternal SARS-CoV-2 infection cases can increase the risk of preterm delivery, premature rupture of membranes, and abnormal fetal heart rate.[6] In cases of severe maternal SARS-CoV-2 infection, delivery can improve the symptoms of severe maternal respiratory disease; consequently, some pregnant women in the third trimester with severe or critical SARS-CoV-2 infection require delivery by cesarean section.[4,7–9] Cases of maternal SARS-CoV-2 infection with comorbidities such as chronic hypertension, preeclampsia, eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), multiple pregnancy, sepsis, shock, acute respiratory distress syndrome, and conditions with the need for assisted mechanical ventilation face increased risks of adverse fetal outcomes including stillbirth and neonatal asphyxia.[10–12]

More than 95% of neonates born to mothers with SARS-CoV-2 infection are uninfected and in a healthy condition.

Neonatal SARS-CoV-2 infections are predominantly transmitted by respiratory tract or contact with infected persons after birth.

Diagnostic criteria

Clinical manifestations of maternal SARS-CoV-2 infection

Clinical manifestations

The symptoms of maternal SARS-CoV-2 infection are similar to those of the general population, including fever, fatigue, nasal congestion, cough, myalgia, sore throat, and runny nose. Some pregnant women develop a partial or complete loss of smell and taste, conjunctivitis, and diarrhea, etc. The most common clinical symptoms are cough and fever.[13,14]

Laboratory tests

(1) Pathogenic tests: The nucleic acid/antigen test is the most common test for COVID-19. Other tests include virus isolation and detection of specific immunoglobulin M (IgM) and IgG antibodies.
(2) The following tests can be performed considering the conditions of the cases: routine blood test, routine coagulation test, cardiac enzymes, liver function, kidney function, cytokines, etc. In the early stage of infection, the total count of peripheral blood leukocytes is normal or decreased, while the lymphocyte count is decreased. Some cases may have elevated liver enzymes, lactate dehydrogenase, myosin, myoglobin, troponin, and ferritin. Most cases have elevated C-reactive protein and blood sedimentation.

Imaging examinations

Low-dose chest X-rays and computed tomography examinations are an important diagnostic basis for assessing lung injury in COVID-19 cases. These imaging examinations can be performed on pregnant women in the second or third trimester under good radiation protection.

Clinical diagnosis and classification of maternal SARS-CoV-2 infections

Diagnosis

Maternal SARS-CoV-2 infection can be diagnosed by drawing on the epidemiological history and clinical manifestations combined with the laboratory and imaging test results:
(1) presenting relevant clinical manifestations of SARS-CoV-2 infection;
(2) presenting one or more of the following pathogenic and serological results: (*a*) positive nucleic acid test for COVID-19, (*b*) positive antigen test for SARS-CoV-2, and (*c*) positive isolation and culture of SARS-CoV-2, and a convalescent SARS-CoV-2-specific IgG antibody level that is at least four times greater than that in the acute period.[13–15]

Clinical classification

(1) Mild infection: clinical symptoms are mild and there is no pulmonary infection visible on imaging examinations.
(2) Moderate infection: cases present fever and respiratory symptoms, such as persistent high fever for more than three days, or/and cough and shortness of breath, but the respiratory rate is less than 30 breaths per minute and fingertip oxygen saturation is greater than 93% when inhaling air at rest. Characteristic pneumonia manifestations of SARS-CoV-2 infection are visible on imaging tests.
(3) Severe infection: cases present any of the following conditions that cannot be explained by other causes:(*a*) respiratory distress with respiratory rate ≥30 breaths per minute, (*b*) arterial oxygen saturation ≤ 93% at rest, (*c*) arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤300 mm Hg, and (*d*) progressive exacerbation of clinical symptoms and lung imaging showing significant progression of 50% of the lesions within 24–48 hours.
(4) Critical infection: presenting one of the following conditions that cannot be explained by other causes: (*a*) respiratory failure requiring mechanical ventilation, (*b*) shock, and (*c*) other organ failure requiring intensive care unit (ICU) monitoring and treatment.[13–15]

Critical cases identification and management

Maternal SARS-CoV-2 infection may increase the risk of hospitalization and ICU admission and may even lead to death in rare cases. Severe SARS-CoV-2 infection is likely to occur if a pregnant woman has not completed the full course of COVID-19 vaccination; is of advanced maternal age; is obese; has a multiple pregnancy; has underlying conditions, such as hypertension, heart disease, chronic obstructive pulmonary disease, and diabetes mellitus; or has pregnancy complications.

In the third trimester of pregnancy, the following indicators should serve as warning signs for exacerbation of the condition and for possible severe illness: progressive exacerbation of hypoxemia or respiratory distress; exacerbation of tissue oxygenation indicators (e.g., fingertip oxygen saturation, oxygenation index) or progressive elevation of lactate; progressive decrease of peripheral blood lymphocyte count, or progressive elevation of inflammatory factors, such as interleukin 6, C-reactive protein, and ferritin; and significant elevation of coagulation-related indicators, such as D-dimer.[16]

Maternal care

Self-monitoring

Pregnant women with SARS-CoV-2 infection should pay attention to self-monitoring while adopting the precautionary measures for preventing the spread of infection.[17] They should monitor their body temperature, heart rate, blood pressure, and the presence of respiratory tract infection symptoms. If possible, peripheral oxygen saturation can also be monitored.[5,18] Pregnant women in the third trimester need to pay attention to fetal movement.

In the following cases, pregnant women with a SARS-CoV-2 infection should seek medical assistance promptly if symptoms are not relieved with symptomatic treatment, there is serious discomfort such as persistent high fever (peak body temperature at 39 °C and above for more than three days), dyspnea, dizziness or worsening headache, heart palpitations, and confusion,[19–21] or if there are abnormal or absent fetal movements or symptoms such as vaginal bleeding or discharge, abdominal pain, and elevated blood pressure.[22,23]

Principles and time points of antenatal care checkups

According to the specific situation of the individual, the dates of antenatal care examinations can be rescheduled if necessary. However, the key dates for some examinations such as NT ultrasound, Down syndrome screening, and midpregnancy

anomaly scan should be confirmed based on communication with the antenatal care hospital and doctor.

The following cases require outpatient consultation: (1) when the symptoms of SARS-CoV-2 infection are severe or not relieved by symptomatic treatment, (2) antenatal care examinations that cannot be rescheduled due to time constraints, and (3) when there are obstetric indications such as abnormal or absent fetal movement, vaginal bleeding or vaginal discharge, abdominal pain, and elevated blood pressure, etc.

Pregnant women should wear N95 masks as standard when they visit the doctor and try to make appointments for registration and examination through online channels, where possible, and may seek doctors' advice through the online platforms, if available and feasible.

Use of medications for the treatment of COVID-19

Symptomatic treatment

Symptomatic treatment of maternal SARS-CoV-2 infection should weigh the pros and cons and carefully consider the effects on the mother, embryo, fetus, newborn, and breastfed infant (Table 1).[24–26]

If using compounded cold medicines, the total daily amount of paracetamol should not exceed 2 g/d. Because some compounded cold medicines contain ingredients that are not recommended for use during pregnancy and lactation (e.g., amantadine and pseudoephedrine), it is recommended to select a single-ingredient medicine for symptomatic treatment during pregnancy and lactation.

In the case of traditional Chinese medicine, the principles of treatment based on syndrome differentiation should be followed for personalized medication. The medications contraindicated for pregnancy should be avoided where possible. If the patient's condition requires such medication, it should only be used after obtaining informed consent from the patient, and the dosage and duration of the medication should be strictly managed to avoid adverse effects on the fetus and fetal movement. The use of antibiotics is generally not advised. In the event of a bacterial coinfection, appropriate antibiotics should be selected under the guidance of doctors to avoid inappropriate or irrational use, especially the combined use of broad-spectrum antibiotics.

Antiviral treatment

Antiviral drugs can reduce the risk of progression to severe disease in patients with mild to moderate SARS-CoV-2 infection who have high-risk factors for disease progression. The NHC's *Diagnosis and Treatment Protocol for COVID-19 (Edition 10 for Trial)* recommends oral antiviral drugs including a nirmatrelvir/ritonavir (NMV/r) combination, azvudine tablets, and molnupiravir capsules.[27]

The NMV/r combination is indicated for adult patients with mild to moderate SARS-CoV-2 infection within five days of onset and who have high-risk factors for progression to severe disease. Dosage: nirmatrelvir 300 mg should be administered concurrently with ritonavir 100 mg every 12 hours for five days. It should be used for pregnant women only if the potential benefits to the pregnant woman outweigh the potential risk to the fetus. If used during breastfeeding, breastfeeding should be suspended during treatment and for seven days after treatment. The dosage of NMV/r should be reduced by half in patients with moderate renal impairment, and it is contraindicated for those with severe liver or renal impairment. The instructions of the NMV/r combination should be read carefully before use and drug interactions should be noted when it is used in combination with other medications.

The use of azivudine tablets and molnupiravir capsules is not recommended for pregnant and lactating women.

Table 1

Symptomatic treatment of SARS-CoV-2 infection.

Symptoms	Generic name of the drug	Pregnancy	Lactation	Common usage and dosage*
Fever/sore throat/myalgia	Paracetamol	Safe to use	Safe to use	Oral: 0.5 g once for fever or pain; can be repeated after 4 to 6 h if fever or pain persists. Total dose should not exceed 2 g in 24 h
	Ibuprofen†	Contraindicated for the first and third trimesters; Safe to use (not to exceed 48 h) in the second trimester	Safe to use	Oral: 0.2 g once for fever or pain; can be repeated after 6–8 h if fever or pain persists. Do not exceed 4 doses per 24 h
Dry cough	Dextromethorphan	Contraindicated for the first trimester	Safe to use	Oral: 15–30 mg once, 3–4 times a day
Cough with phlegm	Acetylcysteine	Safe to use	Safe to use	Oral: 0.2 g once, 3 times a day; Nebulization: 0.3 g once, 1–2 times a day for 5–10 d
	Guaifenesin	Contraindicated for the first trimester	Safe to use	Oral: 0.2 g once, 3–4 times a day
	Ambroxol	Contraindicated for the first trimester	Safe to use	Oral: 30–60 mg once, 3 times a day
Runny nose/nasal congestion	Loratadine	Safe to use	Safe to use	Oral: 10 mg, once a day
	Cetirizine	Safe to use	Safe to use	Oral: 10 mg, once a day
	Chlorpheniramine	Safe to use	Safe to use	Oral: 4 mg once, 1–3 times a day
	Sea water/sea salt water nasal spray	Safe to use	Safe to use	Nasal spray: 1–2 times a day, or as needed
Diarrhea	Oral rehydration salts	Safe to use	Safe to use	Oral: dissolved as directed and taken orally at any time
	Montmorillonite powder	Safe to use	Safe to use	Oral: 3 g once, 3 times a day
	Probiotics	Safe to use	Safe to use	Oral: used according to the specific instructions

*Drugs have different dosages and specifications, so please refer to the drug instructions for specific usage and dosage.

†Some domestic drug instructions recommend contraindication for pregnant and lactating women. *Briggs Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk (12th Edition)* states that human data on the use of ibuprofen in the first and third trimesters indicate a risk but that it can be used during lactation.

h: Hours; d: Days.

Consultation, referral, and management of hospitalized pregnant women

Hospitalized pregnant women with COVID-19 should have their obstetric conditions managed according to the principles of obstetric care, but additional attention should be paid to the SARS-CoV-2 infection, being aware of the progression of the disease and detecting abnormal cardiopulmonary functions and unstable vital signs in a timely manner.[28,29] For women with severe or critical SARS-CoV-2 infections, medications that are safer for pregnant and lactating women should be selected for treatment under the guidance of a multidisciplinary team. In the event that high-risk pregnant women and preterm newborns are in an unstable, severe, or critical condition and the current medical institution does not have an ICU or the capacity to provide multidisciplinary consultation, then the patients can be referred to a medical center specializing in critically ill pregnant women and newborns, which can provide emergency care based on local referral policies.

Hospital birth

Selection of delivery method

For pregnant women with severe and critical SARS-CoV-2 infection, a multidisciplinary treatment team should jointly decide the timing and method of delivery, focusing on assessing the classification, duration, severity, and risk factors of the SARS-CoV-2 infection in pregnant women.

The timing of delivery depends on the health status, complications, and gestational age of the pregnant woman, the condition of the fetus, and the emergency care capacity of the local hospitals. In pregnant women with mild SARS-CoV-2 infection and indications for pregnancy termination, if conditions allow, delivery can be performed after recovery from the infection. For pregnant women with a critical SARS-CoV-2 infection and with refractory hypoxemia, respiratory failure, or exacerbating conditions, the timing of delivery requires careful weighing of maternal and fetal benefits and risks, and full communication between obstetricians, pediatricians, maternal-fetal medicine specialists, and critical care teams.[30]

Special management during labor and 2 hours after delivery

During the first stage of labor, vital signs should be closely monitored, with special emphasis on blood pressure and blood oxygen monitoring, dynamic assessment of the risk of progression to severe and critical conditions, and the provision of emotional and psychological support to the pregnant woman. If feasible, family members should be allowed to accompany pregnant women.

During the second stage of labor, repeated labored breathing and fecal incontinence increase the risk of viral transmission. Therefore, it is recommended to strengthen the personal protection of the health workers during this stage.

During the third stage of labor, postpartum hemorrhage should be prevented. Prompt postpartum assessment of thrombotic risk is required, and anticoagulation therapy should be administered if necessary. Severe and critical cases of COVID-19 often have coagulation disorders, an increased risk of venous thromboembolism, and even pulmonary embolism and sudden death. The decision to use anticoagulation therapy should be based on the specific condition of individual patients.[31] Asymptomatic and mild cases of COVID-19 without other risk factors for thrombosis do not require anticoagulation; severe and critical cases without contraindications to anticoagulation are recommended to receive prophylactic doses of anticoagulation; if no other thrombotic risk exists, anticoagulation can be discontinued after hospital discharge.

Anesthesia and analgesia in cesarean section delivery

SARS-CoV-2 infection is not a contraindication to intraspinal anesthesia and labor analgesia. Labor analgesia can reduce oxygen consumption and the burden on cardiopulmonary function through pain relief. The management of pain in labor also improves the tidal volume of pregnant women, reduces hyperventilation due to pain and anxiety, and reduces the risk of viral transmission. For vaginal delivery or cesarean section delivery, intraspinal anesthesia or analgesia is the preferred labor analgesia in the absence of contraindications to intralesional anesthesia or obstetric contraindications. A thorough assessment of the patient's conditions should be performed, with particular attention to coagulation functions, in addition to respiratory, circulatory, and hepatic and renal function assessment.

General anesthesia should be selected when there is a contraindication to intraspinal anesthesia, an emergency situation, or a severe infection inhibiting the maintenance of adequate oxygenation. A central venous catheter and radial artery catheter should be placed preoperatively according to the needs of the pregnant woman, and close intraoperative monitoring of circulation, respiration, depth of anesthesia, and urine output should be performed. A lung-protective ventilation strategy is recommended, with the additional use of positive end-expiratory pressure or recruitment maneuver to prevent intraoperative pulmonary atelectasis; lidocaine, remifentanil, or dexmedetomidine can be administered during tracheal extubation to avoid choking, and wet gauze can be used to cover the nose and mouth during tracheal extubation to reduce the expulsion of secretions. Regardless of the type of anesthesia used, attention should be paid to monitoring oxygen saturation and maintaining stable blood pressure.[32]

Care of infants born to women with SARS-CoV-2 infection

Feeding

Breastmilk is the preferred food for infants, and breastmilk itself does not transmit virus.[22,33] If rooming-in is practiced, the mother needs to ensure thorough personal protection before breastfeeding, including wearing a mask, washing her hands, and cleaning her breasts. If the mother and infant are separated, breastmilk can be expressed by the mother and then be fed by the caregiver to the infant. The mother should be trained on how to maintain lactation when the mother and infant are separated; the mother should also maintain good personal hygiene such as washing hands and cleaning breasts before expressing breastmilk, and the breast pump should be cleaned and disinfected after use.

Rooming-in of the newborn and the mother

The incidence of postpartum anxiety and depression increases during SARS-CoV-2 infection, and prolonged mother-infant separation can have adverse effects on mothers and infants. Therefore, unnecessary mother-infant separation should be

minimized and mother-infant contact should be allowed on the basis of appropriate protective measures.[34,35] This will promote mother-infant interaction and the establishment of attachment.

After a newborn is delivered from a pregnant woman with COVID-19, a neonatologist should conduct a timely health assessment on the infant. If the newborn is in a good general condition and the mother has apparent manifestation of SARS-CoV-2 infection, temporary separation of the mother and infant may be recommended; if the newborn is in a good general condition and the mother is stable, rooming-in can be practiced, but the conditions of the mother and infant should be observed. Simultaneously, the mother and accompanying family members must wear N95 masks and be informed of the necessary precautions through effective health education.[36]

Key principles in the management of newborns with SARS-CoV-2 infection

Delayed clamping of the umbilical cord, timely cleaning, and assessment of the SARS-CoV-2 infection status should be performed on the newborn immediately after delivery.[37] Respiratory specimens of the newborn taken within 24 hours after birth can be contaminated by the amniotic fluid or vaginal secretions of the mother. Therefore, if nucleic acid or antigen testing is needed, the first test can be performed 24 to 72 hours after birth, depending on the situation of the newborn. If the newborn is exposed to caregivers infected with COVID-19 and develops clinical symptoms such as fever, feeding intolerance, nasal congestion, runny nose, cough, shortness of breath, vomiting, and diarrhea, they should be tested for nucleic acid to confirm the SARS-CoV-2 infection. Once confirmed, the infected infant may be transferred to the neonatal ward for treatment.

COVID-19 vaccination is not recommended for the newborns at present.

Puerperal care

In cases of maternal SARS-CoV-2 infection, mild or asymptomatic individuals who recover well from delivery can be discharged when their temperature is normal for more than 24 hours. If there are pulmonary imaging abnormalities, patients can be discharged when their acute exudative lesions are significantly improved and there are no other complications.[38]

After discharge, in addition to routine obstetric follow-ups, attention should be paid to the presence of high-risk factors for the progression to severe SARS-CoV-2 infection; these factors include postpartum hemorrhage, fatigue, gestational anemia, and concomitant underlying conditions such as obesity and hypertension. Attention should also be paid to the onset or exacerbation of dyspnea, and the onset of neurological symptoms such as dizziness and confusion. Oxygen saturation should be monitored if necessary. Health education should be provided, and the mothers should be advised to take sufficient rest, ensure adequate nutritional intake, and perform necessary monitoring, etc.

In cases of puerperal fever, the mother should receive timely screening and diagnosis of SARS-CoV-2 infection,[39] and the condition needs to be differentiated from common puerperal infections, such as endometritis, surgical site infection, mastitis, influenza, pyelonephritis, and other viral or bacterial respiratory infections. Although assessment of symptoms, physical examination, and laboratory testing can usually differentiate these infections, the possibility of coinfection should be considered.

Psychological guidance and support

As pregnant women are in a unique physiological and psychological period, psychological disorders may increase among cases of maternal SARS-CoV-2 infection, such disorders predominantly manifest as insomnia, anxiety (including panic attacks), depression, hypochondria, and compulsion, etc. Screening and intervention for psychological symptoms of pregnant women should be performed according to the relevant guidelines. For the at-risk pregnant women, such as those with a previous history of depression or anxiety or a family history of mental illness, obstetricians and psychologists can provide maternal care education through online and offline channels; this information can include maternal care messages, the examinations of antenatal care for different gestational age, and the necessary precautions during delivery.

Pregnant women should pay timely visits to psychology and obstetrics outpatient clinics to receive the corresponding level of multidisciplinary consultation and treatment. For pregnant women with mild psychological disorders, the obstetricians and psychologists should cooperate to provide timely nonpharmacological interventions. Pregnant women with moderate or severe psychological disorders can receive in-patient care in specialized wards and specialized hospitals, and the multidisciplinary team psychological consultation and treatment model should be activated to provide nonpharmacological and/or pharmacological interventions. Any pharmacological interventions should consider the safety categories for the use of psychiatric drugs during pregnancy and the condition of each pregnant woman.[40]

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Conflicts of Interest

None.

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