COVID-19 Therapeutics and Considerations for Pregnancy

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INTRODUCTION

The unprecedented impact of the novel Coronavirus Disease 2019 (COVID-19) pandemic has been met with equally unprecedented scientific innovation. More than 3000 vaccine and drug clinical trials are underway or completed,\(^1\) yet 80% excluded pregnant patients,\(^2\) resulting in administration to pregnant patients without research protocol safeguards or delay in the receipt of life-saving interventions. Considerations for the clinical management of COVID-19 disease in pregnancy have been published, and basic tenets remain mostly unchanged.\(^3,4\) However, the data supporting the use of vaccines and therapeutics have evolved and warrant pregnancy-specific consideration.

Perinatal Implications

Multiple studies demonstrate that pregnancy is associated with a higher risk for severe COVID-19 disease, defined by intensive care unit (ICU) admission, mechanical

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Obstet Gynecol Clin N Am 50 (2023) 163–182

https://doi.org/10.1016/j.ogc.2022.10.018

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ventilation, extracorporeal membrane oxygenation (ECMO), and death, compared with nonpregnant persons.\textsuperscript{5,6} Compared with unaffected pregnancies, COVID-19 disease in pregnancy is associated with increased risk for preeclampsia,\textsuperscript{7,8} cesarean delivery, and severe maternal morbidity from direct obstetric causes.\textsuperscript{8} A systematic review including 42 studies comparing fetal and neonatal outcomes in pregnant patients with and without confirmed SARS-CoV-2 infection demonstrated 2-fold increased risk for stillbirth, low birth weight, and prematurity.\textsuperscript{7} Whether there is increased risk for other neonatal complications, such as neonatal ICU admission, respiratory disorders, and hyperbilirubinemia, is controversial and may be mediated by disease severity.\textsuperscript{9} Congenital infection does occur in 1\% to 3\%.\textsuperscript{10–12} There are insufficient data to describe a congenital viral syndrome or to clarify disease severity in infants born with infection. There is a global registry to better understand long-term childhood and adult outcomes following prenatal exposure to SARS-CoV-2 infection.\textsuperscript{13}

\textbf{COVID-19 Drug Treatments}

COVID-19 therapeutics affect the 2 main pathophysiologic processes implicated in disease progression. The early phase is driven by SARS-CoV-2 viral replication, whereas progression to multiorgan involvement in the later phase is driven by cytokine release syndrome. Therefore, therapies that directly target and limit viral replication have the greatest efficacy early in the disease course, whereas immunosuppressive/antiinflammatory therapies are more beneficial in later stages of the disease.

\textbf{Outpatient Treatments}

High-risk, nonhospitalized patients with mild or moderate COVID-19\textsuperscript{14} may be offered secondary preventive therapeutics to reduce the risk of severe disease and death. Pregnant or recently pregnant individuals are included in the “high-risk” criteria, which also includes age greater than or equal to 65 years, Hispanic, non-Hispanic Black, American Indian or Alaska Natives race/ethnicity, and certain medical conditions (eg, active malignancy; chronic lung, liver, or kidney disease; cystic fibrosis; insulin-dependent diabetes mellitus; cardiac conditions; disabilities; primary and secondary immunodeficiency; use of corticosteroids or other immunosuppressive medications). Available antivirals include bebtelovimab, remdesivir, nirmatrelvir/ritonavir, and molnupiravir (Table 1).

\textbf{Bebtelovimab}

Bebtelovimab is a monoclonal antibody (MAb) targeting the highly antigenic and immunogenic surface spike glycoprotein of the SARS-CoV-2 virus. As a drug class, MAbs have low potential for adverse effects (hypersensitivity reaction in < 1\%) or significant drug interactions (not metabolized by cytochrome P450 enzymes). MAbs readily cross the placenta; the degree of fetal transfer is variable and depends on specific drug structure, drug half-life, dose, and the timing of the last dose in relation to the gestational age.\textsuperscript{26} Transfer is minimal during the first trimester and occurs by simple diffusion. By 20 weeks, MAbs are actively transferred in increasing amounts across the placenta, with the highest rate occurring after 36 weeks. Although not empirically studied, this may have added benefit of protecting infants younger than 6 months from severe COVID-19. Nonclinical and observational data have not demonstrated increased risk for birth defects in exposed infants.\textsuperscript{27}

Bebtelovimab is currently recommended because it retains activity against Omicron. Although not studied in phase 3 clinical trials, MAbs used before widespread circulation of Omicron were associated with 70\% relative reduction in COVID-19–related
Table 1
Outpatient therapeutics and considerations in pregnancy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Remdesivir</th>
<th>Nirmatrelvir/Ritonavir</th>
<th>Molnupiravir</th>
<th>Bebtelovimab</th>
<th>Tixagevimab/Cilgavimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class</td>
<td>Antiviral agent RNA polymerase inhibitor</td>
<td>Antiviral agent SARS-CoV-2 main protease inhibitor (Mpro) HIV-1 protease inhibitor and Mpro concentration booster</td>
<td>Antiviral agent &lt; nucleoside inhibitor</td>
<td>Antiviral agent &lt; monoclonal antibody</td>
<td>Antiviral agent &lt; monoclonal antibody</td>
</tr>
<tr>
<td>Dose</td>
<td>Day 1: 200 mg Day 2 and 3: 100 mg</td>
<td>Nirmatrelvir 300 mg (two 150 mg tablets) with ritonavir 100 mg daily for 5 days</td>
<td>800 mg twice daily for 5 d (four 200 mg capsules)</td>
<td>175 mg daily</td>
<td>Tixagevimab 150 mg and cilgavimab 150 mg administered every 6 mo while SARS-CoV-2 in circulation</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intravenous infusion over 30–120 min</td>
<td>Oral (do not crush)</td>
<td>Oral (do not crush)</td>
<td>Intravenous infusion over 30 s</td>
<td>2 separate intramuscular injections in separate sites</td>
</tr>
<tr>
<td>Dose adjustments</td>
<td>Renal: • eGFR &lt; 30 mL/min: theoretic risk SBECID accumulation in kidneys, manufacturer labeling does not recommend, however significant toxicity with 5–10 d</td>
<td>Renal: • eGFR ≥ 30 to &lt; 60 mL/min nirmatrelvir 150 mg with ritonavir 100 mg daily for 5 d • eGFR &lt; 30 mL/min: not recommended</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Agent</th>
<th>Remdesivir</th>
<th>Nirmatrelvir/Ritonavir</th>
<th>Molnupiravir</th>
<th>Bebtelovimab</th>
<th>Tixagevimab/Cilgavimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment unlikely, multiple studies have not shown adverse events. Discuss risk/benefit with patient. Hepatic:</td>
<td>treatment unlikely, multiple studies have not shown adverse events. Discuss risk/benefit with patient. Hepatic:</td>
<td>● ALT &gt;10 times upper limit, consider discontinuation</td>
<td>● Child-Pugh C: not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Chloroquine, hydroxychloroquine, CYP3A inducers</td>
<td>Significant CYP3A interactions; review patient’s other medications for possible temporary discontinuation</td>
<td>Cladribine</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Indication</td>
<td>Mild to moderate COVID-19 or positive direct SARS-CoV-2 viral test &lt;and at high risk for progression to severe disease</td>
<td></td>
<td></td>
<td></td>
<td>Preexposure prophylaxis</td>
</tr>
<tr>
<td>Time frame from symptom onset</td>
<td>≤ 7 d</td>
<td>≤ 5 d</td>
<td>≤ 3–5 d</td>
<td>≤ 7 d</td>
<td>—</td>
</tr>
<tr>
<td>Contraindications and considerations</td>
<td>● Hypersensitivity</td>
<td>● eGFR &lt; 30 mL/min</td>
<td>● May diminish therapeutic effect of cladribine</td>
<td>● Consider local prevalence of SARS-CoV-2 variants and available susceptibility data</td>
<td>● May diminish effect of COVID-19 vaccines</td>
</tr>
<tr>
<td></td>
<td>● Chloroquine or hydroxychloroquine may diminish therapeutic effect of RDV</td>
<td>● Severe hepatic impairment (Child-Pugh class C)</td>
<td>● Evaluate and verify pregnancy status</td>
<td></td>
<td>● Suggest at least 2 wk interval from receipt of COVID-19 vaccine before administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● CYP3A inducers may reduce nirmatrelvir or ritonavir plasma concentrations,</td>
<td>● Use when preferred treatment options unavailable</td>
<td></td>
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</tr>
</tbody>
</table>
CYP3A inducers may decrease serum concentration RDV leading to loss of virologic response and resistance. CYP3A substrates where elevated concentrations are associated with serious/life-threatening reactions (ie, methergine, statins). HIV screening if untested and resistance testing among untreated or nonvirally suppressed patients. Hypersensitivity. Switch to nonhormonal contraceptive.

<table>
<thead>
<tr>
<th>EUA documentation Requirement</th>
<th>No</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
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<td>Patient Fact Sheet</td>
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<tr>
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<td>to report adverse events</td>
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Evidence

<table>
<thead>
<tr>
<th>Primary Trial</th>
<th>PINETREE</th>
<th>EPIC-HR</th>
<th>MOVE-OUT</th>
<th>PROVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population studied</td>
<td>Double-blind, randomized, placebo-controlled trial in symptomatic, unvaccinated, nonhospitalized adults at high risk for COVID-19</td>
<td>Phase 2–3 double-blind, randomized, placebo-controlled trial in symptomatic, unvaccinated, nonhospitalized adults at high risk for COVID-19</td>
<td>Phase 3 double-blind, randomized, placebo-controlled trial in symptomatic, unvaccinated, nonhospitalized adults at high risk for COVID-19</td>
<td>No phase 3 clinical efficacy data, based on in vitro data showing activity against all circulating Omicron subvariants and clinical efficacy</td>
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<th>Bebtelovimab</th>
<th>Tixagevimab/ Cilgavimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to severe disease (n = 562)</td>
<td>progression to severe disease (n = 1379)</td>
<td>progression to severe disease (n = 1433)</td>
<td>data from phase 2 clinical trial in an era when Omicron was not dominant (n = 5197)</td>
<td>followed to 6–7 mo (n = 51197)</td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction (RRR)</td>
<td>87%</td>
<td>88.9%</td>
<td>31% (hazard ratio [HR] 0.69, 95% CI 0.48–1.01)</td>
<td>Not known for bebtelovimab, 85% for sotrovimab</td>
<td>77% (HR 0.23, 95% CI 0.10–0.54)</td>
</tr>
<tr>
<td>Number needed to prevent hospitalization or death</td>
<td>21.7</td>
<td>16</td>
<td>14.7</td>
<td>Not known for bebtelovimab, 17% for sotrovimab</td>
<td>66.7</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Any 42.3%, serious 5% (vs 46.3% and 5% in placebo, respectively); nausea, headache, cough, ↑ALT, ↓creatinine clearance, severe bradycardia, heart failure, acute liver failure</td>
<td>Any 22.6%, serious 2.1% (vs 23.9% and 4.1% in placebo, respectively); treatment discontinuation, dysgeusia, diarrhea, hypertension, ↑ALT, ↓creatinine clearance, angioedema</td>
<td>30.4% vs 33.0% in placebo; diarrhea, nausea, dizziness, urticaria, anaphylaxis, angioedema</td>
<td>22% vs 23% in placebo; diarrhea, headache, nausea, pruritis, rash, vasovagal reaction, hypersensitivity</td>
<td>Any 35.3%, serious 1.4% in both groups; injection site reaction</td>
</tr>
<tr>
<td>Inpatient use</td>
<td>Can continue in the inpatient setting to complete 5 consecutive days of treatment if admitted</td>
<td>Continuation of outpatient therapy allowed if admitted for reasons other than COVID-19</td>
<td>If hospitalization required, complete at provider discretion</td>
<td>Discontinue if hospitalization for disease progression required</td>
<td>N/A</td>
</tr>
<tr>
<td>Pregnancy data</td>
<td>DART</td>
<td>Nirmatrelvir: reduced fetal body weights</td>
<td>Increased risk of miscarriage; malformation of eye, kidney, axial skeleton, and ribs; delayed ossification; decreased fetal birthweight</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No adverse effect on embryo/fetal development</td>
<td>Ritonavir: no adverse developmental outcomes</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Human data | Observational study of 67 pregnant people: no adverse pregnancy outcomes. Insufficient data to identify drug-associated risk of birth defects or miscarriage | Nirmatrelvir: none Ritonavir: observational studies have not identified an increase in risk of major birth defects and are insufficient to identify a drug-associated risk of miscarriage | None |

High risk factors include age > 60 years, obesity (BMI > 30 kg/m²), patient with immunocompromising conditions (B-cell depleting therapies, ie, rituximab, patients receiving tyrosine kinase inhibitors, chimeric antigen receptor T-cell recipients, posthematopoietic cell transplant recipients, active malignancy, lung and solid organ transplant recipients, patients with severe combined primary immunodeficiencies, patients with untreated HIV and CD4 T lymphocyte cell counts < 500 cells/mm³), unvaccinated individuals, cardiovascular conditions (eg, hypertension, myocardial infarct, stroke), diabetes, liver disease, kidney disease.

**Abbreviations:** ALT, alanine transaminase; CYP, cytochrome P450; DART, Development and Reproductive Toxicity; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; FDA, Food and Drug Administration, RDV, remdesivir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBECD, sulfobutylether-beta-cyclodextrin.


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hospitalization or death from any cause, including in pregnant patients. It may be offered to high-risk patients who present more than 5 days from symptom onset or positive viral test when first-line antivirals are not available.

Tixagevimab/cilgavimab reduces the risk of symptomatic COVID-19 by 77% and is the only currently available antiviral for preexposure prophylaxis. It can be offered to uninfected individuals with moderate to severe immune compromise who are unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccine is not recommended. Pregnancy-specific effectiveness data are not available.

**Ritonavir-Boosted Nirmatrelvir**

Nirmatrelvir, which is metabolized by CYP3A enzyme, inhibits viral replication through direct inhibition of the SARS-CoV-2 main protease. Ritonavir is an HIV-1 protease inhibitor, has no activity against SARS-CoV-2, but functions to boost nirmatrelvir plasma levels by inhibition of the CYP3A enzyme. These medications are co-packaged and sold under the commercial name Paxlovid. Paxlovid is 89.1% effective in reducing the incidence of COVID-19–related hospitalization or death in patients treated within 5 days of symptom onset. Preliminary data suggest it retains effectiveness in vaccinated individuals.

Paxlovid is currently the preferred treatment of mild COVID-19 in high-risk individuals and ideally is administered within 5 days of positive test or symptom onset. There are no available human data on the use of nirmatrelvir during pregnancy to evaluate drug-associated risks of major birth defects, miscarriage, adverse maternal or fetal outcomes, or its pharmacokinetics, given the known increase in CYP3A activity in pregnancy. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Although placental transfer of ritonavir occurs, fetal ritonavir concentrations are low.

**Remdesivir**

Remdesivir is an antiviral initially indicated for treatment in hospitalized patients until the PINETREE trial demonstrated that the highest mortality benefit occurred in patients whose treatment was initiated early in the disease course. It is administered as a 3-day infusion and is resource intensive, which limits its use. Remdesivir has not been approved specifically for use in pregnancy. Data suggest a low (16%) rate of serious adverse events and high tolerability, yet efficacy, and pharmacokinetic data are lacking. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network is currently comparing remdesivir pharmacokinetics in pregnant and nonpregnant women of reproductive age who are hospitalized with COVID-19 to assess pregnancy-specific adverse events.

**Molnupiravir**

Molnupiravir is a nucleoside analogue (NA) antiviral that acts by causing chain termination of nascent viral DNA. NAs are currently used to treat viral infections, rheumatologic disorders, and cancer. Despite being named after Mjölnir, the hammer of the god Thor, the observed effect showed that it was only 30% effective in reducing the risk of hospitalization of death, compared with untreated patients. In addition to its reduced efficacy, there are several concerns that limit use in pregnancy. First, the greatest benefit was observed in patients who initiated therapy within 72 hours of symptom onset; however, a readily available diagnostic test is unavailable. Second, mutagenic and carcinogenic toxicity have been demonstrated in mammalian hamster models, but in vivo risk is under debate. Finally, although there are no human
pregnancy data, animal data reported in the Food and Drug Administration’s Emergency Use Authorization suggested risk for embryo toxicity, lethality, mutagenicity, and low birth weight. Nonetheless, as 1 of 2 orally bioavailable therapies for COVID-19, it retains a role in the arsenal. Molnupiravir is recommended when nirmatrelvir or remdesivir are not available or not appropriate, often because of potential drug interactions with ritonavir, and should only be offered to pregnant individuals after consideration of alternative therapies, risk for severe disease, and fetal risk.

**Inpatient Treatments**

Therapeutic management of adults hospitalized for COVID-19 is based on disease severity and includes the use of systemic corticosteroids and antiviral and immunomodulatory therapy (Table 2).

**Corticosteroids**

Corticosteroids are currently the standard-of-care treatments of severe disease for both pregnant and nonpregnant people. Dexamethasone was the first trial-proven beneficial treatment of COVID-19. In the RECOVERY randomized controlled trial, dexamethasone reduced the risk of all-cause mortality in patients requiring invasive mechanical ventilation by 36% compared with placebo. It is administered as a once daily oral or intravenous dose of 6 mg for up to 10 days.

Dexamethasone (and betamethasone) is preferentially administered to women at high risk for preterm birth within 7 days. Unlike other steroids, which are extensively metabolized by placental 11-b-hydroxylase steroid dehydrogenase-2, dexamethasone and betamethasone have high rates of placental transfer and have been shown to reduce the rates of pulmonary, neurologic, and infectious morbidity and mortality associated with prematurity. However, repeated courses have been associated with deleterious effects, such as decreased fetal head circumference, fetal growth restriction, and impaired neurodevelopment. After the RECOVERY trial was published, debate ensued regarding how to manage critically ill pregnant patients, as dexamethasone was the only proven treatment with mortality benefit, yet repeated doses were associated with significant fetal or neonatal adverse outcomes. However, a landmark meta-analysis evaluating dexamethasone, hydrocortisone, and methylprednisolone demonstrated the mortality benefit as a class effect of corticosteroids. Given concerns regarding impact of repeated prenatal steroid exposure on long-term neurodevelopment and the presence of reassuring effectiveness data for other steroids, hydrocortisone or methylprednisolone, rather than dexamethasone, should be administered to pregnant patients with severe COVID-19 meeting criteria. If there is a high likelihood of preterm delivery, clinicians should first administer intravenous dexamethasone or betamethasone, dosed for fetal lung maturity, then complete the steroid course using hydrocortisone or methylprednisolone.

**Remdesivir**

The effectiveness of remdesivir for inpatient adults with severe COVID-19 has been mixed. The Adaptive Covid-19 Treatment Trial showed that remdesivir led to a shorter median time from randomization to recovery (10 days vs 15 days with placebo) and may have reduced the time to hospital discharge (12 days vs 17 days), yet no mortality benefit in mechanically ventilated patients. However, the Solidarity Trial meta-analysis showed a modest mortality benefit (remdesivir 14.6% vs control 16.3%; risk ratio [RR] 0.87, 95% confidence interval [CI] 0.76–0.99, P = .03) and a reduction in need for mechanical ventilation (23.7% vs 27.1%; RR 0.83, 95% CI 0.75–0.93, P = .001). Remdesivir is recommended for hospitalized patients with moderate or
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dexamethasone</th>
<th>Remdesivir</th>
<th>Tocilizumab</th>
<th>Baricitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class</td>
<td>Systemic corticosteroid, antiinflammatory</td>
<td>Antiviral, RNA polymerase inhibitor</td>
<td>Recombinant human monoclonal antibody Interleukin-6 receptor antagonist</td>
<td>Janus kinase 1 and 2 inhibitors, reduces cytokine and growth factor stimulation</td>
</tr>
<tr>
<td>Dose</td>
<td>6 mg daily for 7 d or until discharge</td>
<td>Day 1: 200 mg</td>
<td>Weight &gt; 30 kg: 8 mg/kg</td>
<td>Day 2–10: 100 mg Day 2–10: 100 mg Day 2–10: 100 mg</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intravenous or oral</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Oral</td>
</tr>
<tr>
<td>Oral dispersion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose adjustments</td>
<td>None</td>
<td>None, monitor transaminase levels</td>
<td>Renal:</td>
<td>Renal:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• None</td>
<td>• eGFR &lt; 15 mL/min: not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hepatic:</td>
<td>• Hepatic:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Not recommended for patients with ALT or AST &gt;10 times upper limit</td>
<td>• Treatment interruption if increasing LFTs to exclude diagnosis of drug-induced liver injury</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Multiple considerations CYA3A4 substrate and weak inducer</td>
<td>See Table 1</td>
<td>Uncertain CYP450 metabolism in the setting of severe disease and pregnancy; therefore close drug monitoring recommended Should not be used with other immunomodulators</td>
<td>Increased levels when co-administered with strong OAT3 inhibitors (ie, probenecid) Should not be used with other immunomodulators</td>
</tr>
</tbody>
</table>
**Indication**
Hospitalized patients with severe or critical COVID-19 disease requiring oxygen support
Hospitalized patients who require noninvasive oxygen support
- Given alone in patients requiring supplemental oxygen
- Given with dexamethasone in patients requiring noninvasive oxygen therapy
Severe or critical COVID-19 receiving systemic corticosteroids and receiving supplemental oxygen, mechanical ventilation, and/or ECMO
Severe or critical COVID-19 receiving systemic corticosteroids and requiring supplemental oxygen, mechanical ventilation, and/or ECMO
Considered case-by-case basis in patients with rapidly increasing oxygen requirements and evidence of systemic inflammation

**Contraindications and considerations**
Monitor adverse effects including hyperglycemia, fungal, bacterial, or *Strongyloides* infections (especially if using with baricitinib or tocilizumab), and diffuse multiorgan toxicity

See Table 1

- Known hypersensitivity
- Any non-COVID concurrent active infection, including localized infection
- Absolute neutrophil count < 1000 per mm$^3$, platelet count < 50,000 per mm$^3$, or ALT/AST > 10x upper limit
- None known
- Consider treatment interruption if absolute lymphocyte count < 200 cells per mm$^3$ or absolute neutrophil count < 500 per mm$^3$

**Adverse events**
- Multiple cardiac, dermatologic, endocrine, metabolic, gastrointestinal, hepatic, and psychiatric effects
- Hyperglycemia, pulmonary edema, poor wound healing frequent

See Table 1

- Adverse effects (3%): constipation, anxiety, diarrhea, insomnia, hypertension, nausea
- High risk for serious and fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens
- GI perforation
- Hepatotoxicity
- Transaminitis (18%)
- Neutropenia (2.2%)
- Venous thromboembolism (1.5%)
- Serious opportunistic infections (0.9%)

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### Table 2 (continued)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dexamethasone</th>
<th>Remdesivir</th>
<th>Tocilizumab</th>
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<tbody>
<tr>
<td><strong>Evidence</strong></td>
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</tbody>
</table>
| Effectiveness in general population | Reduction in all cause 28-d mortality[^39] | • Modest mortality benefit in nonmechanically ventilated patients  
  • Shorter median time to recovery  
  • Reduced need for mechanical ventilation | • Reduced all-cause mortality at 28 d  
  • Reduced risk of progression to mechanical ventilation or death  
  • Reduced risk of hemodialysis or hemofiltration  
  • Greater probability of discharge alive at 28 d | • Reduced progression to mechanical ventilation or death  
  • Most pronounced in patients receiving high flow oxygen or noninvasive ventilation |
| Pregnancy considerations | Concern for small head circumference, low birthweight, long-term mental and neurocognitive disorders  
  Alternates:  
  • IV or oral hydrocortisone 5160 mg in divided doses for 7 d or until discharge  
  • IV or oral methylprednisolone 32 mg daily in divided doses for 7 d or until discharge | See Table 1  
  Report of 67 pregnant women treated demonstrated similar recovery rates to nonpregnant and low rate of adverse events[^25] | Human data insufficient to determine drug associated risk for major birth defects and miscarriages  
  Risk for miscarriage at 1.25 times maximum recommended human dose in animal studies  
  May interfere with parturition | Human data insufficient to determine drug associated risk for major birth defects and miscarriages  
  Increased risk of skeletal anomalies and pregnancy loss in animal data |

**Abbreviations:** ALT, alanine transaminase; AST, aspartate transaminase; CYP, cytochrome P450; DART, Development and Reproductive Toxicity; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; FDA, Food and Drug Administration; OAT, ornithine aminotransferase; RDV, remdesivir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Severe disease, not requiring invasive ventilation or ECMO. An intravenous 200 mg loading dose is administered on day 1, followed by 100 mg intravenously from day 2. For patients who require minimal oxygen supplementation, the recommended treatment duration is 5 days. For patients requiring escalating oxygen support, the recommended treatment duration is 10 days.\(^4\)\(^6\) Although efficacy data in pregnant patients are lacking, remdesivir should be offered to pregnant patients who meet clinical criteria.

**Interleukin-6 Inhibitors**

Hyperactivation of the immune response, including release of proinflammatory cytokines such as interleukin-6 (IL-6) is implicated in pathophysiology of severe illness. Tocilizumab is a recombinant humanized MAb that inhibits binding of IL-6 to its receptors.\(^4\)\(^7\)

Tocilizumab has been associated with a 15% to 44% reduction in need for mechanical ventilation and a 15% reduction in all-cause mortality, when given in combination with steroids or remdesivir.\(^4\)\(^8\),\(^4\)\(^9\) It is currently recommended as adjunctive treatment of severe or critically ill patients. The available pregnancy data for tocilizumab are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage with exposure. The Developmental and Reproductive Toxicity (DART) data show embryo-fetal lethality at concentrations 1.25 times higher than the maximum recommended human dose.\(^5\)\(^0\) IL-6 inhibition may theoretically delay parturition through interference with cervical ripening and dilation.

**Janus Kinase Inhibitors**

Janus kinase (JAK) inhibitors reduce cytokine and growth factor stimulation, leading to reduced immune cell function. Baricitinib is currently available on a case-by-case basis in patients with rapidly increasing oxygen requirements and evidence of systemic inflammation. It is orally administered and only given in combination with dexamethasone or another corticosteroid.\(^5\)\(^1\)

The data on effectiveness of JAK inhibitors are inconclusive. The COV-BARRIER trial did not find a statistically significant benefit for baricitinib in patients on low-flow oxygen; however, patients were also receiving remdesivir and steroids.\(^5\)\(^2\)

An increased risk of serious infection (eg, *Strongyloides*, herpes zoster, tuberculosis, protozoal), gastrointestinal perforations, and venous thromboembolism (VTE) has been described in patients receiving either JAK or IL-6 inhibitors. Embryo-fetal toxicities including skeletal anomalies have been observed in animal studies; however, the limited data on use of baricitinib in pregnancy are not sufficient to inform a drug-associated risk for major birth defects or miscarriage.\(^5\)\(^0\)

**Anticoagulation**

Severe and critical COVID-19 is associated with an inflammatory and hypercoagulable state characterized by increased D-dimers, fibrin, fibrin degradation products, and fibrinogen. Yet trials evaluating the efficacy and safety of different antithrombotic regimens in patients with COVID-19 have found little benefit of therapeutic anticoagulation in the treatment of mild, moderate, or severe disease. In addition, a clinically significant increased risk of major bleeding events in patients receiving therapeutic dose anticoagulation has been consistent across all trials.\(^5\)\(^3\)–\(^5\)\(^6\) In mild disease, neither aspirin, prophylactic, or therapeutic coagulation has demonstrated any benefit against risk for symptomatic venous or arterial VTE, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause.\(^5\)\(^7\)
The failure of anticoagulation to demonstrate a benefit suggests that COVID-19 thrombosis is immunologically mediated, rather than through the conventional VTE pathway.

Pregnant patients were excluded from these trials, and pregnancy is known to confer additional increased risk for VTE. The only available data evaluating the combined risks of COVID-19, pregnancy, and venous or arterial thromboembolisms are limited by their retrospective nature and lack of appropriate controls. Based on the available data, there does not seem to be a role for prophylactic anticoagulation in the outpatient setting. Prophylactic anticoagulation should be administered to all hospitalized pregnant patients. The choice to use intermediate dosing should be guided by disease severity, patient mobility, and patient risk factors (ie, body mass index > 30 kg/m², multifetal gestation, personal history of thrombophilia disorder). Therapeutic anticoagulation should be reserved for patients with active VTE.

**Vaccination**

Vaccination is the primary mode of protection against SARS-CoV-2. It is currently recommended that pregnant people receive either of the 2 available mRNA vaccines (Pfizer-BioNTech’s BNT162b2 or Moderna/NIAID’s mRNA-1273). Both vaccines instruct cells to make large amounts of spike protein antigen, mimicking natural infection, but induce a rapid, robust humoral immune response. Other COVID-19 vaccines are available in the United States; however, the COVID-19 protein subunit and adenovirus vector vaccines are not preferred for use in pregnancy.

Initial vaccine data for use in pregnancy were derived from inadvertent inclusion of pregnant persons in clinical trials that demonstrated no increased rates of adverse effects. Subsequently, a report of 3958 participants enrolled in the Centers for Disease Control and Prevention’s V-safe Surveillance System and Pregnancy Registry demonstrated pregnancy outcomes such as miscarriage, stillbirth, congenital anomalies, small for gestational age, and preterm birth did not differ significantly in vaccinated patients when compared against historic controls. In addition, reactogenicity and immunogenicity data were reassuring. The most common events, injection-site pain, fatigue, headache, myalgia, and fever, were more prevalent following the second dose and occurred much less frequently in pregnant, compared with nonpregnant women. Multiple other epidemiologic studies have failed to identify an association of COVID-19 vaccination with adverse fetal/neonatal outcomes such as stillbirth, prematurity, or congenital anomalies.

COVID-19 mRNA vaccines elicit similar immune responses in pregnant and nonpregnant adults. A prospective study enrolled 103 women, 30 of whom were pregnant and 16 lactating. Binding, neutralizing, and functional nonneutralizing antibody responses as well as CD4 and CD8 T cell responses in pregnant, lactating, and nonpregnant women following vaccination were present in equal amounts and higher than immune response following natural infection. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk.

Vaccination is equally effective in protection against severe disease and averting COVID-19–related pregnancy complications. An observational cohort of 10,861 vaccinated pregnant patients matched to 10,861 unvaccinated pregnant without prior history of infection showed 89% effectiveness against hospitalization and severe disease 7 to 77 days after the second dose. Another study demonstrating protection from adverse pregnancy outcomes included 1332 vaccinated patients and 8760 incompletely vaccinated or unvaccinated patients and found a higher association with stillbirth in unvaccinated patients with infection versus vaccinated patients with breakthrough infection.
Finally, maternal vaccination is associated with neonatal benefit through passive immunity. Infants younger than 6 months are especially vulnerable given dampened immunity. Transplacental antibody transfer is an important source of protection from COVID-19 in this group. Studies have demonstrated that infant concentrations are increased and more persistent following maternal vaccination compared with maternal infection, especially when delivery occurs at least 1 week following the second mRNA dose. A large, multicenter, case-controlled trial of 1000 mother-infant pairs, half of whom had received COVID-19 vaccination during pregnancy, demonstrated that maternal vaccine effectiveness against COVID-19–associated hospitalization among infants was 52% and against ICU admission for infants was 70%. These data support current recommendations for COVID-19 vaccination for all persons who are pregnant or considering pregnancy or lactating.

The current immunization schedule for persons 18 years of age or older include a 2-dose primary series with either monovalent mRNA COVID-19 vaccine or the monovalent protein subunit vaccine, given 4 to 8 weeks or 3 weeks apart, respectively. A single-dose mRNA bivalent booster vaccine should be given 8 weeks following. Vaccination is also recommended in previously infected individuals.

SUMMARY

Despite substantial research and therapeutic developments arising out of necessity during the global pandemic, there are still many unanswered questions. Data on how pregnancy affects the pharmacokinetics or effectiveness of current interventions are limited. It is unclear how in utero exposure to SARS-CoV-2 versus treatments affect long-term child development.

Clinicians must therefore be prepared to discuss the evidence for safety, effectiveness, maternal and fetal risks with nontreatment, and potential for harms with treatment options during pregnancy. In addition, clinicians should be empowered to advocate for inclusion and access to live-saving interventions for their pregnant patients.

CLINICS CARE POINTS

- Most pregnant patients with COVID-19 will require supportive care, yet disease in pregnancy is associated with worsened maternal, fetal, and obstetric outcomes.
- COVID-19 mRNA vaccines are safe and recommended in pregnancy.
- For pregnant patients with COVID-19 with moderate disease or at risk for moderate-severe disease, treatment with Paxlovid is preferred in the absence of medical or pharmacologic contraindications, followed by remdesivir. Patients should be counseled regarding the lack of pregnancy-specific data and low theoretical risk of harm.
- For patients with moderate-severe disease regarding inpatient management, first-line treatment with steroids is recommended. To reduce unintended adverse fetal exposure, prednisone or methylprednisolone should be considered over dexamethasone.

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