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SARS-CoV-2 Infection and COVID-19 During Pregnancy: A Multidisciplinary Review

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Abstract

The global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has been associated with worse outcomes in several patient populations, including the elderly and those with chronic comorbidities. Data from previous pandemics and seasonal influenza suggest that pregnant women may be at increased risk for infection-associated morbidity and mortality. Physiologic changes in normal pregnancy and metabolic and vascular changes in high-risk pregnancies may affect the pathogenesis or exacerbate the clinical presentation of COVID-19. Specifically, SARS-CoV-2 enters the cell via the angiotensin-converting enzyme 2 (ACE2) receptor, which is upregulated in normal pregnancy. Upregulation of ACE2 mediates conversion of angiotensin II (vasoconstrictor) to angiotensin-(1-7) (vasodilator) and contributes to relatively low blood pressures, despite upregulation of other components of the renin-angiotensin-aldosterone system. As a result of higher ACE2 expression, pregnant women may be at elevated risk for complications from SARS-CoV-2 infection. Upon binding to ACE2, SARS-CoV-2 causes its downregulation, thus lowering angiotensin-(1-7) levels, which can mimic/worsen the vasoconstriction, inflammation, and pro-coagulopathic effects that occur in preeclampsia. Indeed, early reports suggest that, among other adverse outcomes, preeclampsia may be more common in pregnant women with COVID-19. Medical therapy, during pregnancy and breastfeeding, relies on medications with proven safety, but safety data are often missing for medications in the early stages of clinical trials. We summarize guidelines for medical/obstetric care and outline future directions for optimization of treatment and preventive strategies for pregnant patients with COVID-19 with the understanding that relevant data are limited and rapidly changing.

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Coronaviruses are a family of enveloped, single-stranded, positive-strand RNA viruses characterized by spherical morphologic features with surface spike projections. Human coronaviruses are divided into alphacoronaviruses and betacoronaviruses. The rapid emergence and human-to-human transmission of a virulent novel lineage B betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in the global pandemic of coronavirus disease 2019 (COVID-19) associated with considerable morbidity and mortality.[1,2] Worldwide population studies to date have identified several patient characteristics, including age and comorbid conditions, as risk factors for poor outcomes, but data on pregnant patients are limited. Based on data from previous pandemics, pregnant women[3] are at higher risk for acquiring infection and dying compared with nonpregnant women. The current review provides a multidisciplinary summary of the course and management of COVID-19 during pregnancy using an evidence base that has been published since

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identification of the first patients in Wuhan, China, in December 2019.

TAXONOMY AND PHYLOGENY OF SELECT HUMAN CORONAVIRUSES

Virion and Viral Life Cycle

The capsid of SARS-CoV-2 contains an RNA genome complexed with a nucleocapsid protein. The membrane surrounding this nucleocapsid contains 3 proteins common to all coronaviruses: spike protein, membrane protein M, and small membrane protein E (Figure 1A).[4] Viral entry occurs via 2 routes. The first occurs when the spike protein attaches to the angiotensin-converting enzyme 2 (ACE2) receptor, releasing the viral genome and nucleocapsid protein into the host cell cytoplasm.[5] The other pathway is the direct plasma membrane route via transmembrane serine protease 2 (TMPRSS2), which allows for proteolytic cleavage of the spike protein and mediation of fusion with the cell membrane.[6] Intracellularly, the viral genome is translated into a replicase to produce more genome RNA, messenger RNA, and viral protein. Viral membrane proteins M, N, and E assemble on intracellular membranes. The nucleocapsid protein and viral RNA complex form a helical capsid structure, which buds between the endoplasmic reticulum and the Golgi apparatus. Mature viral particles are packaged in vesicles, transported to the cell membrane, and released from the cell (Figure 1B).[5]

Viral Tropism and Normal and High-Risk Pregnancies

The ACE2 enzyme plays a key role in the conversion of angiotensin Ang I to Ang-(1-9) and Ang II to Ang-(1-7) (vasodilatory, antithrombotic, and anti-inflammatory activities) (Figure 2). The hormonal profile of normal gestation is characterized by an early increase of all the components of the renin-angiotensin-aldosterone system (RAAS), including ACE2.[7] This raises the possibility that pregnant women may be at a greater risk for SARS-CoV-2 infection. In addition, low blood pressure in pregnant women is maintained through a balance between being refractory to the pressor effects of Ang II and increased levels of Ang-(1-7), which exhibit systemic vasodilatory responses.[8,9] In preeclampsia, a pregnancy-specific hypertensive disorder that affects 3.5% of all pregnancies[10] clinically is characterized by multisystem involvement and, commonly, proteinuria; this balance is lost, with an overexaggerated Ang II blood pressure response.[11] Preeclampsia has also been associated with decreased maternal plasma Ang-(1-7) levels.[9] Because SARS-CoV-2 not only binds to ACE2 but also causes its downregulation,[12] infections during pregnancy may potentiate the RAAS abnormalities, ie, increased Ang II relative to decreased Ang-(1-7), that are present in preeclampsia. COVID-19 and preeclampsia share additional common mechanisms, including endothelial cell dysfunction and coagulation abnormalities. Notably, ACE2 receptors are also expressed by endothelial cells,[13] and endothelial cell infection and immune cell–mediated endothelial injury have been recently described in COVID-19.[14] Because

ARTICLE HIGHLIGHTS

- Physiologic, metabolic, and vascular changes in normal and high-risk pregnancies may affect risks for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and modify/exacerbate the clinical presentation of coronavirus disease 2019 (COVID-19).
- Pregnant women may be at greater risk for SARS-CoV-2 infection, with more severe COVID-19 symptoms and worse pregnancy outcomes.
- Studies to date have reported higher risks of pregnancy complications, including preterm birth and preeclampsia, as well as higher rates of cesarean delivery.
- Pharmacologic therapy is limited to medications with proven safety during pregnancy and lactation; safety data are often unavailable for medications in the early stages of clinical trials.
- The current recommendations are based on a limited number of studies. Future large, likely multicenter, studies will be critical in improving our understanding of the pathophysiology and clinical characteristics of COVID-19 and pregnancy, which may optimize COVID-19 preventive and treatment strategies during normal and high-risk pregnancies.

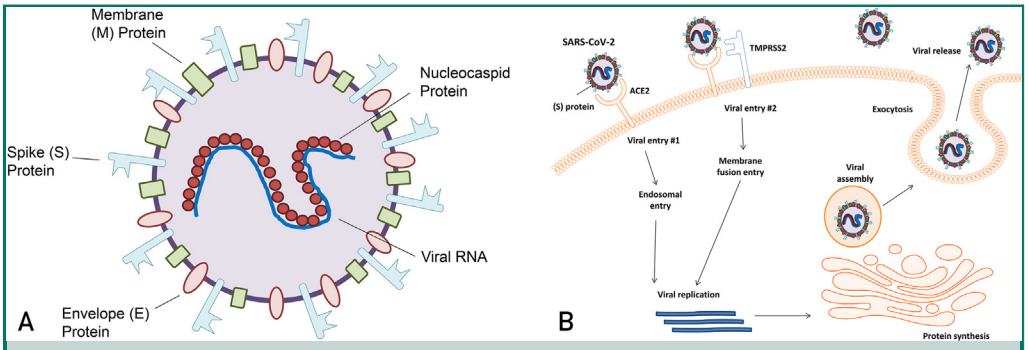

FIGURE 1. Features and life cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A, Structure of the SARS-CoV-2 viron. B, Viral entry methods and replication of SARS-CoV-2.

the hallmark of preeclampsia is endothelial dysfunction,[15] infection with SARS-CoV-2 during pregnancy could mimic and/or initiate microvascular dysfunction by causing endotheliitis. Systemic inflammation and microcirculatory dysfunction, characterized by vasoconstriction and resultant ischemia, ensue. This can further contribute to a procoagulopathic state, as demonstrated by high rates of deep vein thrombosis, stroke, and pulmonary embolism, which are increasingly reported in patients with COVID-19.[16-18] Infection with SARS-CoV-2 during pregnancy can be particularly prothrombotic because coagulation abnormalities may potentiate a hypercoagulable state, which is already present in uncomplicated pregnancy and exacerbated by preeclampsia.[15] Similarly, complement activation, which is present in both preeclampsia[19] and COVID-19,[20] may result in particularly severe thrombotic vascular injury when these disease states are present concurrently. In summary, RAAS abnormalities, endothelial dysfunction, complement activation, and the pro-coagulopathic effects of COVID-19 are similar to those occurring in preeclamptic pregnancies, potentially resulting in progressive vascular damage. Therefore, pregnancy and its complications represent a vulnerable state for invasive infection with SARS-CoV-2, reflecting several overlapping cellular mechanisms.

In addition to the direct cytotoxic effect of the virus, tissue injury in COVID-19 is mediated through an excessive inflammatory response, commonly referred to as cytokine storm. Cytokine storm is mediated via immune responses, which are significantly modified in pregnancy, and may contribute to COVID-19 laboratory and clinical characteristics during pregnancy.

IMMUNE RESPONSES TO COVID-19

During pregnancy, the maternal immune system must adjust to tolerate the semiallogeneic fetus while maintaining its ability to respond to pathogenic insult.[21,22] This is also known as T helper 2 polarization. However, near the end of pregnancy a switch to T helper 1 immunity occurs and the maternal immune system becomes proinflammatory, leading to the sequence of events that occur before parturition (ie, cervical dilation, contractions). Data on immune responses to SARS-CoV-2 in pregnant women are lacking at this time, and data from previous pandemics, suggest that pregnancy may increase the risk of acquiring infection and dying compared with nonpregnant women.[3] The timing of infection during gestation may induce differences in maternal immune responses, viral clearance, and, ultimately, perinatal outcomes. Because the first and third trimesters are proinflammatory to promote implantation and labor,[23] pregnant women infected with SARS-CoV-2 during these trimesters may be at higher risk for exaggerated responses to virus (cytokine storm). Furthermore, high levels of stress and inflammation occur during labor, and the physiologic changes that occur in a mother's body after the baby is born could

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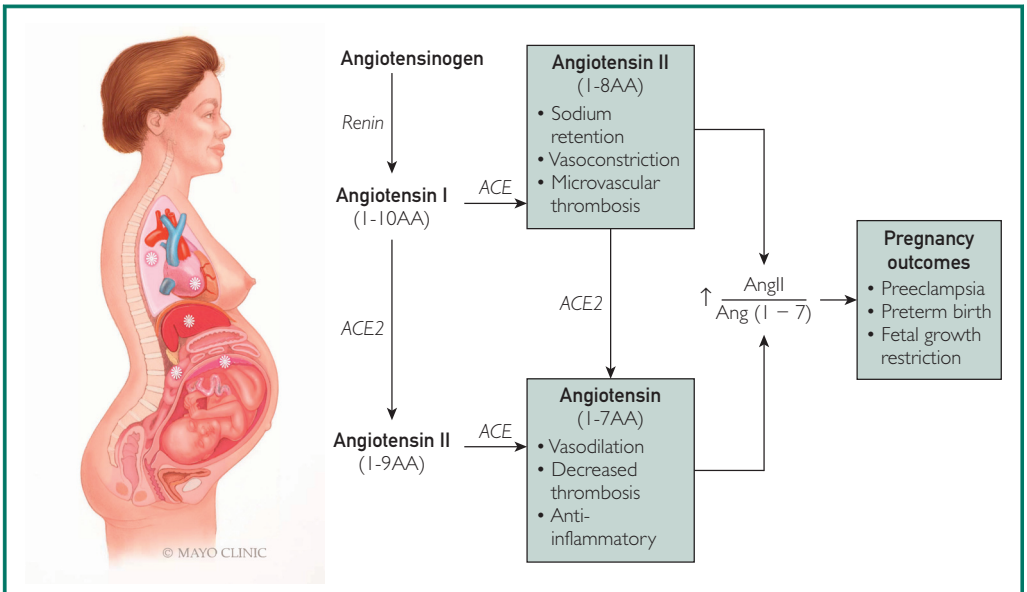

FIGURE 2. Pregnancy, coronavirus disease 2019 (COVID-19), and mechanisms of vascular damage. Upregulation of angiotensin-converting enzyme 2 (ACE2) receptor in pregnancy may increase the risk of severe acute respiratory syndrome coronavirus 2 infection. Binding of virus to ACE2 causes its down-regulation and may increase angiotensin (Ang) II relative to Ang-(1-7), thus favoring vasoconstriction, which can mimic/worsen vascular dysfunction in preeclampsia.

lead to poor maternal COVID-19 outcomes postpartum. This has been observed clinically, where pregnant women with mild symptoms on admission to the hospital for delivery required postpartum hospital admission for respiratory symptoms.[24,25]

Conflicting data exist regarding vertical transmission of the virus; however, research on other coronavirus infections during pregnancy suggests that *in utero* transmission does not occur. Mouse models and epidemiologic data have shown that inflammatory immune responses generated by viral infection during pregnancy can result in negative effects on fetal brain development.[26-28] During the H1N1 pandemic, infected women had higher rates of preterm birth.[29] Therefore, although placental transmission of the virus may not occur with SARS-CoV-2 infection, other short- and long-term effects from inflammation may adversely affect the developing fetus. These require further characterization. Maternal immunity may be passed on to protect the fetus, conferring passive immunity. Immunoglobulin G specific to the 2003 SARS-CoV outbreak strain was found not only in maternal blood, but also in amniotic fluid and cord blood.[30] Another possible source of antibodies could be breast milk, but this has yet to be determined.

MATERNAL PHYSIOLOGY AND CLINICAL CHARACTERISTICS OF COVID-19 DURING PREGNANCY

Significant physiologic changes to respiration occur during pregnancy,[31] including increased secretions and congestion in the upper airways, increased chest wall circumference, and upward displacement of the diaphragm. These changes result in decreased residual volume and increased tidal volume and air trapping, slightly decreased airway resistance, stable diffusion capacity, increased minute ventilation, and increased chemosensitivity to carbon dioxide. Hemodynamic changes include increased plasma volume of 20% to 50%, increased cardiac output, and decreased vascular resistance.[31] These changes result in a state of physiologic dyspnea and respiratory alkalosis as well as an increased susceptibility to respiratory pathogens. As has been seen with other viral

respiratory infections, the early symptoms of SARS-CoV-2 infection may mimic physiologic dyspnea in pregnancy, which could result in delayed diagnosis and more severe disease.[32]

Pregnant women with SARS-CoV-2 infection may experience more severe symptoms compared with nonpregnant women. Existing limited data have reported on rapid deterioration in women who had no symptoms on arrival and were subsequently diagnosed as having severe COVID-19.[24] In some, but not all, patients, maternal comorbidities were present (hypertension, diabetes, cholestasis of pregnancy).[24,33] Case reports have also described cases of quickly worsening maternal status with the ultimate diagnosis of cardiomyopathy.[34] Unfortunately, these rapidly progressive maternal complications have led to a high rate of cesarean deliveries (CDs) for either worsening maternal status or nonreassuring fetal status secondary to the worsening maternal clinical state.

Preeclampsia is an example of a common pregnancy-related complication that may be exacerbated by, or may exacerbate, COVID-19, as previously discussed. The picture becomes further complicated because the two processes share common laboratory abnormalities. Thus, it may be difficult to discern whether certain abnormal laboratory findings are due to SARS-CoV-2 infection or preeclampsia, and this interplay may have treatment implications. For example, thrombocytopenia[35] and liver function abnormalities,[36] both of which are diagnostic criteria for preeclampsia with severe features, are also associated with worsening COVID-19.

MATERNAL DISEASE AND OUTCOMES

Physiologic changes in normal pregnancy and metabolic and vascular changes in high-risk pregnancies may affect the pathogenesis or exacerbate the clinical presentation of COVID-19 during pregnancy. A systematic review by Di Mascio et al[37] evaluating and comparing obstetric outcomes in combined coronavirus infections (SARS, Middle East respiratory syndrome, and SARS-CoV-2) found that SARS-CoV-2 alone resulted in higher rates of preterm birth (24.3% [95% CI, 12.5% to 38.6%] for <37 weeks' gestation and 21.8% [95% CI, 12.5% to 32.9%] for <34 weeks' gestation), preeclampsia (16.2% [95% CI, 4.2% to 34.1%]), and CD (83.9% [95% CI, 73.8% to 91.9%]).

As of April 22, 2020, a total of 23 studies[25,34,38-58] (excluding overlapping of case reports) addressing obstetrical and neonatal outcomes of SARS-CoV-2 infection in pregnancy have been published in English. These studies span January 1, 2020, to April 22, 2020, and include 185 patients. The abstracted information is presented in Table 1, which summarizes maternal and neonatal outcomes. Briefly, most of the diagnoses occurred in the third trimester. Fever was the most common presenting symptom, followed by cough, dyspnea, and gastrointestinal alterations. Slightly more than 25% of patients were asymptomatic at diagnosis. The most common laboratory findings were lymphopenia and neutrophilia. Pneumonia was a common diagnosis (40%), and a small percentage (3.24%) required intensive care unit admission.

Management of patients varied according to institution. Most were treated with medications that are considered to be relatively safe during pregnancy: antibiotics (cefoperazone, sulbactam, ceftriaxone, cefazolin, and azithromycin), antiviral therapy (lopinavir, ritonavir, oseltamivir, and ganciclovir), and a few were treated with corticosteroids (dexamethasone, methylprednisolone).

Due to the high false-negative rates of the nasopharyngeal swab for the quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for the SARS-CoV-2 test,[59] computed tomography may be required to confirm the diagnosis in cases of high suspicion, as seen in 4 cases reported by Wu et al.[53] There were no patients who delivered before 28 weeks' gestation, and most patients delivered at 36 0/7 weeks or later. The impact of infection on timing of delivery is still unclear. Liu et al[41] reported a 46% preterm labor rate between 32 and 36 weeks of gestation in 10 patients admitted with positive SARS-CoV-2 infection, and Zhang et al[44] reported no difference in mean ± SD gestational age at delivery for 16 women with SARS-CoV-2 infection (38.7±1.4 weeks) and 45 women without SARS-CoV-2 infection (37.9±1.6 weeks).

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TABLE 1. Summary of Maternal and Neonatal Outcomes During the COVID-19 Pandemic[a,b]

Characteristic	Value (N=185)
Maternal data	
Age (y), mean (range)	29.6 (20-41)
Trimester (No./total No. [%])	
First	3/185 (1.62)
Second	5/185 (2.70)
Third	177/185 (95.68)
Signs and symptoms (No./total No. [%])	
Fever	90/169 (53.25)
Pneumonia	75/184 (40.76)
Cough	56/169 (33.13)
Asymptomatic	44/169 (26.03)
Dyspnea/shortness of breath	22/169 (13.01)
Gastrointestinal alterations	9/169 (5.32)
ICU admission	6/185 (3.24)
Diagnostic method (No./total No. [%])	
qRT-PCR SARS-CoV-2 only	179/185 (96.75)
CT changes only	6/185 (3.24)
qRT-PCR SARS-CoV-2 and CT changes	100/185 (54.05)
Laboratory alterations	
Lymphopenia	32/93 (34.40)
Neutrophilia	8/93 (8.60)
Interventions (No./total No. [%])	
Antibiotics	64/145 (44.13)
Supportive measures	41/145 (28.27)
Antiviral therapy	39/145 (26.90)
Corticosteroids	12/145 (8.28)
Obstetric comorbidities (No./total No. [%])[c]	
Gestational hypertension	6/182 (3.29)
Preeclampsia	4/182 (2.20)
Gestational diabetes	11/182 (6.04)
Prelabor rupture of membranes	13/184 (7.07)
Fetal distress	23/184 (12.50)
Patient status (No./total No. [%])	
Delivered	152/185 (82.16)
Still pregnant	33/185 (17.83)
Mode of delivery (No./total No. [%])	
Cesarean delivery	129/152 (84.86)
Vaginal delivery	19/152 (12.50)
Pregnancy termination	4/152 (2.63)
Gestational age at delivery of viable pregnancies (No./total No. [%])	
<28 wk	0/148 (0.00)
28-31 6/7 wk	2/148 (1.35)
32-35 6/7 wk	26/148 (17.56)
≥36 wk	96/148 (64.86)
Missing data	24/148 (16.21)

Neonatal data	
Neonates reported (No./total No. [%])	
Total	146 (100)
Live births	145/146 (99.31)
Stillbirths	1/146 (0.68)
Comorbidities after live birth (No./total No. [%])	
Neonatal ICU admission	27/145 (18.62)
Low birth weight	15/145 (10.34)
Pneumonia	9/145 (6.20)
qRT-PCR SARS-CoV-2 positive	2/145 (1.37)
Neonatal death	1/145 (0.69)

[a]COVID-19 = coronavirus disease 2019; CT = computed tomography; ICU = intensive care unit; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[b]Note that certain parameters were not evaluated or reported in all patients, so the denominators used for calculations represent only the numbers for which data are available.
[c]Thirty-three of 185 patients (17.8%) were still pregnant at the end of this study; therefore, rates of complications occurring in late pregnancy or close to delivery, such as preeclampsia, might have been underestimated.

A systematic review by Zaigham and Andersson[60] including 108 pregnant women reported that CD was the most common mode of delivery, with a rate of 92%. It can be speculated that SARS-CoV-2 infections are more likely to result in maternal hypoxia or increased oxygen requirements, resulting in a nonreassuring fetal heart tracing, warranting expedited delivery. There may also be lack of SARS-CoV-2 screening in some health care settings, resulting in selection bias for CD in severe cases. The indication for CD needs to be further evaluated because current guidelines indicate that SARS-CoV-2 infection alone is not an indication for CD.[61,62]

A recent multicenter cohort study of severe COVID-19 in pregnant patients from 12 US institutions reported that patients were usually admitted to the hospital with severe disease 7 days after the onset of symptoms and typically were intubated 2 days after admission.[63] Fifty percent of women required delivery, resulting in a high rate of preterm birth.

NEONATAL OUTCOMES

Neonatal outcomes are shown in Table 1. There was 1 reported stillbirth[41] (<1%) due to severe maternal disease with multiple organ failure and 1 neonatal death[38] (<1%) due to refractory shock with multiple organ failure after delivery at 34 5/7 weeks' gestation. Among the 145 live births, 2 neonates tested positive for SARS-CoV-2 infection. Both did well with supportive therapy and observation and were discharged from the hospital in stable condition.[48,58]

Di Mascio et al[37] reported increased perinatal mortality and higher rates of neonatal intensive care unit admissions, but all neonates tested negative for SARS-CoV-2 infection. Chen et al[43] confirmed no morphologic changes related to infection in 3 placentas of COVID-19–positive mothers. All 3 neonates also tested negative for SARS-CoV-2. Although these findings are consistent with reports suggesting minimal to no risk of vertical transmission,[42,43,64] Penfield et al[65] reported positive SARS-CoV-2 results in 3 of 11 placental swabs from COVID-19–positive mothers. All 3 of the neonates also tested negative. Whether vertical transmission truly occurred, or whether neonates were swabbed too early (during the incubation period) is unclear.

Shah et al[66] published a well-structured classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates that gives the opportunity to consider the risk of maternal to fetal or neonatal transmission beyond just vertical transmission. The classification includes congenital infection from intrauterine death/stillbirth, congenital infection in live-born infants, neonatal infection acquired intrapartum, or neonatal infection acquired postnatally. In addition, several professional societies have provided guidelines for the management of

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TABLE 2. Consensus on Recommendations Classified by Phase of Care of Pregnancy

Antepartum care

Title	Prenatal infection screening	Prenatal appointment	US frequency	US equipment/patient rooms	Antenatal surveillance	Antenatal corticosteroids	GBS screening
Consensus on recommendations	Triage symptomatic patients via telehealth Test anyone with new flulike symptoms Prioritize high-risk patients: older, immunocompromised, advanced HIV, homeless, hemodialysis Use drive-through or standalone testing area All suspected cases should be screened using qRT-PCR Symptomatic patients should be treated as positive until results are back Repeat testing in 24 h if negative but still high suspicion	Elective and nonurgent appointments should be postponed or completed by telehealth Encourage use of telehealth for all visits HCW meetings should be conducted via virtual/audio platform, if feasible Reserve F2F visits for 11-13, 20, 28, 36 wk and weekly after 37 wk Complete laboratory tests and US on same visit day Limit support person at outpatient F2F visits	Consensus: Continue US as medically indicated when possible SMFM suggestions: Combine dating and nuchal translucency US in first trimester Anatomy scan at 20-22 wk Consider stopping serial CL after anatomy US if transvaginal US CL ≥35 mm, previous preterm birth at >34 wk Body mass index >40: schedule at 22 wk to reduce risk of suboptimal views/need for follow-up Single growth F/U at 32 wk Low-lying placenta F/U 34-36 wk	Must be cleaned with disinfectant per manufacturer guidelines after EVERY use Deep clean all instruments and room in the case of a positive patient	Reserve for medically indicated screening Limit NST <32 wk Twice weekly NST only for fetal growth restriction with abnormal umbilical arterial Doppler studies, complicated monochorionic twins, or Kell-sensitized patients with significant titers If patient needs US, perform biophysical profile instead of NST Kick counts instead of NST for low-risk patients Daily NST if patient hospitalized	Should continue if <34 wk, even if tested positive for COVID-19 Balance risks and benefits for 34 0/7 to 36 6/7 wk Other modifications should be individualized	As indicated between 36 0/7 and 37 6/7 wk gestation Consider grouping with other visits in the same time frame Patients can self-collect with proper instructions if the resources and infrastructure allow

Intrapartum care

Title	Predelivery preparation/ screening	Delivery location	Delivery time	Mode of delivery	Support person	Obstetric analgesia and anesthesia	Oxygen use	Second stage of labor	Third stage of labor	Umbilical cord clamping	PPE
Consensus on recommendations	Social distancing and off work for 2 wk before anticipated delivery (start at ~37 wk) Screen patient and partner on phone day before admission Limit HCW staffing to only essential staff	Designated isolation room, for suspected or confirmed cases of COVID-19	Based on routine obstetric indications Early delivery should be considered for critically ill patients No contraindications to IOL unless there are limited beds	Based on routine obstetric indications COVID-19 infection is not an indication for CD Expedite delivery by CD in the setting of fetal distress or maternal deterioration Water births should be avoided	Allowed 1 consistent asymptomatic support person	No evidence against regional or general anesthesia Epidural analgesia is recommended to women with suspected or confirmed COVID-19 to minimize the need for GA if urgent delivery is needed Avoid use of nitrous oxide	Do not use oxygen for intrauterine resuscitation Consider aerosolizing HCWs must wear appropriate PPE (N95)	Do not delay pushing Consider shortening with operative delivery to minimize aerosolization and maternal respiratory effort	Consider active management to reduce blood loss (national blood shortage)	Delayed cord clamping is still recommended in the absence of contraindications Avoid delayed cord clamping in confirmed and suspected cases	-Asymptomatic or negative patients: Patient and provider wear surgical mask Aerosolizing procedures: N95 for patient and N95, gown, gloves, face shield for provider

	Postpartum care					
Title	Placental and fetal tissue	Length of stay	Breastfeeding	Skin to skin	Postpartum pain control	Postpartum visit
Consensus on recommendations	ISUOG recommendations: Should be handled as infectious tissue in positive patients Consider qRT-PCR on placenta	Expedited discharge should be considered if stable. VD → 1 d CD → 2 d	Limited evidence to advise against breastfeeding Advise patients to (1) practice respiratory hygiene during feeding, (2) wear a mask, (3) wash hands before and after touching the baby, (4) routinely clean and disinfect surfaces they have touched During separation, encourage dedicated breast pumping	Routine precautionary separation of a healthy baby and mother is not advised Encourage good hygiene and appropriate PPE for COVID-19–positive patients	No contraindication to NSAID use	Encourage telehealth for postpartum visit Limit F2F visits only for medically necessary concerns

CD = cesarean delivery; CL = cervical length; COVID-19 = coronavirus disease 2019; F2F = face to face; F/U = follow-up; GA = general anesthesia; GBS = group B streptococcus; HCW = health care worker; HIV = human immunodeficiency virus; IOL = induction of labor; ISUOG = International Society of Ultrasound in Obstetrics and Gynecology; NSAID = nonsteroidal anti-inflammatory drug; NST = nonstress test; PPE = personal protective equipment; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction; SMFM = Society for Maternal-Fetal Medicine; US = ultrasonography; VD = vaginal delivery.

COVID-19 during pregnancy. The overall summaries from these professional bodies are consistent, with some variation in the strength of recommendations.[119]

CURRENT GUIDELINES FOR COVID-19 MANAGEMENT IN PREGNANCY

Professional perinatal societies, including the Society for Maternal-Fetal Medicine (SMFM)[62,67] and the American College of Obstetricians and Gynecologists (ACOG)[68,69] from the United States, the Royal College of Obstetricians and Gynaecologists (RCOG)[61] from the United Kingdom, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG),[70] the Centers for Disease Control and Prevention (CDC),[71,72] and the World Health Organization (WHO),[73] have developed guidelines for the care of pregnant patients. Herein we summarize the most current guidelines, updated as of April 22, 2020. A total of 9 papers were identified from 6 societies: SMFM, ACOG, RCOG, ISUOG, CDC, and WHO.

A summary of these guidelines is outlined in Table 2, divided into three sections: antepartum, intrapartum, and postpartum care. The guidelines provide practical management recommendations that institutions can adapt to their infrastructures and resource availability. The recommendations from the SMFM focus on high-risk pregnancies, and those from the ACOG and the RCOG focus on all pregnancies. The WHO and the CDC focus on recommendations that can be generalized across all patient populations, and ISUOG focuses on sonography and care of ultrasound equipment.

Prenatal/Antepartum Care

The consensus among all societies recommends the use of telehealth for prenatal visits. Ultrasound and antenatal surveillance should be combined with visits for laboratory tests or prenatal care. Patients should be screened for symptoms, travel history, and contact history before any face-to-face visits; those who are symptomatic or meet the criteria should undergo testing for SARS-CoV-2 using qRT-PCR. Appropriate personal protective equipment (PPE) should be worn by patients

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and health care workers. Administration of antenatal corticosteroids for fetal lung maturation should still be considered if a pregnancy is between 24 0/7 and 33 6/7 weeks' gestation, but the risk/benefit balance needs to be discussed by the multidisciplinary team. Data on the use of corticosteroids during late preterm (34 0/7 to 36 6/7 weeks) are still controversial, but routine administration is not advised.[67]

Intrapartum Care

Institutions should have a designated area for triaging, screening, and admitting SARS-CoV-2—positive patients. The mode and timing of delivery should follow routine obstetric indications, keeping in mind that COVID-19 alone is not an indication for CD, unless there is fetal distress or deteriorating maternal clinical status. Societies recommend that only 1 consistent healthy asymptomatic individual providing support should be present during labor and delivery. Aerosol-generating procedures, including forceful pushing during the second stage of labor and oxygen supplementation for intrauterine resuscitation, should be limited and appropriate PPE (N95) worn. Water births are contraindicated due to the limited ability to monitor mother and baby, and the risk of fecal transmission.

Postpartum Care

Breastfeeding should not be discouraged, and mother and baby separation is not advised, unless the mother is acutely ill. Mothers are advised to follow appropriate respiratory hygiene by wearing masks during skin-to-skin contact and breastfeeding. Mothers should wash hands before handling their babies or touching pumps or bottles and should avoid coughing while their babies are feeding. All surfaces and breast pumps should be sanitized after each use. In an effort to limit infection exposure, hospital length of stay should be decreased to 1 day for vaginal deliveries and 2 days for CDs. Postpartum visits should be performed through telehealth and patients advised to continue compliance with social distancing after discharge. The method of telehealth should be individualized based on institution resources and availability.

IMPLICATIONS OF COVID-19 IN SPECIAL PREGNANT PATIENT POPULATIONS

Evidence on the potential outcomes of SARS-CoV-2 infection in pregnancies already complicated by congenital anomalies is lacking. Given the severity of some potentially life-threatening congenital conditions as well as the disease-altering effects of fetal interventions, these procedures are considered urgent essential medical services. Therefore, necessary adjustments to the prenatal evaluation and selection of fetal intervention candidates have been proposed to better adapt this essential service to the ongoing pandemic. Perhaps the most important factor to consider is the potential risk of vertical transmission induced by the invasive nature of these procedures.

There is no definitive evidence of in utero transmission from SARS-CoV-2 to date. Some case reports[48,51,58] have reported possible vertical transmission due to positive amniotic fluid SARS-CoV-2 PCR test results, but most of the limited patient series reported in the literature indicate a low to negligible risk.[74,75] Evidence is rapidly accumulating, and this consensus may change as more patients with COVID-19 in pregnancy are reported.

Prenatal Diagnosis

In the event of a suspected or confirmed fetal anomaly, additional evaluation (fetal echocardiography, amniocentesis, chorionic villus sampling [CVS], or cordocentesis) may be indicated to identify patients who could benefit from fetal interventions.

Prenatal diagnostic evaluations may be classified as invasive or noninvasive depending on the risk of vertical transmission and exposure of patients and health care workers to SARS-CoV-2. Imaging studies, including ultrasonography and fetal echocardiography, are considered noninvasive (with no risk of vertical transmission), but specific precautions, including hygiene and use of appropriate PPE, should be applied to the patient and examiner, as well as proper care of the sonogram and ultrasound suite.[76] For

patients with suspected or confirmed SARS-CoV-2 infection, consideration should be given to postponing prenatal imaging until asymptomatic, if safely feasible.

Invasive diagnostic tests (CVS, amniocentesis, and cordocentesis) are associated with a theoretical risk of vertical transmission because these procedures may directly correlate with the risk of fetomaternal hemorrhage.[74] Chorionic villus sampling, which is usually performed between 10 0/7 and 13 6/7 weeks' gestation, may be offered to patients with a low risk of SARS-CoV-2 infection (asymptomatic or negative screening result). For symptomatic patients with suspected or confirmed SARS-CoV-2, invasive diagnostic tests can be delayed if safely feasible. If genetic testing cannot be delayed, amniocentesis (usually performed after 14 0/7 weeks' gestation) should be performed instead of CVS owing to the theoretical lower risk of vertical transmission if transplacental access is avoided. Amniocentesis can also be offered to all asymptomatic or confirmed SARS-CoV-2—negative patients.[74] Fetal blood sampling/transfusion is another invasive procedure with a theoretical risk of vertical transmission. This intervention may be offered to patients with confirmed negative SARS-CoV-2 PCR but should be delayed (if feasible and safe) in those who are symptomatic or positive for SARS-CoV-2.[74]

Fetal Therapy

The Mayo Clinic Fetal Center follows the recommendations of the North American Fetal Therapy Network (NAFTNet), which currently recommends that fetal interventions be provided as much as resources allow due to the time-sensitive nature of conditions amenable to fetal therapy.[77] Specific institutional policies may vary, but, in general, all fetal interventions that have been established as the standard of care (for select patients) should continue to be provided, taking the necessary perioperative precautions. Conversely, innovative or experimental procedures that are yet to show proven benefit should be individualized. In general, for patients with asymptomatic SARS-CoV-2 infection, fetal intervention can be offered. For symptomatic patients, it is recommended that fetal therapy be postponed until maternal conditions stabilize and patients have recovered from the disease. Some examples of fetal surgeries that are still currently offered at Mayo Clinic include fetoscopic laser ablation of placental anastomoses for twin-to-twin transfusion syndrome,[78] in utero repair of spina bifida,[79] intrauterine fetal blood transfusion,[80] in utero intervention for lower urinary tract obstruction,[81] fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia,[82] in utero procedure for fetal tumors associated with hydrops,[83] and in utero intervention for severe congenital heart defects.[84]

TREATMENT OF COVID-19 IN PREGNANT PATIENTS

No drugs have been proved to be effective and safe to use for the treatment of COVID-19 to date. Table 3 outlines the medications or therapies used in various research protocols under investigation, as well as their safety for use in pregnancy. In addition, because the pro-coagulatory state of pregnancy may contribute to thrombotic risks associated with COVID-19, thromboprophylaxis, which is currently advised for patients with COVID-19,[113] should be considered for pregnant patients as well.

There are 6 candidate vaccines under phase 1 or 2 clinical trials and 77 more candidate vaccines in preclinical evaluation as of April 23, 2020.[114] Many vaccines use the spike protein (S protein) as their platform and present as forms of recombinant protein-based vaccines, live attenuated vaccines, inactive viral vaccines, and viral-vector—based vaccines.[115] Live attenuated vaccines are generally contraindicated in pregnancy, but exceptions may be made during pandemic situations (exception for smallpox vaccine). As with any drug under development, assessment for safety in pregnancy is conducted after initial safety data become available from clinical studies.[116] Although it is essential to guarantee safety, an unfortunate impact of delaying research in pregnancy is that vaccinations for pregnant women may also be delayed. This is especially problematic during a pandemic or epidemic, as evident from lessons learned from the Ebola outbreak.[117]

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TABLE 3. Treatment Options for COVID-19

Treatment strategy	Mechanism of action	Effectiveness	Safety in pregnancy
HCQ/chloroquine[85]	Reduces inflammatory cytokines[86]; interferes with ACE2 receptor synthesis.[87,88]	Reduction of body temperature recovery time and cough remission, pneumonia recovery, improved CT findings, nasopharyngeal viral clearance.[89-91]	Generally considered safe in pregnancy and frequently used for patients with autoimmune disease.[92] Efficacy unproven. Concern for prolonged QTc.
HCQ and azithromycin	Reduction of viral replication and IL-6 and IL-8 production.[87,93]	Improved nasopharyngeal viral clearance.[90]	HCQ: as above. Azithromycin: considered safe.[94]
Lopinavir/rotinavir	Inhibition of 3-chymotrypsin-like protease.[86,95,96]	Reduced mortality.[97]	Good safety profile in pregnant patients with HIV.[98]
Remdesivir	Inhibition of viral RNA-dependent RNA polymerase.[99]	Clinical trial still underway. Reduction in duration of hospital stay and mortality.[100]	Not yet FDA approved.
Anakinra	IL-1 inhibitor.	Clinical trial still underway.	Insufficient data to determine risk in pregnancy.[101]
Siltuximab	Human-mouse chimeric monoclonal antibody against IL-6.	Improvement in clinical condition in one-third of patients.[102]	Insufficient data to determine risk in pregnancy.[103]
Sarilumab	Recombinant IL-6 receptor monoclonal antibody.	No data yet from randomized clinical trials or observational studies.[85]	Insufficient data to determine risk in pregnancy.[85]
Tocilizumab	Recombinant IL-6 receptor monoclonal antibody.	No data yet from randomized clinical trials or observational studies.[85]	Insufficient data to determine risk in pregnancy.[85]
Interferon	Antiviral cytokines.	No data yet from randomized clinical trials or observational studies.[85]	Varying adverse effect profiles in various preparations.
Corticosteroid	Anti-inflammatory actions.[104]	Reduced mortality in patients with ARDS.[105] Faster improvement in patients with severe COVID pneumonia.[106]	Considered safe, approved for lung maturation in preterm birth.[107]
ACE inhibitors or angiotensin receptor blockers	ACE2 receptor is the cell receptor for viral entry for COVID-19 virus.[108,109]	No data yet from randomized clinical trials or observational studies[85]	Contraindicated in pregnancy.[110,111]
Convalescent plasma	Convalescent plasma from recently recovered donors targeting COVID-19 virus.	10 Patients with clinically severe COVID-19 were given 200 mL of convalescent plasma. Increase in oxyhemoglobin saturation by day 3, and improved lymphocyte count as well as CRP levels were noted.Several studies are currently underway.[112]	No data on safety in pregnancy. However, specific immunoglobulins as for varicella are used in pregnancy.[103]

ACE = angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CT = computed tomography; FDA = Food and Drug Administration; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; IL = interleukin.

FUTURE PERSPECTIVES

The presented data are preliminary, collected over 4 months and likely to change once large data sets become available. However, the projected course of COVID-19 on the morbidity and mortality of pregnant patients during these challenging times is unprecedented. Racial disparities are known to exist in the obstetric literature.[118] Global health crises subject racial and ethnic minorities, as well as patients with immunocompromised comorbidities, to poorer outcomes. We

envision that national and international perinatal societies will focus on the unique challenges faced by vulnerable patient populations that are burdened with physical, emotional, and social crises, with a focus on improving outcomes for all pregnant patients.

CONCLUSION

Given differing physiology during gestation, pregnancy represents a vulnerable state that may be associated with a greater risk of SARS-CoV-2 infection and subsequent worse COVID-19 outcomes. Global efforts to fast track publication of data on COVID-19 in pregnancy, albeit limited, have allowed us to form a framework to care for these patients. Early reports suggest higher rates of preeclampsia and other pregnancy-related complications with SARS-CoV-2 infection during pregnancy, thus adding urgency to the pursuit of research into optimal COVID-19 treatment and preventive strategies during pregnancy.

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Abbreviations and Acronyms: **ACE2** = angiotensin-converting enzyme 2; **ACOG** = American College of Obstetricians and Gynecologists; **Ang** = angiotensin; **ARDS** = acute respiratory distress syndrome; **CD** = cesarean delivery; **CDC** = Centers for Disease Control and Prevention; **CL** = cervical length; **COVID-19** = coronavirus disease 2019; **CRP** = C-reactive protein; **CT** = computed tomography; **CVS** = chorionic villus sampling; **F2F** = face to face; **FDA** = Food and Drug Administration; **F/U** = follow-up; **GA** = general anesthesia; **GBS** = group B streptococcus; **HCQ** = hydroxychloroquine; **HCW** = health care worker; **HIV** = human immunodeficiency virus; **ICU** = intensive care unit; **IL** = interleukin; **IOL** = induction of labor; **ISUOG** = International Society of Ultrasound in Obstetrics and Gynecology; **NAFTNet** = North American Fetal Therapy Network; **NSAID** = nonsteroidal anti-inflammatory drug; **NST** = nonstress test; **PPE** = personal protective equipment; **qRT-PCR** = quantitative reverse transcriptase polymerase chain reaction; **RAAS** = renin-angiotensin-aldosterone system; **RCOG** = Royal College of Obstetricians and Gynaecologists; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SMFM** = Society for Maternal-Fetal Medicine; **TMPRSS2** = transmembrane serine protease 2; **US** = ultrasonography; **VD** = vaginal delivery; **WHO** = World Health Organization

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