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Coronavirus disease 2019 (COVID-19) pandemic and pregnancy

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Introduction
A critical component in the management of any communicable disease threat is the care of vulnerable populations. Pregnant women are known to be disproportionately affected by respiratory illnesses, which are associated with increased infectious morbidity and high maternal mortality rates. Although most human coronavirus infections are mild, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics of the past two decades have been especially grave, with approximately one-third of infected pregnant women dying from the illness.1,2

The current pneumonia outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, and is predicted to peak around April 2020, without a significant reduction in transmissibility.3 With its indiscriminate and sustained spread across continents, we are likely to see women with COVID-19 canvassed across all trimesters of pregnancy. In this article, we summarize the clinical features of pregnant women with COVID-19, and present a pragmatic and integrated framework that addresses the obstetric complexities of managing this disease in pregnancy.

Clinically Relevant Virology
SARS-CoV-2, a novel enveloped RNA betacoronavirus, infects host respiratory epithelial cells through angiotensin-
converting enzyme 2 (ACE2), a membrane-bound aminopeptidase that functions as its putative receptor. Although the expression of ACE2 is predominantly within type II alveolar cells of the lung, the receptor is also present in several extrapulmonary sites across the aerodigestive tract, including the mucosa of the oral cavity. Patients with COVID-19 therefore manifest a spectrum of upper and lower respiratory tract symptoms. Sexual diamorphism has been suggested, but not proved; cellular studies reveal that the expression of ACE2 is attenuated in females, in keeping with the epidemiological observation that the majority of COVID-19 infections to date have occurred in men.

Physiological Susceptibility to COVID-19
Cardiorespiratory system
Approximately 80% of infections in COVID-19 are mild or asymptomatic; 15% are severe, requiring supplemental oxygen; and 5% are critical, requiring mechanical ventilation. Changes to the cardiorespiratory and immune systems in pregnancy increase a woman’s susceptibility to severe infection and hypoxic compromise, but may also delay diagnosis and source control in those with only innocuous upper respiratory tract symptoms such as sore throat and nasal congestion; the latter are seen in 5% of patients with COVID-19.
Gestational rhinitis, due to estrogen-mediated hyperemia of the nasopharynx, usually affects one-fifth of healthy women in late pregnancy and results in marked nasal congestion and rhinorrhea; these features may mask the coryzal symptoms of COVID-19, leading to unchecked viral shedding and community transmission.

Shortness of breath occurs in 18% of patients with COVID-19. However, physiologic dyspnea due to increased maternal oxygen demands from heightened metabolism, gestational anemia, and fetal oxygen consumption is common in pregnancy and must be distinguished from pathologic breathlessness. In addition, pulmonary volumes are altered: functional residual capacity, end-expiratory volumes, and residual volumes decrease steadily from early pregnancy due to diaphragmatic splitting by the gravid uterus, resulting in reduced total lung capacity at term and an inability to clear pulmonary secretions effectively. This is pertinent, as COVID-19 pneumonia rapidly progresses from focal to diffuse bilateral consolidation of lung parenchyma, which, in the context of the pulmonary changes described above, would more readily predispose to hypoxemic respiratory failure in pregnancy.

**Immune system**

Cytokines produced by T-helper (Th) lymphocytes regulate immunity and inflammation. Th1-type cytokines are microbicidal and proinflammatory and chiefly include interferon-γ (IFN-γ), interleukin (IL)−1α, IL-1β, IL-6, and IL-12. In contrast, Th2-type cytokines are anti-inflammatory and comprise IL-4, IL-10, IL-13, and transforming growth factor−β (TGF-β). In pregnancy, the attenuation in cell-mediated immunity by Th1 cells due to the physiological shift to a Th2 dominant environment contributes to overall infectious morbidity by increasing maternal susceptibility to intracellular pathogens such as viruses.

Interestingly, the cytokine profiles in SARS-CoV and SARS-CoV-2 infections in nonpregnant patients may be extrapolated to account for the differences in disease severity in affected pregnancies. Patients with SARS showed preferential activation of Th1 immunity, resulting in the marked elevation of proinflammatory cytokines (IFN-γ, IL-1β, IL-6, and IL-12) for at least 2 weeks after disease onset, leading to extensive lung damage. In contrast, patients with COVID-19 demonstrated activation of both Th1 and Th2 immunity over similar periods in the disease course, culminating in the presence of IFN-γ and IL-1β in addition to IL-4 and IL-10. In addition, elevated levels of IL-6 (a predominantly Th1 response) are associated with a significantly increased risk of mortality in COVID-19 patients.

Murine studies of influenza have demonstrated that pregnancy increases influenza-related pathology via disrupted viral clearance, increased pulmonary IL-6, IL-1α, and Granulocyte-colony-stimulating factor (G-CSF) expression and enhanced physiological stress in the lungs, influenced by changes in prostaglandin and progesterone levels. However, in COVID-19, a range of immune responses has been described, and early adaptive immune responses may be predictive of milder disease severity. We postulate that changes in the hormonal milieu in pregnancy, which influence immunological responses to viral pathogens together with the physiological transition to a Th2 environment favoring the expression of anti-inflammatory cytokines (IL-4 and IL-10) and other unidentified immune adaptations, may serve as the predominant immune response to SARS-CoV-2, resulting in the lesser severity of COVID-19 compared to that in nonpregnant individuals. These immune responses should be further characterized in gravidas and nongravidas with COVID-19 of different disease severities.

**Clinical Features**

Similar to nonpregnant patients, the predominant features of COVID-19 in pregnant patients are fever, cough, dyspnea, and lymphopenia (Table 1).

**Diagnosis and Imaging**

A real-time reverse transcription polymerase chain reaction (RT-PCR) assay is the current gold standard for detecting SARS-CoV-2 from respiratory specimens in patients with suspected COVID-19. At present, it is available in 84 public health laboratories in the United States; these provide in-state testing capacity in all 50 states and the District of Columbia. The test uses specific primers and probes that target the RNA-dependent RNA polymerase (RdRp), envelope, and nucleocapsid genes of SARS-CoV-2, among which the RdRp assay has the highest analytical sensitivity (3.8 RNA copies/reaction at 95% detection probability). As RT-PCR is a quantitative method in which the amplification of DNA is detected in real time, the determination of viral load in COVID-19 is theoretically possible. However, this usually requires laboratories to develop in-house test kits and to validate them with internal controls.

In contrast, most commercially available assays for COVID-19 provide qualitative results, and false-negative results may be due to a low viral load. The practical limitations of RT-PCR testing include the need for a biosafety level-2 (BSL-2) facility, a requirement for kits with specific reagents and primers, the need to maintain a cold chain (as the specimens require storage at 2−8°C), and the use of strict, validated protocols for testing; consequently, countries with resource limitations or acute spikes in the numbers of suspected cases may not be able to meet these demands. However, there are no good alternatives: antigen—antibody detection tests are not validated, and viral culture is impractical, as it takes at least 3 days for SARS-CoV-2 to cause cytopathic effects in selected cell lines (VeroE6 and Huh7 cells). In addition, viral culture will require a BSL-3 facility, which are usually found only in tertiary medical or university research centers.

Chest imaging may aid, but not replace, molecular confirmation of COVID-19. The predominant findings are peripheral airspace shadowing on a plain chest radiograph (Figure 1) and bilateral, multi-lobar ground-glass opacities or consolidation on a computed tomography (CT) scan of the
chest; these features are nonspecific and appear to be similar in pregnancy. Using RT-PCR as a reference, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a CT chest in diagnosing COVID-19 are 97%, 25%, 65%, and 83%, respectively. However, when CT scans are performed in pregnancy, concerns regarding the teratogenic effects of ionizing radiation on the fetus are inevitable. It is reassuring that the fetal radiation dose for a routine CT chest is 0.03 mGy, and exposure to radiation doses of <50 mGy is not associated with an increased risk of fetal anomalies or pregnancy loss. Although intravenous iodinated contrast medium crosses the placenta, studies have not demonstrated teratogenicity or thyroid dysfunction in the newborn.

### Complications in Pregnancy

The outcomes of coronavirus infections in pregnancy are summarized in Table 1. Hitherto, COVID-19 outcomes for the mother appear more promising compared to those of SARS and MERS. Pooled data reveal a case fatality rate of 0%, 18%, and 25% for COVID-19, SARS, and MERS, respectively; in the latter 2 disease syndromes, progressive respiratory failure and severe sepsis were the most frequent causes. This is not surprising, given the predisposition to superimposed bacterial infections due to direct mucosal injury, dysregulation of immune responses, and alterations to the respiratory microbiome after viral pneumonia. Postnatal maternal deterioration can still occur, necessitating continued monitoring.

Fetal complications of COVID-19 include miscarriage (2%), intrauterine growth restriction (IUGR; 10%), and preterm birth (39%). Fever, with a median temperature of 38.1°C—39.0°C, is the prevailing symptom in COVID-19.

#### TABLE 1

Features of COVID-19 in pregnancy stratified against SARS and MERS

| Characteristics | COVID-19 | SARS | MERS |
|-----------------|----------|------|------|
| No. of cases    | 55       | 17   | 12   |
| Age (y)         | 23–40    | 27–44| 31–39|
| Gestational age at infection (wk) | All were in the third trimester except 2 women who were <28 wk gestation | 4–32 | 4–38 |
| Respiratory comorbidities (n) | None | Asthma (1) | Asthma (1), pulmonary fibrosis (1) |
| Symptoms        |          |      |      |
| Fever (%)       | 84a      | 100  | 58   |
| Cough (%)       | 28a      | 76   | 67   |
| Dyspnea (%)     | 18a      | 35   | 58   |
| Investigationsa |          |      |      |
| CXR/CT evidence of pneumonia | 76a | 100b | 100b |
| Leukocytosis (%)| 38a      | 40b  | 50b  |
| Lymphopenia (%) | 22a      | 67b  | 50b  |
| Thrombocytopenia (%) | 13a | 36b | 50b |
| Maternal complications |      |      |      |
| Mortality (%)   | 0        | 18   | 25   |
| Mechanical ventilation (%) | 2 | 35 | 41 |
| Fetal complications |      |      |      |
| Miscarriage/stillbirth (%) | 2 | 25c | 18b |
| IUGR (%)        | 9        | 13c  | 9c   |
| Preterm birth (%)| 43      | 25c  | 27c  |
| Neonatal complications |      |      |      |
| Neonatal death (%) | 2 | 0c  | 9c   |

Data shown in the table are pooled from references18,35–39,75 (COVID-19);1,78–90 (SARS);2,27,29,83–87 (MERS). COVID-19, coronavirus disease 2019; CT, computed tomography; CXR, chest X-ray; IUGR, intrauterine growth restriction; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

a CXR/CT evidence of pneumonia included ground-glass opacities, focal or bilateral patchy shadowing, and interstitial abnormalities. Leukocytosis was defined as a white blood cell count of >11,000/mm³. Lymphopenia was defined as a lymphocyte count of <1000/mm³. Thrombocytopenia was defined as a platelet count of <150,000/mm³. Patients whose data were not reported were excluded from the calculations; 1 One patient who aborted her pregnancy was excluded from the calculations.

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**FIGURE 1**

Chest radiograph in COVID-19

An erect plain radiograph of the chest in a nonpregnant woman from Singapore with laboratory confirmed COVID-19 demonstrates bilateral and peripherally distributed air-space opacities.

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Cohort studies in patients with other infections have not shown increased risks of congenital anomalies from maternal pyrexia in the first trimester, although childhood inattention disorders are more common, possibly related to hyperthermic injury to fetal neurons.

**Vertical Transmission**

There is a theoretical risk of vertical transmission, similar to that seen in SARS, as the ACE2 receptor is widely expressed in the placenta, with a similar receptor-binding domain structure between SARS-CoV and SARS-CoV-2. Most recently, 2 neonates from COVID-19—infected mothers are said to have tested positive for SARS-CoV-2 shortly following delivery, casting concerns about the possibility of vertical transmission. However, there have been no confirmed instances of vertical transmission among the 46 other neonates born to COVID-19—infected mothers reported thus far, supported in turn by evidence demonstrating an absence of viral isolates in the amniotic fluid, cord blood, breast milk, and neonatal throat swabs in a subset of these patients. It is notable, however, that the overwhelming majority of these women acquired COVID-19 in the third trimester; there are currently no data on perinatal outcomes when the infection is acquired in early pregnancy. Regardless of the risk, it is reassuring that COVID-19 appears to manifest as a mild respiratory disease in the pediatric population.

**Treatment**

**Current approach**

Symptomatic treatment and pregnancy-specific management of complications such as sepsis and acute respiratory distress syndrome (ARDS) comprise the current standards of care. A high Sequential Organ Failure Assessment (SOFA) score and D-dimer levels of >1 μg/mL on admission predict increased mortality in nonpregnant patients with COVID-19. However, D-dimer levels are difficult to interpret, as the values are usually raised in pregnancy, such that only 84%, 33%, and 1% of women in the first, second, and third trimesters, respectively would have normal results based on conventional thresholds. The SOFA score should also be adjusted to reflect the influence of pregnancy on hemodynamics and renal blood flow, such as by using a creatinine level of >1.02 mg/dL (instead of >1.20 mg/dL) to signify renal dysfunction. In addition, mechanical ventilation requires achieving higher maternal oxygen (target PaO₂ >70 mmHg instead of 55–80 mm Hg) and lower carbon dioxide levels (target PaCO₂ 28–32 mmHg) to maintain placental perfusion and prevent fetal hypoxemia and acidosis.

We concur with the WHO recommendation against the routine use of systemic corticosteroids, as it appears to delay viral clearance with no survival benefit. Although neither hydrocortisone nor methylprednisolone readily crosses the placenta, prolonged exposure predisposes to maternal hyperglycemia; this is immunosuppressive and sustains the replication of viral viruses within pulmonary epithelial cells. However, in cases of expedited preterm delivery for obstetric or medical indications, the decision to use corticosteroids to accelerate fetal maturity and to minimize peripartum complications should be individualized. Good obstetric practice should prevail, and urgent delivery should not be delayed.

**Options for antiviral therapy**

The Monitored Emergency Use of Unregistered Interventions (MEURI) framework from the WHO should guide the ethical use of nonlicensed drugs in pregnancy during pandemics. Recent studies have identified remdesivir and chloroquine as strong candidate drugs for the treatment of COVID-19. Remdesivir is a novel, broad-acting antiviral nucleotide prodrug that effectively inhibits replication of SARS-CoV-2 in vitro and that of related coronaviruses including MERS-CoV in nonhuman primates. Its use appears to be safe in human pregnancies, and phase 3 trials evaluating efficacy in COVID-19 are currently underway in the United States (ClinicalTrials.gov number NCT04280705) and China (ClinicalTrials.gov number NCT04252664 and NCT04257656).

Chloroquine phosphate is a ubiquitous antimalarial quinolone compound with broad spectrum antiviral and immunomodulating activity. It has been shown to block coronavirus infection by increasing the endosomal pH required for cell fusion and by interrupting the glycosylation of cellular receptors of SARS-CoV in cell culture. Unpublished data from multicenter clinical trials across China have demonstrated that the drug appears to be effective in accelerating the clinical, radiological, and serological resolution of COVID-19. Although chloroquine and its metabolites cross the placenta, it may be safely used in all trimesters of pregnancy, with no increased risk of adverse perinatal outcomes. However, it is worth noting that chloroquine is a drug with a large volume of distribution, and pharmacokinetic studies have shown significantly lower plasma drug concentrations in pregnancy, which suggests the need for a higher dose in COVID-19 (at least 500 mg twice daily).

A relevant side effect of high-dose chloroquine, however, is systolic hypotension, which may exacerbate the hemodynamic changes from supine aortocaval compression by a gravid uterus.

In addition, as all betacoronaviruses including SARS-CoV, SARS-CoV-2 and MERS-CoV contain 2 cysteine proteases that process the viral polyproteins necessary for their replication, viral protease inhibitors such as lopinavir-ritonavir (LPV/r) have shown some benefit in the adjunct management of COVID-19. Although not studied specifically in pregnant women with respiratory infections, LPV/r is known to be safe: an analysis of population-based surveillance data of LPV/r exposure in HIV-positive pregnancies found no increase in the risk of fetal anomalies, preterm birth, or low-birthweight infants.

Conversely, ribavirin, an antiviral guanosine analogue commonly used in coronavirus treatment cocktails, is teratogenic: it induces miscarriage as well as craniofacial and limb defects in the embryos of pregnant mice exposed...
to doses >25 mg/kg, and should be avoided, especially in early pregnancy. Similarly, baricitinib, a Janus kinase inhibitor, has been identified through machine learning as a potential drug for the treatment of COVID-19 by inhibiting the endocytosis of SARS-CoV-2 into pulmonary cells. However, we opine that baricitinib is contraindicated in pregnancy, as animal studies have demonstrated embryotoxicity.

Currently, there are no approved vaccines for the prevention of COVID-19, although several are under development but will not be available for some time. An open-label, phase 1 clinical trial in nonpregnant women and men evaluating a candidate vaccine, mRNA-1273, led by the U.S. National Institutes of Health (NIH), commenced recruitment on March 16, 2020 (ClinicalTrials.gov number NCT 04283461). The safety and immunogenicity of this lipid nanoparticle (LNP)—encapsulated mRNA-based vaccine in pregnancy is, at present, unknown.

Obstetric Management

Antenatal care

In a pandemic, social distancing measures have proven to be effective in reducing disease transmission. Obstetric care can be served by this model, as our own experience attests, by streamlining medical care providers into self-sufficient groups, each minimally comprising the attending, resident, intern, and nursing or midwifery staff (Figure 2). The individual teams function independently and provide inpatient labor and delivery services, outpatient antenatal care, or surgical services, including treating women with suspected or confirmed COVID-19 infection with full personal protective equipment (PPE) compliance. If a team member is exposed to or infected with COVID-19, that individual’s team will be quarantined for at least 2 weeks; workforce segregation thus ensures adequate clinical coverage by unaffected teams in this event. Although inter-hospital movement of doctors and patients is restricted, approved urgent inter-
FIGURE 3
Labor ward triage

Pregnant woman presents to labor ward

History of travel to a foreign country (including healthcare facilities) reporting local transmission within 14 days preceding symptom onset
or
Close contact* with a suspected or confirmed COVID-19 patient
or
Newly diagnosed COVID-19

Does patient have fever?

Does patient have respiratory symptoms (e.g., cough and SOB)?

No

Low risk

• Routine peripartum care
• Conduct delivery with surgical mask, face shield and surgical gown

Yes

Moderate risk

• Isolate in designated negative pressure room in labour ward
• Send off COVID-19 swab for RT-PCR
• Vaginal delivery permitted
• Surgical mask or N95 for delivery
• Cesarean section in standard OR

High risk

• Isolate in designated negative pressure room in labour ward
• Send off COVID-19 swab for RT-PCR (unless already diagnosed)
• Vaginal delivery permitted
• Low threshold for cesarean section and ICU care if maternal or fetal compromise
• N95 or PAPR for delivery
• Cesarean section in negative pressure OR
• Low threshold for ICU care if clinically deteriorates

No

Yes

*Schematic representation demonstrating a model for stratifying risk in obstetric patients presenting to the labor floor.
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hospital transfer of prenatal patients to tertiary maternity units takes place with full adherence to infection control measures, including isolation when necessary. Ambulatory clinical care is increasingly conducted on Health Insurance Portability and Accountability Act (HIPAA)-compliant telemedicine video conferencing platforms (Zoom Video Communications Inc, San Jose, CA), which allow joint management decisions to be made with primary care providers in real time.

**Fetal surveillance**

Protracted respiratory compromise increases the risk of fetal growth restriction due to maternal hypoxia, which drives the release of potent vasoconstrictors such as endothelin-1 and hypoxia-inducible factor, resulting in placental hypoperfusion and reduced oxygen delivery to the fetus. Given that intrauterine growth restriction (IUGR) complicates approximately 10% of pregnancies with COVID-19 (Table 1), we would monitor the fetus with at least 1 ultrasound assessment of growth following maternal recovery. After sonographic evaluation in high-risk patients, the ultrasound transducers should be disinfected according to the manufacturer’s recommendations.

**Labor, delivery, and breastfeeding**

Women who arrive at the labor ward must be stratified, based on local case definitions, into low, moderate, or high risk for COVID-19 infection, to determine the disposition of the patient and type of infection control precautions required of the healthcare staff (Figure 3).

The mode of delivery is directed by obstetric factors and clinical urgency. As there is no convincing evidence of vertical transmission, vaginal delivery is not contraindicated in patients with COVID-19. When emergent delivery is required in a critically ill parturient, a cesarean delivery is most appropriate; these indications include rapid maternal deterioration, difficulty with mechanical ventilation due to the gravid uterus, and fetal compromise. Delivery, including cesarean delivery, should be carried out with respiratory precautions using full personal protective equipment (PPE) and in rooms with negative pressure ventilation.

Patient self-administered inhalation of nitrous oxide and oxygen (Entonox) is a widely used labor analgesic. However, respiratory viruses contaminating the gas delivery apparatus may be a neglected source of cross-infection, and birth attendants should be aware of decontamination guidelines, which include the cleaning of the expiratory valve between patients, and the use of a microbiological filter (pore size <0.05 μm) between the mouthpiece or facemask. Similarly, in a woman with suspected or confirmed COVID-19 requiring supplemental oxygen in labor, a surgical mask should be worn over the nasal cannula, as humidifying oxygen results in the aerosolization (or spray) of infectious particles to a radius of about 0.4 meters, with a resultant risk of nosocomial droplet infection.

Although the data do not suggest a risk of vertical transmission, delayed clamping of the umbilical cord and skin-to-skin contact should be avoided following delivery, extrapolating from recommendations by the Canadian Society of Obstetricians and Gynecologists guidelines for SARS in pregnancy.

Breastfeeding is not contraindicated, based on current published guidelines, a retrospective analysis of COVID-19 in pregnancy showed that none of the women had detectable viral loads of SARS-CoV-2 in breastmilk. Regardless, if the patient chooses to breastfeed, she should wear a face mask because of the close proximity between mother and child, to reduce the risk of droplet transmission. The presence of

### TABLE 2

| Risk          | Examples of clinical encounters in obstetrics                                                                 | Recommended PPE<sup>a</sup> for staff attending to patient with COVID-19                                                                                  |
|---------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Low risk      | • Any transient encounter >2 meters/6 feet away from patient                                                                 | o None; standard precautions and surgical mask suffice                                                                                               |
| Moderate risk | • Obstetric (including vaginal) examination<br> • Ultrasonography (including vaginal scans)<br> • Vaginal or cesarean delivery | o Surgical cap<br> o Gloves<br> o Face shield or goggles<br> o Gown with long sleeves<br> o Surgical mask or N95/FFP2 respirator                                                                 |
| High risk     | • Use of supplemental oxygen<sup>b</sup> in labor: nasal cannula, face mask, air-entrainment mask, or non-rebreather mask<br> • Maternal collapse: cardiopulmonary resuscitation<sup>b</sup> and endotracheal intubation<sup>c</sup> | o Surgical cap<br> o Gloves<br> o Face shield or goggles<br> o Gown with long sleeves<br> o N95/FFP2 respirator or PAPR with HEPA filter (consider if the healthcare worker herself is pregnant) |

COVID-19, coronavirus disease 2019; HEPA, high-efficiency particulate air; PAPR, powered air-purifying respirator.

<sup>a</sup> Personal protective equipment; defined by the Occupational Safety and Health Administration (OSHA) as specialized clothing or equipment, worn by an employee for protection against infectious materials. These include respirators, goggles and protective attire. <sup>b</sup> Aerosol-generating procedures (AGPs).

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coronavirus antibodies in breastmilk depends on the gestation at which maternal infection occurred and if there was any preceding use of high-dose corticosteroids which could suppress maternal antibody responses.71

**Personal Protective Equipment**

The safety of healthcare providers is of the utmost importance in any pandemic, and the type of personal protective equipment (PPE) necessary depends on the degree of perceived risk (Table 2). Surgical face masks are appropriate for general clinical duties, as randomized trial data have shown them to be as effective as N95 respirators in preventing droplet transmission in influenza.71

**N95 respirators in pregnancy**

The use of N95 respirators (also known as FFP2 masks) is recommended by the CDC for healthcare providers with high-risk exposure to patients with suspected or proven COVID-19.72 However, these filtering facepiece respirators are associated with resistance to airflow and increased static dead space volumes, which may affect maternal cardiorespiratory function and fetal oxygenation when worn for prolonged periods.

Controlled clinical studies73,74 of nurses wearing N95 respirators during an hour of physical activity in their second and third trimesters of pregnancy demonstrated reduced tidal volume (23%) and minute ventilation (26%), resulting in lower oxygen uptake (14%) and increased carbon dioxide production (9%) due to labored breathing. Although there were no changes in fetal heart rate, maternal capillary lactate levels, or oxygen saturations, we caution against the use of N95 respirators in pregnant healthcare workers with growth-restricted fetuses, and recommend that they be exempted from frontline duty during the COVID-19 outbreak. Powered air-purifying respirators (PAPR) with high-efficiency particulate air (HEPA) filters, with less airway resistance, are a reasonable alternative.

**Conclusion**

Pregnant women represent a uniquely vulnerable group in any infectious disease outbreak because of their altered physiology, susceptibility to infections, and compromised mechanical and immunological functions. The need to safeguard the fetus adds to the challenge of managing their health. Special precautions are required to minimize cross-infection of healthcare providers while performing procedures that require close physical contact and promote droplet exposure, such as vaginal delivery. Much of the obstetric management is based on consensus and best practice recommendations, as clinical efficacy data regarding antiviral therapy and corticosteroid use is evolving. This narrative represents an integrated framework to provide an appropriate level of care for these patients and hospital staff during the COVID-19 pandemic.

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**USEFUL RESOURCES**

**U.S. CDC COVID-19 Resource Page:** [https://www.cdc.gov/coronavirus/2019-ncov/index.html](https://www.cdc.gov/coronavirus/2019-ncov/index.html)

**JAMA COVID-19 Resource Page:** [https://jamanetwork.com/journals/jama/pages/coronavirus-alert](https://jamanetwork.com/journals/jama/pages/coronavirus-alert)

**Report of WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19):** [https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf](https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf)

**Practical Advice for Healthcare Workers: COVID-19 and Pregnancy – Gianlugi Pilu, MD, University of Bologna:** [https://m.facebook.com/watch/?v=1118006391865743&_rdr](https://m.facebook.com/watch/?v=1118006391865743&_rdr)

**How to use PPE:** [https://www.cdc.gov/hai/pdfs/ppe/PPEslides6-29-04.pdf](https://www.cdc.gov/hai/pdfs/ppe/PPEslides6-29-04.pdf)

**REFERENCES**

1. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004;191:292–7.
2. Alfaraj SH, Al-Tawiql JA, Memish ZA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection during pregnancy: report of two cases and review of the literature. J Microbiol Immunol Infect 2019;52:501–3.
3. WHO Director-General’s opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at: [https://www.who.int/dg/speeches/detail/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 March 12, 2020.
4. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 2020;395(10225):689–97.
5. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8.
6. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. bioRxiv 2020 [Epub ahead of print].
7. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020 [Epub ahead of print].
8. World Health Organization (WHO). WHO coronavirus disease 2019 (COVID-19) situation report 46. Available at: [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04add_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04add_2). Accessed March 14, 2020.
9. Nelson-Piercy C. Respiratory disease. In: Handbook of obstetric medicine. Boca Raton, FL: CRC Press; 2015. p. 63–84.
10. Gardner MO, Doyle NM. Asthma in pregnancy. Obstet Gynecol Clin North Am 2004;31:385–413.
11. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425–34.
12. Berger A. Th1 and Th2 responses: what are they? BMJ 2000;321:424.
13. Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004;136:95–103.
14. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
15. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intens Care Med 2020;46:846–8.
16. Littauer EQ, Esser ES, Antao OQ, Vassileeva EV, Compans RW, Skoutzou I. H1N1 influenza virus infection results in adverse pregnancy outcomes by disrupting tissue-specific hormonal regulation. PLoS Pathog 2017;13:e1006757.
17. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med 2020;26:453–5.
18. Chen H, Guo JMS, Chen W, 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.

19. Cormia VM, Landt O, Kaaser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020 [Epub ahead of print].

20. Accessed Middle East respiratory syndrome coronavirus: Acute respiratory distress syndrome in pregnancy. Lancet 2020;395(10226):1847–70.

21. Zhou P, Zhou P, Yang XL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.

22. Kong W, Aragaw PP. Chest imaging appearance of COVID-19 infection. Radiology 2020 [Epub ahead of print].

23. AIT, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020 [Epub ahead of print].

24. ACOG. Guidelines for diagnostic imaging during pregnancy and lactation. ACOG Committee opinion number 723. October 2017. Available at: https://www.acog.org/clinical-guidance-and-publications/committees-opinions-committee-on-obstetric-practice-guidelines-for-diagnostic-imaging-during-pregnancy-and-lactation?l=1&MobileSet=false. Accessed February 20, 2020.

25. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 2009;169:2078–86.

26. Wong SF, Chow KM, de Swiet M. Severe acute respiratory syndrome and pregnancy. BJOG 2003;110:641–2.

27. Assini A, Abedi GR, Al Masri M, Bin Saeed A, Gerber SI, Watson JT. Middle East respiratory syndrome coronavirus infection during pregnancy: a report of 5 cases from Saudi Arabia. Clin Infect Dis 2016;63:9513.

28. Hanada S, Pirzadah M, Carver KY, Deng JC. Respiratory viral infection-induced microbime alterations and secondary bacterial pneumonia. Front Immunol 2018;9:2640.

29. Malik A, El Masry KM, Ravi M, Sayed F, Middle East respiratory syndrome coronavirus during pregnancy, Abu Dhabi, United Arab Emirates, 2013. Emerg Infect Dis 2016;22:515–7.

30. Saes L, Urhoq J, Kjaergaard J, et al. Fever in pregnancy and the risk of congenital malformations: a cohort study. BMC Pregnancy Childbirth 2017;17:413.

31. Gustavson K, Ask H, Ystrom E, et al. Maternal fever during pregnancy and offspring attention deficit hyperactivity disorder. Sci Rep 2019;9:9519.

32. Levy A, Yagi B, Bursztyn M, Barkalla R, Scharf S, Yagi C. ACE2 expression and activity are enhanced during pregnancy. Am J Physiol Regul Integr Comp Physiol 2008;295:1953–61.

33. Woodward A. A pregnant mother infected with the coronavirus gave birth, and her baby tested positive 30 hours later. Available at: https://www.bussinesinsider.com/vuhan-coronavirus-in-infant-born-from-infected-mother-2020-2. Accessed March 15, 2020.

34. Murphy S. Newborn baby tests positive for coronavirus in London. Available at: https://www.theguardian.com/world/2020/mar/14/newborn-baby-tests-positive-for-coronavirus-in-london. Accessed March 15, 2020.

35. LUY, Zhao R, Zheng S, et al. Lack of viral transmission of severe acute respiratory syndrome coronavirus 2, China. Emerg Infect Dis 2020;26.

36. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect 2020 [Epub ahead of print].

37. Zhu H, Zhu H, Wang L, Fang C, Peng S. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9:51–60.

38. Zhang L, Zhang L, Jiang Y, et al. Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province. Zhonghua Fu Ke Za Zhi 2020;55:E009.

39. Chen S, Chen S, Huang B, et al. Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. Zhonghua Bing Li Xue Za Zhi 2020;49:E005.

40. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). Front Pediatr 2020 [Epub ahead of print].

41. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fcal viral shedding. Nat Med 2020;26:502–5.

42. Cai J, Xu J, Lin D, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis 2020 [Epub ahead of print].

43. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.

44. Kovac M, Mikovic Z, Rakovic L, et al. The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol 2010;148:27–30.

45. Plante LA, Pacheco LD, Louis JM. SMFM consult series #47: sepsis during pregnancy and puerperium. Am J Obstet Gynecol 2019;220: B2.

46. Dhariani K, Narendra DM, Kalpathali KG. Acute respiratory distress syndrome in pregnancy. In: Phelan JP, Foley MR, Saade GR, Dildy GA, Belfort MA, eds. Critical care obstet- rics. Hoboken, NJ: Wiley-Blackwell; 2019. p. 403–18.

47. World Health Organization (WHO). Novel coronavirus technical guidance: patient management. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management. Accessed February 20, 2020.

48. Huime KD, Gallo LA, Short KR. Influenza virus and glycemic variability in diabetes: a killer combination? Front Microbiol 2017;8:861.

49. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71.

50. de Wit E, Feldmann F, Cronin J, et al. Potential therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A 2020;117:6771–6.

51. Mulangiu S, Dodd DL, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381: 2293–303.

52. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72–3.

53. Karunajeeva HA, Saliman S, Mueller I, et al. Pharmacokinetics of chloroquine and mono-desethylchloroquine in pregnancy. Antimicrob Agents Chemother 2010;54:1186–92.

54. Kilanski A, Milech AM, Deng X, Baker SC. Assessing activity and inhibition of Middle East respiratory syndrome coronavirus papain-like and 3C-like proteases using luciferase-based biosensors. J Virol 2013;87:11955–62.

55. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59: 252–6.

56. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained lopinavir/ritonavir combination and the increase of eosinophil may predict the outcome of COVID-19 progression. Int J Infect Dis 2020;95:183–91.

57. Tookey PA, Thorne C, van Wyk J, Norton M. Maternal and foetal outcomes among 4118 women with HIV infection treated with lopinavir/ritonavir during pregnancy: analysis of population-based surveillance data from the national study of HIV in pregnancy and child- hood in the United Kingdom and Ireland. BMC Infect Dis 2016;16:65–75.

58. Kochhar DM, Penner JD, Knudsen TB. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. Toxicol Appl Pharm 1989;52: 99–112.

59. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV. Proc Natl Acad Sci U S A 2020;117:6771–6.

60. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017;13:234–43.

61. United States Centers for Disease Control and Prevention (CDC). Interim guidance for businesses and employers. Plan, prepare and respond to coronavirus disease 2019. Available at: https://www.cdc.gov/coronavirus/2019-ncov/community/guidance-business-response.html. Accessed March 14, 2020.
62. James JL, Stone PR, Chamley LW. The regulation of trophoblast differentiation by oxygen in the first trimester of pregnancy. Hum Reprod Update 2006;12:137–44.
63. Basseal JM, Westerway SC, Juraja M, et al. Guidelines for reprocessing ultrasound transducers. Aust J Ultrasound Med 2017;20:30–40.
64. Maxwell C, McGeer A, Tai KFY, Sermer M. No. 225—management guidelines for obstetric patients and neonates born to mothers with suspected or probable severe acute respiratory syndrome (SARS). J Obstet Gynaecol Can 2017;39:130–7.
65. Chilvers RJ, Weisz M. Entonox equipment as a potential source of cross-infection. Anaesthesia 2000;55:176–9.
66. Hui DSC, Chan MTV, Chow B. Aerosol dispersion during various respiratory therapies: a risk assessment model of nosocomial infection to health care workers. Hong Kong Med J 2014;20:9–13.
67. Pilu G. AJOG presents: Practical advice for healthcare workers: COVID-19 and pregnancy—information for healthcare workers serving in obstetric units. Available at: https://m.facebook.com/watch/?v¼1118006391865743 &_rdr. Accessed March 15, 2020.
68. United States Centers for Disease Control and Prevention (CDC). Interim guidance on breastfeeding for a mother confirmed or under investigation for COVID-19. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov-specific-groups/pregnancy-guidance-breastfeeding.html. Accessed February 22, 2020.
69. Royal College of Obstetricians and Gynaecologists, United Kingdom. Coronavirus (COVID-19) infection in pregnancy, Information for healthcare professionals. Published March 13, 2020. Available at: https://www.rcog.org.uk/coronavirus-pregnancy. Accessed March 10, 2020.
70. Woo PCY, Lau SKP, Wong BHL, et al. Longitudinal profile of immunoglobulin G (IgG), IgM, and IgA antibodies against the severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein in patients with pneumonia due to the SARS coronavirus. Clin Vaccine Immunol 2004;11:665–8.
71. Radonovich LJ, Simberkoff MS, Besseens MT, et al. N95 respirators vs medical masks for preventing laboratory-confirmed influenza in health care personnel. JAMA 2019;322:824–33.
72. United States Centers for Disease Control and Prevention (CDC). Interim infection prevention and control recommendations for patients with confirmed coronavirus disease 2019 (COVID-19) or persons under investigation for COVID-19 in healthcare settings. 2020. Available at: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html. Accessed February 22, 2020.
73. Tong PS, Ng K, Loke AP, et al. Respiratory consequences of N95-type mask usage in pregnant healthcare workers—a controlled clinical study. Antimicrob Resist Infect Control 2015;4:48–57.
74. Roberge RJ, Kim JH, Powell JB. N95 respirator use during advanced pregnancy. Am J Infect Control 2014;42:1097–100.
75. Giao J. What are the risks of COVID-19 infection in pregnant women? Lancet 2020;395:760–2.
76. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses 2020;12:194.
77. Rasmussen SA, Smulian JC, Lednicky JA, et al. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol 2020;222:415–26.
78. Jiang X, Gao X, Zheng H, et al. Specific immunoglobulin G antibody detected in umbilical blood and amniotic fluid from a pregnant woman infected by the coronavirus associated with severe acute respiratory syndrome. Clin Diagn Lab Immunol 2004;11:1182–4.
79. Robertson CA, Lowther SA, Birch T, et al. SARS and pregnancy: a case report. Emerg Infect Dis 2004;10:345–8.
80. Stockman LJ, Lowther SA, Coy K, Saw J, Parashar UD. SARS during pregnancy, United States. Emerg Infect Dis 2004;10:1899–90.
81. Yudin MH, Steele DM, Sgro MD, Read SE, Kopplin P, Gough KA. Severe acute respiratory syndrome in pregnancy. Obstet Gynecol 2005;105:124–7.
82. Lau KK, Yu WC, Chu CM, Lau ST, et al. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 2004;10:342–4.
83. Alserehi H, Wali G, Alshukairi A, Alraddadi B. Impact of Middle East respiratory syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC Infect Dis 2016;16:105.
84. Jeong SY, Sung SI, Sung JH, et al. MERS-CoV infection in a pregnant woman in Korea. J Korean Med Sci 2017;32:1717–20.
85. Payne DC, Iblan I, Alqarawi S, et al. Stillbirth during infection with Middle East respiratory syndrome coronavirus. J Infect Dis 2014;209:1870–2.
86. Park MH, Kim HR, Choi DH, et al. Emergency cesarean section in an epidemic of the Middle East respiratory syndrome: a case report. Korean J Anesthesiol 2016;69:287–91.
87. Racelis S, de los Reyes VC, Sucaldito MN, et al. Contact tracing the first Middle East respiratory syndrome case in the Philippines. Western Pac Surveill Response J 2015;27:3–7.