Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy

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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 (R0) 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-1α (alarmin) and IL-1β
- 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

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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 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 pandemic[3] 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 diamorphism 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 pregnancy[9] 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 cytokines[12] are microbicidal and proinflammatory and chiefly include gamma interferon (IFN-γ), interleukin (IL)-1α, IL-1β, IL-6 and IL-12. In contrast, Th2-type cytokines[12] are anti-inflammatory and comprise IL-4, IL-10, IL-13 and transforming growth factor beta (TGF-ß). In pregnancy, the attenuation in cell-mediated immunity by Th1 cells due to the physiological shift to a Th2 dominant environment[9] 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 (IFNγ, IL-1β, 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 IFNγ and IL-1β 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-1α, 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 pathogens[16] 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[18] 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^{o}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^{o}C, is the prevailing symptom[7] 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 μg/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 mg/dL (instead of > 1.20 mg/dL) to signify renal dysfunction.[46] Additionally, mechanical ventilation requires achieving higher maternal oxygen (target PaO_2 > 70 mmHg instead of 55 – 80 mmHg) and lower carbon dioxide levels (target $PaCO_2$ 28 – 32 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 chloroquine[50] 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 pregnancies[52] 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 China[53] 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 studies[54] 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 learning[60] 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 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.

Useful resources

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

JAMA COVID-19 Resource Page:

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

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

How to use PPE: https://www.cdc.gov/hai/pdfs/ppe/PPEslides6-29-04.pdf

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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.

[a]Leukocytosis 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)

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

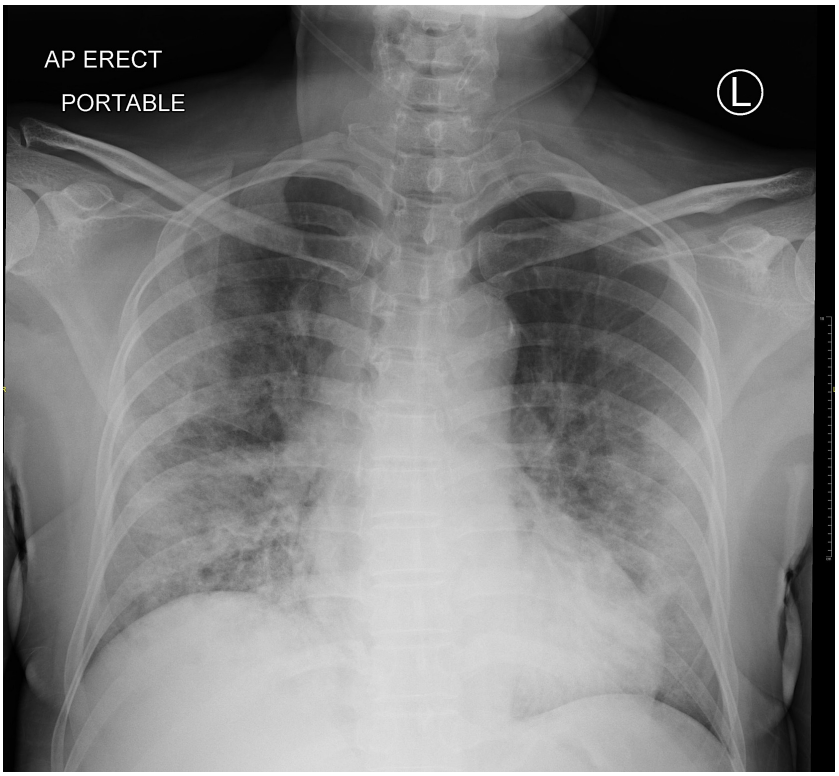
Risk	Examples of clinical encounters in obstetrics	Recommended PPE* for staff attending to the patient with COVID-19
Low risk	• Any transient encounter > 2 meters/6 feet away from patient	○ None; standard precautions and surgical mask suffice
Moderate risk	• Obstetric (including vaginal) examination • 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 1- Plain radiograph in COVID-19



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 1 – Model for workplace segregation in obstetric units during a pandemic

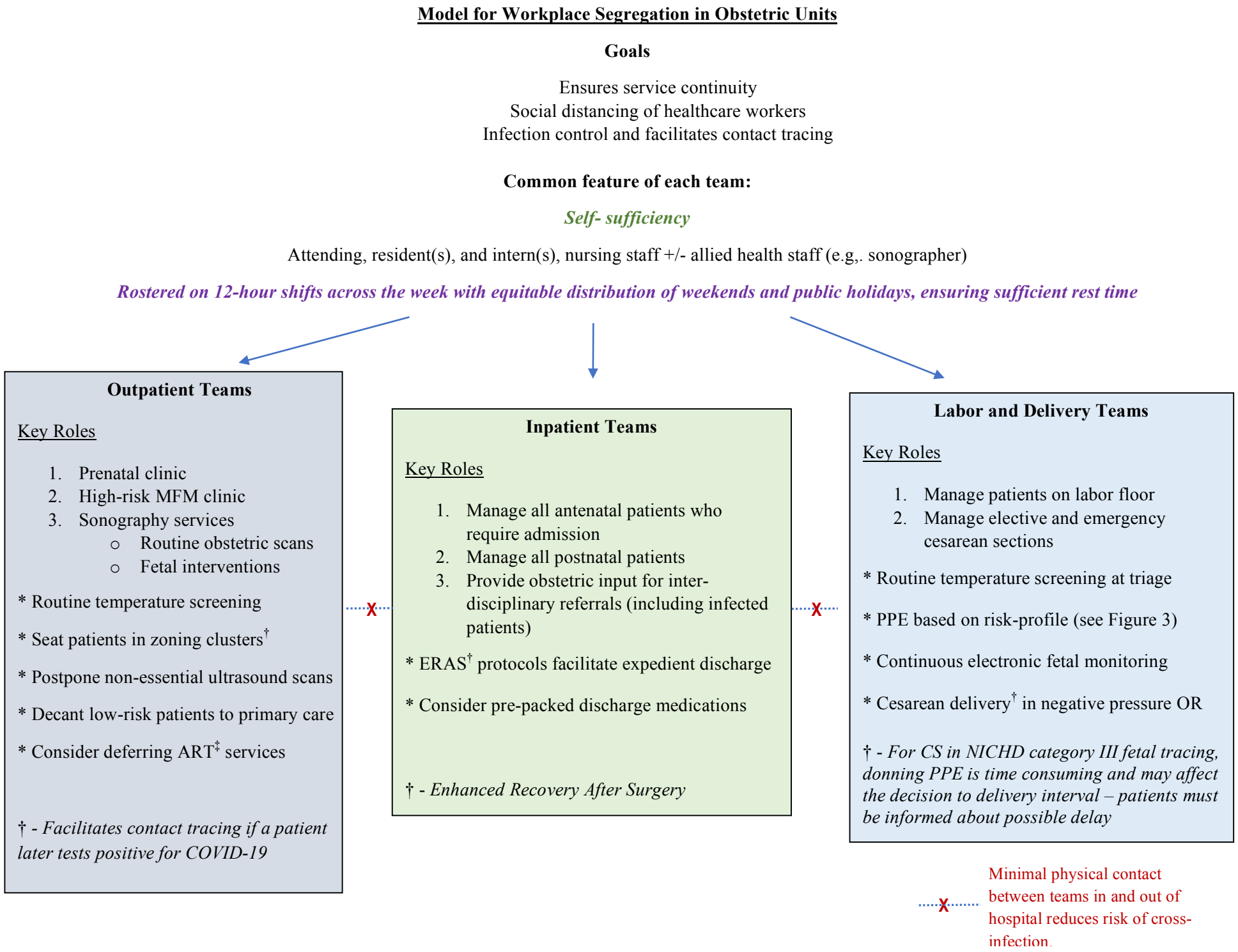
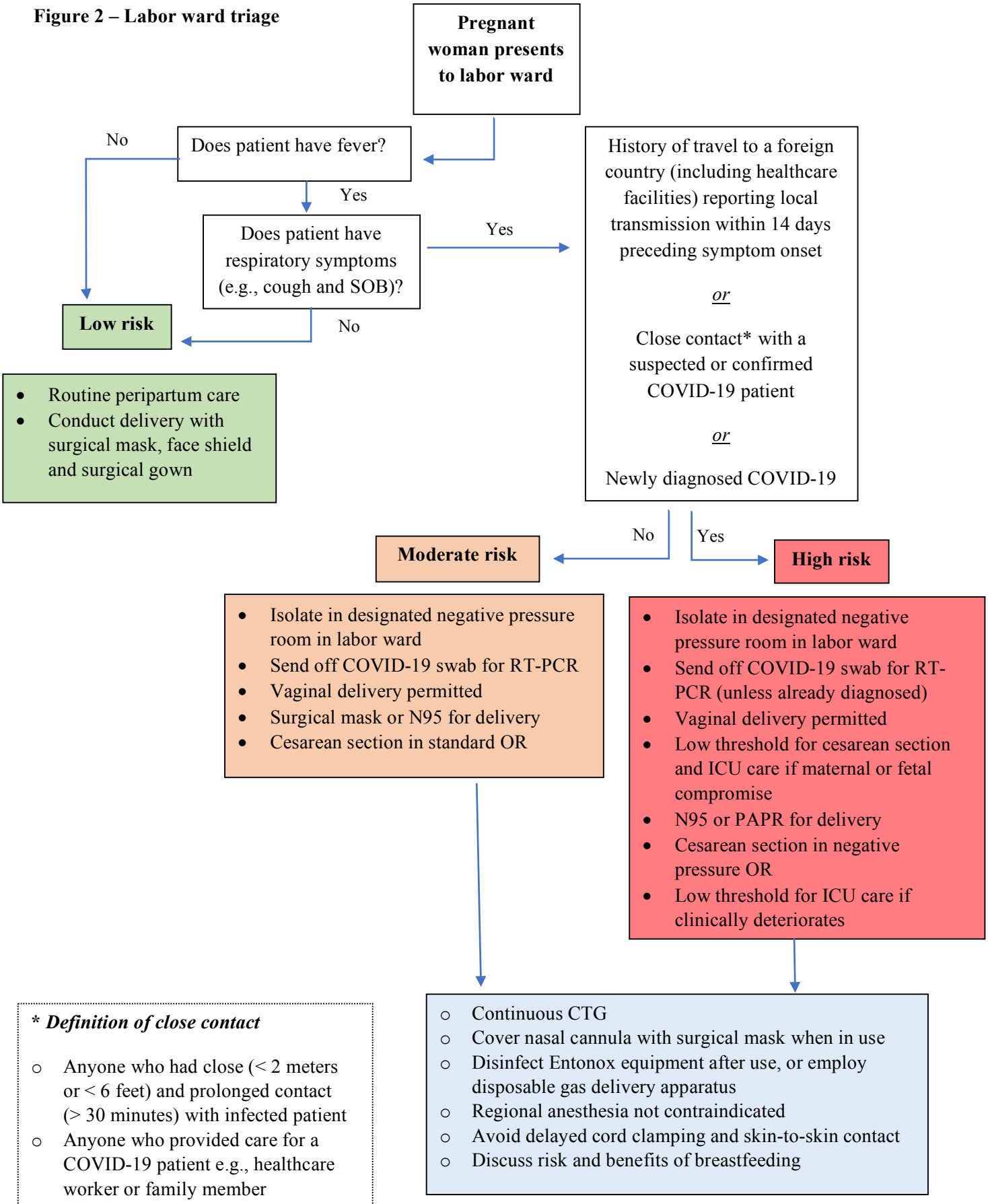


Figure 2 – Labor ward triage



**** Definition of close contact***

- Anyone who had close (< 2 meters or < 6 feet) and prolonged contact (> 30 minutes) with infected patient
- Anyone who provided care for a COVID-19 patient e.g., healthcare worker or family member
- Anyone who stayed within the same premises as a COVID-19 patient

Adapted from the Singapore Ministry of Health (MOH)

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