

1 **Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy**

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47 **Condensation:** Navigating the pathophysiology, diagnosis and obstetric care of pregnant
48 women with COVID-19 infection

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67 **Abstract**

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

79 Pregnant women and their fetuses represent a high-risk population during infectious
80 disease outbreaks. To date, the outcomes of 55 pregnant women infected with COVID-19 and
81 46 neonates have been reported in the literature, with no definite evidence of vertical
82 transmission. Physiological and mechanical changes in pregnancy increase susceptibility to
83 infections in general, particularly when the cardiorespiratory system is affected, and encourage
84 rapid progression to respiratory failure in the gravida. Furthermore, the pregnancy bias towards
85 T-helper 2 (Th2) system dominance which protects the fetus, leaves the mother vulnerable to
86 viral infections, which are more effectively contained by the Th1 system. These unique
87 challenges mandate an integrated approach to pregnancies affected by SARS-CoV-2.

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

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

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116 **Glossary of terms**

- 117 • ACE2: Angiotensin--converting enzyme 2 – the functional receptor of SARS-CoV-2
- 118 • BSL-2: Biosafety level 2 – a laboratory accredited for working with microbes that pose
- 119 a moderate health hazard
- 120 • BSL-3: Biosafety level 3 - a laboratory accredited for working with microbes that pose
- 121 a threat of serious or lethal disease through inhalation
- 122 • CDC: United States Centers for Disease Control and Prevention
- 123 • COVID-19: Coronavirus Disease 2019 (previously called 2019 novel coronavirus
- 124 (2019-nCoV)
- 125 • End expiratory volume: Volume of air that can be exhaled at the end of expiration
- 126 • FFP2: Filtering facepiece respirator that removes at least 92 percent of very small (0.3
- 127 micron) test particles; the European equivalent of an N95 respirator
- 128 • Functional residual capacity: Volume of air in the lungs at the end of expiration; it is
- 129 the sum of residual volume and end expiratory volume
- 130 • Huh7 cells: Lineage of cells used in cell culture, derived from human liver cell line
- 131 • IFN- γ : Interferon gamma – proinflammatory cytokine produced by Th1 lymphocytes
- 132 • IL-1: Interleukin-1 – proinflammatory cytokine produced by Th1 lymphocytes; IL-1
- 133 comprises 11 members, including two with potent inflammatory activity, IL-1 α
- 134 (alarmin) and IL-1 β
- 135 • IL-4: Interleukin-4 – anti-inflammatory cytokine produced by Th2 lymphocytes
- 136 • IL-6: Interleukin-6 – proinflammatory cytokine produced by Th1 lymphocytes; also
- 137 has anti-inflammatory properties
- 138 • IL-10: Interleukin10 - anti-inflammatory cytokine produced by Th2 lymphocytes

- 139 • IL-12: Interleukin-12 – proinflammatory cytokine produced by Th1 lymphocytes
- 140 • MERS: Middle East Respiratory Syndrome
- 141 MERS-CoV: Middle East Respiratory Syndrome coronavirus – the virus that causes
- 142 MERS
- 143 • Minute ventilation: Volume of air the patient moves in one minute; it is the product of
- 144 respiratory rate and tidal volume
- 145 • N95 respirator: Respiratory protective device that removes at least 95 percent of very
- 146 small (0.3 micron) test particles; the American equivalent of an FFP2 respirator
- 147 • Negative pressure room: Room that maintains a lower air pressure inside the treatment
- 148 area than that of the surrounding environment, thus preventing internal air from
- 149 circulating back out
- 150 • R0: Basic reproduction number, which refers to the average number of secondary
- 151 infections produced by each new case of infection in a population where everyone is
- 152 susceptible.
- 153 • Residual volume: Volume of air in the lungs at the end of a maximal exhalation
- 154 • RT-PCR: Reverse transcription polymerase chain reaction
- 155 • SARS: Severe Acute Respiratory Syndrome
- 156 • SARS-CoV: Severe acute respiratory syndrome coronavirus – virus that causes SARS
- 157 • SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2 virus – virus that
- 158 causes COVID-19
- 159 • SOFA score: Sequential organ failure assessment score – to determine the degree of
- 160 end-organ dysfunction during sepsis; a score of 2-points or more is associated with a
- 161 10% mortality rate
- 162 • Tidal volume: Volume of air moved into or out of the lungs during quiet breathing

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

165 • WHO – World Health Organization

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183 **Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy**

184 **Introduction**

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

192 The current pneumonia outbreak of coronavirus disease 2019 (COVID-19), caused by
193 the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared a
194 pandemic³ by the World Health Organization (WHO) on March 11, 2020 and is predicted to
195 peak around April 2020, without a significant reduction in transmissibility.⁴ With its
196 indiscriminate and sustained spread across continents, we are likely to see women with
197 COVID-19 canvassed across all trimesters of pregnancy. In this article, we summarize the
198 clinical features of pregnant women with COVID-19 and present a pragmatic and integrated
199 framework that addresses the obstetric complexities of managing this disease in pregnancy.

200 **Clinically relevant virology**

201 SARS-CoV-2, a novel enveloped RNA betacoronavirus, infects host respiratory epithelial cells
202 through angiotensin--converting enzyme 2 (ACE2) - a membrane-bound aminopeptidase
203 which functions as its putative receptor. Whilst the expression of ACE2 is predominantly
204 within type II alveolar cells of the lung, the receptor is also present in several extrapulmonary
205 sites across the aerodigestive tract, including the mucosa of the oral cavity.⁵ Patients with
206 COVID-19 would therefore manifest a spectrum of upper and lower respiratory tract

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

210 **Physiological susceptibility to COVID-19**

211 Cardiorespiratory system

212 Approximately 80% of infections in COVID-19 are mild or asymptomatic, 15% are severe
213 requiring supplemental oxygen and 5% are critical requiring mechanical ventilation.⁸ Changes
214 to the cardiorespiratory and immune systems in pregnancy increase a woman's susceptibility
215 to severe infection and hypoxic compromise, but may also delay diagnosis and source control
216 in those with only innocuous upper respiratory tract symptoms such as sore-throat and nasal
217 congestion – the latter is seen in 5% of patients with COVID-19.⁷ Gestational rhinitis, due to
218 estrogen-mediated hyperemia of the nasopharynx, usually affects a fifth of healthy women in
219 late pregnancy and results in marked nasal congestion and rhinorrhea – these features may
220 mask the coryzal symptoms of COVID-19, leading to unchecked viral shedding and
221 community transmission.

222 Shortness of breath occurs in 18% of patients with COVID-19.⁷ However, physiologic
223 dyspnea due to increased maternal oxygen demands from heightened metabolism, gestational
224 anemia and fetal oxygen consumption is common in pregnancy⁹ and must be distinguished
225 from pathologic breathlessness. Additionally, pulmonary volumes are altered – functional
226 residual capacity, end expiratory volumes and residual volumes decrease steadily from early
227 pregnancy due to diaphragmatic splinting by the gravid uterus, resulting in reduced total lung
228 capacity at term and an inability to clear pulmonary secretions effectively.¹⁰ This is pertinent,
229 as COVID-19 pneumonia rapidly progresses from focal to diffuse bilateral consolidation of

230 lung parenchyma,¹¹ which in the context of the pulmonary changes described above, would
231 more readily predispose to hypoxemic respiratory failure in pregnancy.

232 Immune system

233 Cytokines produced by T-helper (Th) lymphocytes regulate immunity and inflammation. Th1-
234 type cytokines¹² are microbicidal and proinflammatory and chiefly include gamma interferon
235 (IFN- γ), interleukin (IL)-1 α , IL-1 β , IL-6 and IL-12. In contrast, Th2-type cytokines¹² are anti-
236 inflammatory and comprise IL-4, IL-10, IL-13 and transforming growth factor beta (TGF- β).
237 In pregnancy, the attenuation in cell-mediated immunity by Th1 cells due to the physiological
238 shift to a Th2 dominant environment⁹ contributes to overall infectious morbidity by increasing
239 maternal susceptibility to intracellular pathogens like viruses.

240 Interestingly, the cytokine profiles in SARS-CoV and SARS-CoV-2 infections in non-
241 pregnant patients may be extrapolated to account for the differences in disease severity in
242 affected pregnancies. Patients with SARS showed preferential activation of Th1 immunity
243 resulting in the marked elevation of proinflammatory cytokines (IFN γ , IL-1 β , IL-6 and IL-12)
244 for at least two weeks after disease onset, leading to extensive lung damage.¹³ In contrast,
245 patients with COVID-19 demonstrated activation of both Th1 and Th2 immunity over similar
246 periods in the disease course, culminating in the presence of IFN γ and IL-1 β in addition to IL-
247 4 and IL-10.¹⁴ Additionally, elevated levels of IL-6 (which is a predominantly Th1 response),
248 is associated with a significantly increased risk of mortality in COVID-19 patients.¹⁵

249 Murine studies of influenza have demonstrated that pregnancy increases influenza-
250 related pathology via disrupted viral clearance, increased pulmonary IL-6, IL-1 α , and G-CSF
251 expression and enhanced physiological stress in the lungs, influenced by changes in
252 prostaglandin and progesterone levels.¹⁶ However in COVID-19, a range of immune responses
253 has been described, and early adaptive immune responses may be predictive of milder disease

254 severity.¹⁷ We postulate that changes in the hormonal milieu in pregnancy which influence
255 immunological responses to viral pathogens¹⁶ together with the physiological transition to a
256 Th2 environment favoring the expression of anti-inflammatory cytokines (IL-4 and IL-10) and
257 other unidentified immune adaptations may serve as the predominant immune response to
258 SARS-CoV-2, resulting in the lesser severity of COVID-19¹⁸ compared to non-pregnant
259 individuals. These immune responses should be further characterized in gravidas and non-
260 gravidas with COVID-19 of different disease severities.

261 **Clinical features**

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

264 **Diagnosis and imaging**

265 A real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay is the current gold
266 standard for detecting SARS-CoV-2 from respiratory specimens in patients with suspected
267 COVID-19. At present, it is available in 84 public health laboratories in the U.S - these provide
268 in-state testing capacity in all 50 states and the District of Columbia. The test utilizes specific
269 primers and probes that target the RNA-dependent RNA polymerase (RdRp), envelope and
270 nucleocapsid genes of SARS-CoV-2, among which the RdRp assay has the highest analytical
271 sensitivity (3.8 RNA copies/reaction at 95% detection probability).¹⁹ As RT-PCR is a
272 quantitative method where the amplification of DNA is detected in real-time, the determination
273 of viral load in COVID-19 is theoretically possible. However, this usually requires laboratories
274 to develop in-house test kits and validate them with internal controls.²⁰

275 In contrast, most commercially available assays for COVID-19 provide qualitative
276 results and false-negatives may be due to a low viral load. The practical limitations of RT-PCR
277 testing include the need for a biosafety level-2 (BSL-2) facility, a requirement for kits with

278 specific reagents and primers, the need to maintain a cold chain (as the specimens require
279 storage at 2 – 8°C) and the use of strict, validated protocols for testing – consequently, countries
280 with resource limitations or acute spikes in the numbers of suspected cases may not be able to
281 meet these demands. However, there are no good alternatives: antigen-antibody detection tests
282 are not validated, and viral culture is impractical, as it takes at least three days for SARS-CoV-
283 2 to cause cytopathic effects in selected cell lines (VeroE6 and Huh7 cells).²¹ In addition, viral
284 culture will require a BSL-3 facility, which are usually only found in tertiary medical or
285 university research centers.

286 Chest imaging may aid but not replace molecular confirmation of COVID-19. The
287 predominant findings are peripheral airspace shadowing on a plain chest radiograph (Figure 1)
288 and bilateral, multi-lobar ground-glass opacities or consolidation on computed tomography
289 (CT) scan of the chest;^{22,23} these features are non-specific and appear to be similar in
290 pregnancy.¹⁸ Using RT-PCR as a reference, the sensitivity, specificity, positive predictive
291 value (PPV) and negative predictive (NPV) value of a CT chest in diagnosing COVID-19 in
292 China are 97%, 25%, 65% and 83% respectively.²⁴ However, when CT scans are performed in
293 pregnancy, concerns regarding the teratogenic effects of ionizing radiation on the fetus are
294 inevitable. Reassuringly, the fetal radiation dose for a routine CT chest is 0.03 mGy – exposure
295 to radiation doses < 50 mGy is not associated with an increased risk of fetal anomalies or
296 pregnancy loss.²⁵ Although intravenous iodinated contrast media crosses the placenta, studies
297 have not demonstrated teratogenicity or thyroid dysfunction in the newborn.²⁶

298 **Complications in pregnancy**

299 The outcomes of coronavirus infections in pregnancy are summarized in Table 1. Hitherto,
300 COVID-19 outcomes for the mother appear more promising compared to SARS and MERS.
301 Pooled data reveals a case fatality rate of 0%, 18% and 25% for COVID-19, SARS and MERS

302 respectively – in the latter two, progressive respiratory failure and severe sepsis were the most
303 frequent causes.^{27,28} This is unsurprising, given the predisposition to superimposed bacterial
304 infections due to direct mucosal injury, dysregulation of immune responses and alterations to
305 the respiratory microbiome after viral pneumonia.²⁹ Postnatal maternal deterioration can still
306 occur,³⁰ necessitating continued monitoring.

307 Fetal complications of COVID-19 include miscarriage (2%), intrauterine growth
308 restriction (IUGR; 10%) and pre-term birth (39%). Fever, with a median temperature of 38.1-
309 39.0°C, is the prevailing symptom⁷ in COVID-19; cohort studies in patients with other
310 infections have not shown increased risks of congenital anomalies from maternal pyrexia in
311 the first trimester,³¹ although childhood inattention disorders are more common, possibly
312 related to hyperthermic injury to fetal neurons.³²

313 **Vertical Transmission**

314 There is a theoretical risk of vertical transmission, similar to that seen in SARS, as the ACE2
315 receptor is widely expressed in the placenta,³³ with a similar receptor-binding domain structure
316 between SARS-CoV-1 and SARS-CoV-2. Most recently, two neonates from COVID-19
317 infected mothers are said to have tested positive for SARS-CoV-2 shortly following delivery,
318 casting concerns about the possibility of vertical transmission.^{34,35} However, there have been
319 no confirmed instances of vertical transmission among the 46 other neonates^{18, 36-41} born to
320 COVID-19 infected mothers reported thus far, supported in turn by evidence demonstrating an
321 absence of viral isolates in the amniotic fluid, cord blood, breast milk and neonatal throat swabs
322 in a subset of these patients.¹⁸ It is notable, however, that the overwhelming majority of these
323 women acquired COVID-19 in the third trimester – there is currently no data on perinatal
324 outcome when the infection is acquired in early pregnancy. Regardless of the risk, it is

325 reassuring that COVID-19 appears to manifest as a mild respiratory disease in the pediatric
326 population.^{42,43}

327 **Treatment**

328 Current approach

329 Symptomatic treatment and pregnancy-specific management of complications such as sepsis
330 and acute respiratory distress syndrome (ARDS) comprise the current standards of care. A high
331 Sequential Organ Failure Assessment (SOFA) score and D-dimer levels $> 1 \mu\text{g/mL}$ on
332 admission predict increased mortality in non-pregnant patients with COVID-19.⁴⁴ However,
333 D-dimer levels are difficult to interpret as the values are usually raised in pregnancy, such that
334 only 84%, 33% and 1% of women in the first, second and third trimesters respectively would
335 have normal results based on conventional thresholds.⁴⁵ The SOFA score should also be
336 adjusted to reflect the influence of pregnancy on hemodynamics and renal blood flow, such as
337 utilizing a creatinine level $> 1.02 \text{ mg/dL}$ (instead of $> 1.20 \text{ mg/dL}$) to signify renal
338 dysfunction.⁴⁶ Additionally, mechanical ventilation requires achieving higher maternal oxygen
339 (target $\text{PaO}_2 > 70 \text{ mmHg}$ instead of $55 - 80 \text{ mmHg}$) and lower carbon dioxide levels (target
340 $\text{PaCO}_2 28 - 32 \text{ mmHg}$)⁴⁷ to maintain placental perfusion and prevent fetal hypoxemia and
341 acidosis.

342 We concur with the WHO recommendation against the routine use of systemic
343 corticosteroids, as it appears to delay viral clearance with no survival benefit.⁴⁸ Although
344 neither hydrocortisone nor methylprednisolone readily crosses the placenta, prolonged
345 exposure predisposes to maternal hyperglycemia - this is immunosuppressive and sustains the
346 replication of respiratory viruses within pulmonary epithelial cells.⁴⁹ However, in cases of
347 expedited preterm delivery for obstetric or medical indications, the decision to use
348 corticosteroids to accelerate fetal maturity and minimise peripartum complications should be

349 individualised. Good obstetric practice should prevail and urgent delivery should not be
350 delayed.

351 Options for antiviral therapy

352 The Monitored Emergency Use of Unregistered Interventions (MEURI) framework from the
353 WHO should guide the ethical use of non-licensed drugs in pregnancy during pandemics.
354 Recent studies have identified remdesivir and chloroquine⁵⁰ as strong candidate drugs for the
355 treatment of COVID-19. Remdesivir is a novel, broad-acting antiviral nucleotide prodrug
356 which effectively inhibits replication of SARS-CoV-2 in-vitro and that of related coronaviruses
357 including MERS-CoV in non-human primates.⁵¹ Its use appears to be safe in human
358 pregnancies⁵² and phase 3 trials evaluating efficacy in COVID-19 are currently underway in
359 the United States (ClinicalTrials.gov number NCT04280705) and China (ClinicalTrials.gov
360 number NCT04252664 and NCT04257656).

361 Chloroquine phosphate is a ubiquitous antimalarial quinolone compound with broad
362 spectrum antiviral and immunomodulating activity. It has been shown to block coronavirus
363 infection by increasing the endosomal pH required for cell fusion and by interrupting the
364 glycosylation of cellular receptors of SARS-CoV in cell culture.⁵⁰ Unpublished data from
365 multicenter clinical trials across China⁵³ have demonstrated that the drug appears effective in
366 accelerating the clinical, radiological and serological resolution of COVID-19. Although
367 chloroquine and its metabolites cross the placenta, it may be safely used in all trimesters of
368 pregnancy with no increased risk of adverse perinatal outcomes. However, it is worthwhile
369 noting that chloroquine is a drug with a large volume of distribution and pharmacokinetic
370 studies⁵⁴ have shown significantly lower plasma drug concentrations in pregnancy, which
371 suggests the need for a higher dose in COVID-19 (at least 500 mg twice daily).⁵³ A relevant
372 side effect of high dose chloroquine however, is systolic hypotension which may exacerbate
373 the hemodynamic changes from supine aortocaval compression by a gravid uterus.

374 Additionally, as all betacoronaviruses including MERS-CoV, SARS-CoV and SARS-
375 CoV-2 contain two cysteine proteases that process the viral polypeptides necessary for their
376 replication,^{55,56} viral protease inhibitors such as lopinavir-ritonavir (LPV/r) have shown some
377 benefit in the adjunct management of COVID-19.⁵⁷ Although not studied specifically in
378 pregnant women with respiratory infections, LPV/r is known to be safe – an analysis of
379 population-based surveillance data of LPV/r exposure in HIV-positive pregnancies found no
380 increase in the risk of fetal anomalies, preterm birth or low birth weight infants.⁵⁸

381 Conversely, ribavirin, an antiviral guanosine analogue commonly used in coronavirus
382 treatment cocktails,^{1,30} is teratogenic: it induces miscarriage, craniofacial and limb defects in
383 the embryos of pregnant mice exposed to doses exceeding 25 mg/kg,⁵⁹ and should be avoided,
384 especially in early pregnancy. Similarly, baricitinib – a Janus kinase inhibitor – has been
385 identified through machine learning⁶⁰ as a potential drug for the treatment of COVID-19 by
386 inhibiting the endocytosis of SARS-CoV-2 into pulmonary cells. However, we opine that
387 baricitinib is contraindicated in pregnancy as animal studies have demonstrated
388 embryotoxicity.⁶¹

389 Currently, there no approved vaccines for the prevention of COVID-19, although
390 several are under development but will not be available for some time. An open-label, phase I
391 clinical trial in non-pregnant women and men evaluating a candidate vaccine, mRNA-1273,
392 led by the U.S. National Institutes of Health (NIH) has commenced recruitment on March 16,
393 2020 (ClinicalTrials.gov number NCT 04283461). The safety and immunogenicity of this lipid
394 nanoparticle (LNP)-encapsulated mRNA-based vaccine in pregnancy is, at present, unknown.

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398 **Obstetric management**

399 Antenatal care

400 In a pandemic, social distancing measures have proven to be effective in reducing disease
401 transmission.⁶² Obstetric care can be served by this model, as our own experience attests to, by
402 streamlining medical care providers into self-sufficient groups, each minimally comprising the
403 attending, resident, intern and nursing or midwifery staff (Figure 2). The individual teams
404 function independently and provide inpatient labour and delivery services, outpatient antenatal
405 care, or surgical services, including treating women with suspected or confirmed COVID-19
406 infection with full personal protective equipment (PPE) compliance. If a team member is
407 exposed to or infected with COVID-19, their team will be quarantined for at least 2 weeks;
408 workforce segregation thus ensures adequate clinical coverage by non-affected teams in this
409 event. While inter-hospital movement of doctors and patients is restricted, approved urgent
410 inter-hospital transfer of prenatal patients to tertiary maternity units takes place with full
411 adherence to infection control measures, including isolation when necessary. Ambulatory
412 clinical care is increasingly conducted on Health Insurance Portability and Accountability Act
413 (HIPAA)-compliant telemedicine video conferencing platforms (Zoom Video
414 Communications Inc, San Jose, CA) which allows joint management decisions to be made with
415 primary care providers in real time.

416 Fetal surveillance

417 Protracted respiratory compromise increases the risk of fetal growth restriction due to maternal
418 hypoxia which drives the release of potent vasoconstrictors such as endothelin-1 and hypoxia-
419 inducible factor, resulting in placental hypoperfusion and reduced oxygen delivery to the
420 fetus.⁶³ Given that IUGR complicates approximately 10% of pregnancies with COVID-19, we
421 would monitor the fetus with at least one ultrasound assessment of growth following maternal

422 recovery. Following sonographic evaluation in high-risk patients, the ultrasound transducers
423 should be disinfected according to the manufacturer's recommendations.⁶⁴

424 Labor, delivery and breastfeeding

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

428 The mode of delivery is directed by obstetric factors and clinical urgency. As there is
429 no convincing evidence of vertical transmission,¹⁸ vaginal delivery is not contraindicated in
430 patients with COVID-19. When emergent delivery is required in a critically ill parturient, a
431 cesarean section is most appropriate – these indications include rapid maternal deterioration,
432 difficulty with mechanical ventilation due to the gravid uterus, and fetal compromise. Delivery,
433 including cesarean sections, should be carried out with respiratory precautions using full
434 personal protective equipment (PPE) and in rooms with negative pressure ventilation.⁶⁵

435 Patient self-administered inhalation of nitrous oxide and oxygen (Entonox) is a widely
436 used labor analgesic. However, respiratory viruses contaminating the gas delivery apparatus
437 may be a neglected source of cross-infection and birth attendants should be aware of
438 decontamination guidelines, which include the cleaning of the expiratory valve between
439 patients, and the use of a microbiological filter (pore size < 0.05µm) between the mouthpiece
440 or facemask.⁶⁶ Similarly, in a woman with suspected or confirmed COVID-19 requiring
441 supplemental oxygen in labor, a surgical mask should worn over the nasal cannula, as
442 humidifying oxygen results in the aerosolization (or spray) of infectious particles to a radius of
443 about 0.4 meters, with a resultant risk of nosocomial droplet infection.^{67,68}

444 Although the data do not suggest a risk of vertical transmission, delayed clamping of
445 the umbilical cord and skin-to-skin contact should be avoided following delivery, extrapolating

446 from recommendations by the Canadian Society of Obstetricians and Gynecologists guidelines
447 for SARS in pregnancy.⁶⁵

448 Breastfeeding is not contraindicated, based on current published guidelines^{69,70} – a
449 retrospective analysis of COVID-19 in pregnancy showed that none of the women had
450 detectable viral loads of SARS-CoV-2 in breastmilk.¹⁸ Regardless, if the patient chooses to
451 breastfeed, a face mask should be worn due to the close proximity between mother and child
452 to reduce the risk of droplet transmission. The presence of coronavirus antibodies in breastmilk
453 depends on the gestation at which maternal infection occurred and if there was any preceding
454 use of high-dose corticosteroids which could suppress maternal antibody responses.⁷¹

455

456 **Personal protective equipment (PPE)**

457 The safety of healthcare providers is of utmost importance in any pandemic and the type of
458 PPE necessary depends on the degree of perceived risk (Table 2). Surgical face masks are
459 appropriate for general clinical duties as randomized trial data have shown them to be as
460 effective as N95 respirators in preventing droplet transmission in influenza.⁷²

461 N95 respirators in pregnancy

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

467 Controlled clinical studies^{74,75} of nurses wearing N95 respirators during an hour of
468 physical activity in their second and third trimesters of pregnancy demonstrated reduced tidal
469 volume (23%) and minute ventilation (26%), resulting in lower oxygen uptake (14%) and
470 increased carbon dioxide production (9%) due to labored breathing. Although there were no

471 changes in fetal heart rate, maternal capillary lactate levels or oxygen saturations, we caution
472 against the use of N95 respirators in pregnant healthcare workers with growth-restricted fetuses
473 and recommend that they be exempted from frontline duty during the COVID-19 outbreak.
474 Powered air-purifying respirators (PAPR) with high-efficiency particulate air (HEPA) filters,
475 with less airway resistance, are a reasonable alternative.

476 **Conclusion**

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

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493 **Useful resources**

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

496 **JAMA COVID-19 Resource Page:**
497 <https://jamanetwork.com/journals/jama/pages/coronavirus-alert>

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

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

503 **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.

^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)

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

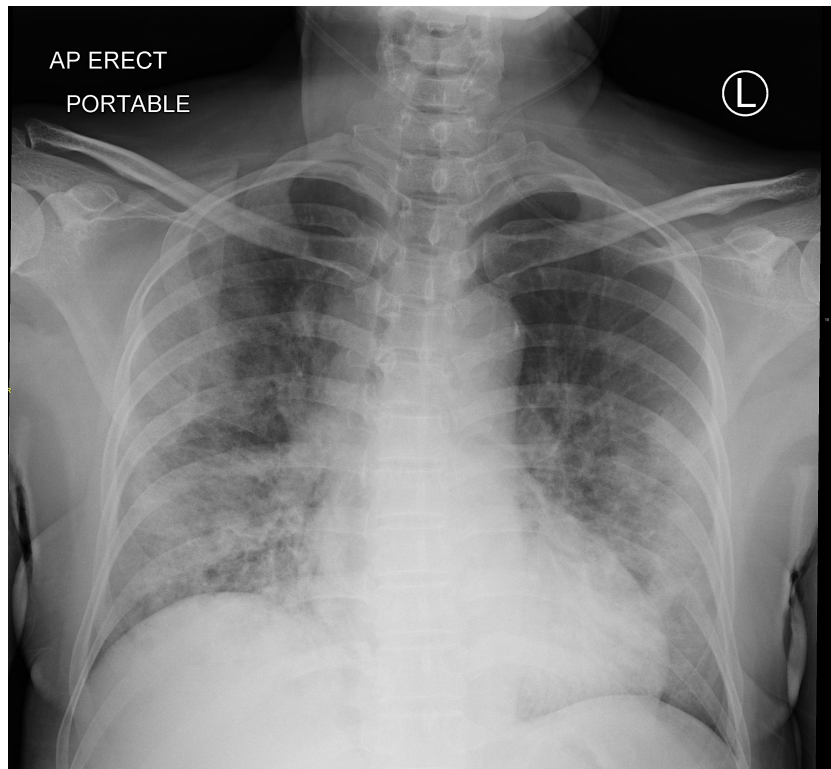
Risk	Examples of clinical encounters in obstetrics	Recommended PPE* for staff attending to the patient with COVID-19
Low risk	<ul style="list-style-type: none"> • Any transient encounter > 2 meters/6 feet away from patient 	<ul style="list-style-type: none"> ○ None; standard precautions and surgical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

Model for Workplace Segregation in Obstetric Units

Goals

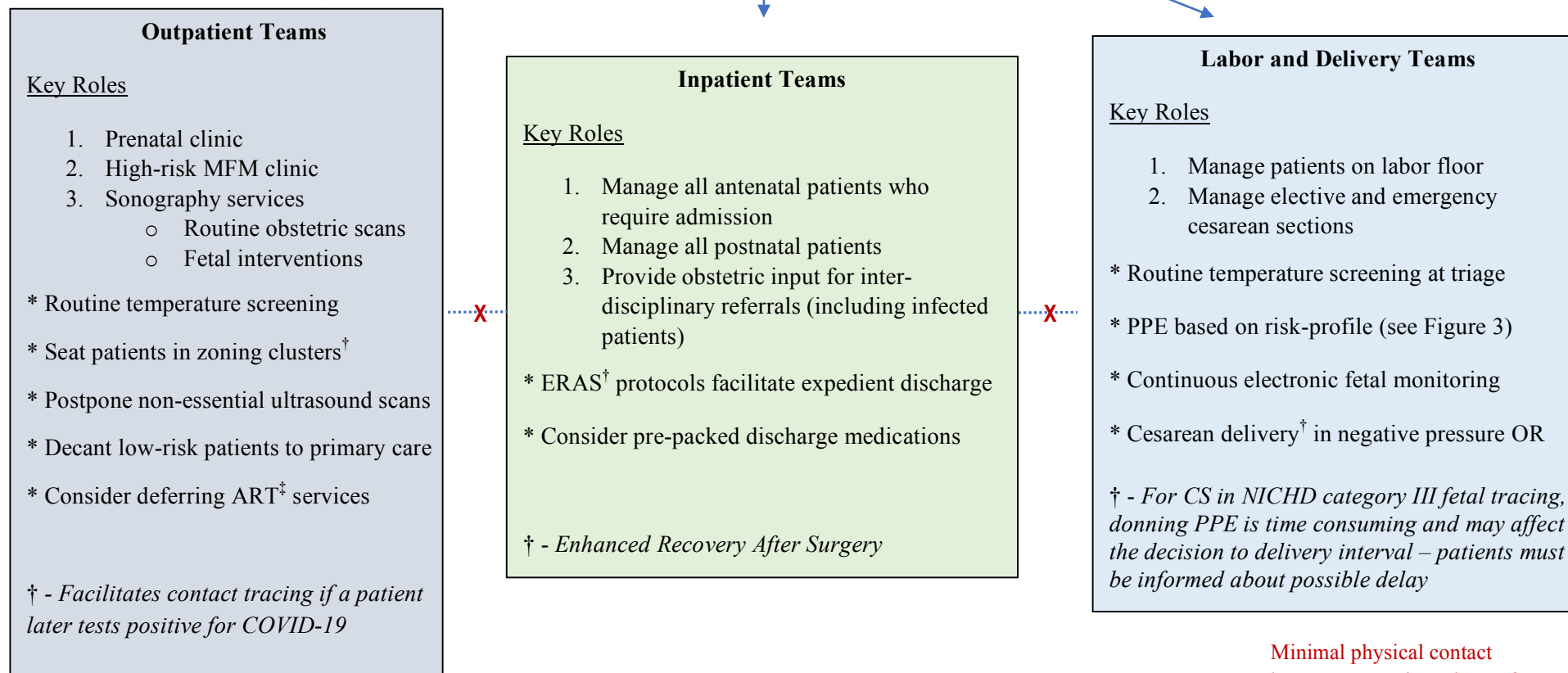
- Ensures service continuity
- Social distancing of healthcare workers
- Infection control and facilitates contact tracing

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



Minimal physical contact between teams in and out of hospital reduces risk of cross-infection.

Figure 2 – Labor ward triage

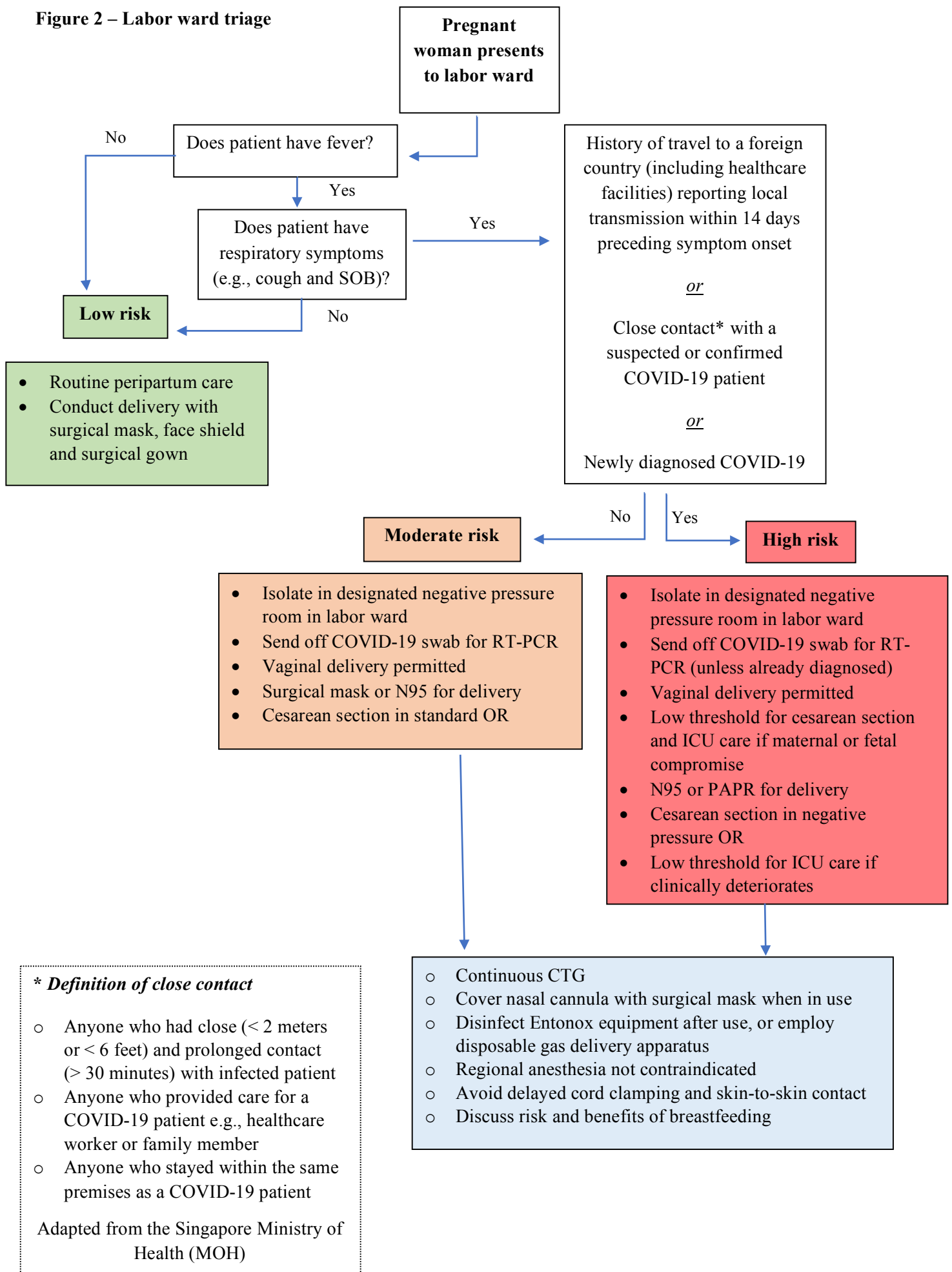


Figure legends

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