Coronavirus Disease-2019 in Pregnancy

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KEYWORDS

• Acute respiratory distress syndrome • COVID-19 • Perinatal outcomes • Pregnancy • SARS-CoV-2

KEY POINTS

- Pregnant women are susceptible to coronavirus disease-2019 (COVID-19) and are at higher risk of complications than the general population.
- COVID-19 infection during pregnancy severely affects maternal health, increasing the risk of hospitalization, the requirement of mechanical ventilatory support, and maternal death.
- COVID-19 infection during pregnancy increases the risk of pregnancy complications such as preeclampsia and preterm birth.
- Despite the lack of evidence in obstetrics, pharmacologic and nonpharmacological therapies during pregnancy diminish severe complications and should be balanced against the potential risks.
- Vaccination during pregnancy is safe and reduces the risk of severe disease.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection during pregnancy is associated with severe complications and adverse effects for the mother, fetus, and neonate.[1,2] Pregnancy constitutes a risk factor for hospitalization, intensive care admission, and death among COVID-19 women of reproductive age.[3] The physiologic adaptations in the respiratory system during pregnancy impose a significant challenge in managing pregnant women who develop acute respiratory distress syndrome (ARDS) in the context of COVID-19 infection.[4] In addition, the thromboembolic risk of pregnancy increases the likelihood of thrombosis, including pulmonary embolism.[5]

Even though this situation was identified during the pandemic, many pregnant women died without access to intensive care units (ICus).[6] COVID-19 infection might increase the risk of preterm delivery and stillbirth.[7] Conversely, inconsistent evidence suggests that vertical transmission is probable but infrequent.[8] Despite all pregnancy-related complications during the COVID-19 pandemic, many pregnant patients decline to be vaccinated, assuming uncertainty regarding the safety and protection against current variants. This review summarizes the lessons learned in assessing, managing, and caring for pregnant patients with COVID-19 infection.

Epidemiology

The epidemiology of COVID-19, including its complications, should be demarcated to the historical moment (prevaccination or postvaccination), the geographic region, and the predominant COVID-19 variant, among others. Global maternal and fetal outcomes have worsened during the COVID-19 pandemic, increasing maternal deaths, stillbirth, ruptured ectopic pregnancies, and maternal depression in many regions. Some of these outcomes show a considerable disparity between low–middle-income (LMICs) and high-income countries (HICs). Comorbidities such as diabetes, hypertension, and asthma were more frequent in HICs. In contrast, others, such as hypothyroidism, anemia, and coinfections, were more prevalent in LMICs, and the overall risk of adverse pregnancy outcomes was higher in LMICs than in

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HICs, including abortion, stillbirths, and maternal death. Significant perinatal adverse events, such as neonatal deaths, pneumonia, and neonatal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, are generally reported in LMICs.[9]

Nevertheless, some lessons were learned after the worst period of the pandemic, highlighting an urgent need to prioritize safe, accessible, and equitable maternity care in response to this pandemic and future health crises.[7] COVID-19 affected antenatal care by decreasing the number of visits and unscheduled care and increasing virtual or remote antenatal care and hospitalizations. This suggests that reduced maternity health-care-seeking and health care providers during the COVID-19 pandemic influenced the pregnancy outcomes observed during the pandemic.[10] In LMICs, evidence describing telemedicine services did not show the expected benefit in the pregnant population by supplementing the existing protocols in antenatal care.[11]

CLINICAL RELEVANCE

Risk Factors for Severe Coronavirus Disease-2019 During Pregnancy

The evidence regarding COVID-19 and pregnancy has changed with the advance of the pandemic. The evidence suggests that some risk factors, including comorbidities and ethnicity, increase the likelihood of pregnant women being symptomatic.[12] Preexisting diabetes (not gestational diabetes) was associated with severe COVID-19 in pregnancy (odds ratio [OR]: 2.12; 95% confidence interval [CI]: 1.62 to 2.78).[13] In SARS-CoV-2 (+) pregnant women, Rh- status was associated with a lower risk of symptomatic COVID-19, with an increase in obstetric hemorrhage and preterm premature rupture of membranes in pregnant women with Rh+ and blood A group, respectively.[14] A systematic review and meta-analysis focused on the relationship between comorbidities and COVID-19 severity, including 13 studies and 154 deceased patients. The presence of at least one severe comorbidity showed a twofold increased risk of death. Overall, overweight (body mass index > 25 kg/m^2) and obesity doubled the risk of death, with no differences in gestational diabetes or asthma. ICU admission was related to fivefold increased risk of death, with no difference in respiratory support or mechanical ventilation.[15] Another study showed the main predictors of mortality (increase in the odds of maternal mortality (OR: 1.15, [95% CI: 1.05 to 1.26]) were the need for invasive mechanical ventilation and a more prolonged ICU stay.[16]

Pathophysiology of Coronavirus Disease-2019 Complications in Pregnancy

During the pandemic, pregnant women were at significant risk of presenting with more severe forms of COVID-19 infection and a high risk of pregnancy complications.[17] COVID-19 causes a severe systemic inflammatory response associated with vascular alterations that could be of particular interest considering the physiologic changes in the immune, respiratory, cardiovascular, coagulation, and renal systems during pregnancy.[18] Alterations of the respiratory system include mucosal edema, capillary engorgement of nasal and oropharyngeal mucosa, and laryngeal tissues. In addition, the diaphragm is displaced 4 cm upward, decreasing functional residual capacity by 10% to 25% at term. In the cardiovascular system, there is a reduction in systemic vascular resistance that allows the homeostatic control of pregnancy-related hemodynamic changes, an increase in cardiac output, an expanded blood volume, and a decrease in blood pressure. Based on these changes, despite the low level of evidence and some debate raised by the difficulties in achieving improvements in oxygenation during COVID-19, many experts and clinical societies propose an O_2 saturation (SpO_2) at $\geq$ 95%.[19]

SARS-CoV-2 causes severe alterations in the cardiovascular system, including the recruitment of inflammatory leukocytes in the vascular tissue, leading to tissue damage and cytokine release, followed by disseminated intravascular coagulation. To an extent, specific clinical responses of pregnant women to COVID-19 could be related to changes in the levels of ACE2 with reduced sensitivity to Ang II.[20] In terms of severity, thrombotic microangiopathy was invoked as one of the mechanisms in severe COVID-19 cases. The protease ADAMTS13 (A Disintegrin-like and Metalloprotease with thrombospondin type 1 motif no. 13) is a marker of microangiopathy responsible for controlling von Willebrand multimer size. Recent evidence shows an imbalance of the von Willebrand/ADAMTS13 axis in pregnant women with COVID-19, indicating that nulliparous women group O showed Willebrand/ADAMTS-13 ratios significantly lower than those in non-O. In this population, the Willebrand to ADAMTS13 ratio was associated with preterm delivery.[21]

Obstetric Complications Associated with Coronavirus Disease-2019 During Pregnancy

Infection in pregnant women was associated with a higher risk of adverse pregnancy outcomes, such as fetal growth restriction, premature rupture

of membranes, fetal distress, preterm birth (delivery before 37 weeks of gestation), spontaneous abortion, and stillbirth.[2] SARS-CoV-2 during pregnancy was associated with a higher risk of developing preeclampsia.[22,23] **Table 1** describes accumulative evidence from a total of 706 pregnant women with COVID-19 in 18 countries, demonstrating that the risk of obstetric complications varies according to symptom status.[2] An observational cohort study from the United States involving 683,905 patients, including the pre- and postpandemic periods (2019 to 2021), showed that women with COVID-19 were more likely to experience both early and late preterm birth, preeclampsia, disseminated intravascular coagulopathy, pulmonary edema, the need for invasive mechanical ventilation and in-hospital mortality than women without COVID-19.[24]

In pregnant patients with COVID-19, the cesarean section rate was high, and iatrogenic preterm birth was reported to be as high as 25%.[25] A recent meta-analysis including 42 studies and 438,548 pregnant women reported that COVID-19 during pregnancy increased the risk of preeclampsia (OR: 2.11), preterm birth (OR: 1.82), and stillbirth (OR: 2.11).[26] Another meta-analysis including 790,754 pregnant women also described an increased risk of preeclampsia in patients infected with SARS-CoV-2.[23] A meta-analysis including 45 studies with a low-to-moderate risk of bias reported 1,843,665 pregnancies during the pandemic (2020) and 23,564,552 pregnancies during a variable pre-pandemic period (from 2002 to 2019, depending on the studies included). This meta-analysis did not find a difference in the odds of stillbirth between the pandemic and pre-pandemic periods, with an increase in mean birth weight during the pandemic compared with the pre-pandemic period and a reduction in unadjusted but not adjusted estimates of preterm birth.[16]

Fetal and Neonatal Disease

A link between fetal or neonatal disease and COVID-19 has not been well elucidated. During the pandemic, some data support that being pregnant with COVID-19 increases the risk of adverse pregnancy and birth outcomes and a low risk of congenital transmission.[27] Pregnant women who test positive for COVID-19 seem to be at a higher risk of lower birth weight and premature birth.[28] In a recent publication, the overall miscarriage rate in pregnant women with COVID-19 ranged between 15.3% (95% CI: 10.94 to 20.59) and 23.1% (95% CI: 13.17 to 34.95), a miscarriage rate within the normal population range.[29]

The vertical transmission of SARS-CoV-2 has been reported but remains highly debated.[30] A recent assessment of 177 pregnancies with a confirmed infection by reverse transcriptase-PCR using nasopharyngeal swabs within the first 24 to 48 hours of life and after 2 weeks of life showed that 5.1% of babies were SARS-CoV-2 positive in the neonatal period, with 1.7% considered intrauterine and 3.4% considered intrapartum or early postnatal transmission cases.[31] **Table 2** shows the rate of positivity of SARS-CoV-2 according to the type of biological sample. Thus, although rare, the intrauterine transmission of SARS-CoV-2 is possible, with early postnatal transmission occurring more frequently. SARS-CoV-2 has been isolated in the human placenta.[32] Many placentas showed histopathologic findings in pregnant women with COVID-19, suggesting placental hypoperfusion and inflammation (**Fig. 1**).[31,33] Angiotensin-converting enzyme 2 (ACE2) is the receptor of SARS-CoV-2, the placental mRNA expression of ACE2 is gestational age-dependent and plays a key role in pregnancy infection and complications.[34] Infected newborns reported in the literature remained asymptomatic or had mild symptoms resolved during follow-up.[35]

EVALUATION

Clinical Assessment and Disease Severity

Most pregnant women with COVID-19 present with mild-to-moderate symptoms (81% to 86% of cases) and are monitored as outpatients for 7 to 14 days after the onset of symptoms.[36] More than 70% of infected women were in their third trimester, with no evidence that supports an association between gestational age and COVID-19 mortality and morbidity.[37] However, SARS-CoV-2 was more severe in pregnant women than in the general population, with an increased risk of hospital admission, with 5% developing a severe form requiring ICU admission and approximately 35% requiring intubation, with a maternal mortality of close to 2.7%.[25] The most common symptoms were fever, cough, chest pain, dyspnea, and fatigue.[38]

Pregnant patients appear to present more commonly with more advanced COVID-19 chest tomography findings than the general adult population, but characteristic laboratory abnormalities are similar to the general population.[38] Early in 2020, the World Health Organization (WHO) proposed a guideline describing a clinical categorization of COVID-19 that has been used indistinctly for the obstetric population. This illness severity in COVID-19 defined patients as critical (criteria for ARDS, sepsis, septic shock, and the provision

Table 1
According to symptom status, the risk ratio for maternal, and perinatal outcomes among pregnant women with coronavirus disease-2019

	Risk Ratio (95% Confidence Interval)
Asymptomatic	
Preeclampsia	1.63 (1.01 to 2.63)
Preterm birth	0.99 (0.72 to 1.36)
Severe perinatal morbidity and mortality index	1.08 (0.69 to 1.69)
Severe neonatal morbidity index	1.42 (0.465 to 3.08)
Maternal morbidity and mortality index	1.24 (1.0 to 1.54)
Any symptoms	
Preeclampsia	2.00 (1.34 to 2.99)
Preterm birth	2.76 (1.77 to 4.30)
Severe perinatal morbidity and mortality index	2.79 (1.57 to 4.95)
Severe neonatal morbidity index	4.66 (1.93 to 11.3)
Maternal morbidity and mortality index	1.76 (1.49 to 2.08)

Maternal morbidity and mortality index includes at least one of the following complications during pregnancy: vaginal bleeding, pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP, preterm labor, infections requiring antibiotics or maternal death, admission to intensive care unit, or referral for higher dependency care. *Severe neonatal morbidity index* includes at least one of the following morbidities: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, or retinopathy of prematurity. *The severe perinatal morbidity* and mortality index includes any morbidities listed in the SNMI, intrauterine or neonatal death, or neonatal intensive care unit stay >7 d.

(*Data from* Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study [published correction appears in JAMA Pediatr. 2022 Jan 1;176(1):104]. JAMA Pediatr. 2021;175(8):817-826.)

of invasive or noninvasive mechanical ventilation or vasopressor therapy), severe (oxygen saturation < 90% on room air, signs of pneumonia, or severe respiratory distress) and nonsevere (in the absence of any severe or critical COVID-19).[39] International societies, including the Society for Maternal and Fetal Medicine (SMFM) and the Royal College of Obstetricians and Gynecologists (RCOG), proposed a disease severity classification based on oxygenation (**Box 1**). Almost half of all patients with COVID-19 admitted to the ICU developed persistent critical illness, requiring high resource utilization. Refractory hypoxemia remained significantly associated with mortality, yet evidence-based ARDS interventions, particularly prone positioning in the late second and third trimesters, were either not implemented or delayed, resulting in worse outcomes. Real-time service evaluation techniques offer opportunities to assess the level of care and improve the protocolized implementation of evidence-based ARDS interventions, which might be associated with improvements in survival.[40]

THERAPEUTIC OPTIONS

General Considerations

Clinical guidelines have made several recommendations for pregnancy during COVID-19: (1) hospitalization only for severe disease; (2) fetal growth scan after SARS-COV-2 infection; and (3) thromboprophylaxis with low molecular weight heparin (LMWH). In addition, a general agreement, supported by all current guidelines, is not to recommend cesarean section solely for maternal COVID-19 infection. A vaccine booster is recommended 6 months after the primary vaccination series. Inpatient management depends on disease severity. To assess clinical deterioration, the SMFM suggests a vital sign assessment every 4 to 8 hours for patients in the general ward and every 2 to 4 hours in cases of severe disease. Continuous monitoring (invasive or noninvasive) in critical illness is preferred as indicated or depending on hospital resources and policies. The inability to maintain oxygen saturation >94% with supplemental oxygen therapy, hemodynamic instability, or the presence of warning signs through any early warning systems (EWSs) should be indications for ICU consultation and transfer. Furthermore, some current and validated obstetric warning systems include SpO_2 as a crucial parameter to identify patients at risk of rapid deterioration.[41]

Pharmacologic Interventions

Six studies involving a total of 599 women reported pharmacologic treatment of COVID-19 in

Table 2
Rate of positivity for severe acute respiratory syndrome coronavirus 2 in maternal, fetal, and neonatal biological samples among pregnant women with coronavirus disease-2019

Sample Site	% (*n*/*N*)
Nasopharyngeal swab	2.88 (27/936)
Placenta	7.69 (2/26)
Cord blood	2.94 (1/34)
Amniotic fluid	0 (0/51)
Neonatal urine sample	0 (0/17)
Neonatal rectal swab	9.67(3/31)
IgM neonatal serology	3.66 (3/82)

Data from Kotlyar AM, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2021;224(1):35-53.e3.

pregnancy that included antiviral therapy, systemic corticosteroids, antibiotics, and immunotherapy; however, the types and doses of the medications were not specified.[42] Antenatal corticosteroids may be used routinely for fetal lung maturation between 24 and 34 weeks. However, clinicians should make decisions in those < 24 or > 34 weeks of gestation on a case-by-case basis. Magnesium sulfate may be used cautiously for seizure prevention in the context of severe preeclampsia and fetal neuroprotection to reduce the risk of cerebral palsy associated with prematurity in those with hypoxia and renal compromise. Thromboprophylaxis in pregnant patients with COVID-19 should consider disease severity, the timing of delivery to disease onset, inpatient vs. outpatient status, underlying comorbidities, and contraindications to the use of anticoagulation.[43] To date, corticosteroids, particularly dexamethasone, are the most proven and recommended treatment for pregnant patients with COVID-19 who are mechanically ventilated or require supplemental oxygen.[44] Although no subgroup analysis was performed on pregnant women, the RCOG and the WHO stated that no harm is expected from steroid use. Concerns about pregnancy safety led to recommending prednisolone as the first choice instead of dexamethasone because prednisolone is extensively metabolized in the placenta, with minimal transfer to the fetus. Other

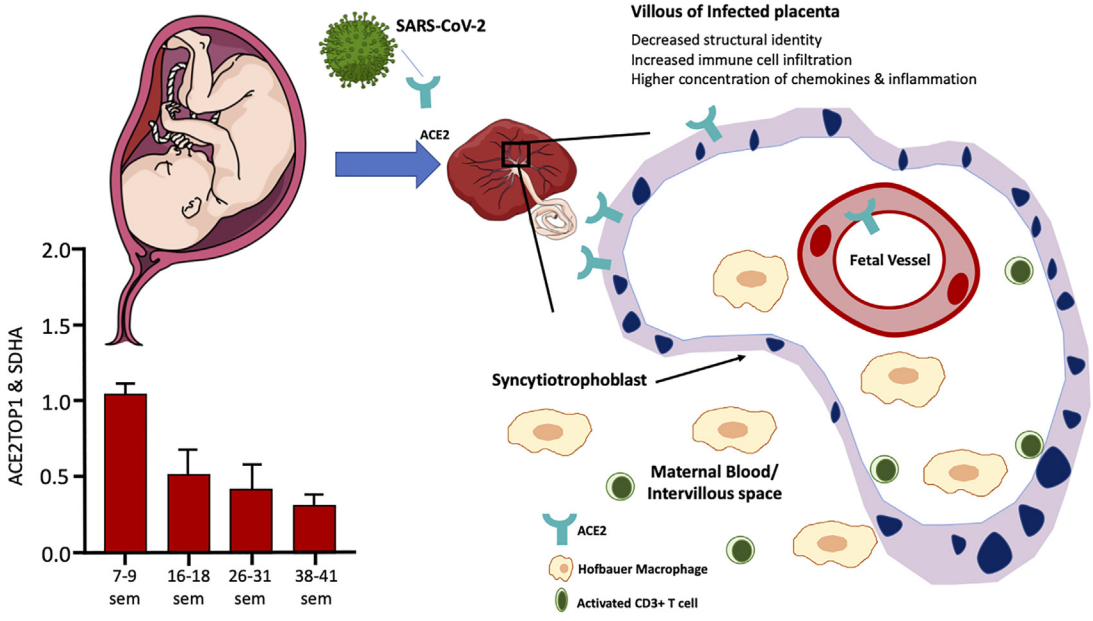

Fig. 1. Inflammatory responses in the placenta upon SARS-CoV-2 infection. Infected placentas show extensive infiltration of maternal immune cells. Angiotensin-converting enzyme 2 (ACE2) is the receptor of SARS-CoV-2 and plays a key role in pregnancy infection and complications. The placental mRNA expression of ACE2 is gestational age-dependent, increasing from the first- (7 to 9 weeks) through the third trimester (38 to 41 weeks). ACE2 is highly expressed in maternal-fetal interface cells, including stromal cells and perivascular cells of decidua, the cytotrophoblast, and syncytiotrophoblast in the placenta. In response to maternal-fetal infection, the syncytiotrophoblast shows increased chemokines and inflammatory markers expression.[33,34] ACE2, angiotensin-converting enzyme 2; SDHA, succinate-ubiquinone oxidoreductase; TOP1, topoisomerase 1. (*Adapted from* Argueta LB, Lacko LA, Bram Y, et al. Inflammatory responses in the placenta upon SARS-CoV-2 infection late in pregnancy. iScience. 2022;25(5):104223.)

Box 1
COVID-19 classification based on maternal oxygenation

Asymptomatic:

A positive test with no symptoms.

Mild disease:

A positive test, but not requiring oxygen and no evidence of sepsis.

Moderate

A positive test and symptoms of lower respiratory tract infection (dyspnea, abnormal blood gases, and persistent fever) but without oxygen desaturation (SpO_2 < 94% at room air) or requiring oxygen therapy to achieve this oxygen level.

Severe:

A positive test and tachypnea (respiratory rate >30 breaths per minute, SpO_2 < 94% at room air or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mm Hg).

Critical:

A positive test and multiorgan dysfunction, septic shock, or need for respiratory support with high flow nasal cannula (HFNC), noninvasive or invasive mechanical ventilation (NIMV and IMV).

Adapted from the Society for Maternal and Fetal Medicine (SMFM) and the Royal College of Obstetricians and Gynecologists (RCOG). Available at: https://www.smfm.org/. Accessed Sep 7 2022.

options are methylprednisolone or hydrocortisone for pregnant women.[45]

Antivirals with different mechanisms of action, such as protease inhibitors and nucleotide or nucleoside analogs, have been proposed for COVID-19 treatment.[46] Although the efficacy and safety profile of remdesivir among pregnant women remains inconclusive, a recent systematic review reporting nine case reports and case series showed clinical recovery after remdesivir treatments.[47] Remdesivir improved the clinical condition of pregnant patients with COVID-19, especially those with a better clinical status at baseline and who received treatment earlier in the course of the disease.[47,48] The current WHO guidelines updates the use of remdesivir for patients with nonsevere COVID-19: its use reduces hospital admission in the highest risk group, although with little or no impact on mortality.[49] Adverse reactions and transaminase enzyme levels should be followed after remdesivir administration; the most common adverse event following remdesivir treatment is transaminitis.[47]

There are sufficient data on the role of tocilizumab, an interleukin-6 antagonist, in improving outcomes, including survival, in hospitalized patients with hypoxia with evidence of systemic inflammation. Tocilizumab improved survival and clinical outcomes in hospitalized COVID-19 patients with hypoxia and systemic inflammation.[50] Based on these results, the National Institute for Health and Care Excellence (NICE) guidance recommends using tocilizumab in hospitalized patients who have or had completed a course of steroids, an increase in C-reactive protein (CRP) > 75, the need for supplemental oxygen, or within 48 h of initiating mechanical ventilation. Data on the use of tocilizumab in pregnancy are scarce, but no adverse effects have been reported. The RCOG recommends offering tocilizumab to pregnant women when they fit the criteria. The decision should involve a multidisciplinary team (MDT) to analyze whether the benefits outweigh the risks.[51]

Although hydroxychloroquine and lopinavir/ritonavir are used during pregnancy and lactation within clinical trials, data from nonpregnant populations have not shown benefits. Although some studies describe the effects of hydroxychloroquine and antibiotics, this has now been shown not to be beneficial and is not recommended for either nonpregnant patients or pregnant women. Adverse events with treatment were three-fold higher than placebo, but very few serious adverse events were found.[52] Case reports suggest that convalescent plasma administered to pregnant women with severe COVID-19 benefits both the mother and the fetus. However, these studies suffer from relevant reporting bias.[53] Clinical trials to investigate the use of convalescent plasma for COVID-19 during pregnancy are lacking. More recent evidence showed no benefit, including in pregnant and nonpregnant populations.[54]

The use of convalescent plasma in patients who tested negative for anti-SARS-CoV-2 antibodies at baseline has not been associated with improved survival (RR 0.94, 95% CI 0.87 to 1.02). In patients with COVID-19, treatment with convalescent plasma, compared with control, was not associated with lower all-cause mortality or improved disease progression, irrespective of disease severity and baseline antibody status.[53] Immunomodulators (tacrolimus), interferon, and inhaled nitric oxide in pregnancy and lactation are not routinely recommended and need further evaluation.[55]

Nonpharmacological Interventions for Coronavirus Disease-2019 in Pregnancy

In the context of moderate to severe COVID-19 infection, the same treatment principles apply to pregnant women and nonpregnant patients regarding nonpharmacological interventions, such as oxygen supplementation or mechanical ventilation. However, invasive mechanical ventilation is arduous in pregnant patients. This is due to the increased demand for oxygen in pregnancy secondary to a higher metabolic rate and increased oxygen consumption. The gravid uterus contributes to ventilatory impairment, and achieving the required volumes during mechanical ventilation can be challenging.[56]

Prone positioning has been proven to help ventilate patients in the presence of ARDS. Although no trials include pregnant women, techniques describe how proning can be performed in this group of patients. For example, some authors describe how they place pillows in a specific way to put the pregnant woman in a comfortable position without compromising the pregnancy.[57] However, this should not be practiced in patients with a wound from a recent cesarean section (first 2 weeks) or when pregnancy is over 34 weeks pregnant; the heavily pregnant uterus can make this position more difficult. Furthermore, after 24 to 28 weeks, there is the risk of aortocaval compression when proning a pregnant woman.

Oxygen Therapy, High Flow Nasal Cannula, and Ventilatory Support

International guidelines recommend maintaining a $SpO_2 > 94\%$ in pregnancy. Another recommendation focuses on supplemental oxygen modalities, including a face mask or high-flow nasal cannula (HFNC). Using HFNC in patients with severe COVID-19 decreased the need for mechanical ventilation support and time for clinical recovery. Despite these benefits, pregnancy-specific or COVID-19-related interventions are poorly reported in the published literature. None of the randomized trials using HFNC reported outcomes in pregnant women or pregnancy was an exclusion criterion.[58] Comparative data for pregnant women for treatments proven effective in the general population lack clinically meaningful interpretation. Thus, despite a potential benefit, there is little evidence to support recommendations regarding using HFNC in obstetrics.

Eleven studies reported nonpharmacological interventions, of which mechanical ventilation was reported in six studies and oxygen administration in eight. In total, 1738 women were included in these studies; 240 were exposed to interventions, 28 patients had mechanical ventilation, and 212 had oxygen administration.[42] Prone positioning remains a well-proven intervention in ARDS and should be considered in pregnant women when indicated. We recognize that proning might not be effective in all cases. However, prone positioning is an option to improve oxygenation in patients with moderate to severe hypoxemia ($PaFiO_2 \leq 150$ mm Hg) before considering delivering a premature infant or maternal cannulation for extracorporeal membrane oxygenation (ECMO).[57] The use of ECMO in pregnancy has increased, and evidence supports its use, feasibility, and favorable outcomes. A recent publication, including six ECMO centers from three different continents and 60 cases over 10 years, describes a maternal survival rate of 87% with an acceptable neonatal outcome.[59] In summary, proven therapies from the nonpregnant critically ill COVID-19 patient population can be extrapolated to critically ill pregnant patients, resulting in good maternal ICU survival and limited extreme premature delivery. Furthermore, in very premature gestations (<32 weeks), the continuation of pregnancy during mechanical ventilation and prone positioning is feasible with good fetal monitoring (**Fig. 2**).[60]

Delivery and Anesthesia

Pregnancy-specific interventions, including delivery or anesthesia, were related to the severity of COVID-19. Scientific societies such as the Society for Obstetric Anesthesia and Perinatology (SOAP) and the SMFM issued recommendations for types of anesthesia for pregnant women with COVID-19. However, no trials have been conducted regarding the management or outcomes of such women. The liberal use of neuraxial labor analgesia may reduce the need for emergency general anesthesia.[61] A systematic review found an association between having a cesarean section and being admitted to the ICU or having COVID-19 pneumonia. The decision to proceed with a cesarean section may be prompted by the need to improve ventilation.[42] In the event of cesarean delivery, neuraxial anesthesia was performed over general anesthesia.[62]

PREVENTION

Vaccination in Pregnancy and Lactation

SARS-CoV-2 mRNA vaccines are the most important strategy for preventing maternal illness.[63] Vaccination prevented pregnant women from SARS-CoV-2 infection (OR: 0.50 [95% CI: 0.35 to 0.79]) and COVID-19-related hospitalization (OR: 0.50 [95% CI: 0.31 to 0.82]). Messenger RNA

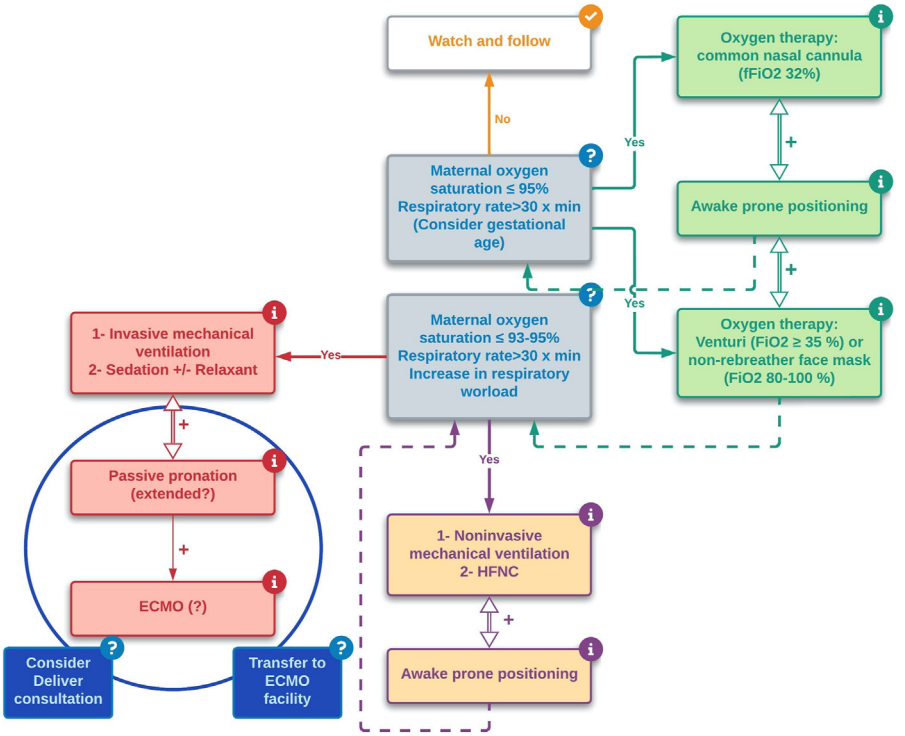

Fig. 2. Flowchart of management of severely critically ill pregnant women with COVID-19.

vaccines reduced the risk of infection in pregnant women (OR: 0.13 [95% CI: 0.03 to 0.57]).[64] Moreover, COVID-19 mRNA vaccination in pregnancy seems safe and is associated with a reduction in stillbirth.[65] However, excluding pregnant women from the initial COVID-19 vaccine trials resulted in a significant hesitancy to accept COVID-19 vaccination among pregnant women around the globe.[66] Worldwide analyses have reported an acceptance rate of 50% in pregnant women and 60% in breastfeeding women.[67] Safety concerns are the most common reason for the decline in COVID-19 vaccination during pregnancy.[68] There is evidence that administering a COVID-19 vaccine is safe and poses no additional risk to the breastfeeding woman or the breastfed baby.[63,69] After COVID-19 vaccination, pregnant patients develop a robust immune response, conferring protective immunity to newborns through breast milk and placental transfer and providing humoral immunity to the infant against COVID-19.[70–74]

In a population-based study including 24,288 singleton livebirths, the risk of preterm birth and small birth weight were similar between newborns prenatally exposed and unexposed to maternal vaccination.[75] Furthermore, the rate of congenital malformations in the exposed population was not higher than that in the unexposed population.[75] Therefore, professional associations and government health authorities should recommend COVID-19 vaccines to breastfeeding women, as the potential benefits of maternal vaccination outweigh the risks.[76] Vaccination campaigns are urgently needed to drive more confidence into the vaccine to help reduce the spread of the infection and the possible consequences during pregnancy.[67] However, pros and cons should be discussed extensively with both parents.[77]

SUMMARY

Although there is conflicting evidence, pregnant women were a potentially vulnerable population during the COVID-19 pandemic, with a significant risk of developing severe forms of COVID-19 and pregnancy complications. International guidelines recommend maintaining a SpO_2 >94% in pregnancy and supplemental oxygen delivery with a face mask or HFNC. Most COVID-19 pregnant women present with mild to moderate symptoms and can be monitored as outpatients for 7 to 14 days after the onset of symptoms. However, SARS-CoV-2 is more severe in pregnant women than in the general population, with an increased risk of hospital admission and severe forms requiring ICU admission, intubation, and mechanical ventilation. Finally, SARS-CoV-2 mRNA vaccines are the most important strategy for preventing maternal illness.

CLINICS CARE POINTS

- Coronavirus disease-2019 (COVID-19) infection during pregnancy is associated with severe complications and adverse effects for the mother, fetus, and neonate.
- Although there is conflicting evidence, pregnant women were a potentially vulnerable population during the COVID-19 pandemic, with a significant risk of presenting with severe COVID-19 and pregnancy complications. In addition, pregnancy is a risk factor for hospitalization, intensive care admission, and death among COVID-19 women of reproductive age.
- International societies have proposed a disease severity classification based on oxygen requirement and saturation. In addition, treatment recommendations do not differ significantly from the general population.
- SARS-CoV-2 mRNA vaccines are an essential strategy for preventing maternal illness and should be encouraged in all pregnant women.

DISCLOSURE

The authors have no relevant conflicts of interest.

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