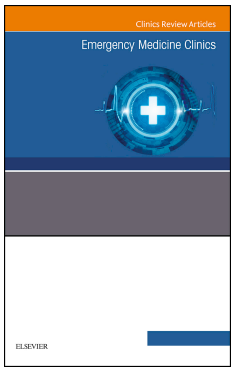
# Journal Pre-proof




Management of COVID-19 Infection in Pregnancy

Vivian Lam, MD MPH, Kami M. Hu, MD FAAEM, FACEP

PII: S0733-8627(22)00114-6

DOI: https://doi.org/10.1016/j.emc.2022.12.004

Reference: EMC 1366

To appear in: *EMERGENCY MEDICINE CLINICS OF NORTH AMERICA*

Please cite this article as: Lam V, Hu KM, Management of COVID-19 Infection in Pregnancy, *EMERGENCY MEDICINE CLINICS OF NORTH AMERICA* (2023), doi: https://doi.org/10.1016/j.emc.2022.12.004.

# Management of COVID-19 Infection in Pregnancy

Vivian Lam, MD MPH
Department of Internal Medicine, Section of Critical Care Medicine
Advocate Christ Medical Center
4440 W 95th Street, Suite AIP
Oak Lawn, IL 60453
Vivian.Lam@aah.org

Kami M. Hu, MD FAAEM, FACEP *_Corresponding author_
Department of Emergency Medicine, Department of Internal Medicine, Division of Pulmonary & Critical Care
University of Maryland School of Medicine
110 S. Paca Street, 6th Floor Suite 200
Baltimore, MD 21201
(667) 214-2208
khu@som.umaryland.edu
@kwhomd

## DISCLOSURES

- Dr. Hu served as a site sub-investigator in the Advarra-sponsored INSIGHT trial, evaluating use of anti-COVID intravenous immunoglobulin for the treatment of COVID-19 infection.
- Dr. Lam has no conflicts of interest to disclose.

## SYNOPSIS

While the majority of pregnant patients who contract SARS-CoV-2 will have a mild course of illness, pregnant patients with COVID-19 are more likely than their nonpregnant counterparts to develop severe illness with an increased risk of poor maternal and fetal outcomes. While the extent of research in this specific patient population remains limited, there are tenets of care with which physicians and other providers must be familiar to increase the chances of better outcomes for the two patients in their care.

**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 COVID-19 infection.
- While 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 ≥ 95% or PaO2 > 70 mmHg), leading to achievement of “severe illness” status and need for adjustments to therapeutic decisions earlier than nonpregnant counterparts with COVID-19 infection.

- The basic tenets of COVID-19-related ARDS 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 ECMO cannulation. Referral to an ECMO-capable institution should be considered for pregnant patients with refractory hypoxia despite maximum therapy.

## INTRODUCTION

The COVID-19 pandemic has had far-reaching impacts on the provision of healthcare to many populations. As providers learned in real-time how to care for allcomers 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.

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 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 on the basis of pregnancy.

## EVALUATION

The level of diagnostic evaluation in pregnant patients presenting with a viral syndrome suspicious for 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, while symptoms of *per os* intolerance and diarrhea may require bloodwork and critical illness requires much more.

Specific considerations in pregnant individuals include determination of fetal wellbeing. 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 informs further care. Finally, evaluation for exertional hypoxia is necessary in 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: **Table 1.** COVID-19 Infection Severity Classification[7])*

## COVID-19 THERAPEUTICS

This chapter 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 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 management of symptomatic outpatients with risk of progression to severe disease, ritonavir-boosted nimatrelvir decreases risk of 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 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 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 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. While 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 severe disease unable to receive other therapies, especially during later gestation after embryogenesis.[7]

**Monoclonal Antibodies**

A variety of SARS-COV-2-targeting monoclonal antibodies are available for use to prevent the progression of COVID-19 disease severity. Bebtelovimab is currently the only antibody currently under an emergency use authorization (EUA) by the FDA for use in the treatment of COVID-19, while 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 is 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 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**

*JAK Inhibitors (baricitinib, 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 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]

*IL-6 Inhibitors (toclizumab, sarilumab)*

Tocilizumab is the primary 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 (6mg daily for 10 days).[5] In the case that steroids are indicated for fetal lung maturity (<34 weeks), the SMFM recommends dosing of dexamethasone 6mg IM every 12h for 48h prior to the 6mg 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 20mg dexamethasone daily for 5 days followed by 10mg 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, while 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 mmHg.[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 mmHg.[5] While nonpregnant patients would be classified as having 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.

*COVID-Specific Therapies*

Most pregnant patients with COVID-19 infection experience mild illness.[2] While pregnancy is a standalone risk factor for progression to severe infection, many patients and their physicians may opt to defer specific COVID therapies when 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 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 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.

*COVID-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 ≥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. Due to risk of fetal distress with maternal hypoxia and need for quick intervention with decompensation, pregnant patients who have reached fetal viability and have severe disease should be hospitalized in a facility with ready obstetric and neonatal intensive care capability.

**Critical disease**

Critical disease describes 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 & Breathing*

The physiologic changes of pregnancy result in a decreased functional reserve with increased oxygen demand; prompt respiratory support to achieve saturations ≥95% is crucial to avoid fetal distress and poor outcomes. HFNC has previously been associated with reduced rate of intubation and ICU mortality compared to NIV in general populations of acute respiratory failure.[58] In COVID-19 infection, there are limited data regarding the selection of HFNC compared to 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. While 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 mmHg 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 mmHg seem 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. While 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 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.

*COVID-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 risk of decompensation and maternal and fetal mortality are high.

ECMO should be considered as a rescue strategy in pregnant patients with COVID-19 ARDS and refractory hypoxia (PaO2 <70 mmHg or PaO2:FiO2 ratio <150) or hypercapnia (pH <7.2 or PCO2 > 80 mmHg 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 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.

## Conclusions

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 with respect to 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.

## References

1. Overton EE, Goffman D, Friedman AM. The Epidemiology of COVID-19 in Pregnancy. Clinical Obstetrics and Gynecology. 2022;65(1):110-122.
2. Schell RC, Macias DA, Garner WH et al. Examining the impact of trimester of diagnosis on COVID-19 disease progression in pregnancy. Am J Obstet Gynecol MFM. 2022;4(6):100728.
3. Zambrano LD, Ellington S, Strid P et al. CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status – United States, January 22-October 3, 2020. US Dept of HHS/CDC MMWR. 2020;69(44):1641-1647.
4. Khan DSA, Pirzada AN, Ali A et al. The Differences in Clinical Presentation, Management, and Prognosis of Laboratory-Confirmed COVID-19 between Pregnant and Non-Pregnant Women: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2021;18:5613.
5. Halscott T, Vaught J, SMFM COVID-19 Task Force. Society for Maternal-Fetal Medicine Management Considerations for Pregnant Patients With COVID-19. Society for Maternal-Fetal Medicine. Available at https://www.smfm.org/covidclinical. Accessed 21 Nov 2022.
6. American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetricians-gynecologists, obstetrics. Washington, DC: ACOG; 2020. Available at: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed 15 Oct 2022.
7. National Institutes of Health COVID-19 Treatment Guidelines Panel. Special Considerations in Pregnancy. Updated 26 Sept 2022. Available at:

https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy/. Accessed 21 Nov 2022.
8. Therapeutics and COVID-19: Living guideline, 22 April 2022. Geneva: World Health Organization; 2022 (WHO/ 2019-nCoV/therapeutics/2022.3). Licence: CC BY-NC-SA 3.0 IGO.
9. Tremblay E, Thérasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics. 2012;32(3):897-911.
10. 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.
11. Hammond J, Leister-Tebbe H, Gardner A, et al.; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-1408.
12. Catlin NR, Bowman CJ, Campion SN, et al. Reproductive and developmental safety of nirmatrelvir (PF-07321332), an oral SARS-CoV-2 $M^{pro}$ inhibitor in animal models. Reprod Toxicol. 2022;108:56-61.
13. Loza A, Farias R, Gavin N, et al. Short-term Pregnancy Outcomes After Nirmatrelvir-Ritonavir Treatment for Mild-to-Moderate Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2022;140(3):447-449.
14. Beigel JH, Tomashek KM, Dodd LE, et al. for the ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 – Final Report. N Engl J Med. 2020;383:1813-26.
15. Gottlieb RL, Vaca CE, Paredes R, et al. for the PINETREE Investigators. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2022;386:305-315.
16. Eid J, Abdelwahab M, Colburn N, et al. Early Administration of Remdesivir and Intensive Care Unit Admission in Hospitalized Pregnant Individuals With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2022;139(4):619-621.
17. Saroyo YB, Rumondang A, Febriana IS, et al. Remdesivir Treatment for COVID 19 in Pregnant Patients with Moderate to Severe Symptoms: Serial Case Report. Infect Dis Rep. 2021;13:437–443.
18. Budi DS, Pratama NR, Wafa IA, et al. Remdesivir for pregnancy: A systematic review of antiviral therapy for COVID-19. Heliyon. 2022 Jan;8(1):e08835.
19. Singh AK, Singh A, Singh R, et al. Remdesivir in COVID-19: a critical review of pharmacology, pre-clinical and clinical studies. Diabetes Metab Syndr. 2020;14(4):641–648.
20. Mulangu S, Dodd LE, Davey RT,Jr. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381:2293–2303.
21. Waters MD, Warren S, Hughes C, et al. Human genetic risk of treatment with antiviral nucleoside analog drugs that induce lethal mutagenesis: The special case of molnupiravir. Environ Mol Mutagen. 2022;63(1):37-63.
22. Montgomery H, Hobbs FDR, Padilla F, et al.; TACKLE study group. Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2022;10(10):985-996.
23. Ginde AA, Paredes R, Murray TA, et al.; ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. Lancet Respir Med. 2022;10(10):972-984.
24. U.S. Food and Drug Administration. Coronavirus (COVID-19) Drugs. Updated 9 Nov 2022. Available at: https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs. Accessed 21 Nov 2022.

25. Hirshberg JS, Cooke E, Oakes MC, et al. Monoclonal antibody treatment of symptomatic COVID-19 in pregnancy: initial report. Am J Obstet Gynecol. 2021;225(6):688–689.
26. Mayer C, VanHise K, Caskey R, Naqvi M, Burwick RM. Monoclonal Antibodies Casirivimab and Imdevimab in Pregnancy for Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2021;138(6):937-939.
27. Thilagar BP, Ghosh AK, Nguyen J, et al. Anti-spike monoclonal antibody therapy in pregnant women with mild-to-moderate coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2022;139(4):616–618.
28. Chang MH, Cowman K, Guo Y, et al. A real-world assessment of tolerability and treatment outcomes of COVID-19 monoclonal antibodies administered in pregnancy. Am J Obstet Gynecol. 2022;226(5):743–745.
29. Richley M, Rao RR, Afshar Y, et al. Neutralizing monoclonal antibodies for coronavirus disease 2019 (COVID-19) in pregnancy: a case series. Obstet Gynecol. 2022;139(3):368–372.
30. Buonomo AR, Esposito N, Di Filippo I, et al. Safety and efficacy of anti-SARS-CoV-2 monoclonal antibodies in pregnancy. Expert Opin Drug Saf. 2022 Sep;21(9):1137-1141.
31. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2022; Version 10.1.1. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 22 Nov 2022.
32. Marconi VC, Ramanan AV, de Bono S, et al. on behalf of the COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo- controlled phase 3 trial. Lancet Respir Med. 2021;9:1407–18.
33. Kalil AC, Patterson TF, Mehta AK, et al. for the ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384:795-807.
34. Guimaraes PO, Quirk D, Furtado RH, et al. for the STOP-COVID Trial Investigators. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385:406-415.
35. Gouverneur A, Avouac J, Prati C, et al. JAK inhibitors and risk of major cardiovascular events or venous thromboembolism: a self-controlled case series study. Eur J Clin Pharmacol. 2022;78(12):1981-1990.
36. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of Pregnancies With Maternal/Paternal Exposure in the Tofacitinib Safety Databases for Ulcerative Colitis. Inflamm Bowel Dis. 2018;24(12):2494-2500.
37. Clowse ME, Feldman SR, Isaacs JD, et al. Pregnancy Outcomes in the Tofacitinib Safety Databases for Rheumatoid Arthritis and Psoriasis. Drug Saf. 2016;39(8):755-62.
38. Costanzo G, Firinu D, Losa F, et al. Baricitinib exposure during pregnancy in rheumatoid arthritis. Ther Adv Musculoskelet Dis. 2020;12:1759720X19899296.
39. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637–1645.
40. Gordon AC, Mouncey PR, Al-Beidh F, et al.; The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384:1491-502.
41. Nakajima K, Watanabe O, Mochizuki M, et al. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. Mod Rheumatol. 2016;26(5):667-671.

42. Hoeltzenbein M, Beck E, Rajwanshi R, et al. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. Semin Arthritis Rheum. 2016;46(2):238-245.
43. Jimenez-Lozano I, Caro-Teller JM, Fernandez-Hidalgo N, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study. J Clin Pharm Ther. 2021;46:1062-1070.
44. Jorgensen SCJ, Lapinsky SE. Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review. Clin Microbiol Infect. 2022;28:51-55.
45. Abdullah S, Bashir N, Mahmood N. Use of intravenous tocilizumab in pregnancy for severe coronavirus disease 2019 pneumonia: two case reports. J Med Case Reports. 2021;15:426.
46. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384:693-704.
47. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. The Lancet Respiratory Medicine. February 2020;e(3):267-276.
48. Tomazini BM, Maia IS, Cavalcanti AB, et al. for the COALITION COVID-19 Brazil III Investigators. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020;324(13):1307-1316.
49. Sterne JAC, Murthy S, Diaz JV; REACT Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-1341.
50. Granholm A, Munch MW, Myatra SN, et al. Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. Intensive Care Med. 2022;48(1):45-55.
51. Hu KM, Hong AS. Resuscitating the Crashing Pregnant Patient. Emerg Med Clin North Am. 2020;38(4):903-917.
52. Wang C, Xu YJ, Shi Y, et al. Verification on the Developmental Toxicity of Short-term Exposure to Phenol in Rats. Biomed Environ Sci. 2020;33(6):403-413.
53. Guerin C, Reignier J, Richard J-C, et al. for the PROSEVA Study Group. Prone Positioning in Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2013;368:2159-2168.
54. Thompson AE, Ranard BL, Wei Y, Jelic S. Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure. JAMA Intern Med. 2020;180(11):1537–1539.
55. Ehrmann S, Li J, Ibarra-Estrata M, et al. for the Awake Prone Positioning Meta-Trial Group. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet Respir Med. 2021;9:1387–95.
56. Pourdowlat G, Mikaeilvand A, Eftekhariyazdi M, et al. Prone-Position Ventilation in a Pregnant Woman with Severe COVID-19 Infection Associated with Acute Respiratory Distress Syndrome. Tanaffos. 2020;19(2):152-5.
57. Alhazzani W, Parhar KKS, Weatherald J, et al. Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial. JAMA. 2022;327(21):2104–13.
58. Ni Y-N, Luo J, Yu H, et al. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med. 2018;36:226-233.
59. Riera J, Barbeta E, Tormos A, et al. CiberesUCICOVID Consortium. Effects of intubation timing in patients with COVID-19 throughout the four waves of the pandemic: a matched analysis. Eur Respir J. 2022;:2201426.

60. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. 2015 Apr;41(4):623-32.
61. Nishikimi M, Nishida K, Shindo Y, et al;. Failure of non-invasive respiratory support after 6 hours from initiation is associated with ICU mortality. PLoS One. 2021 Apr 30;16(4):e0251030.
62. Oxford-Horrey C, Savage M, Prabhu M, et al. Putting It All Together: Clinical Considerations in the Care of Critically Ill Obstetric Patients with COVID-19. Am J Perinatol. 2020;37(10):1044-1051.
63. Chanques G, Constantin JM, Devlin JW, et al. Analgesia and sedation in patients with ARDS. Intensive Care Med. 2020;46(12):2342-56.
64. Stephens RJ, Evans EM, Pajor MJ, et al. A dual-center cohort study on the association between early deep sedation and clinical outcomes in mechanically ventilated patients during the COVID-19 pandemic: The COVID-SED study. Crit Care. 2022;26(1):179.
65. Stephens RJ, Ablordeppey E, Drewry AM, et al. Analgosedation Practices and the Impact of Sedation Depth on Clinical Outcomes Among Patients Requiring Mechanical Ventilation in the ED: A Cohort Study. Chest. 2017;152(5):963-71.
66. Wiedemann H P, Wheeler A P, Bernard G R et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–2575.
67. Manuck TA, Rice MM, Bailit JL, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol. 2016;215(1):103.e1-103.e14.
68. Chong J, Ahmed S, Hill K. Acute Respiratory Distress Syndrome in a pregnant patient with COVID-19 improved after delivery: A case report and brief review. Respir Med Case Rep. 2020;31:101171.
69. Pineles BL, Stephens A, Narendran LM, et al. Does delivery affect time to recovery in COVID-19-related ARDS during pregnancy? Am J Obstet Gynecol.2021;224(2):S498–9.

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

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

**Table 1.** COVID-19 Infection Severity Classification

| Drug Class | Name | Indication | Dose | Side Effects | Pregnancy Consideration |
|---|---|---|---|---|---|
| Antivirals | Nirmatrelvir/ Ritonavir (Paxlovid) | mild/moderate severity at high risk for severe illness<br><br>≤5 days onset | 100mg twice daily for 5 days<br><br>eGFR ≥30 to 60 mL/min: Nirmatrelvir 150mg/RTV 100mg twice daily for 5 days | . Hypertension<br>. Myalgias<br>. Angioedema; hypersensitivity reactions | Nirmatrelvir: no safety data RTV considered safe<br><br>Not recommended by WHO |
| | Remdesivir | Mild/moderate severity at high risk for severe illness<br><br>Severe illness not on MV/ECMO<br><br>≤7 days onset | 200mg IV on day 1, then IV daily<br><br>Mild/moderate: 3 days<br><br>Severe: 5-10 days | No increase from placebo | Considered safe<br>Requires multiple IV doses |
| | Molnupiravir | Outpatients with mild/moderate severity at high risk for severe illness<br><br>≤5 days onset | 800mg twice daily for 5 days | No increase from placebo | NIH/SMFM: last option if other therapies unavailable<br><br>Not recommended by WHO or FDA |
| Monoclonal Antibodies | Bebtelovimab | Outpatients with mild/moderate severity at high risk for severe illness<br><br>≤7 days onset | 175mg IV over 30 seconds | Hypersensitivity reactions<br><br>No increase from placebo | 2nd line therapy<br>Limited data<br>Generally considered safe |
| | Tixagevimab/ Cilgavimab (Evusheld) | Not currently recommended for treatment given low efficacy against circulating variants | | | |
| | Casirivimab/ Imdevimab (REGEN-COV) | | | | |
| | Sotrovimab | | | | |
| Steroids | Dexamethasone | Severe/critical illness | 6mg daily for 10 days<br><br>ARDS: 20mg IV daily x 5 days then 10mg 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<br><br>≤ 7 days onset | 4mg PO daily for 14 days or until hospital discharge<br><br>eGFR 30-59: 2mg daily<br>eGFR 15-29: 1mg daily<br>eGFR <15: not for use | No increase from placebo<br><br>. Cytopenias<br>. Transaminitis<br>. Thrombosis | No safety data |
| | Tofacitinib | Severe/critical illness with baricitinib unavailable<br><br>(no set limit) | 10mg twice daily for 14 days or until hospital discharge<br><br>eGFR <30: 5mg twice daily<br>ESRD: 5mg twice daily, give dose after HD on HD days | . Thrombosis<br>. Cardiovascular events<br>. GI perforation | No evidence of fetal adverse effects<br><br>Must use with VTE prophylaxis |
| IL-6 Receptor Antagonists | Tocilizumab | Severe/critical illness | 8mg/kg IV once (maximum dose 800mg) | . Transaminitis<br>. Activation of latent infection | Animal studies with evidence of fetal toxicity at high doses<br><br>Appears safe in COVID-19 |
| | Sarilumab | Severe/critical illness with tocilizumab unavailable | 400mg IV once | . Cytopenias<br>. Transaminitis<br>. Activation of latent infection | No human safety data<br>Appears safe in animals |

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

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

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

Abbreviations: WHO, World Health Organization; NIH, National Institutes of Health COVID-19 Treatment Guidelines; SMFM, Society for Maternal Fetal Medicine (*follows NIH Clinical Guidelines)

[1] Pregnancy-specific recommendation

[2] C-reactive protein >75 mg/L

**Table 3.** Major recommendations for COVID-19 therapy based on severity of illness[5,8,10,31]