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Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy

Dr Pradip Dashraath, MBBS MMed (O&G) MRCOG, Dr Wong Jing Lin Jeslyn, MBBS MMed (O&G) MRCOG, Dr Lim Mei Xian Karen, MBBS MMed (O&G) MRCOG, Dr Lim Li Min, MBBS MMed (O&G) MRCOG, Dr Li Sarah, MBChB MPH MMed (O&G) MRCOG, Prof Arijit Biswas, MBBS MD FRCOG, A/Prof Mahesh Arjandas Choolani, MBBS PhD FRCOG, A/Prof Citra Mattar, MBBS MRANZCOG PhD, A/Prof Su Lin Lin, MBBS MMed (O&G) MRCOG

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Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy**Names of authors:** (surnames underlined>Dr Pradip Dashraath*, MBBS MMed (O&G) MRCOG¹Dr Wong Jing Lin Jeslyn* MBBS MMed (O&G) MRCOG¹ | * Joint-first authorsDr Lim Mei Xian Karen, MBBS MMed (O&G) MRCOG¹Dr Lim Li Min, MBBS MMed (O&G) MRCOG¹Dr Li Sarah, MBChB MPH MMed (O&G) MRCOG¹Prof Arijit Biswas, MBBS MD FRCOG^{1,2}A/Prof Mahesh Arjandas Choolani, MBBS PhD FRCOG^{1,2}A/Prof Citra Mattar, MBBS MRANZCOG PhD^{1,2}A/Prof Su Lin Lin, MBBS MMed (O&G) MRCOG^{1,2}**Institution:**¹ Department of Obstetrics & Gynaecology, National University Hospital, Singapore² Yong Loo Lin School of Medicine, National University of Singapore

Author contributions: Pradip Dashraath and Wong Jing Lin Jeslyn contributed substantially and equally. Each of us was involved in the writing and revision of the manuscript. All authors read and approved the final version.

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Corresponding author:

Pradip Dashraath, MBBS MMed (O&G) MRCOG

Mailing address: National University of Singapore, Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, 1E Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228

Email address: pradip_dashraath_vijayakumar@nuhs.edu.sg

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Abstract

The current coronavirus disease 2019 (COVID-19) pneumonia pandemic, caused by the severe acute respiratory syndrome 2 (SARS-CoV-2) virus, is spreading globally at an accelerated rate, with a basic reproduction number (R_0) of 2 – 2.5, indicating that 2 – 3 persons will be infected from an index patient. A serious public health emergency, it is particularly deadly in vulnerable populations and communities in which healthcare providers are insufficiently prepared to manage the infection. As of March 16, 2020, there are more than 180,000 confirmed cases of COVID-19 worldwide, with over 7,000 related deaths. The SARS-CoV-2 virus has been isolated from asymptomatic individuals, and affected patients continue to be infectious two weeks after cessation of symptoms. The substantial morbidity and socioeconomic impact have necessitated drastic measures across all continents, including nationwide lockdowns and border closures.

Pregnant women and their fetuses represent a high-risk population during infectious disease outbreaks. To date, the outcomes of 55 pregnant women infected with COVID-19 and 46 neonates have been reported in the literature, with no definite evidence of vertical transmission. Physiological and mechanical changes in pregnancy increase susceptibility to infections in general, particularly when the cardiorespiratory system is affected, and encourage rapid progression to respiratory failure in the gravida. Furthermore, the pregnancy bias towards T-helper 2 (Th2) system dominance which protects the fetus, leaves the mother vulnerable to viral infections, which are more effectively contained by the Th1 system. These unique challenges mandate an integrated approach to pregnancies affected by SARS-CoV-2.

Here we present a review of COVID-19 in pregnancy, bringing together the various factors integral to the understanding of pathophysiology and susceptibility, diagnostic challenges with real-time reverse transcriptase polymerase chain reaction (RT-PCR) assays, therapeutic controversies, intrauterine transmission and maternal-fetal complications. We discuss the latest options in antiviral therapy and vaccine development, including the novel use of chloroquine in the management of COVID-19. Fetal surveillance, in view of the

predisposition to growth restriction and special considerations during labor and delivery are addressed. Additionally, we focus on keeping frontline obstetric care providers safe while continuing to provide essential services. Our clinical service model is built around the principles of workplace segregation, responsible social distancing, containment of cross-infection to healthcare providers, judicious use of personal protective equipment and telemedicine. Our aim is to share a framework which can be adopted by tertiary maternity units managing pregnant women in the flux of a pandemic while maintaining the safety of the patient and healthcare provider at its core.

Glossary of terms

- ACE2: Angiotensin--converting enzyme 2 – the functional receptor of SARS-CoV-2
- BSL-2: Biosafety level 2 – a laboratory accredited for working with microbes that pose a moderate health hazard
- BSL-3: Biosafety level 3 - a laboratory accredited for working with microbes that pose a threat of serious or lethal disease through inhalation
- CDC: United States Centers for Disease Control and Prevention
- COVID-19: Coronavirus Disease 2019 (previously called 2019 novel coronavirus (2019-nCoV))
- End expiratory volume: Volume of air that can be exhaled at the end of expiration
- FFP2: Filtering facepiece respirator that removes at least 92 percent of very small (0.3 micron) test particles; the European equivalent of an N95 respirator
- Functional residual capacity: Volume of air in the lungs at the end of expiration; it is the sum of residual volume and end expiratory volume
- Huh7 cells: Lineage of cells used in cell culture, derived from human liver cell line
- IFN- γ : Interferon gamma – proinflammatory cytokine produced by Th1 lymphocytes
- IL-1: Interleukin-1 – proinflammatory cytokine produced by Th1 lymphocytes; IL-1 comprises 11 members, including two with potent inflammatory activity, IL-1 α (alarmin) and IL-1 β
- IL-4: Interleukin-4 – anti-inflammatory cytokine produced by Th2 lymphocytes
- IL-6: Interleukin-6 – proinflammatory cytokine produced by Th1 lymphocytes; also has anti-inflammatory properties
- IL-10: Interleukin10 - anti-inflammatory cytokine produced by Th2 lymphocytes

- IL-12: Interleukin-12 – proinflammatory cytokine produced by Th1 lymphocytes
- MERS: Middle East Respiratory Syndrome
- MERS-CoV: Middle East Respiratory Syndrome coronavirus – the virus that causes MERS
- Minute ventilation: Volume of air the patient moves in one minute; it is the product of respiratory rate and tidal volume
- N95 respirator: Respiratory protective device that removes at least 95 percent of very small (0.3 micron) test particles; the American equivalent of an FFP2 respirator
- Negative pressure room: Room that maintains a lower air pressure inside the treatment area than that of the surrounding environment, thus preventing internal air from circulating back out
- R0: Basic reproduction number, which refers to the average number of secondary infections produced by each new case of infection in a population where everyone is susceptible.
- Residual volume: Volume of air in the lungs at the end of a maximal exhalation
- RT-PCR: Reverse transcription polymerase chain reaction
- SARS: Severe Acute Respiratory Syndrome
- SARS-CoV: Severe acute respiratory syndrome coronavirus – virus that causes SARS
- SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2 virus – virus that causes COVID-19
- SOFA score: Sequential organ failure assessment score – to determine the degree of end-organ dysfunction during sepsis; a score of 2-points or more is associated with a 10% mortality rate
- Tidal volume: Volume of air moved into or out of the lungs during quiet breathing

- VeroE6 cells: Lineage of cells used in cell culture, derived from monkey kidney epithelial cells and are suited for propagating viruses that replicate slowly

- WHO – World Health Organization

Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy

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 were especially grave, with approximately a 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), has been declared a pandemic³ by the World Health Organization (WHO) on March 11, 2020 and is predicted to peak around April 2020, without a significant reduction in transmissibility.⁴ 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 which functions as its putative receptor. Whilst 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.⁵ Patients with COVID-19 would therefore manifest a spectrum of upper and lower respiratory

tract symptoms. Sexual dimorphism has been suggested, but not proven - cellular studies reveal that the expression of ACE2 is attenuated in females,⁶ in keeping with the epidemiological observation that the majority of COVID-19 infections to date have occurred in men.⁷

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.⁸ 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 is seen in 5% of patients with COVID-19.⁷ Gestational rhinitis, due to estrogen-mediated hyperemia of the nasopharynx, usually affects a 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-19.⁷ However, physiologic dyspnea due to increased maternal oxygen demands from heightened metabolism, gestational anemia and fetal oxygen consumption is common in pregnancy⁹ and must be distinguished from pathologic breathlessness. Additionally, pulmonary volumes are altered – functional residual capacity, end expiratory volumes and residual volumes decrease steadily from early pregnancy due to diaphragmatic splinting by the gravid uterus, resulting in reduced total lung capacity at term and an inability to clear pulmonary secretions effectively.¹⁰ This is pertinent, as COVID-19 pneumonia rapidly progresses from focal to diffuse bilateral consolidation of

lung parenchyma,¹¹ 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 cytokines¹² are microbicidal and proinflammatory and chiefly include gamma interferon (IFN- γ), interleukin (IL)-1 α , IL-1 β , IL-6 and IL-12. In contrast, Th2-type cytokines¹² are anti-inflammatory and comprise IL-4, IL-10, IL-13 and transforming growth factor beta (TGF- β). In pregnancy, the attenuation in cell-mediated immunity by Th1 cells due to the physiological shift to a Th2 dominant environment⁹ contributes to overall infectious morbidity by increasing maternal susceptibility to intracellular pathogens like viruses.

Interestingly, the cytokine profiles in SARS-CoV and SARS-CoV-2 infections in non-pregnant 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-1 β , IL-6 and IL-12) for at least two weeks after disease onset, leading to extensive lung damage.¹³ 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-1 β in addition to IL-4 and IL-10.¹⁴ Additionally, elevated levels of IL-6 (which is a predominantly Th1 response), is associated with a significantly increased risk of mortality in COVID-19 patients.¹⁵

Murine studies of influenza have demonstrated that pregnancy increases influenza-related pathology via disrupted viral clearance, increased pulmonary IL-6, IL-1 α , and G-CSF expression and enhanced physiological stress in the lungs, influenced by changes in

prostaglandin and progesterone levels.¹⁶ However in COVID-19, a range of immune responses has been described, and early adaptive immune responses may be predictive of milder disease severity.¹⁷ We postulate that changes in the hormonal milieu in pregnancy which influence immunological responses to viral pathogens¹⁶ 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-19¹⁸ compared to non-pregnant individuals. These immune responses should be further characterized in gravidas and non-gravidas with COVID-19 of different disease severities.

Clinical features

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

Diagnosis and imaging

A real-time reverse transcriptase 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 U.S - these provide in-state testing capacity in all 50 states and the District of Columbia. The test utilizes 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).¹⁹ As RT-PCR is a quantitative method where 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 validate them with internal controls.²⁰

In contrast, most commercially available assays for COVID-19 provide qualitative results and false-negatives 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 three days for SARS-CoV-2 to cause cytopathic effects in selected cell lines (VeroE6 and Huh7 cells).²¹ In addition, viral culture will require a BSL-3 facility, which are usually only found 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 computed tomography (CT) scan of the chest;^{22,23} these features are non-specific and appear to be similar in pregnancy.¹⁸ Using RT-PCR as a reference, the sensitivity, specificity, positive predictive value (PPV) and negative predictive (NPV) value of a CT chest in diagnosing COVID-19 in China are 97%, 25%, 65% and 83% respectively.²⁴ However, when CT scans are performed in pregnancy, concerns regarding the teratogenic effects of ionizing radiation on the fetus are inevitable. Reassuringly, the fetal radiation dose for a routine CT chest is 0.03 mGy – exposure to radiation doses < 50 mGy is not associated with an increased risk of fetal anomalies or pregnancy loss.²⁵ Although intravenous iodinated contrast media crosses the placenta, studies have not demonstrated teratogenicity or thyroid dysfunction in the newborn.²⁶

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 SARS and MERS. Pooled data reveals a case fatality rate of 0%, 18% and 25% for COVID-19, SARS and MERS respectively – in the latter two, progressive respiratory failure and severe sepsis were the most frequent causes.^{27,28} This is unsurprising, 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.²⁹ Postnatal maternal deterioration can still occur,³⁰ necessitating continued monitoring.

Fetal complications of COVID-19 include miscarriage (2%), intrauterine growth restriction (IUGR; 10%) and pre-term birth (39%). Fever, with a median temperature of 38.1-39.0°C, is the prevailing symptom⁷ in COVID-19; cohort studies in patients with other infections have not shown increased risks of congenital anomalies from maternal pyrexia in the first trimester,³¹ although childhood inattention disorders are more common, possibly related to hyperthermic injury to fetal neurons.³²

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,³³ with a similar receptor-binding domain structure between SARS-CoV-1 and SARS-CoV-2. Most recently, two 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.^{34,35} However, there have been no confirmed instances of vertical transmission among the 46 other neonates^{18, 36-41} 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.¹⁸ It is notable, however,

that the overwhelming majority of these women acquired COVID-19 in the third trimester – there is currently no data on perinatal outcome 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.^{42,43}

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 $> 1 \mu\text{g/mL}$ on admission predict increased mortality in non-pregnant patients with COVID-19.⁴⁴ 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.⁴⁵ The SOFA score should also be adjusted to reflect the influence of pregnancy on hemodynamics and renal blood flow, such as utilizing a creatinine level $> 1.02 \text{ mg/dL}$ (instead of $> 1.20 \text{ mg/dL}$) to signify renal dysfunction.⁴⁶ Additionally, mechanical ventilation requires achieving higher maternal oxygen (target $\text{PaO}_2 > 70 \text{ mmHg}$ instead of $55 - 80 \text{ mmHg}$) and lower carbon dioxide levels (target $\text{PaCO}_2 28 - 32 \text{ mmHg}$)⁴⁷ 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.⁴⁸ Although neither hydrocortisone nor methylprednisolone readily crosses the placenta, prolonged exposure predisposes to maternal hyperglycemia - this is immunosuppressive and sustains the replication of respiratory viruses within pulmonary epithelial cells.⁴⁹ However, in cases of

expedited preterm delivery for obstetric or medical indications, the decision to use corticosteroids to accelerate fetal maturity and minimise peripartum complications should be individualised. 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 non-licensed drugs in pregnancy during pandemics. Recent studies have identified remdesivir and chloroquine⁵⁰ as strong candidate drugs for the treatment of COVID-19. Remdesivir is a novel, broad-acting antiviral nucleotide prodrug which effectively inhibits replication of SARS-CoV-2 in-vitro and that of related coronaviruses including MERS-CoV in non-human primates.⁵¹ Its use appears to be safe in human pregnancies⁵² 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.⁵⁰ Unpublished data from multicenter clinical trials across China⁵³ have demonstrated that the drug appears 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 worthwhile noting that chloroquine is a drug with a large volume of distribution and pharmacokinetic studies⁵⁴ 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).⁵³ 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.

Additionally, as all betacoronaviruses including MERS-CoV, SARS-CoV and SARS-CoV-2 contain two cysteine proteases that process the viral polypeptides necessary for their replication,^{55,56} viral protease inhibitors such as lopinavir-ritonavir (LPV/r) have shown some benefit in the adjunct management of COVID-19.⁵⁷ 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 birth weight infants.⁵⁸

Conversely, ribavirin, an antiviral guanosine analogue commonly used in coronavirus treatment cocktails,^{1,30} is teratogenic: it induces miscarriage, craniofacial and limb defects in the embryos of pregnant mice exposed to doses exceeding 25 mg/kg,⁵⁹ and should be avoided, especially in early pregnancy. Similarly, baricitinib – a Janus kinase inhibitor – has been identified through machine learning⁶⁰ 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.⁶¹

Currently, there 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 non-pregnant women and men evaluating a candidate vaccine, mRNA-1273, led by the U.S. National Institutes of Health (NIH) has 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.⁶² Obstetric care can be served by this model, as our own experience attests to, 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 labour 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, their team will be quarantined for at least 2 weeks; workforce segregation thus ensures adequate clinical coverage by non-affected teams in this event. While inter-hospital movement of doctors and patients is restricted, approved urgent inter-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 allows 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.⁶³ Given that IUGR complicates approximately 10% of pregnancies with COVID-19, we would monitor the fetus with at least one ultrasound assessment of growth following maternal recovery. Following sonographic evaluation in high-risk patients, the ultrasound transducers should be disinfected according to the manufacturer's recommendations.⁶⁴

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 of 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,¹⁸ vaginal delivery is not contraindicated in patients with COVID-19. When emergent delivery is required in a critically ill parturient, a cesarean section is most appropriate – these indications include rapid maternal deterioration, difficulty with mechanical ventilation due to the gravid uterus, and fetal compromise. Delivery, including cesarean sections, should be carried out with respiratory precautions using full personal protective equipment (PPE) and in rooms with negative pressure ventilation.⁶⁵

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 < 0.05µm) between the mouthpiece or facemask.⁶⁶ 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.^{67,68}

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.⁶⁵

Breastfeeding is not contraindicated, based on current published guidelines^{69,70} – a retrospective analysis of COVID-19 in pregnancy showed that none of the women had detectable viral loads of SARS-CoV-2 in breastmilk.¹⁸ Regardless, if the patient chooses to breastfeed, a face mask should be worn due to the close proximity between mother and child to reduce the risk of droplet transmission. The presence of 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 (PPE)

The safety of healthcare providers is of utmost importance in any pandemic and the type of 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.⁷²

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-19.⁷³ 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 studies^{74,75} 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 due to 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 anti-viral 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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502 **Useful resources**503 **U.S. CDC COVID-19 Resource Page:** <https://www.cdc.gov/coronavirus/2019->504 [ncov/index.html](https://www.cdc.gov/coronavirus/2019-ncov/index.html)505 **JAMA COVID-19 Resource Page:**506 <https://jamanetwork.com/journals/jama/pages/coronavirus-alert>507 **Report of WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19):**508 <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19->509 [final-report.pdf](https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf)510 **Practical Advice for Healthcare Workers: COVID-19 and Pregnancy – Gianluigi Pilu,**511 **MD, University of Bologna:** https://m.facebook.com/watch/?v=1118006391865743&_rdr512 **How to use PPE:** <https://www.cdc.gov/hai/pdfs/ppe/PPEslides6-29-04.pdf>

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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-Tawfiq 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>). 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; published online Feb 4. DOI:[https://doi.org/10.1016/S01406736\(20\)30260-9](https://doi.org/10.1016/S01406736(20)30260-9)
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; published online Feb 24. DOI:10.1038/s41368-020-0074-x.

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; published online Jan 26. DOI:10.1101/2020.01.26.919985
7. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; published online Feb 28. DOI: 10.1056/NEJMoa2002032
8. 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=96b04adf_2. Accessed 14 March 2020
9. Nelson-Piercy C. Respiratory disease. In: *Handbook of Obstetric Medicine*. Boca Raton, FL: CRC Press; 2015:63-84.
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; published online Feb 24. DOI:10.1016/S1473-3099(20)30086-4
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; published online Mar 3. DOI:10.1007/s00134-020-05991-x
- 16.** Littauer EQ, Esser ES, Antao OQ, Vassilieva EV, Compans RW, Skountzou I. H1N1 influenza virus infection results in adverse pregnancy outcomes by disrupting tissue-specific hormonal regulation. *PLoS Pathog* 2017;13:e1006757-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; published online Mar 16. DOI: 10.1038/s41591-020-0819-2
- 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; published online Feb 12. DOI: [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3).
- 19.** Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020;25 DOI:10.2807/1560-7917.ES.2020.25.3.2000045
- 20.** Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis* 2020; published online Feb 24. DOI: 10.1016/S14733099(20)30113-4
- 21.** Zhou P, Zhou P, Yang XL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270-73.

- 583 **22.** Kong W, Argawal PP. Chest imaging appearance of COVID-19 infection. Radiology
584 2020;2. DOI:10.1148/ryct.2020200028

- 585 **23.** Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19
586 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; published
587 online Feb 24. DOI:10.1016/S1473-3099(20)30086-4

- 588 **24.** Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in
589 coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology
590 2020; published online Feb 26. DOI:10.1148/radiol.2020200642.

- 591 **25.** Guidelines for diagnostic imaging during pregnancy and lactation. ACOG Committee
592 Opinion, Number 723, October 2017. Available at: [https://www.acog.org/Clinical-](https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Guidelines-for-Diagnostic-Imaging-During-Pregnancy-and-Lactation?IsMobileSet=false)
593 Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-
594 Practice/Guidelines-for-Diagnostic-Imaging-During-Pregnancy-and-
595 Lactation?IsMobileSet=false. Accessed February 20, 2020.

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

- 599 **27.** Wong SF, Chow KM, de Swiet M. Severe acute respiratory syndrome and pregnancy.
600 BJOG 2003;110:641-2.

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

- 604 **29.** Hanada S, Pirzadeh M, Carver KY, Deng JC. Respiratory viral infection-induced
605 microbiome alterations and secondary bacterial pneumonia. *Front Immunol*
606 2018;9:2640.

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

- 610 **31.** Sass L, Urhoj SK, Kjærgaard J, et al. Fever in pregnancy and the risk of congenital
611 malformations: a cohort study. *BMC Pregnancy Childbirth* 2017;17:413. DOI:
612 <https://doi.org/10.1186/s12884-017-1585-0>.

- 613 **32.** Gustavson K, Ask H, Ystrom E, et al. Maternal fever during pregnancy and offspring
614 attention deficit hyperactivity disorder. *Sci Rep* 2019;9:9519, published online Jul 2.
615 DOI: <https://doi.org/10.1038/s41598-019-45920-7>.

- 616 **33.** Levy A, Yagil Y, Bursztyn M, Barkalifa R, Scharf S, Yagil C. ACE2 expression and
617 activity are enhanced during pregnancy. *Am J Physiol Regul Integr Comp Physiol*
618 2008;295:1953-61.

- 619 **34.** Woodward A. A Pregnant Mother Infected with the Coronavirus Gave Birth, and Her
620 Baby Tested Positive 30 Hours Later. Available online:
621 [https://www.businessinsider.com/wuhan-coronavirus-in-infant-born-from-infected-](https://www.businessinsider.com/wuhan-coronavirus-in-infant-born-from-infected-mother-2020-2)
622 [mother-2020-2](https://www.businessinsider.com/wuhan-coronavirus-in-infant-born-from-infected-mother-2020-2). Accessed 15 March 2020.

- 623 **35.** Murphy S. Newborn baby tests positive for coronavirus in London. Available online:
624 [https://www.theguardian.com/world/2020/mar/14/newborn-baby-tests-positive-for-](https://www.theguardian.com/world/2020/mar/14/newborn-baby-tests-positive-for-coronavirus-in-london)
625 [coronavirus-in-london](https://www.theguardian.com/world/2020/mar/14/newborn-baby-tests-positive-for-coronavirus-in-london). Accessed 15 March 2020.

- 626 **36.** Li Y, Zhao R, Zheng S, et al. Lack of Vertical Transmission of Severe Acute
627 Respiratory Syndrome Coronavirus 2, China. *Emerg Infect Dis* 2020;26(6).
- 628 **37.** Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-
629 2 infection during pregnancy. *J Infect* 2020; published online Mar 4.
630 DOI:10.1016/j.jinf.2020.02.028
- 631 **38.** Zhu H, Zhu H, Wang L, Fang C, Peng S. Clinical analysis of 10 neonates born to
632 mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020;9:51-60.
- 633 **39.** Zhang L, Zhang L, Jiang Y, et al. Analysis of the pregnancy outcomes in pregnant
634 women with COVID-19 in Hubei Province. *Zhonghua Fu Chan Ke Za Zhi*
635 2020;55:E009
- 636 **40.** Chen S, Chen S, Huang B, et al. Pregnant women with new coronavirus infection: a
637 clinical characteristics and placental pathological analysis of three cases. *Zhonghua*
638 *Bing Li Xue Za Zhi* 2020;49:E005.
- 639 **41.** Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus
640 (COVID-19). *Front Pediatr* 2020; published online Mar 16. DOI:
641 10.3389/fped.2020.00104
- 642 **42.** Xu, Y., Li, X., Zhu, B. et al. Characteristics of pediatric SARS-CoV-2 infection and
643 potential evidence for persistent fecal viral shedding. *Nat Med* 2020; published online
644 Mar 13. DOI:10.1038/s41591-020-0817-4
- 645 **43.** Cai J, Xu J, Lin D, et al. A case series of children with 2019 novel coronavirus
646 infection: clinical and epidemiological features. *Clin Infect Dis* 2020; published
647 online Feb 28. DOI:10.1093/cid/ciaa198

44. 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; published online Mar 9. DOI:10.1016/S0140-6736(20)30566-3
45. Kovac M, Mikovic Z, Rakicevic 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.
46. Plante LA, Pacheco LD, Louis JM. SMFM Consult Series #47: Sepsis during pregnancy and puerperium. *Am J Obstet Gynecol* 2019;220:B2.
47. Dharani K, Narendra DM, Kalpalatha KG. Acute respiratory distress syndrome in pregnancy. In: Jeffrey P, Phelan LDP, Michael R. Foley, George R. Saade, Gary A Dildy, and Michael A. Belfort, eds. *Critical Care Obstetrics*. Wiley-Blackwell;2019:403-418.
48. 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.
49. Hulme KD, Gallo LA, Short KR. Influenza virus and glycemic variability in diabetes: a killer combination? *Front Microbiol* 2017;8:861. DOI:10.3389/fmicb.2017.00861.
50. 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;30:269–271.

51. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc. Natl. Acad. Sci. U.S.A.* 2020, published online Feb 13. DOI:10.1073/pnas.1922083117.
52. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293-2303.
53. 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.
54. Karunajeewa HA, Salman S, Mueller I, et al. Pharmacokinetics of chloroquine and monodesethylchloroquine in pregnancy. *Antimicrob Agents Chemother* 2010;54:1186-92.
55. Kilianski A, Mielech AM, Deng X, Baker SC. Assessing activity and inhibition of Middle East respiratory syndrome coronavirus papainlike and 3C-like proteases using luciferase-based biosensors. *J Virol* 2013;87:11955-62.
56. 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.
57. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. *Int J Infect Dis* 2020; published online Mar 12, DOI: 10.1016/j.ijid.2020.03.013
58. 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 childhood in the United Kingdom and Ireland. BMC Infect Dis
2016;16:65-75.

59. Kochhar DM, Penner JD, Knudsen TB. Embryotoxic, teratogenic, and metabolic
effects of ribavirin in mice. Toxicol Appl Pharm 1980;52:99-112.

60. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-
nCoV acute respiratory disease. Lancet 2020;395:e30–31, published online Feb 4.
DOI:10.1016/S0140-6736(20)30304-4.

61. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease.
Nat Rev Rheumatol 2017;13:234-243.

62. Interim guidance for businesses and employers. Plan, prepare and respond to
coronavirus disease 2019. United States Centers for Disease Control and Prevention
(CDC). February 26, 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/community/guidance-business-response.html>. Accessed March 14, 2020.

63. 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.

64. Basseal JM, Westerway SC, Juraja M, et al. Guidelines for reprocessing ultrasound
transducers. Australian Journal of Ultrasound in Medicine 2017;20:30-40.

65. 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.

66. Chilvers RJ, Weisz M. Entonox equipment as a potential source of cross-infection.
Anaesthesia 2000;55:176-9.

67. 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
68. Pihu 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/?v=1118006391865743&_rdr. Accessed 15 March 2020
69. Interim guidance on breastfeeding for a mother confirmed or under investigation for COVID-19. United States Centers for Disease Control and Prevention (CDC). February 19, 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/pregnancy-guidance-breastfeeding.html>. Accessed February 22, 2020.
70. Coronavirus (COVID-19) infection in pregnancy. Information for healthcare professionals. Royal College of Obstetricians and Gynaecologists, United Kingdom. Published 13 March 2020.
71. 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.
72. Radonovich LJ, Simberkoff MS, Bessesen MT, et al. N95 respirators vs medical masks for preventing laboratory-confirmed influenza in health care personnel. JAMA 2019;322:824-33.

- 737 **73.** Interim infection prevention and control recommendations for patients with confirmed
738 coronavirus disease 2019 (COVID-19) or persons under investigation for COVID-19
739 in healthcare settings. United States Centers for Disease Control and Prevention
740 (CDC). February 19, 2020. Available at: [https://www.cdc.gov/coronavirus/2019-](https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html)
741 [nCoV/hcp/infection-control.html](https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html). Accessed February 22, 2020.
- 742 **74.** Tong PS, Ng K, Loke AP, et al. Respiratory consequences of N95-type mask usage in
743 pregnant healthcare workers - a controlled clinical study. *Antimicrob Resist Infect*
744 *Control* 2015;4:48-57.
- 745 **75.** Roberge RJ, Kim JH, Powell JB. N95 respirator use during advanced pregnancy. *Am*
746 *J Infect Control* 2014;42:1097-100.
- 747 **76.** Qiao J. What are the risks of COVID-19 infection in pregnant women? *Lancet*
748 2020;395:760-2.
- 749 **77.** Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan)
750 coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and
751 other human coronavirus infections. *Viruses* 2020;194. DOI:10.3390/v12020194
- 752 **78.** Rasmussen SA, Smulian JC, Lednický JA, et al. Coronavirus disease 2019 (COVID-
753 19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol* 2020;
754 published online Feb 24. DOI: 10.1016/j.ajog.2020.02.017
- 755 **79.** Jiang X, Gao X, Zheng H, et al. Specific Immunoglobulin G antibody detected in
756 umbilical blood and amniotic fluid from a pregnant woman infected by the
757 coronavirus associated with severe acute respiratory syndrome. *Clin Diagn Lab*
758 *Immunol* 2004;11:1182-84.

- 759 **80.** Robertson CA, Lowther SA, Birch T, et al. SARS and pregnancy: a case report.
760 Emerg Infect Dis 2004;10:345–8.
- 761 **81.** Stockman LJ, Lowther SA, Coy K, Saw J, Parashar UD. SARS during pregnancy,
762 United States. Emerg Infect Dis 2004;10:1689–90.
- 763 **82.** Yudin MH, Steele DM, Sgro MD, Read SE, Kopplin P, Gough KA. Severe acute
764 respiratory syndrome in pregnancy. Obstet Gynecol 2005;105:124-7.
- 765 **83.** Lau KK, Yu WC, Chu CM, Lau ST et al. Possible central nervous system infection by
766 SARS coronavirus. Emerg Infect Dis 2004;10:342-4.
- 767 **84.** Alserehi H, Wali G, Alshukairi A, Alraddadi B. Impact of Middle East respiratory
768 syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC
769 Infect Dis 2016;16:105 DOI:10.1186/s12879-016-1437-y.
- 770 **85.** Jeong SY, Sung SI, Sung JH, et al. MERS-CoV infection in a pregnant woman in
771 Korea. J Korean Med Sci 2017;32:1717–20.
- 772 **86.** Payne DC, Iblan I, Alqasrawi S, et al. Stillbirth during infection with Middle East
773 respiratory syndrome coronavirus. J Infect Dis 2014;209:1870–2.
- 774 **87.** Park MH, Kim HR, Choi DH et al. Emergency cesarean section in an epidemic of the
775 middle east respiratory syndrome: a case report. Korean J Anesthesiol 2016;69:287-
776 91.
- 777 **88.** Racelis S, de los Reyes VC, Sucaldito MN et al. Contact tracing the first middle east
778 respiratory syndrome case in the Philippines. Western Pac Surveill Response J
779 2015;27:3-7

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Table 1: Clinical features of COVID-19 in pregnancy stratified against SARS and MERS

Characteristics	COVID-19	SARS	MERS
Number of cases	55	17	12
Age (years)	23-40	27-44	31-39
Gestational age at infection (weeks)	All were in the third trimester except 2 women who were less than 28 weeks gestation	4-32	4-38
Respiratory comorbidities (n)	None	Asthma (1)	Asthma (1), Pulmonary fibrosis (1)
Symptoms			
Fever (%)	84*	100	58
Cough (%)	28*	76	67
Dyspnea (%)	18*	35	58
Investigations^a			
CXR/CT evidence of pneumonia	76*	100*	100*
Leukocytosis (%)	38*	40*	50*
Lymphopenia (%)	22*	67*	50*
Thrombocytopenia (%)	13*	36*	50*
Maternal complications			
Mortality (%)	0	18	25
Mechanical ventilation (%)	2	35	41
Fetal complications			
Miscarriage/stillbirth (%)	2	25 [^]	18*
IUGR (%)	9	13 [^]	9*
Preterm birth (%)	43	25 [^]	27*
Neonatal complications			
Neonatal death (%)	2	0 [^]	9*

* Patients whose data was not reported were excluded from the calculations.

[^]1 patient who aborted her pregnancy was excluded from the calculations.

^aLeukocytosis was defined as a white cell count of more than 11,000 per cubic millimeter. Lymphopenia was defined as a lymphocyte count of less than 1000 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter.

CXR/CT evidence of pneumonia included ground-glass opacities, focal or bilateral patchy shadowing and interstitial abnormalities.

SARS, severe acute respiratory syndrome; MERS, middle east respiratory syndrome; CXR, Chest X-Ray; CT, Computed Tomography scan; IUGR, intrauterine growth retardation

Data shown in the table are pooled from references 18, 36-40, 76-78 (COVID-19); 1, 79-83 (SARS); 2, 28, 30, 84-88 (MERS)

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Table 2: PPE for healthcare workers caring for a patient with COVID-19 in pregnancy

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

*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.

[†] Aerosol-generating procedures (AGPs)

[‡] Powered air-purifying respirators with high-efficiency particulate air filter

Figure legends

Figure 1

Title: Plain radiograph in COVID-19

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

Figure 2

Title: Organization of perinatal services

Caption: Schematic demonstrating a model for workplace segregation in obstetric units to allow for service continuity and infection control

Figure 3

Title: Labor ward triage

Caption: Schematic demonstrating a model for stratifying risk in obstetric patients presenting to the labor floor

Table 1: Clinical features of COVID-19 in pregnancy stratified against SARS and MERS

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Neonatal complications			
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Table 2: PPE for healthcare workers caring for a patient with COVID-19 in pregnancy

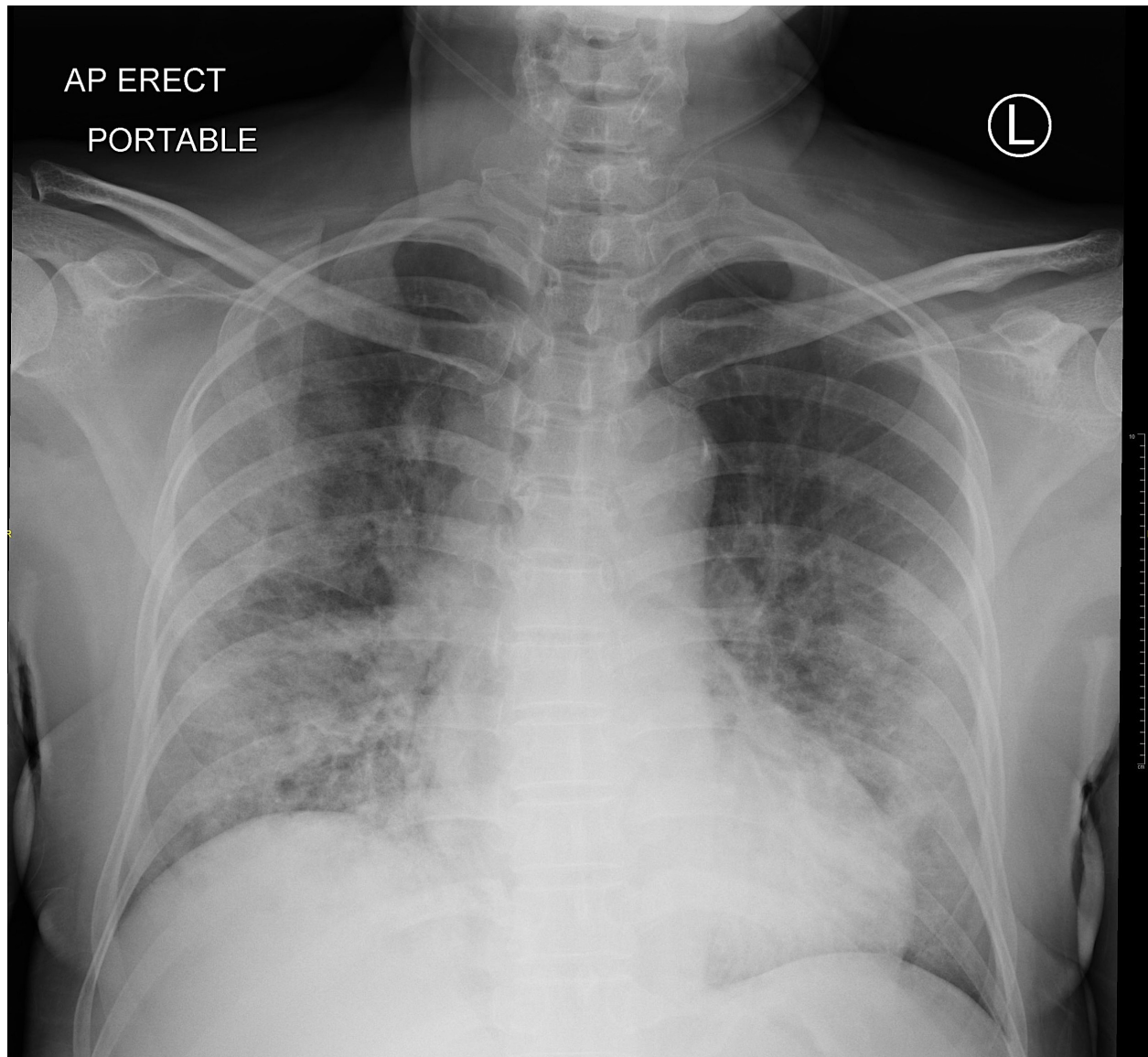
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High risk	- Use of supplemental oxygen in labor[†]: Nasal cannula, face mask, air-entrainment mask or non-rebreather mask - Maternal collapse: Cardiopulmonary[†] resuscitation and endotracheal intubation[†]	- Surgical cap - Gloves - Face shield or goggles - Gown with long sleeves - N95/FFP2 respirator or PAPR with HEPA filter[‡] (consider if the healthcare worker herself is pregnant)

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[†] Aerosol-generating procedures (AGPs)

[‡] Powered air-purifying respirators with high-efficiency particulate air filters

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Model for Workplace Segregation in Obstetric Units

Goals

Ensures service continuity
Social distancing of healthcare workers
Infection control and facilitates contact tracing

Common feature of each team:

Self- sufficiency

Attending, resident(s), and intern(s), nursing staff +/- allied health staff (e.g., sonographer)

Rostered on 12-hour shifts across the week with equitable distribution of weekends and public holidays, ensuring sufficient rest time

