Management of Coronavirus Disease-2019 Infection in Pregnancy

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KEYWORDS

- COVID-19 • SARS-COV-2 • Pregnancy • Antepartum • Obstetrics

KEY POINTS

- Pregnancy is inherently associated with an increased risk of severe illness and poor fetal outcomes related to coronavirus disease-2019 (COVID-19) infection.
- Although evidence for the management of pregnant patients with COVID-19 infection is limited, all major guidelines argue against the withholding of therapeutics solely due to pregnancy.
- Oxygenation goals in pregnancy are higher (saturations $\geq$ 95% or PaO2 > 70 mm Hg), leading to the achievement of "severe illness" status and the need for adjustments to therapeutic decisions earlier than nonpregnant counterparts with COVID-19 infection.
- The basic tenets of COVID-19-related acute respiratory distress syndrome and critical illness management are largely the same for pregnant patients as in nonpregnant patients, with exception of oxygenation goals, lower recommended PCO2 ranges, and a need for fetal monitoring.
- Pregnancy is not a contraindication to extracorporeal membrane oxygenation (ECMO) cannulation. Referral to an ECMO-capable institution should be considered for pregnant patients with refractory hypoxia despite maximum therapy.

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has had far-reaching impacts on the provision of health care to many populations. As providers learned in real-time how to care for all-comers with COVID-19 infection, there came the realization that pregnancy is associated with more severe illness and poor maternal and fetal outcomes. In this light, navigating the literature to determine the appropriate care has been particularly important for physicians caring for pregnant women.

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Epidemiologically, the data suggest that pregnant patients have similar positive test rates to the general local population,[1] and that the majority of pregnant patients with COVID-19 infection experience mild disease.[2] In comparison to their nonpregnant age-matched counterparts; however, pregnant patients have an increased risk of severe illness including intensive care unit (ICU) admission and need for mechanical ventilation and extracorporeal membrane oxygenation (ECMO) support.[1,3,4] Similarly, pregnant patients with COVID-19 have a higher incidence of poor fetal and neonatal outcomes and death than noninfected pregnant patients.[1]

Several groups have provided recommendations for the care of pregnant patients during the COVID pandemic,[5–8] relying on general population data, animal safety studies, and expert opinion. One important overarching theme is clear across them: therapy needed for the management of COVID-19 should not be withheld solely based on pregnancy.

EVALUATION

The level of the diagnostic evaluation in pregnant patients presenting with a viral syndrome suspicious of COVID-19 is essentially the same as for nonpregnant patients and depends on their apparent illness severity and baseline comorbidities. Patients with mild flu-like illness may only need testing to evaluate for flu and COVID, for example, whereas symptoms of *per os* intolerance and diarrhea may require bloodwork, and critical illness requires much more.

Specific considerations in pregnant individuals include the determination of fetal well-being. This evaluation includes asking about abdominal cramping, leakage of vaginal fluid or vaginal bleeding, and presence of fetal movement if gestational age-appropriate, and performing a point-of-care-ultrasound (POCUS) assessment of fetal heart rate. Appropriate chest imaging should not be avoided if indicated, as the radiation exposure is relatively low,[9] and presence of infiltrates inform further care. Finally, evaluation for exertional hypoxia is necessary for any pregnant individual with moderate COVID-19 infection without evident hypoxia at rest.

CLASSIFICATION OF DISEASE SEVERITY

Management of COVID-19 infection is primarily dependent on illness severity. The range of clinical presentation of COVID-19 infection is wide and the definition of illness categories may vary slightly across clinical guidelines and studies. This article uses the definitions as delineated in the National Institutes of Health (NIH) guidelines,[7] (**Table 1**) which are generally accepted by the Society for Maternal-Fetal Medicine (SMFM).[5]

(Placeholder: see **Table 1**. COVID-19 Infection Severity Classification[7]).

Coronavirus Disease-2019 Therapeutics

This article will briefly discuss pharmacologic therapies currently recommended by major societies and panels, which are summarized in **Tables 2** and **3**. Pregnancy remains an independent risk factor for progression to severe disease and adverse outcomes, and both the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have been explicit in their statements that appropriate therapies should not be withheld from pregnant patients.[5,6]

(Placeholder: **Table 2**. Recommended therapies for COVID-19 management).

Antivirals

Nirmatrelvir/ritonavir (paxlovid)

Recommended for the management of symptomatic outpatients with a risk of progression to severe disease,[10] ritonavir-boosted nimatrelvir decreases the risk of

Table 1
Coronavirus disease-2019 infection severity classification

Severity Class	Presentation
Asymptomatic Or Presymptomatic	Positive COVID-19 test without symptoms
Mild	Flu-like symptoms (ex: fever, cough, sore throat, vomiting, diarrhea, malaise) *No* dyspnea or hypoxia and normal chest imaging
Moderate	Evidence of lower respiratory tract disease by symptoms or imaging $SpO_2 \geq 95\%$ on room air
Severe	Respiratory rate > 30 breaths/minute Hypoxia with $SpO_2 < 95\%$ on room air PaO_2 to FiO_2 ratio < 300 Lung involvement on imaging > 50%
Critical	Multisystem organ dysfunction Circulatory shock Respiratory failure requiring HFNC or MV

Abbreviations: FiO_2, fraction of inspired oxygen; HFNC, high flow nasal cannula; MV, mechanical ventilation (invasive or noninvasive); PaO_2, arterial partial pressure of oxygen; SpO_2, oxygen saturation.

hospitalization and mortality in COVID-19 infection.[11] Though the EPIC-HR trial supporting its use excluded pregnant and lactating individuals, the combo is still recommended for patients in this category who are pregnant,[5,7] based on an assessment of the low risk of harm given existing animal safety data[12] and small case series.[13]

Remdesivir

Remdesivir was one of the earliest antivirals available for the management of COVID-19, used in hospitalized patients in the ACTT-1 trial with earlier disease recovery.[14] Remdesivir has also been studied in outpatients at high risk of progression to reduce the risk of hospitalization and death.[15]

In pregnancy specifically, evidence regarding the use of remdesivir to treat COVID-19 is accumulating but is primarily observational. A small study suggested that early administration of remdesivir (within seven days of symptom onset) is associated with a decreased likelihood of progression to critical disease or ICU admission as well as decreased length of hospitalization.[16] A case series of pregnant individuals described clinical improvement and no adverse events after remdesivir,[17] and a recent systematic review noted a high rate of recovery among remdesivir-treated pregnant patients, significantly higher than those not treated.[18] Better outcomes were seen in patients with better baseline health and drug administration within 48 hours of presentation.[18]

Animal reproductive studies have not shown adverse fetal effects,[19] and prior use in the treatment of Ebola-infected pregnant individuals also support its safety.[20] The most demonstrated adverse event is transaminitis, with higher levels seen with 10-day versus 5-day treatment regimens. These lab abnormalities have not resulted in poor clinical outcomes and eventually resolve on cessation of the drug,[18] making it quite reasonable to use remdesivir for a planned 5-day course, with the determination to continue to 10 days if deemed necessary.

Molnupiravir

Molnupiravir is another second-line antiviral therapy with lower efficacy and no human pregnancy data. Although the FDA and WHO recommend against its use in pregnancy due to teratogenicity noted in animal studies,[21] the NIH panel suggests that molnupiravir can be a reasonable last option for pregnant patients at particularly high risk of

Table 2
Recommended therapies for coronavirus disease-2019 management

Drug Class	Name	Indication	Dose	Side Effects	Pregnancy Consideration
Antivirals	Nirmatrelvir/Ritonavir (Paxlovid)	Outpatients with mild/moderate severity at high risk for severe illness ≤5 days onset	Nirmatrelvir 300 mg/RTV 100 mg twice daily for 5 days eGFR ≥30 to 60 mL/min: Nirmatrelvir 150 mg/RTV 100 mg twice daily for 5 days	• GI effects • Hypertension • Myalgias • Angioedema; hypersensitivity reactions	Nirmatrelvir: no safety data RTV considered safe Not recommended by WHO
	Remdesivir	Mild/moderate severity at high risk for severe illness Severe illness not on MV/ECMO ≤7 days onset	200 mg IV on day 1, then IV daily Mild/moderate: 3 days Severe: 5-10 days	No increase from placebo	Considered safe Requires multiple IV doses
	Molnupiravir	Outpatients with mild/moderate severity at high risk for severe illness ≤5 days onset	800 mg twice daily for 5 days	No increase from placebo	NIH/SMFM: last option if other therapies unavailable Not recommended by WHO or FDA
Monoclonal Antibodies	Tixagevimab/Cilgavimab (Evusheld Casirivimab/Imdevimab (REGEN-COV) Sotrovimab	Outpatients with mild/moderate severity at high risk for severe illness ≤7 days onset	175 mg IV over 30 seconds	Hypersensitivity reactions No increase from placebo	2nd line therapy Limited data Generally considered safe
	Bebtelovimab	Not currently recommended for treatment given low efficacy against circulating variants			

Steroids	Dexamethasone	Severe/critical illness	6 mg daily for 10 days ARDS: 20 mg IV daily x 5 days then 10 mg daily x 5 days	Hyperglycemia	Dexamethasone crosses the placenta, risk of neonatal adrenal insufficiency depending on duration/timing of delivery
JAK Inhibitors	Baricitinib	Severe/critical illness ≤ 7 days onset	4 mg PO daily for 14 days or until hospital discharge eGFR 30-59: 2 mg daily eGFR 15-29: 1 mg daily eGFR <15: not for use	No increase from placebo • Cytopenias • Transaminitis • Thrombosis	No safety data
	Tofacitinib	Severe/critical illness with baricitinib unavailable (no set limit)	10 mg twice daily for 14 days or until hospital discharge eGFR <30: 5 mg twice daily ESRD: 5 mg twice daily, give dose after HD on HD days	• Thrombosis • Cardiovascular events • GI perforation	No evidence of fetal adverse effects Must use with VTE prophylaxis
IL-6 Receptor Antagonists	Tocilizumab	Severe/critical illness	8 mg/kg IV once (maximum dose 800 mg)	• Transaminitis • Activation of latent infection	Animal studies with evidence of fetal toxicity at high doses Appears safe in COVID-19
	Sarilumab	Severe/critical illness with tocilizumab unavailable	400 mg IV once	• Cytopenias • Transaminitis • Activation of latent infection	No human safety data Appears safe in animals

Abbreviations: ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FDA, Federal Drug Administration; GI, gastrointestinal; HD, hemodialysis; IL-6, interleukin-6; IV, intravenous; JAK, Janus kinase; kg, kilogram; mg, milligram; mL/min, milliliter per minute; NIH, National Institutes of Health; RTV, ritonavir; SMFM, Society of Maternal Fetal Medicine; WHO, World Health Organization.

Data from [National Institutes of Health COVID-19 Treatment Guidelines Panel. Clinical Management of Adults. Updated 26 Sept 2022. Available at: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/. Accessed 22 Nov 2022.] *and* [Society for Maternal-Fetal Medicine. COVID-19 Outpatient Therapy for Pregnant Patients. Updated 21 Jun 2022. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://s3.amazonaws.com/cdn.smfm.org/media/3526/COVID_treatment_table_6-21-22_%28final%29.pdf. Accessed 22 Nov 2022.]

Table 3
Major recommendations for coronavirus disease-2019 therapy based on severity of illness[5,8,10,31]

Illness Severity	Major Guidelines		
	WHO	**NIH/SMFM[a]**	**IDSA**
Asymptomatic Mild Moderate	High risk: Remdesivir Avoid Nirmatrelvir/Ritonavir and Molnupiravir[b]	High risk, not hospitalized: *Preferred* 1st: Nirmatrelvir/Ritonavir 2nd: Remdesivir *Alternative*: Molnupiravir Hospitalized: Remdesivir	Not hospitalized: Remdesivir *Can consider convalescent plasma if immunosuppressed* High risk: Add Nirmatrelvir/Ritonavir (not Molnupiravir)[b] Hospitalized: Remdesivir
Severe	Dexamethasone AND Tocilizumab (2nd: Sarilumab) AND Baricitinib *Consider addition of Remdesivir*	"Minimal" O2: Remdesivir Conventional O2: Remdesivir AND Dexamethasone Rapid progression/Systemic inflammation[c]: Add Baricitinib or Tocilizumab	Dexamethasone AND Remdesivir AND Baricitinib (2nd: Tofacitinib) Rapid progression/Systemic inflammation[c]: Add Tocilizumab (2nd: Sarilumab)
Critical	Dexamethasone AND Tocilizumab (2nd: Sarilumab) AND Baricitinib	Dexamethasone AND Baricitinib (2nd line: Tofacitinib) OR Tocilizumab (2nd line: Sarilumab) *If not yet requiring MV or ECMO: can add Remdesivir*	Dexamethasone AND Tocilizumab (or 2nd: Sarilumab)

Abbreviations: NIH, National Institutes of Health COVID-19 Treatment Guidelines; SMFM, Society for Maternal Fetal Medicine. WHO, World Health Organization.

[a] Follows NIH Clinical Guidelines.
[b] Pregnancy-specific recommendation.
[c] C-reactive protein >75 mg/L.

severe disease unable to receive other therapies, especially during later gestation after embryogenesis.[7]

Monoclonal Antibodies

A variety of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)-targeting monoclonal antibodies are available for use to prevent the progression of COVID-19 disease severity. Bebtelovimab was the last available antibody under an emergency use authorization (EUA) by the FDA for use in the treatment of COVID-19, but this EUA was rescinded in November 2022 due to lack of efficacy against circulating variants. Tixagevimab/cilgavimab (brand name Evusheld) is under FDA EUA for pre-exposure prophylaxis but not therapy. Of note, European Union's European Medicines Agency supports the use of tixagevimbab/cilgavimab in treatment, due to some existing evidence of its efficacy.[22,23] Diminished efficacy against the newer variants has led to the FDA removing its EUA for the use of casirivimab/imdevimab (REGEN-COV), sotrovimab, and bamlanivimab/etesevimab at this time.[24]

The actual data on bebtelovimab use in pregnancy are limited, with existing literature on monoclonal antibody efficacy and safety in pregnant women generally including the earlier generation antibodies. These studies are primarily retrospective in nature but support clinical efficacy in preventing the progression to severe COVID-19 infection.[25–29] Hypersensitivity reactions, including anaphylaxis, have occurred and remain a risk with monoclonal antibody administration, and one case series reported a subsequent early delivery necessitated by fetal distress,[29] but with this singular exception, the safety profile appears to be relatively favorable.[30]

Immunomodulators

Janus kinase inhibitors (baricitinib and tofacitinib)

Many immunomodulatory drugs have been evaluated for the management of COVID-19. The Janus kinase (JAK) inhibitors baricitinib and tofacitinib are currently recommended by the Infectious Disease Society of America (IDSA) for the treatment of severely to critically ill patients with COVID-19 infection,[31] with a stronger recommendation for baricitinib based on multiple trials in nonpregnant patients indicating decreased need for mechanical ventilation and 60-day mortality, whether used alone or in conjunction with dexamethasone or remdesivir.[32,33] The data for tofacitinib is less robust, but its use was associated with reduced incidence of death or progressive respiratory failure when given in conjunction with dexamethasone.[34]

Although no differences in rates of adverse events were seen in the COVID-19 studies, both drugs have been associated with increased thrombotic risk,[35] a factor of potential concern given the existing increased risk of venous thromboembolism (VTE) in pregnancy. This risk should be considered in the context of JAK inhibitors' potential to reduce both progression to respiratory failure that leads to lengthy immobility as well as the systemic inflammation which is presumed to lead to thrombotic risk in COVID-19 infection. All pregnant patients hospitalized due to COVID-19 infection should receive pharmacologic VTE prophylaxis unless specifically contraindicated.[5,6] Although limited, the existing literature does not support an increased frequency of poor fetal outcomes with maternal baricitinib or tofacitinib use in other autoimmune disorders.[36–38]

Interleukin-6 inhibitors (tocilizumab and sarilumab)

Tocilizumab is the primary interleukin-6 (IL-6) receptor antagonist currently recommended for use.[5–8,31] Used in conjunction with corticosteroids in the treatment of severe to critically ill COVID-19 infection and systemic inflammation (widely defined as a C-reactive protein level >75 mg/L), it has been associated with lower mortality,

decrease in progression to mechanical ventilation, and earlier discharge in the general population.[39,40] The only randomized controlled data in pregnant COVID-19 infection arises from the RECOVERY study, which included 10 pregnant patients.[39]

Clinical safety data for tocilizumab use during pregnancy exist to a small degree in the rheumatologic disease literature.[41,42] There is evidence of higher prematurity and spontaneous abortion rates, but these findings are confounded by concomitant methotrexate use–a known abortifacient–and disease activity in the rheumatologic population. In the limited data from the current pandemic[43–45] there is no evidence of increased congenital malformation risk, although infection has been a continuing concern. One study noted a single CMV reactivation and subsequent congenital CMV,[43] and UK guidelines suggest delay of live vaccines until 6 months of age in case of in utero exposure to tocilizumab.[44]

Corticosteroids

The primary standard medical management of COVID-19 of this severity includes corticosteroids for pregnant patients with saturations of <95% on room air.[46] The RECOVERY trial demonstrating survival benefit with dexamethasone only included 4 pregnant patients,[46] but the marked benefits led to the recommendation that COVID-infected pregnant patients with an oxygen requirement be given steroids according to RECOVERY dosing (6 mg daily for 10 days).[5] In the case that steroids are indicated for fetal lung maturity (<34 weeks), the SMFM recommends dosing of dexamethasone 6 mg IM every 12 h for 48 h before the 6 mg daily dosing for up to 10 days.[5]

Almost coincident with the beginning of the COVID-19 pandemic, the DEXA-ARDS trial was published, adding to the many previous trials with conflicting data regarding steroids in ARDS. DEXA-ARDS demonstrated increased ventilator-free days and decreased mortality among ARDS patients with P:F ratio <200 using a treatment regimen of 20 mg dexamethasone daily for 5 days followed by 10 mg daily for 5 days, without significant adverse effects.[47] With RECOVERY ushering in dexamethasone as a standard treatment for COVID-19 infection, consideration of high-dose dexamethasone for COVID-19-related ARDS seemed natural. In truth, the optimal steroid dose is unclear despite additional signals for benefit in several studies,[48–50] although additional randomized controlled trials are ongoing. Of note, high-dose dexamethasone is not mentioned in guidelines for pregnant individuals with more severe COVID-19 infection.[5]

(Placeholder: **Table 3**. *Recommendations for COVID-19 therapy based on severity of illness*).

MANAGEMENT
Asymptomatic Infection

Pregnant patients with asymptomatic COVID-19 infection, in general, require only maintenance of prenatal and follow-up care. The American College of Obstetricians and Gynecologists (ACOG) has developed recommendations regarding use of telehealth and modification or consolidation of routine prenatal care as necessary to limit exposure to others.[6] Therapies to prevent progression of illness (see **Table 2**) should be strongly considered in all pregnant patients and more so in those with additional risk factors placing them at risk for severe illness. Patients should be advised to follow up closely with their outpatient physician and told when to seek care in case of disease progression.[5,6]

Mild/Moderate Disease

Mild disease involves viral syndromic symptoms without dyspnea, hypoxia, or evidence of lower respiratory tract infection by imaging, whereas moderate disease describes individuals with evidence of lower respiratory disease but without oxygen requirement.

An understanding of oxygenation goals in pregnancy is key to appropriately classify disease severity and therefore management of COVID-19 infections. Goal saturations are higher in pregnant patients due to increased oxygen consumption and occurrence of fetal hypoxia and distress at maternal PaO2 values < 60 mm Hg.[51] In vivo data establishing a PaO2 threshold is limited, but current guidelines continue to recommend a goal saturation of ≥95%, corresponding to a PaO2 ≥70 mm Hg.[5] Although nonpregnant patients would be classified as having a moderate disease with saturations of 94%, in pregnancy this qualifies as severe.

Supportive care

In general, the usual symptomatic management of a viral syndrome can and should be provided: acetaminophen for pain and fever control, increased hydration, and short-term over-the-counter (OTC) decongestants as needed are suitable. Guaifenesin and dextromethorphan are considered safe in pregnancy, as are antihistamines. There are no human studies evaluating the use of phenol throat sprays, but some evidence of fetal toxicity in mice studies,[52] leading to a recommendation to use for only short durations and to gargle and spit rather than swallow the spray.

Coronavirus Disease-specific therapies

Most pregnant patients with COVID-19 infection experience mild illness.[2] Although pregnancy is a standalone risk factor for progression to severe infection, many patients and their physicians may opt to defer specific COVID therapies when the illness is asymptomatic or mild. Emergency physicians should maintain a low threshold to treat those with mild illness but a separate additional risk factor for severe illness, as well as those with the moderate disease even if hospitalization is not required.

Disposition

Low-risk pregnant patients with mild COVID-19 infection can usually be discharged home with appropriate guidance on outpatient follow-up with their obstetrician, appropriate supportive care, and indications for prompt return to the ED. The disposition of patients with lower respiratory disease depends primarily on their overall clinical picture, baseline health, ambulatory status, and ability to care for themselves appropriately at home. Patients with moderate illness may be discharged if they do not experience significant exertional dyspnea and their saturations remain ≥95% on ambulation, if they are able to maintain good oral hydration, and if they have an adequate outpatient follow-up. Otherwise, retention in the hospital for further observation and management is appropriate. Patients requiring hospitalization should be admitted to a facility that can conduct fetal monitoring and provide appropriate obstetric or maternal-fetal medicine consultation if indicated by gestational age and patient-specific risk factors.

Severe Disease

Severe disease is defined as COVID-19 infection with hypoxia requiring supplemental oxygen but not high flow nasal cannula (HFNC) or mechanical ventilation (MV), PaO2/FiO2 ratio < 300, respiratory rate >30 breaths per minute, or >50% lung involvement on imaging.

Coronavirus Disease-specific therapies

Administration of steroids is part of the standard of care for all pregnant patients with COVID-19 infection and an oxygen requirement,[31] with a recommendation to administer in conjunction with remdesivir if within 7 days of symptom onset.[5,10,31] It is worth noting that the current NIH guidelines recommend remdesivir alone without dexamethasone for general patients with a new but "minimal" oxygen requirement,[10] but this

recommendation is not held across all societies and dexamethasone also potentially be indicated for fetal lung maturation depending on the clinical scenario and gestational age.

Current guidelines also recommend initiation of either baricitinib or tocilizumab in patients with rapidly increasing oxygenation needs or laboratory markers demonstrating systemic inflammation.[10,31] Emergency physicians can usually defer this decision to the admitting team or until consultation with pharmacy or the infectious disease specialists can be performed.

Additional considerations

As already discussed, supplemental oxygenation should be given to reach a goal saturation of $\geq$95%. Proning has been associated with improved oxygenation and decreased mortality in intubated patients with severe acute respiratory distress syndrome (ARDS).[53] Similarly, self-proning arose as a therapeutic adjunct early in the COVID-19 pandemic and is a relatively simple intervention that has been proven to increase oxygenation in patients with severe COVID-19,[54–56] but has not been shown to decrease rates of intubation[57] and can be difficult to manage with the gravid abdomen as pregnancy progresses. If the patient is comfortable doing so, it is reasonable to have them rotate through side-lying positions with pillow support or to prone with use of a pregnancy proning pillow,[5] but escalation to needed respiratory supports should not be delayed to see if self-proning will help.

Disposition

Pregnant patients with hypoxia will, of course, require admission. Owing to the risk of fetal distress with maternal hypoxia and need for quick intervention with decompensation, pregnant patients who have reached fetal viability and have the severe disease should be hospitalized in a facility with ready obstetric and neonatal intensive care capability.

Critical Disease

Critical disease describes the requirement of advanced respiratory therapies including HFNC, noninvasive ventilation (NIV), invasive mechanical ventilation (IMV), or ECMO, as well as patients with shock or other organ dysfunction.

Airway and breathing

The physiologic changes of pregnancy result in a decreased functional reserve with increased oxygen demand; prompt respiratory support to achieve saturations $\geq$95% is crucial to avoid fetal distress and poor outcomes. HFNC has previously been associated with a reduced rate of intubation and ICU mortality compared with NIV in general populations of acute respiratory failure.[58] In COVID-19 infection, there are limited data regarding the selection of HFNC compared with NIV. Guidelines suggest initial management with HFNC in COVID-19 infection with acute hypoxemic respiratory failure despite conventional oxygen therapy,[10] although bypassing HFNC for a trial of NIV may be appropriate depending on the patient's mental status, work of breathing, and concern for poor ventilation. No specific recommendations are available for timing of intubation for COVID-19 during pregnancy and must be considered on a case-by-case basis,[5] although delays to needed intubation have been associated with poor outcomes in patients with both COVID[59] and non-COVID respiratory failure.[60,61]

Special considerations in the pregnant population should inform the preparation for endotracheal intubation. The most experienced practitioner should intubate given aforementioned physiologic changes and needs, including reduced functional residual capacity, increased risk of severe hypoxemia and aspiration, likelihood of a more difficult airway and the need to maintain higher maternal oxygen saturation for adequate fetal oxygenation.[51] If the fetus is viable, in addition to standard fetal heart rate and

tocodynamometer monitoring, obstetric and neonatal teams should be present or imminently available, if possible, in case of fetal distress necessitating emergent delivery. Although mechanical ventilation alone is not an indication for delivery, the peri-intubation period presents a time of high risk.

Ventilator management in COVID-19-associated acute respiratory failure should follow the standard guidelines for ventilator management in ARDS. In patients with moderate-severe ARDS, guidelines support a higher PEEP strategy, though this must be assessed based on patient-specific factors some heterogeneity in respiratory failure in COVID-19 patients.[10] With gravid habitus and upward shifting of the diaphragm, a higher PEEP strategy is likely to be beneficial, though there is no formal evidence to support the theory. Minute ventilation is increased in pregnancy, resulting in an average PCO2 of approximately 30 mm Hg and the necessary maternal-fetal gradient to assist in offloading fetal CO2 into the maternal circulation to avoid fetal acidemia. Permissive hypercapnia is a major tenet of lung protective ventilation, but there are no formal studies assessing appropriate PCO2 goals in pregnant ARDS, although values up to 60 mm Hg seems to be reasonably tolerated.[62]

Patients with acute ARDS frequently require sedation and sometimes neuromuscular blockade to tolerate the ventilator settings necessary to improve oxygenation and longer-term outcomes.[63] Deep sedation has been associated with worsened mortality and prolonged mechanical ventilation and hospital length of stay,[64,65] and should *not* be empirically targeted in all patients, but if needed should not be withheld due to concerns of fetal effects.

Circulation

Critical COVID-19 infection can be associated with circulatory shock, whether distributive due to overwhelming systemic inflammation, acidemia, bacterial superinfection, and/or the need to counteract sedative medications that allow ventilator synchrony, or cardiogenic due to myocarditis, or stress-induced versus underlying peripartum cardiomyopathy. Although a fluid restrictive strategy is better for ARDS management,[66] it is important to restore perfusion to the organs, and a 1 or 2-liter bolus of crystalloid is a reasonable initial strategy in light of insensible losses and potential for decreased oral intake or viral gastroenteritis, provided there is no initial concern for cardiogenic shock by physical exam or point-of-care echocardiogram ("echo"). If hypotension persists and patient is volume replete, initiation of vasopressors should be pursued over the additional fluid challenge. Hypotensive patients with signs of volume overload and/or cool extremities and evidence of diminished cardiac function by point-of-care echo should be initiated on inotropic therapy.

Coronavirus Disease-specific therapies

Whether RECOVERY or DEXA-ARDS doses, dexamethasone or an equivalent glucocorticoid, in combination with either baricitinib and/or tocilizumab, are recommended in critically ill patients with COVID-19 infection. see **Table 3**).

Salvage therapy

Critical illness and mechanical ventilation are not specific indications for early delivery, but in patients with severe respiratory failure refractory to maximum therapy beyond 32 weeks gestation, controlled delivery should be considered. After 32 weeks, neonatal major morbidity and mortality are low (8.7% and 0.2%, respectively) with continued decrease as fetal gestational age progresses.[67] Low-level data suggest physiologic improvements in respiratory mechanics in some patients after delivery, although exactly why some benefit and others do not is unclear.[68,69] Delivery could be considered a reasonable option for optimization of both maternal and fetal/neonatal outcomes,

especially in refractory hypoxia and multisystem organ failure, where the risk of decompensation and maternal and fetal mortality is high.

ECMO should be considered as a rescue strategy in pregnant patients with COVID-19 ARDS and refractory hypoxia (PaO2 <70 mm Hg or PaO2:FiO2 ratio <150) or hypercapnia (pH < 7.2 or PCO2 > 80 mm Hg for >6 hours) despite optimal ventilatory management.[5] ECMO cannulation is not in and of itself an indication for delivery, although immediate obstetrical concerns may prompt emergent delivery peri-cannulation; obstetric and neonatal teams should be on hand. If not already at a center with the capability for multidisciplinary ECMO and MFM care, consultation with such a center to assess ECMO candidacy and potential transfer should be considered, especially for those who have not yet reached 32 weeks gestation and should not pursue controlled delivery.

SUMMARY

Recommendations for the optimal care of pregnant patients with COVID-19 infection are mostly extrapolated from study data involving nonpregnant patients, animals, and separate disease states. In general, the management of pregnant patients for both targeted COVID-19 therapies as well as general critical illness mirrors that of nonpregnant patients, and the therapeutic options for each level of illness severity should not be withheld due to gravid state. Ultimately, vaccination is the mainstay of prevention of poor COVID-19 outcomes, and tailoring COVID-19 disease management for pregnant patients will require research to address the many areas of limited evidence.

CLINICS CARE POINTS

- Appropriate COVID therapies should not be withheld solely due to a pregnant state. Up-to-date COVID therapeutic guidlines can be found online on the NIH website: www.covid19treatmentguidelines.nih.gov/.
- For patients requiring hospitalization in their third trimester of pregnancy, transfer to a facility with maternal-fetal medicine and appropriate neonatal intensive care capability should be considered.
- Stabilization of maternal oxygenation and hemodynamics is the best way to stabilize fetal status. While there are no strict criteria to guide timing of intubation, intubation in a controlled setting with the most capable provider is likely to yield the best outcomes.

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