Optimized care of severe and critical COVID-19 during and after Pregnancy

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OBJECTIVES

Supportive Care

Proning

Oxygen Therapy

Thromboprophylaxis
COVID-19 vaccination and pregnancy

COVID-19 vaccination is recommended before and during pregnancy to decrease the risk of severe illness and death in pregnant individuals and to decrease the risk of adverse effects on the fetus, including preterm birth and death.

Published Online: December 10, 2021. doi:10.1001/jama.2021.22679
Population
This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

Disease severity

Non-severe
Absence of signs of severe or critical disease

Severe
Oxygen saturation <90% on room air
Signs of pneumonia
Signs of severe respiratory distress

Critical
Requires life sustaining treatment
Acute respiratory distress syndrome
Sepsis
Septic shock

WHO/2019-nCoV/therapeutics/2021.4
Severity of COVID-19 during pregnancy

- Patients with SpO2 < 94% (in room air, at sea level).
- Relationship between partial arterial pressure and Inspiration fraction of Oxygen (PaO2 / FiO2) < 300 mm Hg,
- Respiratory rate > 30 breaths / min or
- Lung infiltrates more than 50%.

Severity of COVID-19 during pregnancy

- Patients with respiratory distress, septic shock and/or multi-organ dysfunction.

COVID-19 infection during pregnancy

Asymptomatic infection
13.5% in areas with high prevalence of COVID-19

Asymptomatic pregnant women 30% vs 10% in women in reproductive age, non pregnant
Admission in Intensive care unit
(aRR = 1.5, [IC] of 95% = 1.2–1.8)

Mechanical ventilation
(aRR = 1.7, IC of 95% = 1.2–2.4)

Published 2020 Jun 26. doi:10.15585/mmwr.mm6925a1
Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study

1. 7 days after symptoms onset

2. Duration of hospitalization was 6 days (64 pts)

3. Gestational age at onset of symptoms: 29 ± 6 weeks

4. Delivery while active infection in 50%

Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Pandemic</th>
<th>Pre-pandemic</th>
<th>Weight</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Pregnancies</td>
<td>Events</td>
<td>Pregnancies</td>
</tr>
<tr>
<td>LMIC subgroup*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumari et al, 2020²⁵</td>
<td>7</td>
<td>1237018</td>
<td>8</td>
<td>6209</td>
</tr>
<tr>
<td>Lumbreras-Marquez et al, 2020²⁷</td>
<td>523</td>
<td>3527</td>
<td>690</td>
<td>2218650</td>
</tr>
<tr>
<td>Overall total</td>
<td>530</td>
<td>1233491</td>
<td>698</td>
<td>2224859</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2=0; \chi^2=0.06, df=1 (p=0.81); I^2=0\%$
Residual heterogeneity: $\tau^2=NA; \chi^2=0.06, df=1 (p=0.81); I^2=0\%$
Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection The INTERCOVID Multinational Cohort Study

Table 2. Adjusted Associations for Maternal and Perinatal Outcomes Among Women With and Without COVID-19 Diagnosis According to Symptom Statusa

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%)</th>
<th>RR (95% CI)</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MMIb</td>
<td>SNMc</td>
<td>SPMMId</td>
<td>Preterm birthc</td>
<td>Preeclampsia/eclampsia/HELLP</td>
</tr>
<tr>
<td>COVID-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>288 (13.5)</td>
<td>1.24 (1.00-1.54)</td>
<td>1.42 (0.65-3.08)</td>
<td>1.08 (0.69-1.69)</td>
<td>0.99 (0.72-1.36)</td>
<td>1.63 (1.01-2.63)</td>
</tr>
<tr>
<td>Any symptom</td>
<td>418 (19.6)</td>
<td>1.76 (1.49-2.08)</td>
<td>3.45 (2.14-5.56)</td>
<td>3.09 (2.36-4.04)</td>
<td>2.10 (1.67-2.62)</td>
<td>2.00 (1.34-2.99)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diarrhea/vomiting</td>
<td>48 (2.3)</td>
<td>1.36 (0.85-2.19)</td>
<td>4.66 (1.93-11.30)</td>
<td>2.79 (1.57-4.95)</td>
<td>2.76 (1.77-4.30)</td>
<td>0.48 (0.07-3.81)</td>
</tr>
<tr>
<td>With fever</td>
<td>199 (9.3)</td>
<td>1.89 (1.54-2.32)</td>
<td>4.34 (2.53-7.43)</td>
<td>3.81 (2.81-5.17)</td>
<td>2.39 (1.82-3.13)</td>
<td>1.82 (1.08-3.06)</td>
</tr>
<tr>
<td>With shortness of breath</td>
<td>89 (4.2)</td>
<td>2.46 (1.96-3.08)</td>
<td>3.88 (1.78-8.49)</td>
<td>3.86 (2.62-5.67)</td>
<td>2.88 (2.12-3.89)</td>
<td>2.72 (1.59-4.64)</td>
</tr>
<tr>
<td>With fever and shortness of breath</td>
<td>45 (2.1)</td>
<td>2.56 (1.92-3.40)</td>
<td>4.97 (2.11-11.69)</td>
<td>5.09 (3.30-7.86)</td>
<td>3.40 (2.38-4.86)</td>
<td>2.22 (1.06-4.64)</td>
</tr>
</tbody>
</table>

Supportive Care
<table>
<thead>
<tr>
<th>Anticipated outcome</th>
<th>Interventions</th>
</tr>
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</table>
| Reduce days of invasive mechanical ventilation          | • Use weaning protocols that include daily assessment for readiness to breathe spontaneously  
• Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions  
• Early mobilization  
• Implementation of the above as a bundle of care (may also reduce delirium); such as the Awakening and B Coordination, Delirium assessment/management, and Early mobility (ABCDE) |
| Reduce incidence of ventilator-associated pneumonia     | • Oral intubation is preferable to nasal intubation in adolescents and adults  
• Keep patient in semi-recumbent position (head of bed elevation 30–45°)  
• Use a closed suctioning system; periodically drain and discard condensate in tubing  
• Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely  
• Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days |
| Reduce incidence of catheter-related bloodstream infection | • Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed |
| Reduce incidence of pressure ulcers                     | • Turn patient every 2 hours                                                                                                                                                                         |
| Reduce incidence of stress ulcers and GI bleeding       | • Give early enteral nutrition (within 24–48 hours of admission)  
• Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for GI bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score |
| Reduce the development of antimicrobial resistance       | • Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection |
| Reduce the development of adverse drug effects           | • Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, and other side-effects from unnecessary antimicrobial use |
| Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic (173) | • Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance |
Use cautious fluid management in patients with COVID-19 without tissue hypoperfusion and fluid responsiveness.

Remark: Patients with COVID-19 should be treated cautiously with intravenous fluids; aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation (129). This applies to both children and adults.
Therapeutics and COVID-19

Recommendation against

We recommend against administering convalescent plasma for treatment of COVID-19. *(Strong recommendation against)*

For patients with severe or critical COVID-19

Only in research settings

We recommend not to use convalescent plasma for treatment of COVID-19, except in the context of a clinical trial. *(Recommended only in research settings)*
Convalescent Plasma for Pregnant Women with COVID-19: A Systematic Literature Review

Published data may indicate that convalescent plasma, administered to pregnant women with severe COVID-19 brings benefits for the mother and baby. Nevertheless, the quality of the available studies is limited, as most are case reports and, therefore, they have a relevant notification bias.

Conditional recommendation

We suggest treatment with casirivimab and imdevimab, under the condition that the patient has seronegative status. (Conditional recommendation for)

- With benefits of casirivimab and imdevimab observed only in patients with seronegative status, clinicians will need to identify these patients by credible tests available at the point of care to appropriately apply this recommendation (see Evidence to Decision section).
- Treatment with casirivimab and imdevimab is in addition to the current standard of care, which includes corticosteroids and IL-6 receptor blockers.
Monoclonal Antibodies Casirivimab and Imdevimab in Pregnancy for Coronavirus Disease 2019 (COVID-19)

Monoclonal antibody treatment of symptomatic COVID-19 in pregnancy: initial report

Monoclonal antibodies like casirivimab and imdevimab, approved under authorization for Emergency use, must be considered in non-vaccinated pregnant women with mild or moderate COVID-19 to reduce risk of progression in severity of disease.

Therapeutics and COVID-19

For patients with severe and critical COVID-19

**Strong recommendation for**

*We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab).* *(Strong recommendation for)*

*Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19* *(4)*, and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.*

WHO/2019-nCoV/therapeutics/2021.4
Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review

The available data have significant limitations and is not enough to allow to describe the hole spectrum of adverse events associated with the exposure to Tocilizumab during pregnancy and breastfeeding.

Obviously, a more efficient frame of regulations is needed to ensure the equitable inclusion of pregnant women in research trials.

Only in research settings

We recommend not to use ivermectin in patients with COVID-19 except in the context of a clinical trial. *(Recommended only in research settings)*

Recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19. *(Strong recommendation against)*

*Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.*

Recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19. *(Strong recommendation against)*

*Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.*
Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019

Oxygen therapy
The first 24h of admission are crucial to evaluate the clinical progression.

We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support.

**Remark:** Patients may continue to have increased work of breathing or hypoxaemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO₂ 0.60–0.95). Hypoxaemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation (109).
Hospitalization

- Supplemental Oxygen to achieve \( \text{SatO}_2 \geq 95\% \), to ensure oxygen support for the baby to compensate the growing oxygen requirement

We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target \( \text{SpO}_2 \geq 94\% \) and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target \( \text{SpO}_2 > 90\% \) or \( \geq 92-95\% \) in pregnant women.

- Continous monitoring of Oxygen Saturation
- Low threshold to confirm with blood gases the growing oxygen requirements or CO2 retention related with respiratory insufficiency.

Respiratory insufficiency in pregnancy

Observación y seguimiento

Saturación materna ≤ 95%
FR >30 x min
(Considerar edad gestacional)

Oxigenoterapia:
O2 canula nasal
(FiO2 32%)

Pronación espontánea

Saturación materna ≤ 93-95%  
FR >30 x min del trabajo respiratorio

Oxigenoterapia: Ventury (FiO2 ≥ 35 %) o MNR (FiO2 80-100 %)

1- Ventilación mecánica No-invasiva  
2- Canula nasal de alto flujo

Pronación espontánea

doi:10.1016/j.ajog.2020.04.005
1- Ventilación mecánica invasiva
2- Sedación +/- Relajación

Saturación materna ≤ 93-95%
FR >30 x min del trabajo respiratorio

Pronación (extendida?)

ECMO (?)

Desembarazar
Referencia

1- Ventilación mecánica No-invasiva
2- Canula nasal de alto flujo

Pronación espontánea
A Randomized Clinical Trial

A Intubation

Hazard ratio, 0.62 (95% CI, 0.39-0.96); P = .03

Cumulative proportion undergoing intubation

Days after randomization

B Clinical recovery

Hazard ratio, 1.39 (95% CI, 1.00-1.92); P = .047

Cumulative proportion with clinical recovery

Days after randomization

Conditional recommendation

We suggest awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence).

In adult patients with severe ARDS (PAO₂/FIO₂ < 150) prone ventilation for 12–16 hours per day is recommended.

Remarks:
1. Application of prone ventilation is recommended for adult patients, preferably for 16 hours per day, and may be considered for paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely; protocols (including videos) are available (140)(141).
2. There is little evidence on prone positioning in pregnant women with ARDS; this could be considered in early pregnancy. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position.
Prone position

Supine Position ARDS Lung

Ventral Lung
Anterior alveoli
Posterior alveoli
Dorsal Lung

Gravity

Prone Position ARDS Lung

Dorsal Lung
Posterior alveoli
Anterior alveoli
Ventral Lung
Prone Positioning for Pregnant Women With Hypoxemia Due to Coronavirus Disease 2019 (COVID-19)
Maternal and neonatal survival were favorable. Prone position was well-tolerated, but it is not clear the impact of prone position on the delivery in the oxygenation and maternal ventilation.
Thromboprophylaxis
Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported (27)(28)(166)(167)(168).

Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways.

**Thromboprophylaxis**

**Conditional recommendation**

In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing (conditional recommendation, very low certainty).
# Pregnancy and COVID-19: pharmacologic considerations

<table>
<thead>
<tr>
<th>Low-risk pregnancy and low risk for VTE</th>
<th>Isolating at home</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors for VTE and not receiving TP</strong></td>
<td><strong>Continue TP</strong></td>
<td>Hospitalized for non-COVID-19-related reason, but asymptomatic or minor symptoms such as anosmia</td>
</tr>
<tr>
<td><strong>Receiving TP</strong></td>
<td>Conduct risk assessment and consider TP on individual basis</td>
<td>Pneumonia requiring supplementary oxygen but not ventilation</td>
</tr>
</tbody>
</table>

**Antepartum**
- Encourage hydration and mobilization
- Conduct risk assessment and consider TP on individual basis
- Continue TP
- Conduct risk assessment and consider TP on individual basis
- Give TP (LMWH)
- Give TP (LMWH); dose according to local critical care protocol

**Peripartum**
- Not applicable
- Follow local policy for interruption of anticoagulation prior to delivery
- Follow local policy for interruption of anticoagulation prior to delivery
- Follow local policy for interruption of anticoagulation prior to delivery
- Follow local policy for interruption of anticoagulation prior to delivery

**Postpartum (while in hospital)**
- Usual care
- Conduct risk assessment and consider TP on individual basis
- Conduct risk assessment and consider TP on individual basis
- Conduct risk assessment and consider TP on individual basis
- Conduct risk assessment and consider TP on individual basis

**Postpartum (upon discharge)**
- Usual care; encourage hydration and mobilization
- Decision based on primary indication for TP; encourage hydration and mobilization
- Conduct risk assessment and consider extended TP on individual basis; encourage hydration and mobilization
- Conduct risk assessment and consider extended TP on individual basis; encourage hydration and mobilization
- Conduct risk assessment and consider extended TP on individual basis; encourage hydration and mobilization

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<table>
<thead>
<tr>
<th>Prophylactic dose</th>
<th>Cr Clearance &gt;30ml/min</th>
<th>Cr Clearance &lt;30ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>&lt;80Kg: 40mg/sc/OD</td>
<td>&lt;80Kg: 20mg/sc/OD</td>
</tr>
<tr>
<td></td>
<td>80-100Kg: 60mg/sc/OD</td>
<td>&gt;80Kg: 40mg/sc/OD</td>
</tr>
<tr>
<td></td>
<td>&gt;100Kg: 40mg/sc/BD</td>
<td></td>
</tr>
<tr>
<td>Nadroparin</td>
<td>0.3ml /sc/OD</td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5,000 UI/sc/OD</td>
<td></td>
</tr>
</tbody>
</table>
