Severe acute respiratory syndrome coronavirus-2 and the deduction effect of angiotensin-converting enzyme 2 in pregnancy

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Abstract: The 2019 novel coronavirus (2019-nCoV, later named SARS-CoV-2) is a pandemic disease worldwide. The spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is continuing at a rapid speed. Till May 4, 2020, there have been 3,407,747 confirmed cases and 238,198 deaths globally. The common symptoms in pregnant women are fever, cough, and dyspnea. Angiotensin-converting enzyme 2 (ACE2) has transient overexpression and increased activity during pregnancy, which is now confirmed as the receptor of SARS-CoV-2 and plays essential roles in human infection and transmission. There is no evidence that pregnant women are more susceptible to SARS-CoV-2. To date, there is no valid medication or vaccination. The immune suppression or modulation during pregnancy increases the risk of severe pneumonia. Remdesivir is an antiviral medication targeting ribonucleic acid (RNA) synthesis that has clinical improvement in the treatment of SARS-CoV-2. Chloroquine is controversial in its effectiveness and safety to treat SARS-CoV-2. Remdesivir is safe in pregnancy. Chloroquine has not been formally assigned to a pregnancy category by the Food and Drug Administration (FDA). The management strategy includes monitoring fetal heart rate and uterine contractions; early oxygenation if O_2 saturation is less than 95%; empiric antibiotics for prevention of secondary infection; corticosteroid to treat maternal SARS-CoV-2 disease routinely is not suggested, only for fetal lung maturation in selected cases; and consideration of delivery is according to the obstetric indication, gestational age, and severity of the disease. During epidemics, delivery at 32–34 weeks is considered. The indication for the Cesarean section should be flexible to minimize the risk of infection during the delivery. The newborn should be in isolation ward immediately after birth; breastfeeding is not contraindicated but should avoid direct transmission infection.

Keywords: Angiotensin-converting enzyme 2 (ACE2); Antiviral medication; Pregnancy; Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

1. INTRODUCTION

In December 2019, a series of pneumonia with unknown origin was noted in Wuhan, Hubei province, China.[1–5] The Chinese Academy of Engineering announced the source was a novel coronavirus named 2019-new coronavirus (2019-nCoV) by World Health Organization (WHO), later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[6] According to WHO statistics, there were 3,272,202 people infected with 2019-nCoV and 230,104 people died from the disease globally till May 02, 2020. Coronaviruses (CoVs) are enveloped single-strand RNA viruses. There are four genera, alpha CoV, beta CoV, gamma CoV, and delta CoV.[7–9] Before this epidemic of 2019-nCoV, there were six human coronaviruses identified, four of which are in circulation, which causes mild respiratory tract infection. The other two were SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV), which had epidemic pneumonia in 2002 and 2012, respectively.[10] Pregnant women may be infected with such serious respiratory disease, and we here review a limited cases series of pregnant women with SARS and MERS, which can be helpful for pregnant women who are infected with SARS-CoV-2.[11–30]

2. SARS AND MERS IN PREGNANCY

Severe acute respiratory syndrome (SARS) caused by SARS coronavirus (SARS-CoV) erupted in November 2002 in Guangdong province, China. The epidemic occurred in China, Hong-Kong,

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Taiwan, Singapore, and Vietnam. A total of 8098 people were infected, with 774 deaths globally. It was transmitted by respiratory droplets and presented with fever (99%–100%), dry cough (57%–75%), and myalgia (45%–61%).[11,12] The mean incubation period was 4–6 days. Overall, case fatality ratio was approximately 15%.[13–15]

A multicenter observational study in Hong Kong reported outcomes of 12 pregnant women who were infected with SARS-CoV in 2003.[15,16] Three pregnant women died. Seven women were in the first trimester, and four had a spontaneous abortion. Five women were more than 24 weeks of gestational age, and four had preterm delivery. Two of the pregnant women recovered from SARS but had intrauterine growth restriction of the ongoing pregnancy. None of the newborn babies had SARS. Fatality rate (25%), intensive care unit (ICU) admission rate (50%), and mechanical ventilation rate (33%) were higher than nonpregnant women. The pregnant women were treated with broad-spectrum antibiotics, and in severe cases, ribavirin was used.[16] However, ribavirin has a teratogenic effect in animal.[26] Women who are in early pregnancy should consider termination with treating of ribavirin. In a study of placental pathology of patients, there was increased intervillous or subchorionic fibrin and extensive fetal thrombotic vasculopathy, which may result due to the hypoxic respiratory disease.[27–29] Nevertheless, villitis, which is the evidence of maternal hematogenous infection that transmit to the fetus, was not found.[27,30]

MERS is a respiratory disease produced by MERS coronavirus. Since September 2012, 2494 people were diagnosed with MERS coronavirus (MERS-CoV), causing 858 deaths (from WHO).[23] Clinical symptoms vary from mild to severe. They usually begin with fever, cough, chills, sore throat, myalgia, and arthralgia, with rapid progress to dyspnea and pneumonia in the first week (epidemic and emerging coronavirus, SARS, and MERS). The mean incubation period was 5.2 days; the fatality rate was 34.4%. A study reviewed 11 pregnant women infected with MERS-CoV; all the pregnant women were symptomatic, six (54%) patients were admitted to ICU, three (27%) patients died during the hospitalization, and three (27%) infants died.[24,25]

3. SARS-COV-2 AND ANGIOTENSIN-CONVERTING ENZYME 2 IN PREGNANCY

The immunologic change in pregnancy may increase the susceptibility to pathogens.[15,31,32] Pneumonia in pregnant women is more frequent and more severe than in nonpregnant women.[33] About 25% of pregnant women who have pneumonia need mechanical ventilation.[34]

A total of 70 pregnant women with SARS-CoV-2 were eligible for the systematic review.[15,22,35–40] The common symptoms are fever (84%), cough (28%), and dyspnea (18%). Obstetric complications include preterm birth (39%), intrauterine growth restriction (10%), and miscarriage (2%).[22] This study included nine SARS-CoV-2-infected pregnant women in Wuhan, whose amniotic fluid, cord blood, neonatal throat swab, and breast milk were collected. All of the specimens were negative for SARS-CoV-2, which indicates no evidence of vertical transmission.[40] But a study indicated that angiotensin-converting enzyme 2 (ACE2), which is the receptor of SARS-CoV-2, was highly expressed in maternal–fetal interface cells, suggesting the possibility of vertical transmission.[41] More studies to clarify the role of ACE2 in pregnancy are warranted.[42]

The renin–angiotensin system (RAS), or renin–angiotensin–aldosterone system (RAAS), is a hormone system that regulates electrolyte balance, as well as systemic vascular resistance.[43–45] A gradual increase in the different components of the RAS in pregnancy is a physiological condition for maternal–fetal circulation. The effects of the stimulated RAS in normal pregnancy are incompletely realized.[46]

ACE2 is the receptor of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2.[44,45,47] The ACE cleaves angiotensin I to angiotensin II. ACE2 was first identified in the year 2000, which converts angiotensin I to angiotensin 1–9 and angiotensin II to angiotensin 1–7. ACE2 is a negative regulator in the RAAS. It provides a binding site for the S-protein of coronavirus.[48,49] There was structural evidence that the SARS-CoV-2 S protein has a higher affinity to ACE2 than the SARS-CoV S protein.[50] Although ACE2 is the receptor of SARS-CoV-2, it plays a protective role in acute lung injury.[51] Local activation of the RAAS responses to viral insults in pregnancy may mediate vasoconstriction, acute lung injury, adverse myocardial remodeling, preterm birth, intrauterine growth restriction, and miscarriage.[22,52,53] Studies proposed that ACE2 has transient overexpression and increased activity during pregnancy, especially in the placenta.[46,54,55] But if pregnant women are more susceptible to SARS-CoV-2 is currently not known. We proposed the deduction effect of ACE2 in pregnancy (Fig. 1).

4. TREATMENT AND MANAGEMENT

Antiviral medications remdesivir and chloroquine effectively inhibited SARS-CoV-2 *in vitro*.[56] Remdesivir is an antiviral medication targeting RNA synthesis that is used to treat Ebola, SARS, and MERS. A study had used remdesivir on 53 patients with SARS-CoV-2, of which 68% had clinical improvement.[57,58] It is also found to be safe in pregnancy.[59] Chloroquine is an antimalarial drug and sometimes used to treat autoimmune disease. Clinical studies on the use chloroquine to treat SARS-CoV-2 in more than 10 hospitals in China found efficacy in treatment pneumonia.[60] However, a systemic review study had a conservative attitude.[38] Some experts proposed that chloroquine use in SARS-CoV-2 is premature and harmful.[61] It is controversial if chloroquine is effective and safe to treat SARS-CoV-2. However, a large-scale study demonstrated the safety of chloroquine in pregnancy.[62–64] Pregnant women with SARS-CoV-2 infection are considered relatively high risk. The management strategy is shown below.[22,65–68]

- Monitoring fetal heart rate and uterine contractions closely.
- Early oxygenation is considered; if O_2 saturation is less than 95%, mechanical ventilation may be used.
- Empiric antibiotics for prevention of secondary infection.
- Corticosteroid to treat maternal SARS-CoV-2 infection routinely is not suggested, but for fetal lung, maturation is considered by case.
- Consideration of delivery is according to the obstetric indication, gestational age, and severity of the disease, if there are no obstetric indications, and if the maternal infection is critical, early delivery is considered. During such epidemics, delivery at 32–34 weeks is considered. The indication for the cesarean section should be flexible to minimize the risk of infection during the delivery.
- The newborn should be in isolation ward immediately after delivery; breastfeeding is not contraindicated but should avoid direct infection (Fig. 2).

SARS-CoV-2 is an ongoing disease. There is no valid medicine and vaccine for the disease; pregnant women have physiologic changes and immunologically susceptible to infectious disease. Besides, consideration of the safety of the fetus makes the treatment more difficult. The experience of pregnant women in SARS-CoV-2 is limited.

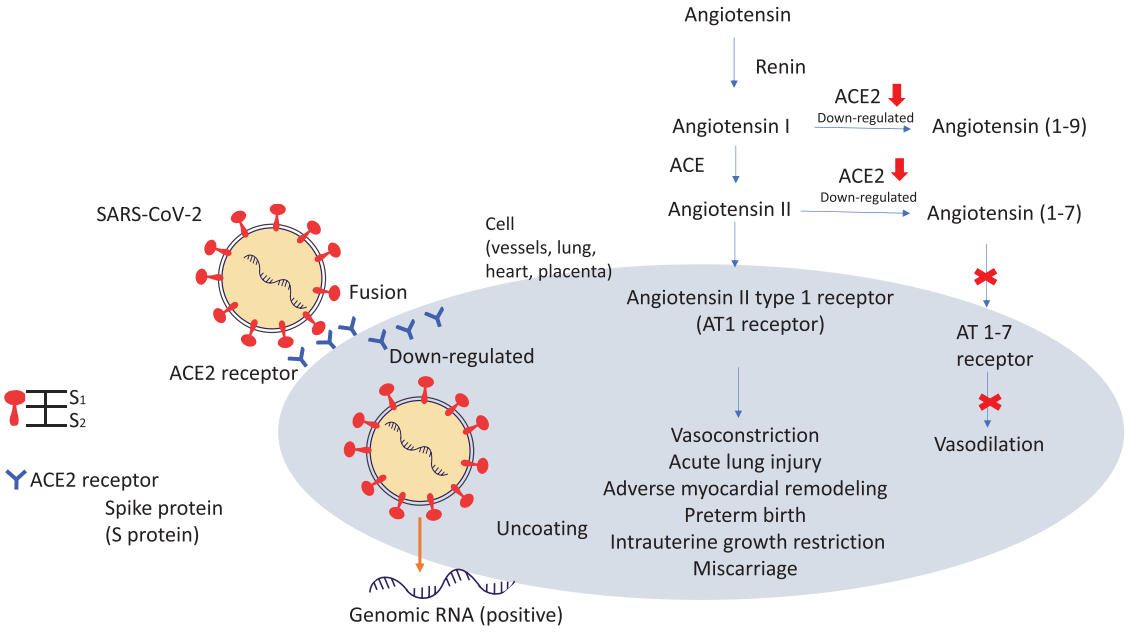

Fig. 1 The interaction between SARS-CoV-2 and the renin-angiotensin system. The SARS-CoV-2 spike protein binding to the ACE2 receptor; S1 subunit binds to host cell and S2 subunit triggers the fusion of the viral envelope and target cell. After entry of the virus particle, surface ACE2 is further downregulated, resulting in unrestrained angiotensin II accumulation.

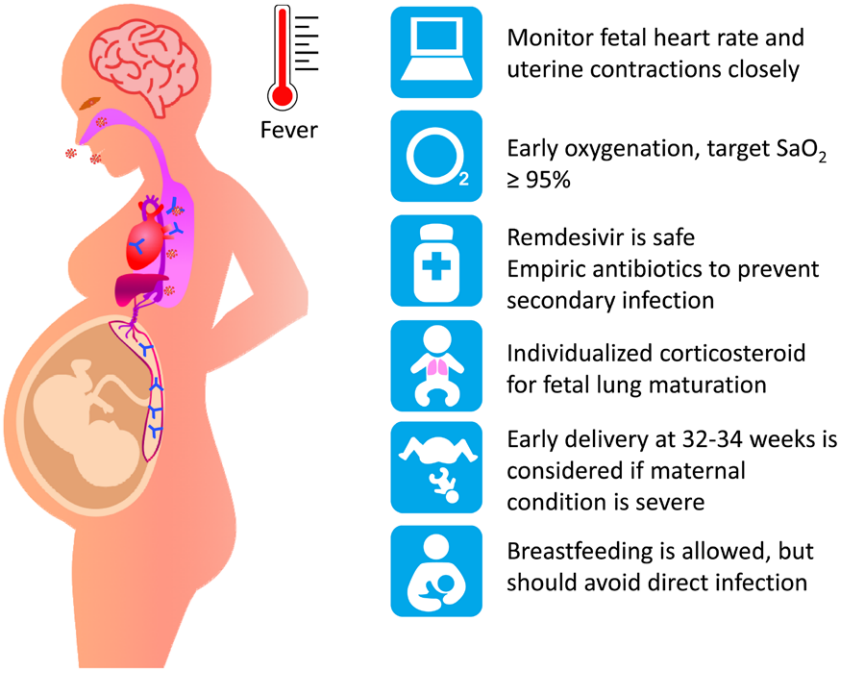

Fig. 2 The transmission pathway and the management of SARS-CoV-2 in pregnancy.

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