



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



COVID-19 in pregnancy and the puerperium: A review for emergency physicians

Marina N. Boushra, MD^a, Alex Koyfman, MD^b, Brit Long, MD^{c,*}

^a Respiratory Institute at The Cleveland Clinic, Cleveland, OH 44106, United States of America

^b The University of Texas Southwestern Medical Center, Department of Emergency Medicine, 5323 Harry Hines Boulevard, Dallas, TX 75390, United States of America

^c Brooke Army Medical Center, Department of Emergency Medicine, 3841 Roger Brooke Dr, Fort Sam Houston, TX 78234, United States of America

ARTICLE INFO

Article history:

Received 7 October 2020

Received in revised form 23 October 2020

Accepted 25 October 2020

Keywords:

Pregnancy

COVID-19

Coronavirus

Infectious disease

ABSTRACT

Background: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel virus responsible for causing the novel coronavirus disease of 2019 (COVID-19).

Objective: This article discusses the clinical manifestations of COVID-19 in pregnant patients, the effects of pregnancy on the course of COVID-19 disease, and the impact of COVID-19 on pregnancy outcomes.

Discussion: The physiological and mechanical changes associated with pregnancy increase maternal susceptibility to infections and complicate intubation and mechanical ventilation. The most common symptoms of COVID-19 in pregnant patients are cough and fever, although many infected individuals are asymptomatic. The majority of pregnant women diagnosed with COVID-19 disease have a mild course of illness and will recover without needing to deliver, but the risks of critical illness and need for mechanical ventilation are increased compared to the general population. Risk factors for death and severe disease include obesity, diabetes, and maternal age > 40 years. Women in their third trimester have the highest risk for critical illness, intensive care unit admission, and need for mechanical ventilation. Adverse fetal outcomes of maternal COVID-19 infection include increased risk of miscarriage, prematurity, and fetal growth restriction. Vertical transmission of SARS-CoV-2 is possible but has not been conclusively proven.

Conclusions: COVID-19 is a potentially deadly infection, but data are limited concerning the pregnant population. Pregnant patients appear to present similarly to the general population, with fever and cough being the most reported symptoms in studies. Knowledge of these presentations and outcomes can assist clinicians caring for these patients.

Published by Elsevier Inc.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel enveloped ribonucleic acid (RNA) virus responsible for causing the novel coronavirus disease of 2019 (COVID-19), a multi-system disease ranging in severity from asymptomatic to fatal [1]. In March 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 a pandemic [2]. Emergency clinicians are frequently the first point of healthcare contact for patients presenting with COVID-19. As such, the burden of counseling on the course of illness, preventative measures, and treatment falls commonly on providers in the emergency department (ED). Additionally, many providers caring for patients infected with SARS-CoV-2 are pregnant or recently-pregnant, and understanding the risks of exposure to COVID-19 can aid allocation of resources and guide protocols to protect them. Pregnant patients are

an especially vulnerable population in the time of the COVID-19 pandemic, and clinician knowledge regarding the disease and its effects on pregnancy can aid emergency physicians in treatment planning and patient counseling.

2. Methods

This narrative review provides a focused overview of COVID-19 in pregnancy for emergency clinicians. The authors searched PubMed and Google Scholar for articles using the Medical Subject Heading (MeSH) compliant keywords “pregnancy” and “COVID-19” or “coronavirus” or “SARS-CoV-2”. The search was conducted from database inception to September 30, 2020. PubMed yielded 1066 articles, and Google Scholar yielded 13,400 articles. Authors evaluated case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews. Authors also reviewed guidelines and supporting citations of included articles. The literature search was restricted to studies published in English, with focus on the emergency medicine and critical care literature. Authors decided

* Corresponding author at: 3841 Roger Brooke Dr, Fort Sam Houston, TX 78234, United States of America

E-mail address: brit.long@yahoo.com (B. Long).

which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. A total of 59 resources were selected for inclusion in this narrative review.

3. Discussion

3.1. Pathophysiology of respiratory illnesses and other coronaviruses in pregnancy

The physiological and mechanical changes associated with pregnancy increase maternal susceptibility to infections in general. Pregnancy is a state of relative immunosuppression, caused by a change in the maternal immune system to prevent rejection of the semiallogenic fetus [3]. This occurs through a hormone-mediated shift from a primarily type 1 T helper cell response to a type 2 T helper cell response, which is more anti-inflammatory in nature [3]. Increased estriol levels also decrease CD4+ and CD8+ T cells, suppress inflammatory cytokine production, and promote the release of anti-inflammatory cytokines [3]. These immunologic shifts, and physiologic changes discussed later, predispose pregnant individuals to a more severe and protracted disease course with respiratory infections [3].

This phenomenon has been well documented with coronavirus infections in the past [4]. Given the relative novelty of the SARS-CoV-2 virus, data regarding its specific pathophysiologic impact in pregnancy are limited. However, recent coronavirus epidemics caused by the Middle Eastern Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV-1) viruses in 2003 and 2012, respectively, can provide valuable information [5,6]. MERS-CoV and SARS-CoV-1 appear to cause more severe disease in pregnant patients compared to SARS-CoV-2 [6]. A 2020 meta-analysis calculated a mortality rate approaching 25–30% in pregnant women with severe SARS-CoV-1 and MERS-CoV, whereas current estimates for SARS-CoV-2 mortality in pregnant women are less than 2% [6].

Data from SARS-CoV-1 and MERS-CoV can also inform the response to SARS-CoV-2 until more specific data are available. In examining the SARS-CoV-1 and MERS-CoV outbreaks, significant morbidity and mortality were most common among patients in the second and third trimesters of pregnancy [5]. Adverse outcomes included miscarriage, small for gestational age neonates, and prematurity [5]. Fever, cough, and fatigue were the most commonly reported symptoms with both SARS-CoV-1 and MERS-CoV [6]. The most common laboratory abnormalities were lymphocytopenia, elevated C-reactive protein (CRP), and leukopenia [6]. A meta-analysis of pregnant women hospitalized for infection with SARS-CoV-1, MERS-CoV, or SARS-CoV-2 noted that 90% of these patients demonstrated radiographic evidence of pneumonia either on plain x-ray or computed tomography (CT), even when asymptomatic [6]. This meta-analysis also noted an increased rate of preterm birth, caesarean delivery, neonatal intensive care unit (NICU) admission, and preeclampsia in women diagnosed with any of the three coronaviruses compared to the general population [6]. There have been no documented cases of vertical transmission of SARS-CoV-1 or MERS-CoV [5,6].

3.2. Clinical manifestations of COVID-19 in pregnancy

Testing in non-pregnant individuals most commonly occurs when they present with symptoms or a concerning contact history, whereas pregnant individuals are often tested for COVID-19 when presenting for care for pregnancy or reasons unrelated to the COVID-19 outbreak [5,6]. A living systematic review of 28 studies including 11,432 patients found that 1 in 10 pregnant or recently-pregnant women presenting or admitted to the hospital tested positive for COVID-19 [7]. Of these, three quarters were asymptomatic, and one in twenty asymptomatic

pregnant women presenting or admitted to the hospital tested positive for COVID-19 [7]. Similar to the general population, the predominant features of symptomatic COVID-19 in pregnant patients were fever, cough, dyspnea, and lymphopenia [7]. The largest cohort study to date reported cough and fever as the most common symptoms in pregnant women presenting with COVID-19, 33% and 29%, respectively, rates similar to the 40% and 39% reported in the Allotey et al. cohort study [7,8]. Compared to non-pregnant women of reproductive age, pregnant or recently-pregnant women with COVID-19 were less likely to report fever or myalgias [7]. A French cohort study suggested that the presence of gastrointestinal symptoms was associated with more severe disease [9]. Symptoms do not appear to differ based on gestational age at the time of presentation [10].

Both leukocytosis and leukopenia occur commonly in pregnant patients with COVID-19. A small case study noted that leukocytosis, lymphopenia, increased neutrophil ratio, and normal presenting temperature were more common in pregnant versus nonpregnant women with COVID-19 [10]. In contrast, a later meta-analysis found leukopenia to be the most common laboratory abnormality in these patients (66.1%) but supported the finding of lymphopenia as a common abnormality (48.3%) [6]. Other common laboratory abnormalities reported in the literature include an elevated CRP, D-dimer, and lactate dehydrogenase (LDH) [10,11]. The most common CT finding of COVID-19 pneumonia in pregnant patients included ground glass opacities and bilateral infiltrates [6,7,10,11]. A meta-analysis of 42 studies comprising 247 pregnant patients with COVID-19 found that focal unilateral or bilateral ground-glass opacities were the most common imaging findings in mild or asymptomatic disease, while all patients with critical illness had diffuse bilateral ground-glass opacities with subpleural involvement and pleural effusion on imaging [5,6]. This study found abnormal imaging in 89% of patients, 8.7% of whom were asymptomatic at the time of imaging [11]. This is similar to studies including patients with SARS-CoV-1 and MERS-CoV, which showed that abnormal imaging findings were common in asymptomatic pregnant patients [5,6].

Given the prevalence of community spread of SARS-CoV-2 and relatively high rates of positive testing in otherwise asymptomatic individuals, it is important to not fall prey to premature closure in pregnant patients who test positive for COVID-19 [12]. Many conditions common to pregnancy can present with fever, cough, or dyspnea, and COVID-19 increases risk for several common pregnancy conditions, including preeclampsia and pulmonary embolism (PE) [7]. The differential diagnosis for the symptoms of COVID-19 in pregnancy is broad and includes PE, cardiomyopathy, pleural or pericardial effusion, pre-eclampsia, gestational rhinitis, physiologic dyspnea, and other etiologies of viral/bacterial pneumonia. Common complications of pregnancy and the puerperium should remain high on the differential for these patients, regardless of the results of COVID-19 testing. Patients should be evaluated for these common conditions based on their history and examination. Table 1 demonstrates the most common signs and symptoms,

Table 1
Clinical Manifestations of COVID-19 in Pregnancy [7,8,11]

Signs/symptoms	Laboratory findings	Imaging findings
Cough	↑/↓ Leukocytes	Unilateral or bilateral ground-glass opacities
Fever	↓ Lymphocytes	Pleural effusions
Dyspnea	↑ CRP	
Myalgias	↑ LDH	
Anosmia / dysgeusia	↑ D-dimer ^a	
Nausea	↑ IL-6 ^a	
Vomiting		
Diarrhea		

^a The combination of elevated D-dimer and IL-6 is a poor prognostic indicator [11].

laboratory findings, and imaging findings in pregnant patients with COVID-19.

3.3. Clinical course and outcomes of COVID-19 in pregnancy

Data on the course of COVID-19 in pregnant women are mixed. Small international case series suggest a similar course of illness in pregnant and non-pregnant women [9,13–16]. Most studies suggest that critical illness is rare in pregnant patients but slightly increased when compared to the general population [8,11,13,17,18]. One study reported that approximately 90% of pregnant women diagnosed with COVID-19 disease recovered without needing to deliver [7]. A meta-analysis of 637 pregnant women with COVID-19 found that 76.5% of patients had mild disease, 15% had severe disease, and 7.7% had critical disease at the time of admission (Table 2) [11]. Of those with mild disease, approximately 3% went on to develop severe or critical infection [11]. Those patients with severe or critical disease accounted for the majority of poor maternal and neonatal outcomes, including maternal death, stillbirth, neonatal death, and NICU admission [11].

Other studies also demonstrate severe outcomes in pregnant patients with COVID-19. While estimated mortality rates for pregnant patients with COVID-19 are 0.6–2%, comparable to the general population, those with critical disease at the time of presentation account for the vast majority of deaths secondary to COVID-19 [7,11]. A recent study found an increased risk of severe illness and mechanical ventilation in pregnant women compared to their non-pregnant counterparts when adjusted for age, race, and co-morbidities [19]. The rate of intensive care admission rises with increasing gestational age, with one study reporting more than 90% of pregnant patients requiring ICU in their third trimester [11]. Data suggest 40% of pregnant patients who died from COVID-19 had obesity, diabetes, or maternal age greater than or equal to 40 years [7,11,17,19]. Complications of severe illness include the need for invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), preterm delivery, and COVID-related cardiomyopathy [19]. Pregnant women with COVID-19 were more likely to require mechanical ventilation and admission to an ICU. Increased maternal age, high body mass index, pre-existing hypertension, and pre-existing diabetes were associated with severe COVID-19, and the presence of maternal co-morbidities was a risk factor for ICU admission and mechanical ventilation [7,8,10,11]. The severity of maternal disease correlated with risk for NICU admission or neonatal death [11]. The combination of elevated D-dimer and interleukin-6 levels was likewise associated with more severe disease and found to be present in 60% of severely ill and 80% of critically ill pregnant women with COVID-19, respectively [11]. Unfortunately, data on baseline levels of these labs in pregnancy are limited, making comparisons difficult. Additionally, COVID-19 is associated with the development of cardiomyopathy in 7–33% of the general population [20,21]. Data on COVID-19 cardiomyopathy in pregnancy are limited, as there is only one small case series reporting on two pregnant patients who developed cardiomyopathy with COVID-19 [22]. Due to lack of data, it is uncertain whether the risk of COVID-19-related cardiomyopathy is increased in pregnant patients compared to the general population.

Table 2
COVID-19 Severity by Clinical Findings [19,23]

Classification	Definition
Asymptomatic	-Positive SARS-CoV-2 testing but no symptoms
Mild	-Fever, cough, headache but no shortness of breath, dyspnea, or abnormal imaging
Moderate	-Clinical or radiographic evidence of mild pneumonia —O ₂ saturation >93% on room air at sea level
Severe	-Dyspnea, respiratory rate ≥ 30/ min, O ₂ saturation ≤ 93%, P:F ratio <300, or >50% lung infiltrates
Critical	-Respiratory failure, septic shock, and/or multiorgan dysfunction

3.4. Effects of COVID-19 on pregnancy and the perinatal period

The PRIORITY study, which included 179 infants born to COVID-positive mothers and 84 infants born to COVID-negative mothers, found no increased risk of preterm birth, NICU admission, and respiratory disease in the COVID-positive cohort, although NICU admission and preterm birth were increased in the sub-group of mothers testing positive 0–14 days before delivery [2,4,8–11,13–15,18,24–26]. The largest cohort study to date followed the courses of 242 COVID-19 positive pregnant women and their 248 infants through the third trimester of pregnancy and one month postpartum [11]. Notable outcomes of this study include a higher rate of caesarean delivery and premature birth in patients hospitalized due to COVID-19 symptoms, findings that have been replicated in several cohort studies and meta-analyses [11]. It is uncertain whether the higher rate of prematurity derives from a need to deliver secondary to COVID-19 related maternal complications or from effects of the disease on the pregnancy. Rates of preterm birth and caesarean delivery are increased in COVID-19 patients regardless of the severity of disease, suggesting that these outcomes may be iatrogenic. One meta-analysis found that preterm delivery occurred in approximately one third of patients with COVID-19 [11]. Of these, 40% were early preterm deliveries (occurring between 24 weeks and 33 weeks 6 days gestation), and 60% were late preterm deliveries (occurring between 34 weeks and 36 weeks 6 days gestation) [11]. Rates of caesarean delivery are extremely high in COVID-19 patients in this meta-analysis, with reported rates of nearly 85% [25,26]. Notably, they also found that the only documented indication for caesarean delivery in approximately half of these cases was maternal COVID-19, again suggesting that this effect may be iatrogenic in nature [11].

Data on fetal complications from COVID-19 are limited. Evidence suggests that miscarriage is more common in patients who became ill in the first trimester compared to the second trimester, with rates of 16.1% and 3.5%, respectively [27–30]. While direct data are not available, abnormal fetal growth due to placental insufficiency is a concern in pregnant patients due to documented uteroplacental vascular malperfusion, intervillous inflammation, and thrombosis of fetal intervillous vessels in maternal COVID-19 infection [8]. This concern derives from 4 studies reporting on the histopathological examinations of 14 placentas from patients with clinically mild COVID-19 which found occlusive fibrin deposition and non-occlusive thrombi with placental hypoperfusion in all specimens [11,31]. Half of these cases resulted in preterm delivery, and one case each of placental abruption, second-trimester miscarriage, and small for gestational age infant were also reported [23–26].

Neonates whose mothers were admitted for the treatment of COVID-19 infection had an odds ratio of 3 of prematurity, regardless of the severity of maternal disease [24]. Spontaneous preterm labor is not increased compared to the general population, and caesarean sections account for nearly all the preterm deliveries reported [7]. Accordingly, most of the complications in neonates born to COVID-19 positive mothers are a result of prematurity rather than COVID-19 infection. Infants with mothers who tested positive closer to delivery were more likely to be admitted to the NICU than those with mothers who tested positive two or more weeks prior to delivery [8]. Stillbirths and neonatal death rates are not increased compared to the general population [8]. In a recent cohort study, nearly a tenth of the neonates born to COVID-19 positive mothers presented to the ED in the first month of life [24]. None tested positive for COVID-19 [32–35]. This is in line with the findings of the PRIORITY study, which reported no cases of pneumonia or lower respiratory disease in neonates born to COVID-positive mothers at 6–8 weeks of age [33,35]. Several case series report mild symptoms in neonates diagnosed with COVID-19 at or shortly after birth [32–35]. The most common findings of COVID-19 in neonates are fever, pneumonia, cyanosis, respiratory distress, and feeding intolerance [8]. The majority of patients in these case series had mild symptoms and favorable outcomes, and most complications were related to prematurity and sepsis, rather than SARS-CoV-2 [11,24].

Vertical transmission of SARS-CoV-2 remains widely debated. No cases of vertical or horizontal transmission were found in the Marin Gabriel et al study [8]. However, Turan et al. reported in their meta-analysis that 2% of infants born to mothers with COVID-19 tested positive 16–24 h after birth by naso- and oropharyngeal swabs; the PRIORITY study reported a similar positivity rate of 1.1% in infants born to COVID-19 infected mothers [11,24]. SARS-CoV-2 virions have also been visualized in the syncytiotrophoblasts and microvilli of the placenta, suggesting that transplacental transfer may be possible [36]. Both Ig-G and Ig-M antibodies against COVID-19 have been found in seronegative neonates born to COVID-19 infected mothers [26,27]. This is notable because Ig-M antibodies cannot cross the placenta, suggesting a fetal immune response against the virus in neonates born to an infected mother. While SARS-CoV-2 has been isolated from maternal vaginal mucosa and stool samples, it has also been isolated from cord blood, placenta, and amniotic fluid, and there are no data to suggest that caesarean delivery is safer or reduces the risk of vertical transmission of SARS-CoV-2 in these patients [11].

3.5. COVID treatments in pregnancy

Human data on the effects of COVID-19 treatments on pregnancy are limited. Current treatments for patients with COVID-19 include dexamethasone, convalescent plasma, and the antiviral medication remdesivir [36]. The RECOVERY trial, which demonstrated a mortality benefit of dexamethasone in patients with COVID-19 who required respiratory support, did include pregnant and breastfeeding patients and reported no pregnancy-associated adverse outcomes [37]. Use of high doses of dexamethasone in early pregnancy has been associated with poor pregnancy outcomes in mice, mares, and dogs [38]. These outcomes included early pregnancy termination, impaired fetal growth, and abnormal placentation [38]. However, the RECOVERY trial utilized dexamethasone 6 mg daily, which is not high dose [37]. Data on the safety and efficacy of convalescent plasma in COVID-19 disease during pregnancy are emerging, and available data on the efficacy of this treatment in the general population currently demonstrate no difference in mortality [39]. Two ongoing trials of convalescent plasma in pregnant patients with COVID-19 disease are ongoing (NCT04397757 and NCT04388527) [40,41]. Documented adverse effects of convalescent plasma use in the general population are rare but include febrile and allergic transfusion reactions, transfusion-related acute lung injury (TRALI), and anaphylaxis [42]. Randomized trials of remdesivir use in COVID-19 have excluded pregnant and breastfeeding women, but the medication was used without documented harm in pregnant women during the Ebola and Marburg virus epidemics [43]. Remdesivir is available for the treatment of severe COVID-19 disease in pregnant women on a compassionate-use basis in the United States at the time of this article's production [44]. Chloroquine/hydroxychloroquine, a popular treatment at the start of the pandemic, is not recommended for use in COVID-19 disease at the time of this review [45,46]. Data from multiple trials have demonstrated no benefit with the use of chloroquine or hydroxychloroquine in COVID-19 [47]. Additionally, these medications are associated with maternal dysrhythmias, and hydroxychloroquine can cross the placenta and accumulate in fetal ocular tissue [48–50]. Given the lack of documented benefit and the known risks of chloroquine/hydroxychloroquine, they are not recommended for use in COVID-19. As pregnancy is a hypercoagulable state, thromboprophylaxis with low-molecular weight heparin in pregnant patients with COVID-19 should be considered, particularly those with elevated d-dimer levels [51]. The decision to start thromboprophylaxis should be made in conjunction with the patient and their obstetrician.

3.6. Respiratory failure in pregnancy

Respiratory failure can complicate the course of COVID-19 in pregnant patients. Emergency physicians should be cognizant of the impact

of the anatomic and physiologic changes of pregnancy on intubation and mechanical ventilation (Table 3). Elevation of the diaphragm by the expanding uterus reduces functional residual capacity [52]. Oxygen consumption and carbon dioxide production are increased in pregnant patients due to the metabolic demands of the fetus [52]. This combination results in a shorter safe apnea time and faster desaturation following induction and paralysis. Pregnant patients are also at increased risk of aspiration secondary to a progesterone-mediated decrease in the tone of the lower esophageal sphincter, which can complicate intubation and positive-pressure ventilation in these patients [11]. This is compounded by edema and hyperemia of the upper airways in pregnant patients, which increase the friability of the upper airways and decrease their caliber [53,54]. Finally, increased progesterone levels result in increased tidal volume and minute ventilation in pregnant patients, inducing a state of respiratory alkalosis that promotes the transfer of oxygen from maternal circulation to the fetus [52–54]. This should be considered when interpreting pre- and post-intubation blood gases, and every effort should be made to match the patient's pre-intubation minute ventilation once mechanical ventilation is initiated to avoid acidosis and fetal harm. While permissive hypercapnia and hypoxia have proven effective in the management of acute respiratory distress syndrome (ARDS) in the general population, it is uncertain how safe this strategy is in pregnant patients, who rely on maternal respiratory alkalosis for transplacental gas transfer to the fetus [52–54]. Data on ECMO as a rescue therapy in pregnant patients with critical COVID-19 are limited, but it may be associated with favorable maternal and fetal outcomes in pregnant patients failing other therapies [11,55]. Because the success of ECMO as a salvage therapy is often dependent on its early use, consultation and potential transfer to an ECMO expert center should be considered in patients with critical disease failing conventional therapy [7,11,55].

3.7. Disposition of COVID-19 pregnant patients and patient counseling

Patients with mild disease and no co-morbidities can generally be discharged home with close return precautions, as approximately 3% will develop more severe disease (Fig. 1) [11]. Consideration should be given to hospitalizing patients with mild disease complicated by one or more comorbidities, as these patients have a higher risk of decompensation and severe disease [16]. Factors associated with more severe disease include obesity, hypertension, diabetes mellitus, maternal age greater than 40 years, and third-trimester pregnancy [16]. Those with severe or critical disease should be hospitalized, preferably at a center that has obstetrics services and an adult and neonatal ICU (Fig. 1) [8].

Table 3

The impact of anatomic and physiologic changes of pregnancy on respiratory failure and intubation

Anatomic/physiologic change	Effect	Practical considerations
Edema and hyperemia of the upper airways	Increased mucosal friability, decreased caliber of upper airways	Consider using a smaller caliber endotracheal tube
Decreased functional residual capacity	Shorter safe apnea time	Expect rapid desaturation; be prepared to intubate immediately after paralyzing
Faster oxygen consumption		
Gravid abdomen	Aortocaval compression with prone positioning	If proning is necessary, offset the gravid uterus with pillows/blankets
Increased tidal volume and minute ventilation	Physiologic respiratory alkalosis	Set ventilator to match patient's pre-intubation minute ventilation
Diminished lower esophageal sphincter tone	Increased aspiration risk	Avoid bagging if possible Consider intubating in an upright position

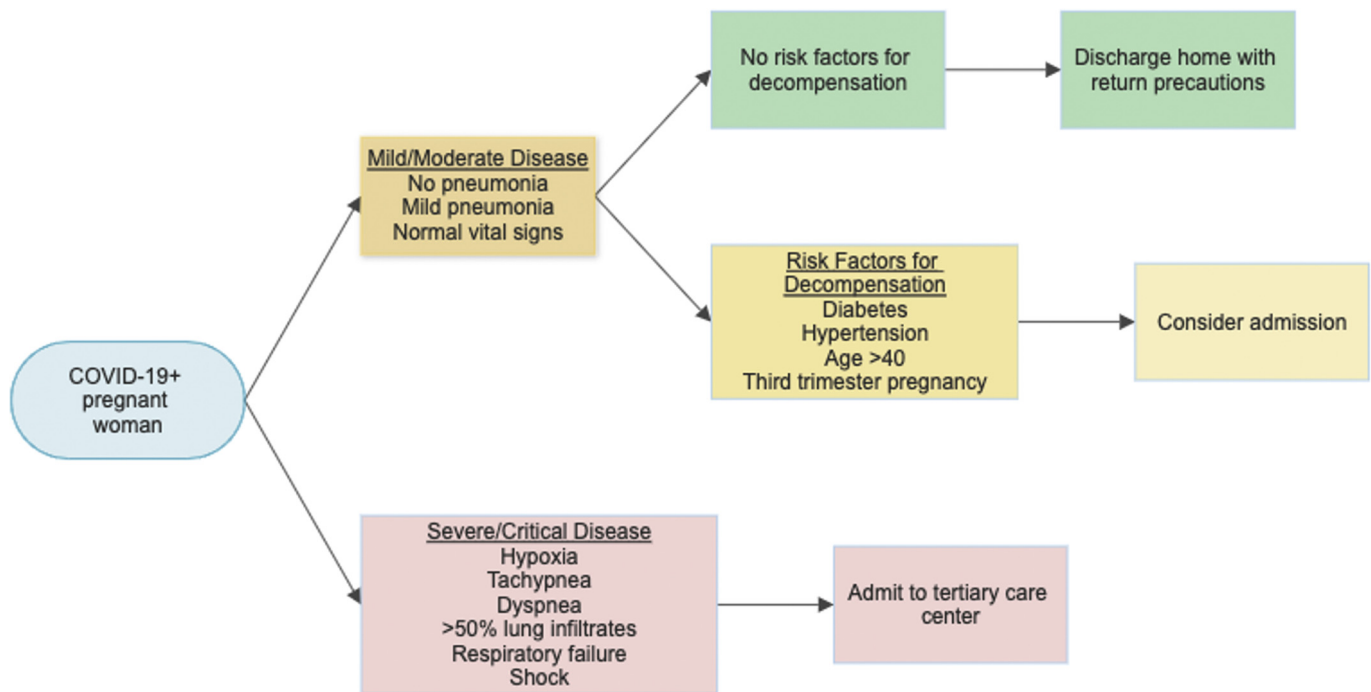


Fig. 1. Algorithm for the disposition of pregnant patients with COVID-19.

3.8. Breastfeeding

Patients diagnosed with COVID-19 in late pregnancy or the puerperium may express concern about breastfeeding. Evidence regarding the transmission of SARS-CoV-2 in breastmilk is limited and therefore insufficient to make a recommendation for or against breastfeeding by COVID-19 infected mothers. Two studies looking at a total of 9 patients found no molecular evidence of the virus in breastmilk, whereas one study reported finding the virus in breastmilk more than one week after delivery [56,57]. Given the paucity of evidence for transmission in breastmilk and the proven benefits of breastfeeding, the WHO and the Centers for Disease Control and Prevention recommend continued breastfeeding by mothers who are COVID-19 positive as long as basic hygiene measures are followed, including the wearing of a facemask by the mother during feeding [58,59]. One study noted a decreased rate of breastfeeding in COVID-19 positive mothers, a factor previously documented to be associated with maternal-newborn separation at birth, which has been common in mothers positive for COVID-19 [8].

4. Conclusion

COVID-19 is a potentially deadly infection, but data are limited concerning the pregnant population. Heterogeneity in study populations, testing protocols, and study results make it difficult to draw widespread conclusions, especially in studies with pregnant and puerperal individuals. Pregnant patients appear to present similarly to the general population, with fever and cough being the most reported symptoms in studies. Other than direct testing, no laboratory or imaging finding is sensitive or specific for the virus. Ground-glass opacities and bilateral infiltrates are the most commonly reported CT findings but are neither sensitive nor specific for COVID-19 infection. Lymphopenia has been commonly reported, as well as leukocytosis and leukopenia. Patients with mild disease and no co-morbidities can be safely discharged home. Close follow-up and return precautions should be provided, as 3% progress to severe or critical illness. Risk factors for death and severe disease include obesity, diabetes, and maternal age > 40 years. Women in their third trimester have the highest risk for critical illness, ICU admission, and need for mechanical ventilation. Evidence for transmission of SARS-CoV-19 through

breastmilk is limited, and current guidelines recommend continued breastfeeding by COVID-19 positive mothers.

Declaration of Competing Interest

NONE for Dr. Boushra, Dr. Koyfman, and Dr. Long.

Acknowledgements

MB, BL, and AK conceived the idea for this manuscript and contributed substantially to the writing and editing of the review. This manuscript did not utilize any grants or funding, and it has not been presented in abstract form. This clinical review has not been published, it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. This review does not reflect the views or opinions of the U.S. government, Department of Defense, U.S. Army, U.S. Air Force, or SAUSHEC EM Residency Program.

References

- [1] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395(10223):470–3. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9).
- [2] WHO Director-General's opening remarks at the media briefing on COVID-19; 11 March 2020 <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020> (Accessed September 29, 2020).
- [3] Mathad JS, Gupta A. Pulmonary infections in pregnancy. *Semin Respir Crit Care Med*. 2017;38(2):174–84. <https://doi.org/10.1055/s-0037-1602375>.
- [4] Perlman S. Another decade, another coronavirus. *N Engl J Med*. 2020;382(8):760–2. <https://doi.org/10.1056/NEJMe2001126>.
- [5] Galang RR, Chang K, Strid P, et al. Severe coronavirus infections in pregnancy: a systematic review. *Obstet Gynecol*. 2020;136(2):262–72. <https://doi.org/10.1097/AOG.0000000000004011>.
- [6] Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical

- maternal-fetal transmission: a systematic review and meta-analysis. *Eur J Med Res*. 2020;25(1):39. <https://doi.org/10.1186/s40001-020-00439-w>.
- [7] Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370. <https://doi.org/10.1136/bmj.m3320>.
 - [8] Gabriel Marin, Miguel A, Mar Reyne Vergeli, Sonia Caserio Carbonero, Sole Laia, Tamara Carrizosa Molina, et al. Maternal, perinatal, and neonatal outcomes with COVID-19: a multicenter study of 242 pregnancies and their 248 infant newborns during their first month of life. *The Pediatric Infectious Disease Journal*. 2020. <https://doi.org/10.1097/INF.0000000000002902> Still in print.
 - [9] Cohen J, Vignaux O, Jacquemard F. Covid-19 in pregnant women: general data from a French national survey. *Eur J Obstet Gynecol Reprod Biol*. 2020;251(1):267–8. <https://doi.org/10.1016/j.ejogrb.2020.06.002>.
 - [10] Liu D, Li L, Wu X, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: a preliminary analysis. *Am J Roentgenol*. 2020; 215(1):127–32. <https://doi.org/10.2214/AJR.20.23072>.
 - [11] Turan O, Hakim A, Dashraath P, Jeslyn WJL, Wright A, Abdul-Kadir R. Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: A systematic review. *Int J Gynecol Obstet*. 2020;151(1). <https://doi.org/10.1002/ijgo.13329> ijgo.13329.
 - [12] Kim GU, Kim MJ, Ra SH, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. *Clin Microbiol Infect*. 2020;26(7). <https://doi.org/10.1016/j.cmi.2020.04.040> 948.e1–948.e3.
 - [13] Hirshberg A, Kern-Goldberger AR, Levine LD, et al. Care of critically ill pregnant patients with coronavirus disease 2019: a case series. *Am J Obstet Gynecol*. 2020;223(2):286–90. <https://doi.org/10.1016/j.ajog.2020.04.029>.
 - [14] Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. *Am J Obstet Gynecol*. 2020;223(1). <https://doi.org/10.1016/j.ajog.2020.04.014> 111.e1–111.e14.
 - [15] Ferrazzi E, Frigerio L, Savasi V, et al. Mode of delivery and clinical findings in COVID-19 infected pregnant women in northern Italy. *SSRN Electron J*. April 2020. <https://doi.org/10.2139/ssrn.3562464>.
 - [16] Salvatori G, de Rose DU, Concato C, et al. Managing COVID-19-positive maternal-infant dyads: an Italian experience. *Breastfeed Med*. 2020;15(5):347–8. <https://doi.org/10.1089/bfm.2020.0095>.
 - [17] San-Juan R, Barbero P, Fernández-Ruiz M, et al. Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: a single-Centre cohort study from Spain. *EClinicalMedicine*. 2020;23:100407. <https://doi.org/10.1016/j.eclinm.2020.100407>.
 - [18] Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. *Arch Pathol Lab Med*. 2020;144(7):799–805. <https://doi.org/10.5858/arpa.2020-0901-SA>.
 - [19] Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status – United States, January 22–June 7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(25): 769–75. <https://doi.org/10.15585/mmwr.mm6925a1>.
 - [20] Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. *Circulation*. 2020;141(20):1648–55. <https://doi.org/10.1161/CIRCULATIONAHA.120.046941>.
 - [21] Thompson JL, Nguyen LM, Noble KN, Aronoff DM. COVID-19-related disease severity in pregnancy. *Am J Reprod Immunol*. September 2020. <https://doi.org/10.1111/aji.13339>.
 - [22] Juusela A, Nazir M, Gimovsky M. Two cases of coronavirus 2019-related cardiomyopathy in pregnancy. *Am J Obstet Gynecol MFM*. 2020;2(2):100113. <https://doi.org/10.1016/j.ajogmf.2020.100113>.
 - [23] What's new | COVID-19 Treatment Guidelines; 2020 <https://www.covid19treatmentguidelines.nih.gov/whats-new/> (Accessed October 18, 2020).
 - [24] Flaherman VJ, Afshar Y, Boscardin J, et al. Infant outcomes following maternal infection with SARS-CoV-2: first report from the PRIORITY study. *Clin Infect Dis*. September 2020. <https://doi.org/10.1093/cid/ciaa1411>.
 - [25] Fenizia C, Biasin M, Cetin I, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. *Nat Commun*. 2020;11(1):5128. <https://doi.org/10.1038/s41467-020-18933-4>.
 - [26] Carosso A, Cosma S, Serafini P, Benedetto C, Mahmood T. How to reduce the potential risk of vertical transmission of SARS-CoV-2 during vaginal delivery? *Eur J Obstet Gynecol Reprod Biol*. 2020;250:246–9. <https://doi.org/10.1016/j.ejogrb.2020.04.065>.
 - [27] Baergen RN, Heller DS. Placental pathology in Covid-19 positive mothers: preliminary findings. *Pediatr Dev Pathol*. 2020;23(3):177–80. <https://doi.org/10.1177/1093526620925569>.
 - [28] Chen S, Huang B, Luo DJ, et al. Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. *Zhonghua bing li xue za zhi = Chinese journal of Pathology*. 2020;49(0). <https://doi.org/10.3760/cmaj.cn112151-20200225-00138> E005.
 - [29] Kuhrt K, McMicking J, Nanda S, Nelson-Piercy C, Shennan A. Placental abruption in a twin pregnancy at 32 weeks' gestation complicated by coronavirus disease 2019 without vertical transmission to the babies. *Am J Obstet Gynecol MFM*. 2020;2(3):100135. <https://doi.org/10.1016/j.ajogmf.2020.100135>.
 - [30] Baud D, Greub G, Favre G, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. *JAMA*. 2020;323(21):2198–200. <https://doi.org/10.1001/jama.2020.7233>.
 - [31] Knight Dphil M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ*. 2020;369:m2107. <https://doi.org/10.1136/bmj.m2107>.
 - [32] Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809–15. [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3).
 - [33] Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. 2020;323(13):1313–4. <https://doi.org/10.1001/jama.2020.2131>.
 - [34] Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;9(1):51–60. <https://doi.org/10.21037/tp.2020.02.06>.
 - [35] Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020; 174(7):722–5. <https://doi.org/10.1001/jamapediatrics.2020.0878>.
 - [36] Tobaqiy M, Qashqary M, Al-Dahery S, et al. Therapeutic management of patients with COVID-19: a systematic review. *Infect Prevent Pract*. 2020;2(3):100061. <https://doi.org/10.1016/j.infpip.2020.100061>.
 - [37] Horby P, Lim WS, Emberson J, et al. Dexamethasone for COVID-19-Preliminary Report Effect of Dexamethasone in Hospitalized Patients with COVID-19-Preliminary Report RECOVERY Collaborative Group*. *medRxiv*. June 2020. <https://doi.org/10.1101/2020.06.22.20137273> 2020.06.22.20137273.
 - [38] Solano ME, Arck PC. Steroids, Pregnancy and Fetal Development. *Front Immunol*. 2020;10:3017. <https://doi.org/10.3389/fimmu.2019.03017>.
 - [39] Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc*. 2020;95(9):1888–97. <https://doi.org/10.1016/j.mayocp.2020.06.028>.
 - [40] COVID-19 Convalescent Plasma for Mechanically Ventilated Population - Full Text View - ClinicalTrials.gov. <https://www.clinicaltrials.gov/ct2/show/NCT04388527>; 2020 (Accessed October 5, 2020).
 - [41] COVID-19 Convalescent Plasma for the Treatment of Hospitalized Patients With Pneumonia Caused by SARS-CoV-2 - Full Text View - ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT04397757>; 2020 (Accessed October 5, 2020).
 - [42] Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2020;2020(7). <https://doi.org/10.1002/14651858.CD013600.pub2>.
 - [43] Mulangu S, Dodd LE, Davey RT, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med*. 2019;381(24):2293–303. <https://doi.org/10.1056/NEJMoa1910993>.
 - [44] Igbinoza I, Miller S, Bianco K, et al. Use of remdesivir for pregnant patients with severe novel coronavirus disease 2019. *Am J Obstet Gynecol*. 2020. <https://doi.org/10.1016/j.ajog.2020.08.001>.
 - [45] Huybrechts KF, Bateman BT, Zhu Y, et al. Hydroxychloroquine early in pregnancy and risk of birth defects. *Am J Obstet Gynecol*. September 2020. <https://doi.org/10.1016/j.ajog.2020.09.007>.
 - [46] Lacroix I, Bénévent J, Damase-Michel C. Chloroquine and hydroxychloroquine during pregnancy: what do we know? *Therapies*. 2020;75(4):384–5. <https://doi.org/10.1016/j.therap.2020.05.004>.
 - [47] Hussain N, Chung E, Heyl J, et al. A Meta-Analysis on the Effects of Hydroxychloroquine on COVID-19. *Cureus*. 2020;12(8). <https://doi.org/10.7759/cureus.10005>.
 - [48] Louchet M, Sibide J, Peytavin G, Picone O, Tréluyer J-M, Mandelbrot L. Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019. *Am J Obstet Gynecol MFM*. 2020;2(3):100159. <https://doi.org/10.1016/j.ajogmf.2020.100159>.
 - [49] Klinger G, Morad Y, Westall CA, et al. Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. *Lancet*. 2001;358(9284): 813–4. [https://doi.org/10.1016/S0140-6736\(01\)06004-4](https://doi.org/10.1016/S0140-6736(01)06004-4).
 - [50] Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature. *J Rheumatol*. 2011;38(12):2504–8. <https://doi.org/10.3899/jrheum.110686>.
 - [51] Carlo Di Renzo G, Giardina I. Coronavirus disease 2019 in pregnancy: Consider thromboembolic disorders and thromboprophylaxis; 2020. <https://doi.org/10.1016/j.ajog>.
 - [52] Schwaiblmair F, Karcz M, Menk M, Papadakis PJ, Dantoni SE. Respiratory failure and mechanical ventilation in the pregnant patient. *Crit Care Clin*. 2016;32(1):85–95. <https://doi.org/10.1016/j.ccc.2015.08.001>.
 - [53] Lapinsky SE. Management of Acute Respiratory Failure in pregnancy. *Semin Respir Crit Care Med*. 2017;38(2):201–7. <https://doi.org/10.1055/s-0037-1600909>.
 - [54] Lucarelli E, Behn C, Lashley S, Smok D, Benito C, Oyelese Y. Mechanical ventilation in pregnancy due to COVID-19: a cohort of three cases. *Am J Perinatol*. 2020;37(1): 1066–9. <https://doi.org/10.1055/s-0040-1713664>.
 - [55] Fiore A, Piscitelli M, Adodo DK, et al. Successful use of extracorporeal membrane oxygenation postpartum as rescue therapy in a woman with COVID-19. *J Cardiothorac Vasc Anesth*. 2020. <https://doi.org/10.1053/j.jvca.2020.07.088>.
 - [56] Groß R, Conzelmann C, Müller JA, et al. Detection of SARS-CoV-2 in human breastmilk. *Lancet*. 2020;395(10239):1757–8. [https://doi.org/10.1016/S0140-6736\(20\)31181-8](https://doi.org/10.1016/S0140-6736(20)31181-8).
 - [57] Gabriel MAM, Martínez AMM, Martínez MEM, Pedroche JA. Negative transmission of SARS-CoV-2 to hand-expressed colostrum from SARS-CoV-2-positive mothers. *Breastfeed Med*. 2020;15(8):492–4. <https://doi.org/10.1089/bfm.2020.0183>.
 - [58] Coronavirus Disease (COVID-19) and Breastfeeding | Breastfeeding | CDC; 2020 <https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/maternal-or-infant-illnesses/covid-19-and-breastfeeding.html> (Accessed September 29, 2020).
 - [59] Breastfeeding and COVID-19: Scientific brief-2-Limitations; 2020. <https://doi.org/10.1101/2020.05.04.20089995>.