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Pregnancy with COVID-19: Management considerations for care of severe and critically ill cases

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Abstract

Pregnant women are a potentially highly vulnerable population due to anatomical, physiological, and immunological changes under the COVID-19 pandemic. Issues related to pregnancy with COVID-19 attracted widespread attention from researchers. A large number of articles were published aiming to elaborate clinical characteristics and outcomes of pregnant women infected with COVID-19, in order to provide evidence for management. The existing data suggest that the overall prognosis of pregnancy with COVID-19 is promising when compared with that of other previous coronaviruses. There is still maternal morbidity and mortality related to COVID-19 reported. However, the optimal management of severe and critically ill cases of COVID-19–infected pregnancy is poorly clarified. The possibility of postpartum exacerbation in pregnancy with COVID-19 is also worthy of attention for obstetricians. This review makes further elaboration of the above issues.

KEYWORDS

COVID-19, Critically ill, Postpartum exacerbation, Pregnancy, Severe

1 | INTRODUCTION

Since the end of 2019, the coronavirus disease 2019 (COVID-19) has been spreading globally, causing over 340 000 deaths.[1] Based on the previous knowledge of two notable coronavirus outbreaks, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), it is suggested that pregnant women are particularly susceptible to adverse outcomes, including the need for endotracheal intubation, admission to an intensive care unit (ICU), acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and even death.[2-4] Also, there is combined with a high incidence of adverse fetal outcomes, including stillbirth, fetal growth restriction, and preterm birth. However, current research suggests that maternal severity with COVID-19 is similar to that of non-pregnant women, with a rate of severe pneumonia at 0%-18%.[5,6] A few critically ill cases have also been reported, causing maternal death and fetal loss. This may indicate that the effect of novel coronavirus (COVID-19) infection on pregnant women may be different from that of SARS and MERS. It is well known that most pregnancy complications, such as hypertensive disorders of pregnancy, will be relieved after the termination of pregnancy. But for COVID-19, we found that postpartum exacerbation presented due to short-term pathophysiological changes immediately after delivery.[7] Gestational weeks of infection, the maturity of the fetus, disease severity, and postpartum exacerbation make the management of severe and critically ill cases of pregnant women with COVID-19 more difficult. This article is mainly to explore those issues and make some clinical suggestions.

2 | THE SEVERITY OF DISEASE IN PREGNANCY WITH COVID-19

As all we know, pregnant women may be more susceptible to respiratory pathogens and pneumonia in pregnancy compared with non-pregnant women due to the physiological adaptations of pregnancy,

such as diaphragmatic elevation, edema of the respiratory tract mucosa, and increased oxygen consumption, as well as pregnancy-related immune alterations.[8-11] These adaptive changes also make women less tolerant of hypoxia.

Over the last several decades, it has been shown that coronaviruses and influenza viruses can cause severe respiratory disease in pregnant women with a high fatality rate. For example, the mortality rate for pregnant women infected with influenza during the 1918 pandemic was 27%.[12] Similarly, regarding the SARS virus, the mortality rate for the general population was 10%, while the maternal rate was 25%, and 33% need mechanical ventilation.[2] In the H1N1 2009 influenza virus outbreak, pregnant women were four times more likely to be hospitalized and were at increased risk of complications when compared to the general population.[13]

However, based on available reports from different countries so far, it seems that SARS-nCoV-2 does not follow the same pathogenic pattern. In the correspondence we published previously,[7] the information of 118 infected pregnant women in Wuhan from the epidemic reporting system of the National Health Commission showed a rate of severe maternal disease at 7.6%. Another report from China which collected data of 116 infected pregnant women came to the same conclusion with a relatively lower severe disease rate (6.9%).[14] In a recently published article from New York City,[15] Breslin et al reported that among 43 pregnant women confirmed with COVID-19, the estimated rate of severe maternal disease approximated that of the non-pregnant population at 9.3%. COVID-19 does not appear to have a higher risk of severe disease in pregnancy than in the general population. However, although there are limited but several reports of severe and critically ill cases with COVID-19. One report from China[16] described a gravida at 34 weeks with severe COVID-19 pneumonia who was performed cesarean section for stillbirth and deteriorated with requiring extracorporeal membrane oxygenation (ECMO). Another report from Iran[17] still described 9 critically ill patients infected with COVID-19, of which 7 cases of maternal deaths and 4 cases of pregnancy loss (stillbirth or neonatal death). These reports suggest that SARS-nCoV-2 infection still has the potential to cause maternal death and adverse outcomes, despite encouraging early experiences, which deserves the attention of obstetricians.

In addition, it is worth noting that asymptomatic infections are presented in pregnant women. Sutton et al[18] conducted a universal screening for SARS-CoV-2 in women admitted for delivery in a hospital of New York City, and showed an asymptomatic infectious rate at 13.7% (among 210 patients). In the report from Breslin et al,[15] 14 (32.6%) of 43 pregnant women were asymptomatic with a positive result of SARS-CoV-2. During the pandemic, maternity care delivered has remained a high priority and pregnant women had to visit doctors for obstetric factors. The presence of asymptomatic infections reminds obstetricians to consider a reasonable screen test to guide the management of pregnancy with COVID-19.

3 | CONSIDERATIONS ON THE DELIVERY MANAGEMENT FOR SEVERE AND CRITICALLY ILL CASES

One of the most difficult yet crucial issues of the management is the determination of delivery timing, especially in the severe and critically ill cases. In the review of the literature, He et al[16] reported a case admitted at 34 weeks gestation with severe COVID-19 pneumonia in Guangdong, China. What is remarkable is the rapid speed of disease development of COVID-19 in the severe and critical cases. In this case, the fetal heart rate pattern was reassuring 2 hours before operation without evidence of hypoxia. At the same time, the maternal blood gas analysis showed hypoxemia with balanced acid-base status. After 2 hours, the operation was performed with a severe asphyxia baby born (Apgar score at 1 minute was 1). The neonate cord blood gas analysis suggested severe metabolic acidosis with a pH value of 6.56. Similarly, the mother developed acidosis 30 minutes after the beginning of operation according to blood gas analysis (pH 7.13). The baby died of severe asphyxia and acidosis which may relate to the mother's rapidly progressing respiratory failure and metabolic disorders. A similar situation also occurred in a critically ill case confirmed with COVID-19 reported by Schnettler et al[19] from Cincinnati, USA, with the development of severe COVID-19 ARDS within 10 hours of admission. Hantoushzadeh et al[17] from Iran presented 9 critically ill cases with 7 maternal deaths. Among them, 6 patients progressed to require mechanical ventilation within 1 week of onset, which highlighted the rapidity of COVID-19 infection in pregnancy. Based on the above limited reports, we learned that for some severe cases, after the onset of disease, they may progress to require mechanical ventilation and intensive care, even result in maternal death within a very short time (1 to 2 weeks).[20] The incidence of fetal or neonatal death was quite high in critically ill cases. This rapidly progressing ARDS puts the fetus at great risk. Therefore, the time window left for us to decide to terminate the pregnancy is relatively short, which also brings great difficulties to our decision-making. Therefore, we recommend to organize a multidisciplinary team in a short period of time after maternal hypoxemia occurs, to assess fetal maturity combined with the evaluation of progression speed of the disease, and make a decision of delivery in time.

It is commonly accepted, based on extremely limited data, that delivery does not improve the respiratory status of pregnant patients with acute respiratory failure.[21] In cases which the fetus is not mature enough to survive, especially less than 24 weeks, and the maternal cardiopulmonary conditions are unstable, the decision to proceed toward delivery may be deferred to avoid the mother's condition deteriorated furtherly. If the pregnant patient's respiratory status is so dire to manage, especially after 28 weeks of gestation, we recommend proceeding with a controlled delivery (like cesarean) to avoid the occurrence of fetal death and achieve possible improvement in maternal cardiopulmonary function. But before the pregnancy termination, it should be necessary to monitor the fetal condition closely due to an extremely high rate of fetal death

in the setting of severe systemic infection. For pregnant women who are stable on conventional oxygen therapy, we suggest a daily non-stress test for fetal monitoring. But for patients who require mechanical ventilation, we suggest continuous monitoring after 28 weeks of gestation to find out the signs of non-reassuring fetal status in time.[22] Regarding the use of steroids for fetal lung maturity in the setting of COVID-19 infection, despite no more data available, we still believe a single course of steroids may be reasonable to give for patients at high risk of preterm birth within seven days.

What indicators can be used to predict the occurrence of rapid ARDS has not yet been determined. In some studies of pregnancy with community-acquired pneumonia, anemia, hypoproteinemia, and low BMI were proved as risk factors for severe community-acquired pneumonia.[23] Among the patients with COVID-19, we also found that level of hemoglobin and albumin was significantly lower in severe cases than that of mild cases,[24] which reminds us to attach importance to the above indicators. But whether correcting the anemia and hypoproteinemia status can benefit, more research evidence is needed. Recently, a risk score based on characteristics of COVID-19 patients at the time of admission to the hospital was developed that may help predict a patient's risk of developing critical illness.[25] In this risk prediction model, 10 variables were independent predictive factors and were included in the risk score. The mean AUC in the development cohort was 0.88 (95% CI, 0.85-0.91), and the AUC in the validation cohort was 0.88 (95% CI, 0.84-0.93). Although whether this risk score is applicable in maternal populations with equal predictive effectiveness is unknown. But this result provides a possibility for clinicians to estimate an individual hospitalized patient's risk of developing the critical illness, which can provide obstetricians with essential information for delivery decision-making.

4 | POSTPARTUM EXACERBATION SHOULD BE ALERT IN MANAGEMENT

In our correspondence, six cases who were mild and one case who was severe at admission all aggravated in one week after delivery.[7] The same phenomenon was observed in other reports through sorting out the timeline of cases. Several severe case reports from Henan[26] and Hubei[27] also manifested postpartum exacerbation. One patient in New York[15] was admitted to hospital because of obstetric factors with mild COVID-19 illness and was discharged after delivery. But she was re-admitted to the hospital 6 days after delivery due to aggravation of the COVID-19 pneumonia. In the report of critically ill cases in Iran,[17] all women have deteriorated after delivery. But we need to be cautious to understand that this condition may attribute to changes in the maternal cardiopulmonary system shortly after delivery or be a part of the natural disease course. It is indeed worth noting that the physiologic adaptations to delivery and the immediate postpartum period had occurred.

One of the most unstable periods of perinatal hemodynamics is three days after delivery. The fluid retention began to return to the body circulation with autotransfusion of up to 500 ml of blood volume, which increased the perfusion of the viscera and the pressure of the pulmonary circulation.[28] In addition, with a surge of catecholaminergic and release of inflammatory mediators within the endothelium, considerable fluid shifts between the interstitial, intracellular, and intravascular compartments which may result in pulmonary edema.

On the other hand, due to hemodilution and excessive consumption and demand, the level of basic albumin in pregnant women is lower than that of non-pregnant women, and studies have shown that the colloidal osmotic pressure after delivery is significantly decreased.[29] Hypoalbuminemia was common in severe cases. Due to the hypoalbuminemia, colloid osmotic pressure decreases furtherly, and excessive amount of fluid outside the pulmonary vessels even infiltrates into the alveoli. Fluid retention in the stroma and alveoli can reduce the gas diffusion and decrease the ratio of ventilating blood flow. Combined with pulmonary injury by virus, pulmonary edema and other pathological changes can serve to exacerbate illness leading to ARDS.[30]

Third, the delivery itself can increase the level of some cytokines such as IL-6 which high expression is related to the increase of incidence rate and mortality of influenza virus during pregnancy.[31] Studies have shown that in SARS-nCov-2 infected patients, cytokine secretion increases, such as IL-6, and the immune system of severe patients will have a fatal cytokine storm.[32] Childbirth may be a promoter of cytokine secretion to affect the illness development.[33,34]

Taking into account the above reasons, in the short period after birth, some patients, especially severe patients, will suffer from an increased risk of illness exacerbation. This provides us with more information on the management of COVID-19 in pregnancy. On the one hand, for severe and critically ill maternal COVID-19 infection, it is necessary to fully consider that the pathophysiological changes in the delivery and postpartum stages may aggravate the condition. Therefore, close observation and timely treatment after birth should be conducted with the change of disease condition in pregnant women with COVID-19.

5 | MATERNAL-FETAL IMMUNITY AND COVID-19 INFECTION

As described in the first part of this article, COVID-19 infection manifested less severe illness than the other coronaviruses which attributed to many factors. One explanation is the different immune states activated by virus infection. The Th1/Th2 immune balance is one of the important immune regulatory mechanisms. Th1 cytokines have antimicrobial and pro-inflammatory properties, while Th2 cytokines have anti-inflammatory properties.[35] In the case of SARS-CoV infection, the immune response of Th1 type is highly activated and lasts for a long time, resulting in a consistently high level of pro-inflammatory cytokine expression for more than 2 weeks since the onset of the disease. The persistence of this intense inflammatory state may be responsible for extensive lung damage.[36] However, unlike SARS-CoV infection, the intensity and duration of Th1 and

Th2 immune responses in SARS-Cov-2 infection are very similar. Not only IFN-γ and IL-1, but also IL-4 and IL-10 are also present in the blood.[37] In the pregnant population, the pregnancy itself does not appear to be an aggravating factor and may also be related to the unique immune status during pregnancy.

As we all know, maternal-fetal immunity is the only paradox that contradicts the classical immunological principles. Fetus is regarded as a semi-allograft, and successful pregnancy depends on the mother's sustained and stable immune tolerance to the fetus.[38] Meanwhile, a series of changes on the status of maternal anti-infective immunity also occur during pregnancy.

During pregnancy, the maternal immune system will make real-time adjustments to resist the invasion of pathogens, manifested as an enhanced response on natural immunity and a decrease in adaptive immune response.[39] This specific change of immune state is believed to be related to the tilt of the immune balance of Th1/Th2 to Th2 which induce immune tolerance to the fetus and placenta. Meanwhile, some studies believe that the immune balance of Th17/Treg also plays an important role in this process.[40,41]

Therefore, in pregnant women with COVID-19, Th2 predominant immune balance and the role of Treg cells may play an important role in preventing excessive systemic inflammatory response and life-threatening complications such as ARDS and MODS.[42] This may explain the clinical observation that the proportion of pregnant women infected with COVID-19 progressing to severe or critical cases is not higher than in the general population.

However, significant increases in plasma cytokines IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα have been observed in a small number of severe or critical cases with COVID-19 infection,[24] possibly due to antibody-dependent enhancement of SARS-CoV-2.[43] Elevated circulating levels of IL-6, a pro-inflammatory cytokine, are associated with an increased risk of death in patients with COVID-19.[24] Cytokines storms observed in severe and critically ill cases in general population still gave us a lot of inspiration to understand the pregnancy-related critically ill cases.

Therefore, from the perspective of reproductive immunology, combined with the characteristics of maternal-fetal immunology and COVID-19 infection, the development of appropriate immunomodulatory drugs for pregnant women may have important guiding significance in preventing fatal systemic inflammatory reaction and organ function injury in severe or critical cases. However, studies on the immunological characteristics of SARS-CoV-2 virus infection in pregnant and puerperal women are very limited, and more clinical and basic studies are needed to further explore this.

6 | CONCLUSION

Although the risk of developing into severe cases in pregnant women with COVID-19 is not higher than that of the general population, the management of severe and critically ill cases still deserves more attention. Rapid clinical decompensation, the occurrence of adverse maternal and neonatal outcomes, and postpartum exacerbation highlight the delivery timing and management considerations during pregnancy and the postpartum period. For the care of severe and critically ill cases, we recommend to organize a multidisciplinary team as soon as possible after maternal hypoxemia occurs, to assess fetal maturity combined with the evaluation of progression speed of the disease, and make a decision of delivery in time. When the fetus is not mature enough to survive, the decision to proceed delivery should be deferred in the setting of severe and critical maternal COVID-19 infection until maternal cardiopulmonary stability can be achieved. In the postpartum period, close observation and timely treatment after birth should be conducted with the change of disease condition in pregnant women with COVID-19. In addition, the immune status of pregnant women infected with COVID-19 should also be considered to provide evidence for optimizing current treatment measures.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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