Management of the COVID-19 Critically Ill Pregnant Woman

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Abstract

The SARS-CoV-2 pandemic has been spreading like wildfire and there is no accurate estimate of the number of pregnant women infected with COVID-19 and how serious the cases are. The evidence thus far has confirmed that SARS-CoV-2 infection in pregnancy results in a spectrum of symptoms ranging from none at all to critical or severe disease. A recent multinational study has reported that 11% of pregnant women infection with COVID-19 are complicated, required admission to the intensive care unit and that the risk of maternal mortality was 0.8%. Other complications included preterm birth and perinatal death which occurred in 26.3% and 4.1% of the cases, respectively. COVID-19 complications during pregnancy need to be identified and addressed early-on during the infection. This narrative review will summarize recommendations for the management of critically ill pregnant women with a diagnosed SARS-CoV-2 infection during the prenatal period. It will provide insight for healthcare providers and clinicians into diagnosis, initial evaluation and classification of severity, indications for hospitalization and intensive care unit admission, and clinical management considerations. The overall recommendation is to provide an individualized plan of care and prolong gestation as much as the status of the mother and fetus allows.

Keywords: COVID-19; SARS-CoV-2; Maternal Infection; Pregnancy; Critical Illness; Clinical Management; Intensive Care; Thrombosis

Abbreviations

ICU: Intensive Care Unit; CDC: Centers for Disease Control and Prevention; RT-PCR: Reverse-Transcriptase Polymerase Chain Reaction; IgG: Immunoglobulin G; IgM: Immunoglobulin M; WBC: White Blood Cell; CRP: C-Reactive Protein; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; LDH: Lactate Dehydrogenase; CT: Computed Tomography; ABGs: Arterial Blood Gases; bpm: Breaths Per Minutes; SpO2: Peripheral Oxygen Saturation; NIH: National Institutes of Health; ARDS: Acute Respiratory Distress Syndrome; PaO2: Partial Pressure of Oxygen; WHO: World Health Organization; PaCO2: Partial Pressure of Carbon Dioxide; ECMO: Extracorporeal Membrane Oxygenation; VTE: Venous Thromboembolism; LMWH: Low Molecular Weight Heparin; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; ACOG: American College of Obstetricians and Gynecologists; SaO2: Oxygen Saturation; c-Section: Cesarean Section

Introduction

The SARS-CoV-2 pandemic has been spreading ferociously and the numbers of those infected have been on the rise. The number of cases of COVID-19 to date has reached a total of 180,000,000 around the world and the death toll so far is around 3,900,000 worldwide [1].
The virus is usually responsible for a mild infectious syndrome, but patients can also develop pneumonia, acute respiratory failure, and other serious complications. Up till now, we do not have an accurate estimate of the number of pregnant women infected with COVID-19 and how severe the cases are.

The evidence thus far has confirmed that SARS-CoV-2 infection in pregnancy results in a spectrum of symptoms ranging from none at all to critical or severe disease [2]. Despite the fact that most pregnant women are asymptomatic [3] and that the risk of critical illness is low, it seems however that pregnant and recently pregnant women are at an increased risk for severe COVID-19 illness as compared to non-pregnant people [4]. The infection appears to increase the possibility of hospital and intensive care unit (ICU) admission, and mechanical ventilation in the pregnant population, in addition to increased risk of preterm delivery. It is unclear however whether the severity of the disease at delivery and trimester of pregnancy impact maternal mortality and morbidity [2].

A recent multinational study by the World Association of Perinatal Medicine Working Group [5], that involved 72 centers in 22 different countries, has reported that 11% of women whose pregnancy was complicated with COVID-19, required admission to the ICU and that the risk of maternal mortality was 0.8%. Other complications included preterm birth which occurred in 26.3% of the cases and perinatal death which affected 4.1% of cases. The risk of vertical transmission however was negligible [5].

The explanation behind this increased susceptibility to SAR-CoV-2 is the anatomical changes that occur in the body during pregnancy. The elevation of the diaphragm level in addition to the increased dimension of the thoracic cage in the transverse diameter may have damaging effects on maternal hypoxia tolerance [6,7]. Furthermore, the changes in lung volume and the increased vasodilatation might increase mucosal edema and secretions in the upper respiratory tract. As for immunology, it seems likely that during pregnancy there is an increased risk of contracting infections caused by intracellular organisms, such as viruses, due to modifications of the cell-mediated immunity [8]. As a matter of fact, these physiological changes - in addition to those that occur in the cardiovascular, and coagulation systems - may present an increased risk of morbidity [9].

COVID-19 complications during pregnancy need to be identified and addressed early-on during the infection. Current guidance documents for the management of COVID-19 in pregnant women provide details for handling pregnant women with a suspected or confirmed diagnosis. In this narrative review, we summarize recommendations for the management of critically ill pregnant women with a diagnosed SARS-CoV-2 infection during the prenatal period. Our aim is to aide healthcare providers and clinicians in promptly evaluating and treating such cases.

Diagnosis

First and foremost, the diagnosis of COVID-19 should be based on signs and symptoms of the disease, testing for SARS-CoV-2, and imaging [10]. The most commonly reported symptoms in pregnant women with COVID-19, as per a report by Centers for Disease Control and Prevention (CDC), were fever and headaches. Other reported symptoms include cough in 50% of the cases, and muscle aches in 37%, among others [4].

Testing for the SARS-CoV-2 virus using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay of swabbed specimens from the respiratory tract [11], remains the gold standard with a reported sensitivity of 89% [10]. There has been a recent shift in attention to testing serum immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies as a fast and precise method of diagnosing patients and those who are asymptomatic. As per the WHO, COVID-19 testing of symptomatic pregnant women may need to be prioritized to allow their timely access to specialized care [12].

A simple blood test might aide in identifying cases of COVID-19. A systematic review conducted by Allotey, et al. (2020), revealed an elevated white blood cell (WBC) count in 27.4% of the patients, elevated C-reactive protein (CRP) in 47%, and lymphopenia in 36% of
pregnant and recently pregnant women with suspected or confirmed COVID-19 [3]. Others have reported elevated aspartate aminotransferase (AST) and alanine transaminase (ALT) and elevated lactate dehydrogenase (LDH) [13]. Some of these irregular laboratory findings however could be normal in pregnancy such as leukocytosis [14], and elevated D-dimer and CRP levels [15] while others overlap with abnormal laboratory findings that are usually observed with some pregnancy-related disorders [14]. It is therefore essential that the clinician be aware of these and take them into consideration when determining infection status of the pregnant woman.

A chest computed tomography (CT) with abdominal shielding could be a useful tool in identifying and assessing pregnant women with COVID-19. Pregnant women suspected of COVID-19 and admitted to the hospital in an area where the virus is endemic can receive low-dose chest CT, even when RT-PCR is negative, knowing that the impact of a chest CT on the fetus is minimal [10,16]. The pooled results of a meta-analysis by Gao, et al. (2020) revealed that among pregnant women with COVID-19, 71% had positive CT findings [17]. Furthermore, Chen, et al. reported that 79% of pregnant infected women who underwent a chest CT had infiltrates in both lungs [18]. Other typical observations of chest CT included multiple, patchy, ground glass opacity, crazy-paving pattern, and consolidation shadows distributed in the peripheral and subpleural areas of both lungs [10].

The critically ill pregnant woman

Initial evaluation and classification of severity

As with other patients, pregnant patients with symptoms compatible with COVID-19, assessing illness severity, underlying comorbidities, and clinical status should be conducted to decide whether in-person assessment for possible hospitalization is needed (Figure 1). Pregnant women who have been exposed to the virus could present with no symptoms, mild symptoms or could have an array of clinical indicators. However rapid clinical deterioration could occur, as pregnant women who are symptomatic are at an increased risk of severe disease as compared to non-pregnant women [4,19].

Figure 1: Algorithm for assessing disease risk of pregnant women with suspected or confirmed COVID-19.

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The initial evaluation for pregnant mothers includes assessing medical history and respiratory compromise that includes a physical examination, such as testing temperature, blood pressure, respiratory rate, and heart rate, and other tests such as oxygen saturation and arterial blood gases (ABGs), and chest x-ray as needed [9,16]. Additionally, an assessment of the pregnancy state to confirm fetal well-being should be conducted. For instance, fetal heart rate auscultation, cardiotocography, or fetal ultrasound should be used to assess fetal viability depending on gestational age and symptoms of the mother. Certain risk factors add to the severity of the disease, including older maternal age (especially those 35 years and older), obesity, and presence of underlying medical co-morbidities; particularly diabetes and hypertension or the presence of more than one comorbidity [20].

If upon initial examination, the mother was noted to have an elevated body temperature of greater than or equal to 38°C, a respiratory rate over 20 breaths per minutes (bpm), a peripheral oxygen saturation ($\text{SpO}_2$) of less than 96%, or presence of dyspnea, then a chest X-ray is needed, taking into consideration protective measures for the fetus [9]. A workup of blood count, kidney function including creatinine, urea, electrolyte panel (sodium, potassium, calcium and magnesium), liver function tests, LDH and CRP, and coagulation tests (prothrombin time and activated partial thromboplastin time) is also advised [9].

Additional laboratory testing could be necessary to determine severe COVID-19 in infected patients, see table 1. However, these laboratory findings have been extrapolated from published cohort studies and have not been clearly demonstrated to have prognostic significance. Yet, they can be used to identify those who may be at risk for severe disease.

<table>
<thead>
<tr>
<th>Laboratory feature</th>
<th>Possible threshold</th>
<th>Normal ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated D-dimer</td>
<td>Above 1000 ng/mL</td>
<td>&lt; 500 ng/mL</td>
</tr>
<tr>
<td>Elevated CRP</td>
<td>Above 100 mg/L</td>
<td>&lt; 8.0 mg/L</td>
</tr>
<tr>
<td>Increase level of LDH</td>
<td>Above 245 units/L</td>
<td>110 to 210 units/L</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>More than twice the normal upper limit</td>
<td>0 to 9 ng/L (troponin T high sensitivity in females)</td>
</tr>
<tr>
<td>Increase in ferritin</td>
<td>Above 500 mcg/L</td>
<td>10 to 200 mcg/L in females</td>
</tr>
<tr>
<td>Elevated CPK</td>
<td>More than twice the normal upper limit</td>
<td>40 to 150 units/L</td>
</tr>
<tr>
<td>Decreased absolute lymphocyte count</td>
<td>Less than 800/microL</td>
<td>1800-7700/microL (older than 21 years)</td>
</tr>
</tbody>
</table>


CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase; CPK: Creatine Phosphokinase.

The specified thresholds are not well established and may not apply if the laboratory does not utilize the same reference values.

Table 1: Laboratory findings associated with severe COVID-19 infection.

There have been several definitions for severity of disease in non-pregnant women. Table 2 summarizes disease classifications as per the National Institutes of Health (NIH), which apply to both pregnant women and non-pregnant individuals [21]. It is worthy to note that a patient’s status may alter over time. Certain considerations should also be accounted for such as the threshold for some interventions. An example of that is oxygen supplementation which is recommended for pregnant women when their $\text{SpO}_2$ is less than 95 percent on room air at sea level to adjust for the physiologic changes in oxygen demand in the pregnant state and to make sure that adequate oxygen is delivered to the fetus [21].

Classification | Symptoms and indications
--- | ---
Asymptomatic or pre-symptomatic | Patient tests positive test for SARS-CoV-2 using a virologic test but has no symptoms indicative of COVID-19.
Mild illness | Patient has any signs and symptoms indicative of COVID-19 such as fever, cough, sore throat, malaise, headache, loss of taste and smell, but with no shortness of breath, dyspnea, or abnormal chest imaging.
Moderate illness | Patient with indication of lower respiratory disease (clinical assessment or imaging) and an SpO₂ ≥ 94 percent on room air*.
Severe illness | Patient with a respiratory frequency of > 30 breaths per minute, SpO₂ < 94% on room air*, a PaO₂/FiO₂ ratio of < 300 mm Hg, or lung infiltrates of more than 50 percent.
Critical illness | Respiratory failure, septic shock, and/or multiple organ dysfunction.


SpO₂: Peripheral saturation of oxygen; PaO₂/FiO₂: Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen. *Room air at sea level.

Table 2: COVID-19 disease severity classification as per National Institutes of Health (NIH) in non-pregnant patients.

Indication for hospitalization and ICU admission

The admission criteria for pregnant women with COVID-19 includes a persistent fever of more than 38°C despite using paracetamol, and an x-ray of the chest that reveals pneumonia. The presence of acute confusion or any end-organ dysfunction, or a urea level of more than 19 mg/dL, or a respiratory rate greater than or equal to 30 bpm or a decreased systolic blood pressure of less than or equal to 90 mmHg or diastolic blood pressure of less than or equal to 60 mmHg are additional indicators for hospitalization [9]. In pregnant women, the presence of co-morbidities like chronic hypertension, pregestational diabetes, or immunosuppression, should also be considered among the criteria for admission [9,14] (Figure 2).

Critically ill pregnant women with severe disease symptoms and respiratory failure, require an admission to the ICU [16]. An admission should be considered in those who present with irregular vital signs, shock or organ failure, gradually decreasing peripheral lymphopenia and inflammatory markers such as CRP or LDH, or rapidly progressing pulmonary lesions over a short duration. The use of mechanical ventilation should be considered in patients with respiratory failure [10] (Figure 2). These patients should be cared for by a multidisciplinary team at a hospital or facility that can conduct maternal and fetal monitoring and offers obstetrical services, in addition to an ICU for adult patients [16].

**Figure 2:** Hospital and ICU admission criteria for pregnant women with COVID-19.
Clinical management recommendations

The same recommendations for managing the non-pregnant patient, also apply in pregnancy [16]. The management plan may include additional considerations such as monitoring the fetus and uterine contractions, based on gestational age, and as deemed appropriate. An individualized delivery plan that has been based on a multidisciplinary team approach that may include consulting with infectious disease specialists, obstetric, pulmonary and critical care medicine, and pediatric specialists should be tailored as needed [16]. Further considerations in the clinical management of the critically ill pregnant woman include:

Respiratory support

Patients with severe COVID-19 disease often present with acute respiratory distress syndrome (ARDS) that could lead to profound acute hypoxic respiratory failure. These cases often need oxygen and respiratory support. The same guidelines that apply to the general public, apply to critically ill pregnant patients, however during pregnancy SpO2 should be kept at 95 percent and above. This is in excess of the oxygen delivery needs of the mother. If SpO2 falls to less than 95 percent, measurement of arterial blood gas may be performed to check the partial pressure of oxygen (PaO2). A PaO2 greater than 70mmHg in pregnant women is necessary to maintain a satisfactory oxygen diffusion gradient from mother to fetus across the placenta. As per the World Health Organization (WHO), maintaining the maternal SpO2 level at a target of 92% to 95% or above is desirable once the patient is stable [12].

Evidence from clinical trials has demonstrated that placing COVID-19 severely ill patients with ARDS in the prone position decreased mortality [22]. Pregnant women suffering from severe respiratory distress can benefit from this approach, although placing a pregnant woman in such a position can prove to be difficult, even if it were a semi-prone positioning during the late pregnancy. Therefore, physiologic changes and risks of pregnancy should be accounted for before implementing [22]. It has been recommended to support the gravid uterus beyond 24 weeks using padding or pillows above and below the uterus to offload it and avoid aortocaval compression [22].

Sometimes using permissive hypercapnia (partial pressure of carbon dioxide (PCO2) < 60 mmHg) and extracorporeal membrane oxygenation (ECMO), are needed for management of ARDS without any fetal compromise. However, high positive end-expiratory pressure conditions (> 10 mmHg) require close continuous monitoring of both the mother and fetus, because they decrease preload and cardiac output [14].

Antithrombotic therapy and VTE prophylaxis

The evidence gathered so far suggests that COVID-19 infected pregnant women might be at increased risk of developing venous thromboembolism (VTE) as compared to uninfected pregnant women [23]. Pregnancy in itself is a physiological prothrombotic state, that if coupled with reduced mobility and dehydration can add to the risk. An observational cohort study of disease severity and perinatal outcomes revealed that the incidence of VTE was 6.0% (95% CI 2 - 11) among those with severe-critical illness [24]. Unless it is contraindicated, a prophylactic-dose of anticoagulation is recommended for pregnant patients hospitalized for severe COVID-19 [25].

Unfractioned heparin and low molecular weight heparin (LMWH) do not cross the placenta and hence do not lead to teratogenicity or fetal bleeding [26]. However, use of unfractioned heparin is preferred over LMWH for pregnant patients near delivery as it is easily overturned. The recommended dosage of unfractioned heparin in the first trimester is 5000 units, the second trimester is 7500 to 10,000 units, and the third trimester is 10,000 units, administered subcutaneously every 12 hours. Otherwise, pregnant patients who are remote from delivery could be given prophylactic- or intermediate-dose LMWH. When pharmacologic prophylaxis is contraindicated, intermittent pneumatic compression is suggested [14]. It is not recommended to use direct-acting oral anticoagulants during pregnancy as safety data are still lacking [25].

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Glucocorticoid’s administration

It has recently been reported that COVID-19 pregnant women who receive oxygen supplementation benefit from use of an early short course of glucocorticoids if they meet the criteria for use of glucocorticoids to treat COVID-19 [27]. Moreover, in order to induce fetal lung maturity, the same dosage of glucocorticoids should be administered (dexamethasone four doses of 6 mg intravenously 12 hours apart over two days). The treatment should be continued for 10 days unless the patient is discharged. Methylprednisolone or hydrocortisone can alternatively be used, however, the efficacy of administering such steroids for decreasing maternal mortality is still unclear [27].

NSAIDs and acetaminophen administration

Nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly used to treat fever and pain, have been anecdotally reported to have possible negative effects in patients infected with COVID-19. There have also been reassuring findings where no evidence of a harmful effect was observed [28]. There are no recommendations for avoiding NSAIDS when clinically indicated. It is preferable to use the lowest effective dose for less than 48 hours, keeping in mind gestational age-related potential fetal toxicity [14].

The potential concern of using acetaminophen is hepatic toxicity. Hence, it can be used as an antipyretic and analgesic, provided that the patient has normal liver function tests. Its use in the first trimester is safe, with a protective effect from COVID-19 related hyperthermia that may however increase the risk of congenital abnormalities especially neural tube defects or miscarriage [14]. Still, a recent review has shown that the incidence of these outcomes in relation to COVID-19 infection has not increased [29].

Antiviral drug therapy

There is no approved treatment for COVID-19 so far. There are a number of approved therapies for other indications that are being used and evaluated for treatment of COVID-19, however their use remains investigational. The American College of Obstetricians and Gynecologists (ACOG) recommended use of antiviral therapy for pregnant women with suspected or confirmed influenza in 2018 [30], although more research into their use is needed. The following considerations need to be assessed when antiviral drugs are used for treatment of COVID-19 in pregnant women:

- Remdesivir: This antiviral is recommended for pregnant woman who qualify for its use and to whom the drug is available. Studies have reported activity against SARS-CoV-2 and other related corona viruses in vitro [31,32]. There have been no reports of fetal toxicity when used in some pregnant women infected with Ebola and Marburg virus [33].

- Ribavirin is an investigational drug for COVID-19, known to be teratogenic, and should be avoided in infected pregnant women [14].

- Baricitinib is available for emergency use in combination with remdesivir but its use as the primary treatment is not recommended. Decisions about its administration in pregnant women need to be weighed, given its potential benefit to the mother and its theoretical risk on the fetus [14]. Based on its molecular weight, baricitinib may cross the placenta and therefore decisions towards its use depend on the severity of the mother’s case, gestational age, and any underlying risk factors. There is limited data to ascertain a drug-associated risk for major birth defects or miscarriage.

Chloroquine therapy

Chloroquine, also used for COVID-19 has shown apparent efficacy in its treatment [31,34]; some studies have shown that chloroquine and hydroxychloroquine had exceptional maternal and fetal safety and are therefore worthy of consideration for use in COVID-19 infected
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pregnant women [30,31]. Use of high-dose chloroquine could cause a reduction in systolic blood pressure, thus leading to aggravation of the supine hypotensive syndrome observed from aortocaval compression by the gravid uterus when the woman lies in the supine position [32].

Convalescent plasma

Convalescent plasma, collected from the human plasma of individuals who have recovered from COVID-19, may contain antibodies against the virus and that could be a treatment option for patients infected with COVID-19. Convalescent plasma has been administered to some pregnant patients with COVID-19 with or without additional drug therapy [35,36]. There is increasing evidence recently however that there is no clinical benefit for this approach [37].

Fetal monitoring

In general, the WHO recommends that after resuscitation and stabilization of the pregnant patient, then fetal well-being should be monitored [12]. Wireless external fetal monitoring system for fetal heart tracing became popular during the COVID-19 pandemic. For hospitalized patients, the monitor can be continuously used, particularly in unstable patients in whom emergency cesarean section (c-section) is indicated due to abnormal fetal heart tracing. In patients with stable oxygen saturation (SaO2), an abnormal non-stress test can be performed one to two times a day. Another application of this digital monitoring is for remote fetal assessment of discharged patients who are at risk of preterm labor [14].

Invasive fetal procedures could aggravate COVID-19 infection, and hence can result in increased morbidity and mortality to both the mother and fetus. It is therefore recommended that they be conducted only if they arise from life-threatening conditions and are not elective [29].

Timing and mode of delivery

Timing and mode of delivery should be individualized for patients with severe illness, as there are multiple issues to consider, as well as the mother’s preference. The WHO recommends that a c-section should only be conducted when medically indicated. The decision to terminate the pregnancy and perform emergency delivery is challenging and should take into consideration the gestational age, the severity status of the mother’s infection, and the viability of the fetus [12].

Despite the increased oxygen needs and reduced functional residual capacity of the lungs that are associated with the pregnant status, and which could lead to worsening of the mother’s situation, it is not known whether delivering the critically ill mother would lead to an improvement in her health [38]. Add to that the increased risk of postnatal transmission of SARS-CoV-2 to the fetus in the delivery room. Also, prematurity could affect the transfer of antibodies from the mother to the fetus; immunoglobulins from the mother reach about 50% of their level at 28 - 30 weeks of gestation [29].

In COVID-19 hospitalized pregnant patients with severe disease, but who are not intubated, some recommendations have supported considerations of delivery in those pregnant beyond 32 to 34 weeks if the mother’s status is worsening. As for those who are intubated, the timing of delivery is delicate. Some recommendations advocate delivery after 32 to 34 weeks of gestation if the patient is stable, with the intent of avoiding pregnancy-related issues should the maternal status become worse. This could however aggravate the mother’s condition. Others consider delivery only for mothers with worsening critical illness and those with refractory hypoxemic respiratory failure [14].

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As for critically ill intubated mothers who are less than 30 to 32 weeks gestation, it is advised to continue maternal support with monitoring of the fetus, as long as the mother is stable, or her condition is improving. This will prevent neonatal morbidity or mortality and also probably avert maternal mortality as a result of premature labor [14]. Postpartum maternal and infant care is outside the scope of this review.

Follow-up after recovery

Pregnant women who have recovered from COVID-19 generally require outpatient follow-up within a few days of discharge whether at the healthcare facility in person or via telehealth. As for fetal monitoring, suboptimal fetal growth due to placental insufficiency is a plausible consequence of COVID-19 especially since some studies have observed fetal and/or maternal malperfusion following the mother’s infection with COVID-19 [39,40].

In the absence of robust data, the current recommendations are that pregnant women with confirmed infection should have at least one ultrasound assessment of the amniotic fluid volume as of the third trimester of pregnancy and after a minimum of 14 days following clearing of symptoms or 21 days after the first fetal biometry ultrasound. Pregnant women infected in their first trimester or early on in their second trimester should have a detailed fetal morphology scan, a component of their regular prenatal care, between 18 and 23 weeks of gestation [14].

Conclusion

Overall, gestational weeks should be prolonged as much as possible, if the status of the mother and fetus allows. It is essential that the healthcare practitioner properly evaluate the infected mother and individualize the care plan, taking into consideration all obstetric indications, to be the best fit for the pregnant woman and her fetus. Finally, it is worthy to note that since COVID-19 is a rapidly evolving virus, the above review of management of critically ill pregnant women may become out-of-date as new data and findings relevant to pregnant women and COVID-19 becomes available.

Bibliography


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