INTERIM GUIDANCE

ISUOG Interim Guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium: information for healthcare professionals – an update

In response to the World Health Organization (WHO) statements and international concerns regarding the coronavirus disease 2019 (COVID-19) outbreak, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) is issuing the following guidance for management during pregnancy and puerperium.

Given the uncertainty regarding many aspects of the clinical course of COVID-19 in pregnancy, frequently updated information may help obstetricians and ultrasound practitioners in counseling pregnant women and further improve our understanding of the pathophysiology of COVID-19 infection in pregnancy.
This statement, an update on our previous Interim Guidance[1] (see Appendix S1), is not intended to replace other previously published interim guidance on evaluation and management of COVID-19-exposed pregnant women and should be considered in conjunction with relevant advice from organizations such as:

American College of Obstetricians and Gynecologists (ACOG): https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics
Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/pregnancy-faq.html
European Centre for Disease Prevention and Control (ECDC): https://www.ecdc.europa.eu
Indicazioni ad interim della Societa Italiana di Neonatologia (SIN): https://www.sin-neonatologia.it/pdf/covid19/ALLATTAMENTO%20e%20INFEZIONE%20da%20SARS-CoV-2%20Indicazioni%20ad%20interim%20della%20Società%20Italiana%20di%20Neonatologia%20SIN.pdf
International Federation of Gynecology and Obstetrics (FIGO): https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.13156
Ministry of Health, Brazil: https://www.conasems.org.br/wp-content/uploads/2020/03/guia_de_vigilancia_2020.pdf)
National Health Commission of the People's Republic of China: http://www.nhc.gov.cn
Pan American Health Organization (PAHO): http://www.paho.org

Perinatal Medicine Branch of Chinese Medical Association https://mp.weixin.qq.com/s/11hbxlPh317es1XtfWG2qg
Public Health England: https://www.gov.uk/guidance/coronavirus-covid-19-information-for-the-public
Royal College of Obstetricians and Gynaecologists (RCOG): https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/
Santé Publique France: https://www.santepubliquefrance.fr/
Sociedad Española de Ginecología y Obstetricia S.E.G.O.: https://mcusercontent.com/fbf1db3cf76a76d43c634a0e7/files/1abd1fa8-1a6f-409d-b622-c50e2b29eca9/RECOMENDACIONES_PARA_LA_PREVENCIO_N_DE_LA_INFECCIO_N_Y_EL_CONTROL_DE_LA_ENFERMEDAD_POR_CORONAVIRUS_2019_COVID_19_EN_LA_PACIENTE_OBSTE_TRICA.pdf
Society for Maternal-Fetal Medicine: https://www.smfm.org/covidclinical
World Health Organisation (WHO): https://www.who.int/emergencies/diseases/novel-coronavirus-2019

BACKGROUND

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health emergency. Since the first case of COVID-19 pneumonia was reported in Wuhan, Hubei Province, China, in December 2019, the infection has spread rapidly to the rest of China and beyond[2,3].

Coronaviruses are enveloped, non-segmented, positive-sense ribonucleic acid (RNA) viruses belonging to the family Coronaviridae, order Nidovirales[4]. The epidemics of the two β-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have caused more than 10 000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV[5–8]. SARS-CoV-2 belongs to the same β-coronavirus subgroup and it has genome similarity of about 80% and 50% with SARS-CoV and MERS-CoV, respectively[9].

SARS-CoV-2 is spread by respiratory droplets and direct contact (when body fluids of an infected person have touched another person's eyes, nose or mouth, or an open cut, wound or abrasion). It should be noted that SARS-CoV-2 has been found in a laboratory environment to be viable on plastic and stainless-steel surfaces for up to 72 hours, whereas on copper and cardboard it is viable for up to 24 hours[10]. SARS-CoV-2 also remains viable and infectious in aerosols for hours, raising the possibility of airborne transmission. The Report of the World Health Organization (WHO)-China Joint Mission on Coronavirus Disease 2019 (COVID-19)[11] estimated a high R_0 (reproduction number) of 2–2.5. The latest report from WHO[12], on April 10th, estimated the global mortality rate of COVID-19 to be 6.1%. However, other reports, which utilized appropriate adjustment for the case ascertainment rate and the time lag between onset of symptoms and death, suggested the mortality rate to be lower, at 1.4%[13].

Huang *et al*.[14] first reported on a cohort of 41 patients with laboratory-confirmed COVID-19 pneumonia. They described the epidemiological, clinical, laboratory and radiological characteristics, as well as treatment and clinical outcome of the patients. Subsequent studies with larger sample sizes have shown similar findings[15,16]. The most common symptoms reported are fever (88.5%) and cough (68.6%)[17]. Myalgia or fatigue (35.8%), expectoration (28.2%) and dyspnea (21.9%) are also reported[17]. Diarrhea (4.8%) and nausea and vomiting (3.9%) are less common[17]. Breslin *et al*.[18] observed similar COVID-19 severity in pregnant patients (86.0% mild disease, 9.3% severe disease and 4.7% critical disease) to that reported in non-pregnant patients[16]. On admission, ground-glass opacity is the most common radiologic finding on computed tomography (CT) of the chest (56.4%)[16]. No radiographic or CT abnormality was found in 157 of 877 (17.9%) patients with non-severe disease and in five of 173 (2.9%) patients with severe disease. Lymphocytopenia was reported to be present in 64.5% of patients on admission[17]. Elevated C-reactive protein and lactic

dehydrogenase were observed in 44.3% and 28.3% of patients, respectively. Furthermore, they screened asymptomatic pregnant patients admitted to the labor ward, and found that 32.6% of them tested positive; however, 71.4% of these patients developed symptoms during admission or early postpartum[18].

Universal testing for COVID-19 remains a topic of debate and its need is determined mainly by local protocol and prevalence of the disease. A recent study from New York, USA, reported that a relatively large proportion (13.5%) of patients without any symptoms admitted for delivery tested positive for SARS-CoV-2[19]. Of these patients, 10% developed fever before discharge from the hospital. This indicates the potential problem with triaging patients based merely on symptoms in areas with widespread community infection.

Pregnancy is a physiological state that predisposes women to respiratory complications of viral infection. Due to the physiological changes in their immune and cardiopulmonary systems, pregnant women are more likely to develop severe illness after infection with respiratory viruses[20]. In 2009, pregnant women accounted for 1% of patients infected with influenza A subtype H1N1 virus, but they accounted for 5% of H1N1-related deaths[21]. In addition, SARS-CoV and MERS-CoV are both known to be responsible for severe complications during pregnancy, including the need for endotracheal intubation, admission to an intensive care unit (ICU), renal failure and death[8,22]. The case fatality rate of SARS-CoV infection among pregnant women is up to 25%[8]. Currently, however, there is no evidence that pregnant women are more susceptible to SARS-CoV-2 or that those with COVID-19 are more prone to developing severe pneumonia[18,23–28].

Over and above the impact of COVID-19 on a pregnant woman, there are concerns relating to the potential effect on fetal and neonatal outcome; therefore, pregnant women require special attention in relation to prevention, diagnosis and management. Based on the limited information available as yet and our knowledge of other similar viral pulmonary infections, the following expert opinions are offered to guide clinical management.

DIAGNOSIS OF INFECTION AND CLINICAL CLASSIFICATION

Case definitions are those included in the WHO's interim guidance, 'Global surveillance for COVID-19 caused by human infection with COVID-19 virus'[29].

Suspected case

- A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness of breath)) AND a history of travel to or

residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR

- A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact*, below) in the last 14 days prior to symptom onset; OR
- A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness of breath) AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

*A contact is defined as a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case, within 1 meter and for more than 15 min;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease, without using proper personal protective equipment (PPE);
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured from 2 days before to 14 days after the date on which the sample that led to confirmation was taken.

Probable case

- A suspected case for whom laboratory testing for COVID-19 is inconclusive; OR
- A suspected case for whom testing could not be performed, for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19, irrespective of clinical signs and symptoms.

Evidence suggests that a proportion of transmissions occur from cases with no or mild symptoms that do not provoke healthcare-seeking behavior[30]. Under these circumstances, in areas in which local transmission occurs, an increasing number of cases without a defined chain of transmission is observed and a lower threshold for suspicion in patients with severe acute respiratory infection may be recommended by health authorities[31].

Any suspected case should be tested for SARS-CoV-2 using available molecular tests, such as quantitative reverse transcription polymerase chain reaction (qRT-PCR). Lower-respiratory-tract specimens likely have a higher diagnostic value compared with upper-respiratory-tract specimens for detecting SARS-CoV-2. The WHO recommends

that, if possible, lower-respiratory-tract specimens, such as sputum, endotracheal aspirate or bronchoalveolar lavage, be collected for SARS-CoV-2 testing[32]. If patients do not have signs or symptoms of lower-respiratory-tract disease or specimen collection for lower-respiratory-tract disease is clinically indicated but collection is not possible, upper-respiratory-tract specimens of combined nasopharyngeal and oropharyngeal swabs should be collected. If initial testing is negative in a patient who is strongly suspected of having COVID-19, the patient should be resampled, with a sampling time interval of at least 1 day, and specimens collected from multiple respiratory-tract sites (nose, sputum, endotracheal aspirate). Additional specimens, such as blood, urine and stool, may be collected to monitor the presence of virus and the shedding of virus from different body compartments. When qRT-PCR analysis is negative for two consecutive tests, COVID-19 can be ruled out.

The WHO has provided guidance on the rational use of PPE for COVID-19[33]. When conducting aerosol-generating procedures (e.g. tracheal intubation, non-invasive ventilation, cardiopulmonary resuscitation, manual ventilation before intubation), healthcare workers are advised to use respirators (e.g. fit-tested N95, FFP2 or equivalent standard) with their PPE[33,34]. The Centers for Disease Control and Prevention (CDC) additionally considers procedures that are likely to induce coughing (e.g. sputum induction, collection of nasopharyngeal swabs and suctioning) as aerosol-generating procedures and CDC guidance includes the option of using a powered air-purifying respirator[34,35].

CHEST IMAGING DURING PREGNANCY

Computed tomography (CT)

Chest imaging, especially CT scan, is essential for evaluation of the clinical condition of a pregnant woman with COVID-19[36–38]. Fetal growth restriction (FGR), microcephaly and intellectual disability are the most common adverse effects from high-dose (> 610 mGy) radiation exposure[39,40]. According to the American College of Radiology and American College of Obstetricians and Gynecologists, when a pregnant woman undergoes a single chest X-ray examination, the radiation dose to the fetus is 0.0005–0.01 mGy, which is negligible, while the radiation dose to the fetus is 0.01–0.66 mGy from a single chest CT or CT pulmonary angiogram[41–43].

Chest CT scanning has high sensitivity (97%) for diagnosis of COVID-19[38]. In a pregnant woman with suspected COVID-19, a chest CT scan may be considered as a primary tool for the detection of COVID-19 in epidemic areas[38]. Informed consent should be acquired (shared decision-making) and a radiation shield applied over the gravid uterus. Because of the logistics involved in performing a CT scan on critically ill patients, and the need for thorough cleaning of the CT unit after imaging a COVID-19 patient, a portable chest X-ray is an acceptable alternative to a CT scan.

A CT pulmonary angiogram is generally used in preference to a ventilation/perfusion scan on clinical suspicion of pulmonary embolus and should not be withheld during pregnancy.

Ultrasound

During the COVID-19 pandemic, it has been proposed that ultrasound examination of the lungs of a pregnant woman with suspected COVID-19 could be carried out at the same time as the obstetric scan, in order to minimize the risk of radiation as well as streamlining the clinical assessment of these pregnant patients. This mode of lung imaging could be considered when chest X-ray and CT scan are not available. However, management should be determined by the clinical features and severity of the disease, and not based merely on diagnostic imaging. A practical guide on how to perform lung ultrasound examination in pregnant women with suspected COVID-19 was published recently[44]. In brief, the lung ultrasound scan can be performed with any type of machine and any type of transducer (including linear, convex and microconvex). Detailed guidance regarding cleaning of ultrasound equipment and transducers in the context of COVID-19 has been provided in the article, 'ISUOG Safety Committee Position Statement: safe performance of obstetrics and gynecological scans and equipment cleaning in the context of COVID-19'[45].

On ultrasound, horizontal 'A-lines' are the hallmark of the normal lung. When the lung loses normal aeration, but is not completely consolidated, it generates different shapes and lengths of vertical artifacts, usually called 'B-lines'. When the density of the peripheral lung parenchyma is increased, ultrasound examination shows a white area (the so-called 'ultrasonographic white lung'), in which neither A-lines nor separated B-lines are visible. Consolidation appears as an irregular hypoechoic area, and pleural effusion appears anechoic. An accompanying videoclip and images demonstrating these findings can be found in the original article[44].

Following the obstetric abdominal ultrasound examination, with the patient in a supine position, the examiner can simply move the probe from the abdomen to the chest, scanning the anterior and lateral areas of the thorax. The examination should cover the whole pulmonary area, from basal to upper areas of the thorax. Four vertical lines (right mid-axillary line, right parasternal line, left parasternal line and left mid-axillary line) can be followed in order to perform a systematic examination. With the patient in a sitting or lateral position, the posterior paravertebral surface of the thorax should then be scanned, from basal to upper areas or along posterior-axillary lines according to the patient's position.

TREATMENT DURING PREGNANCY

Triage of patients

Refer to Appendix 1. Triage of pregnant patients who potentially have COVID-19 is of great importance, reducing the risk for patients and healthcare workers alike[23]. Setting up a triage station outside the obstetric ward and outpatient clinic is essential, allowing for systematic and thorough screening (see Appendix 2) for symptoms (e.g. fever, cough, sore throat) and risk factors (based on any significant travel history, occupation, contact and cluster (TOCC)). Temperature should be checked. When concern is raised about a potential COVID-19 patient, i.e. due to symptoms and/or TOCC risk factors, a surgical face mask should be put on the patient and she should be separated from other patients, preferably in an isolated COVID-19 unit. Healthcare workers should don appropriate PPE for the management of suspected/probable/confirmed COVID-19 pregnant women[33,45,46].

Place of care

Refer to Appendix 3. Suspected, probable and confirmed cases of COVID-19 should ideally be managed by designated tertiary hospitals with effective isolation facilities and protection equipment[47]. Suspected/probable cases should be treated in isolation and confirmed cases should be managed in a negative-pressure isolation room, when available; otherwise, designated COVID-19 units can help reduce spread by cohorting affected patients with dedicated staffing. Designated hospitals should set up a dedicated operating room and a neonatal isolation ward. Ideally, the operating room and neonatal isolation ward should have negative-pressure ventilation. When it is not possible to set up negative-pressure ventilation for operating rooms, it is advisable to discuss with the hospital engineer whether it is appropriate to switch off their positive-pressure ventilation. All attending medical staff should don PPE (fit-tested N95, FFP2 or equivalent standard respirator, eye protection (goggles and/or face shield), disposable fluid-resistant and impermeable protective gown and double gloves) when providing care for confirmed cases of COVID-19[33,35,48].

However, in areas with widespread local transmission of the disease, health services may be unable to provide such levels of care to all suspected, probable or confirmed cases. Pregnant women with a mild clinical presentation may not initially require hospital admission, and home confinement can be considered, provided that this is possible logistically and that monitoring of the woman's condition can be ensured[49]. If negative-pressure isolation rooms are not available, patients should be isolated in single rooms, or grouped together once COVID-19 has been confirmed.

For transfer of confirmed cases, the attending medical team should don PPE and keep themselves and their patient a minimum distance of 2 meters, or 6 feet, from any individuals without PPE.

Referral to intensive care unit (ICU)

When an inpatient has confirmed COVID-19, vigilant maternal monitoring (including oxygen saturation monitoring) is of paramount importance, allowing for rapid initiation of supportive care[23]. Although not yet validated in COVID-19 pregnant patients, a modified early obstetric warning score (MEOWS) can be used to enable early recognition of critical illness[50,51]. An adapted MEOWS chart is provided in Appendix 4. When the maternal condition requires additional care, this should not be withheld due to pregnancy; respiratory indications for transfer to an isolated negative-pressure room in the ICU include pulmonary edema, need for airway protection and necessity of mechanical ventilation[50]. Patients with hypoxemic respiratory failure should be admitted to the ICU as soon as possible. Multidisciplinary care (obstetricians, maternal–fetal-medicine subspecialists, intensivists, obstetric anesthetists, internal-medicine or respiratory physicians, midwives, virologists, microbiologists, neonatologists, infectious-disease specialists) is essential, particularly because some pregnancy-related diseases can cause findings similar to those of severe COVID-19 (e.g. pulmonary embolism) and because the physiologic changes of pregnancy may affect management (e.g. optimal maternal positioning, changes in respiratory physiology affecting appropriate ventilator settings).

Suspected/probable cases

General treatment

Particular attention should be paid to fluid and electrolyte balance; symptoms should be treated, for example with antipyretic medicines.

Surveillance

Maternal vital signs (preferably using MEOWS) and oxygen saturation level should be monitored vigilantly to minimize maternal hypoxia; arterial blood-gas analysis should be conducted; repeat chest imaging (when indicated) should be performed; complete blood count should be evaluated regularly, with renal- and liver-function testing and coagulation testing.

Confirmed cases

Non-severe disease

(1) The approach to symptomatic treatment and surveillance is the same as for suspected/probable cases. Conservative fluid administration is advised[23,52]. Fluid balance should be evaluated regularly to minimize the risk of fluid overload[53]. Isotonic crystalloid fluid is the first choice of fluid to be administered. (2) Currently there is no proven antiviral treatment for COVID-19 patients, although a number of drugs are being trialed therapeutically in patients with severe symptoms. Decisions regarding antivirals, antimalarials and antibiotics should be undertaken in conjunction with local infectious-disease experts, and with the obstetrician providing advice on potential maternal or fetal effects of any treatment regimen. A summary of potential treatments, including hydroxychloroquine, lopinavir/ritonavir, interferon β-1b, tocilizumab, azithromycin and remdesivir, is provided in Appendix S2. (3) In non-pregnant patients,

comorbidities such as hypertension or diabetes seem to increase the risk for progression to severe disease, with poorer clinical outcome[54]. Therefore, it is advisable to monitor closely pregnant patients with these comorbidities and to be aware of this increased risk.

Severe and critical disease

(1) The degree of severity of COVID-19 pneumonia is defined by the Infectious Diseases Society of America/American Thoracic Society guidelines for community-acquired pneumonia (Appendix S3)[55,56]. (2) Severe pneumonia is associated with a high maternal and perinatal mortality rate; there is, therefore, a requirement for aggressive treatment, including supporting measures with hydration, oxygen therapy and chest physiotherapy. The case should be managed in a negative-pressure isolation room in the ICU, with the woman in a semi-recumbent or prone position, if feasible. Support of should be provided by a multidisciplinary team[57]. (3) Antibacterial treatment: appropriate antibiotic treatment in combination with antiviral treatment should be used promptly when there is suspected or confirmed secondary bacterial infection, following discussion with microbiologists. (4) Blood-pressure monitoring and fluid-balance management: in patients without septic shock, conservative fluid-management measures should be undertaken[58]. Excessive fluid can worsen hypoxemia in severe disease without shock[23,52]. In patients with septic shock, fluid resuscitation and inotropes are required to maintain an average arterial pressure ≥ 65 mmHg and a lactate level < 2 mmol/L[23,50]. The Hour-1 Surviving Sepsis Campaign bundle of care is a concise and practical approach to initial care for (suspected) sepsis[59]. This Bundle of Care is provided in Appendix S4. The WHO advises administration of 250–500 mL crystalloid intravenous fluid in the first 15–30 min, as a bolus[23]. (5) Oxygen therapy: supplemental oxygen should be used to maintain oxygen saturation > 94%[23,60]; oxygen should be given promptly to patients with hypoxemia and/or shock, and the method of ventilation should be according to the patient's condition and following guidance from the intensivists and obstetric anesthetists[23]. Accelerated hypoxemia in pregnancy is possible, due to increased oxygen consumption and reduced functional residual capacity[51]. The intensivist should remain aware of a higher likelihood of difficult intubation and greater risk of aspiration during pregnancy. (6) Medically indicated preterm delivery should be considered by the multidisciplinary team on a case-by-case basis. Early delivery may aid ventilation, allowing for prone ventilation if required. (7) Even in confirmed COVID-19 patients, other causes for maternal collapse should be examined[51].

MANAGEMENT DURING PREGNANCY

It has been reported that viral pneumonia in pregnant women is associated with an increased risk of preterm birth, FGR and perinatal mortality[61]. Based on nationwide population-based data, it was demonstrated that pregnant women with other viral pneumonias (*n* = 1462) had an increased risk of preterm birth, FGR and having a newborn with low birth weight and Apgar score < 7 at 5 min, compared with those

without pneumonia (n = 7310)[62]. A case series of 12 pregnant women with SARS-CoV in Hong Kong, China, reported three maternal deaths, that four of seven patients who presented in the first trimester had spontaneous miscarriage, four of five patients who presented after 24 weeks had preterm birth and two mothers recovered without delivery, but their ongoing pregnancies were complicated by FGR[8]. Currently, there are limited data regarding the impact on the fetus of maternal SARS-CoV-2 infection. There is an apparent increase of iatrogenic preterm birth but not of spontaneous preterm birth; therefore, cervical-length screening is not recommended.

Fever is common in COVID-19 patients. Previous data have demonstrated that maternal fever in early pregnancy can cause congenital structural abnormalities involving the neural tube, heart, kidney and other organs[63–65]. However, another study, including 80 321 pregnant women, reported that the rate of fever in early pregnancy was 10%, while the incidence of fetal malformation in this group was 3.7%[66]. Among the 77 344 viable pregnancies with data collected at 16–29 weeks of gestation, in the 8321 pregnant women with a reported temperature > 38°C lasting 1–4 days in early pregnancy, compared to those without a fever in early pregnancy, the overall risk of fetal malformation was not increased (odds ratio = 0.99 (95% CI, 0.88–1.12))[66]. Previous studies have reported no evidence of congenital infection with SARS-CoV, and currently there are no data on the risk of congenital malformation when SARS-CoV-2 infection is acquired during the first or early second trimester of pregnancy[67].

Outpatient antenatal care

If appropriate, giving advice via telephone or videoconferencing to patients with suspected/probable/confirmed COVID-19 can be considered[53]. When the patient has to be seen in hospital, early triage and isolation measures should be applied; all healthcare workers attending these patients should wear appropriate PPE[33,35]. A negative-pressure room is advised for confirmed cases. However, if this is not available, a dedicated single consultation room, with any unnecessary equipment having been removed, is advised. Thorough disinfection between patients, according to local protocols, is essential, especially of high-touch surfaces[45,52].

Inpatient antenatal care

Hospital admission might be required in pregnant patients with suspected/probable/confirmed COVID-19, either because of the disease itself or for obstetric reasons. A separate (part of the) obstetric ward should be reserved for these patients, preferably with negative-pressure rooms for confirmed cases. This ward should use dedicated equipment, such as cardiotocography (CTG) or ultrasound machines[45]. This equipment should not leave the room/ward without appropriate disinfection.

Prompt review by senior team members and, if necessary, multidisciplinary review, is advised for these patients[53]. Although they are in an isolated ward, woman-centered and skilled care with psychosocial support remains important[23]. Additionally,

thromboprophylaxis must be considered for all pregnant women who are managed as inpatients, especially in those with severe disease, unless delivery is imminent (within 12 hours)[23,51,53]. The Royal College of Obstetricians and Gynaecologists advises prophylactic low-molecular-weight heparin for all pregnant women admitted with COVID-19 and this should also be considered in outpatient self-isolating patients on a case-by-case basis, according to risk factors[53]. However, when the patient decompensates rapidly, a thorough risk–benefit analysis should be made regarding the administration of thromboprophylaxis, due to safety concerns regarding its use in conjunction with neuraxial analgesia.

Fetal monitoring and ultrasound

Following maternal assessment, CTG for fetal heart-rate (FHR) monitoring, at an appropriate gestational age according to local practice, should be undertaken, as well as ultrasound assessment of fetal growth and amniotic fluid volume, with umbilical artery Doppler if necessary. In severe COVID-19 cases, the fetal scan can be performed once the patient is stabilized. All sonographers/sonologists should don appropriate PPE when undertaking the ultrasound scan[35]. Detailed guidance regarding cleaning of ultrasound equipment and transducers in the context of COVID-19 has been provided in the ISUOG Safety Committee Position Statement on 'safe performance of obstetric and gynecological scans and equipment cleaning in the context of COVID-19'[45].

Pregnant women with confirmed infection who are asymptomatic, or recovering from mild illness, should be monitored with 4-weekly ultrasound assessments of fetal growth and amniotic fluid volume, with umbilical-artery Doppler if necessary[68,69]. When the infection is acquired in the first or early second trimester of pregnancy, a detailed morphology scan at 18–23 weeks of gestation is indicated, and these pregnancies should be monitored carefully after recovery.

The pregnancy should be managed according to the clinical findings, regardless of the timing of infection during pregnancy. All clinical visits for obstetric emergencies should be carried out in agreement with current local guidelines. All routine follow-up appointments should be postponed by 14 days or until positive test results (or two consecutive negative test results) are available. Details on how to prioritize obstetric ultrasound services are provided in a separate document[70].

MANAGEMENT DURING CHILDBIRTH

Refer to Appendix 3. COVID-19 itself is not an indication for delivery, unless there is a need to improve maternal oxygenation. For suspected, probable and confirmed cases of COVID-19, delivery should be conducted in a negative-pressure isolation room whenever possible. The timing and mode of delivery should be individualized,

dependent mainly on the clinical status of the patient, gestational age and fetal condition[53]. In the event that an infected woman has spontaneous onset of labor with optimal progress, she could be allowed to deliver vaginally[47]. Continuous fetal and frequent maternal monitoring is essential in these patients. Therefore, as well as for the protection of the medical team, given evidence of virus in feces and the inability of healthcare workers to use adequate PPE during the delivery, water birth should be avoided[53,71].

Shortening the second stage by operative vaginal delivery can be considered, as active pushing while wearing a surgical mask may be difficult for the woman to achieve[72]. With respect to a pregnant woman without a diagnosis of COVID-19, but who might be a silent carrier of the virus, we urge caution regarding the practice of active pushing while wearing a surgical mask, as it is unclear if there is an increased risk of exposure to any healthcare professional attending the delivery without PPE, because forceful exhalation may significantly reduce the effectiveness of a mask in preventing the spread of the virus by respiratory droplets[72]. During labor, excessive intravenous fluid should be avoided, especially when administering oxytocin, since this could worsen fluid overload due to its antidiuretic effect[73]. Oxytocin should be administered in an isotonic crystalloid such as 0.9% NaCl solution. Induction of labor can be considered when the cervix is favorable, but there should be a low threshold to expedite the delivery when there is fetal distress, poor progress in labor and/or deterioration in maternal condition.

Septic shock, acute organ failure or fetal distress should prompt emergency Cesarean delivery (or termination, if legal, before fetal viability)[69]. Donning PPE is time-consuming, and this may impact on the decision-to-delivery interval, but it must be done. Women and their families should be told about this possible delay, which may be of particular importance in Category-1 Cesarean delivery.

Both regional anesthesia and general anesthesia can be considered, depending on the clinical condition of the patient and after consultation with the obstetric anesthetist. As general anesthesia is considered an aerosol-generating procedure, regional anesthesia is preferred. When appropriate, consider an early epidural for a laboring woman with confirmed COVID-19. Concerning the presence of a birth-partner during childbirth, we advise adherence to local protocols. It is advisable to give the asymptomatic birth-partner a surgical face mask and they must follow strict hand hygiene[53]. However, when the partner is symptomatic, they must remain in isolation and therefore cannot attend the delivery.

For preterm cases requiring delivery between 24 and 33 + 6 weeks of gestation, we urge caution regarding the use of antenatal steroids (dexamethasone or betamethasone) for fetal lung maturation in a critically ill patient, because this can potentially worsen the clinical condition and the administration of antenatal steroids might delay the delivery that is necessary for management of the patient, especially

when there is a need to improve maternal oxygenation[74]. The use of antenatal steroids should be considered according to risk–benefit analysis and in discussion with infectious-disease specialists, maternal–fetal-medicine subspecialists and neonatologists[57,75]. We advise against the use of steroids in women at risk for late preterm delivery (between 34 and 36 weeks of gestation). Such risk–benefit analysis and discussion should likewise be applied to the use of tocolysis in case of women presenting with spontaneous preterm labor.

Miscarried embryos/fetuses and placentae of COVID-19 pregnant women should be treated as infectious tissues and they should be disposed of appropriately.

NEONATAL IMPACT AND CARE

Risk of vertical transmission

At present, it is uncertain whether there is a risk of vertical mother-to-baby transmission. In two studies, with a combined total of ten pregnant women with COVID-19 in the third trimester, amniotic fluid, cord blood and neonatal throat-swab samples tested negative for SARS-CoV-2, suggesting there was no evidence of vertical transmission in women who developed COVID-19 pneumonia in late pregnancy[26,76]. Furthermore, the study by Qiu *et al.* demonstrated that vaginal secretion samples tested negative for SARS-CoV-2 RNA[77]. Notably, in a neonate born to a pregnant woman with COVID-19 that tested positive for SARS-CoV-2 RNA in the pharyngeal swab sample 36 hours after birth, it was subsequently confirmed that qRT-PCR testing of the placenta and cord blood was negative for SARS-CoV-2, suggesting that intrauterine vertical transmission might not have occurred[27,78].

Two studies have recently explored the possibility of vertical transmission of SARS-CoV-2 in a combined total of seven affected pregnancies by testing for SARS-CoV-2-specific antibodies (immunoglobulins G and M (IgG and IgM)) in neonatal serum samples[79,80]. Their conclusion, that SARS-CoV-2 could be transmitted *in utero*, was based on the presence of IgM antibodies, detected by recently developed automated chemiluminescence immunoassays, in blood drawn from three neonates following birth. However, for all three, the neonatal respiratory samples tested negative for SARS-CoV-2 RNA. In the study by Dong *et al.*, the observed rapid decline in the infant (within 14 days) of SARS-CoV-2 IgG levels, along with a decline in IgM antibodies, strongly suggests that neonatal SARS-CoV-2 IgG antibodies were derived transplacentally from the mother, and not actively induced by the presumed neonatal infection[80].

In order to further investigate the possibility of vertical transmission of SARS-CoV-2, appropriately matched biological samples, including cord blood, placental tissue, amniotic fluid and amnion–chorion-interface swab, should be collected immediately after delivery, using aseptic technique, from women with COVID-19[81]. A neonatal

pharyngeal swab can also be collected. If possible, testing for SARS-CoV-2 of the miscarried fetus/placenta of COVID-19 pregnant women should be undertaken. In addition to testing for SARS-CoV-2 RNA by qRT-PCR, serological testing could be an important supplement in order to clarify the issue of vertical transmission of the virus. Longitudinal follow-up for 6–18 months of infants born to COVID-19 women should be undertaken[81].

Neonatal management

Regarding neonatal management of suspected, probable and confirmed cases of maternal COVID-19, the umbilical cord should be clamped promptly, and the neonate should be transferred to the resuscitation area for assessment by the attending pediatric team. There should be different healthcare workers taking care of mother and baby in order to minimize the risk of cross-contamination. There is insufficient evidence regarding whether delayed cord clamping increases the risk of infection to the newborn via direct contact[75]. In units in which delayed cord clamping is recommended, clinicians should consider carefully whether this practice should be continued. There is also currently insufficient evidence regarding the safety of breastfeeding and the need for mother/baby separation[26,82]. If the mother is severely or critically ill, separation appears to be the best option, with attempts to express breastmilk in order to maintain milk production. For this, there should be a dedicated breast pump and the machine must be washed thoroughly, according to the manufacturer's recommendations, after each use[83]. If the patient is asymptomatic or mildly affected, breastfeeding and colocation (also called rooming-in) can be considered by the mother in coordination with healthcare providers, or may be necessary if facility limitations prevent mother/baby separation. Since the main concern is that the virus may be transmitted by respiratory droplets rather than breastmilk, breastfeeding mothers should ensure to wash their hands and wear a three-ply surgical mask before touching the baby. In case of rooming-in, the baby's cot should be kept at least 2 meters from the mother's bed, and a physical barrier such as a curtain or glass may be used[84,85].

The need to separate mothers with COVID-19 from their newborns, with the consequence that they are unable to breastfeed directly, may impede early bonding as well as establishment of lactation[86]. These factors will inevitably cause additional stress for mothers in the postpartum period. As well as caring for their physical wellbeing, medical teams should consider the mental wellbeing of these mothers, showing appropriate concern and providing support when needed[23,86].

GENERAL PRECAUTIONS

At the time of writing, there are no effective drugs or vaccines to prevent COVID-19. Therefore, personal protection should be considered in order to minimize the risk of contracting the virus.

Patients and healthcare providers

a. Good personal hygiene should be maintained: during the COVID-19 epidemic period, close contact with others should be consciously avoided, participation in any gathering in which a distance of at least 2 meters between individuals cannot be maintained should be avoided, attention should be paid to hand washing and hand sanitizer (with 70% alcohol concentration) used frequently[33,87].
b. A three-ply surgical mask should be worn when visiting a hospital or other high-risk area.
c. Medical assistance should be sought promptly for timely diagnosis and treatment when symptoms such as fever and cough are experienced.

Healthcare providers

a. Consider provision of educational information (brochures, posters) should be considered in waiting areas.
b. Triage plans for screening should be set up. In units in which triage areas have been set up, staff should have appropriate PPE and be strictly compliant with hand hygiene.
c. All pregnant patients who present to the hospital and for outpatient visits should be assessed and screened for symptoms and risk factors based on TOCC (Appendix 2).
d. Pregnant patients with known TOCC risk factors and those with mild or asymptomatic COVID-19 should delay any antenatal visits and routine ultrasound assessment by 14 days if advisable.
e. The number of visitors to the department should be reduced.
f. In units in which routine group-B streptococcus (GBS) screening is practiced, acquisition of vaginal and/or anal swabs should be delayed by 14 days in pregnant women with symptoms and/or TOCC risk factors or should be performed only after a suspected/probable case tests negative or after recovery in a confirmed case. Intrapartum prophylactic antibiotic cover for women with ante- or intrapartum risk factors for GBS is an alternative.
g. On presentation to triage areas, pregnant patients with symptoms and/or TOCC risk factors should be placed in an isolation room for further assessment.
h. Medical staff who are caring for suspected, probable or confirmed cases of COVID-19 patients should be monitored closely for fever or other signs of infection and should not be working if they have any COVID-19 symptoms. Common symptoms at onset of illness include fever, dry cough, myalgia, fatigue, dyspnea and anorexia. Ideally, medical staff assigned to care for suspected, probable or confirmed cases of COVID-19 should minimize contact with other patients and colleagues, with the aim of reducing the risk of exposure and potential transmission.
i. Medical staff who have been exposed unexpectedly, while without PPE, to a COVID-19 pregnant patient, should be quarantined or self-isolate for 14 days.

j. Pregnant healthcare professionals should follow risk-assessment and infection-control guidelines following exposure to patients with suspected, probable or confirmed COVID-19.

KEY POINTS FOR CONSIDERATION

1. Pregnant women with confirmed COVID-19 should ideally be managed by designated tertiary hospitals, and they should be informed of the risk of adverse pregnancy outcome.
2. Negative-pressure isolation rooms should be set up for safe labor, delivery (including Cesarean section) and postpartum (including neonatal) care.
3. During the COVID-19 epidemic period, a detailed history regarding TOCC and clinical manifestations should be acquired routinely from all pregnant women attending for routine care.
4. Chest imaging, especially CT scan, should be included in the work-up of pregnant women with suspected, probable or confirmed COVID-19.
5. Suspected/probable cases should be treated in isolation and confirmed cases should be managed in a negative-pressure isolation room. A woman with confirmed infection who is critically ill should be admitted to a negative-pressure isolation room in the ICU.
6. Antenatal examination and delivery of pregnant women infected with COVID-19 should be carried out in a negative-pressure isolation room on the labor ward. Human traffic around this room should be limited when it is occupied by an infected patient.
7. All medical staff involved in management of infected women should don appropriate PPE (fit-tested N95, FFP2 or equivalent standard respirator, eye protection (goggles and/or face shield), disposable fluid-resistant and impermeable protective gown disposable fluid-resistant and impermeable protective gown and double gloves) as required.
8. Management of COVID-19 pregnant women should be undertaken by a multidisciplinary team (obstetricians, maternal–fetal-medicine subspecialists, intensivists, obstetric anesthetists, midwives, internal-medicine or respiratory physicians, virologists, microbiologists, neonatologists, infectious-disease specialists).
9. Vigilant maternal monitoring (including oxygen-saturation monitoring) of all COVID-19 patients is paramount, allowing for rapid commencement of supportive care. The use of a MEOWS chart is recommended.
10. Timing and mode of delivery should be individualized, dependent mainly on the clinical status of the patient, gestational age and fetal condition.
11. Both regional anesthesia and general anesthesia can be considered, depending on the clinical condition of the patient and after consultation with the obstetric anesthetist. If possible, regional anesthesia is preferable due to a lower risk of transmission in comparison with general anesthesia.

12. At present, limited data suggest that there is no evidence of vertical mother-to-baby transmission in women who develop COVID-19 in late pregnancy, although case reports of potential vertical transmission are emerging.
13. There is currently insufficient evidence regarding the safety of breastfeeding and the need for mother/baby separation. If the mother is severely or critically ill, separation appears to be the best option, with attempts to express breastmilk in order to maintain milk production. If the patient is asymptomatic or mildly affected, breastfeeding and colocation (rooming-in) can be considered by the mother in coordination with healthcare providers.
14. Healthcare professionals engaged in obstetric care and those who perform obstetric ultrasound examinations should be trained and fitted appropriately for PPE.
15. We strongly recommend submitting cases to local, regional or international registries for COVID-19-infected pregnant women, with the aim of answering the many clinical and scientific questions in relation to the impact of COVID-19 during pregnancy.

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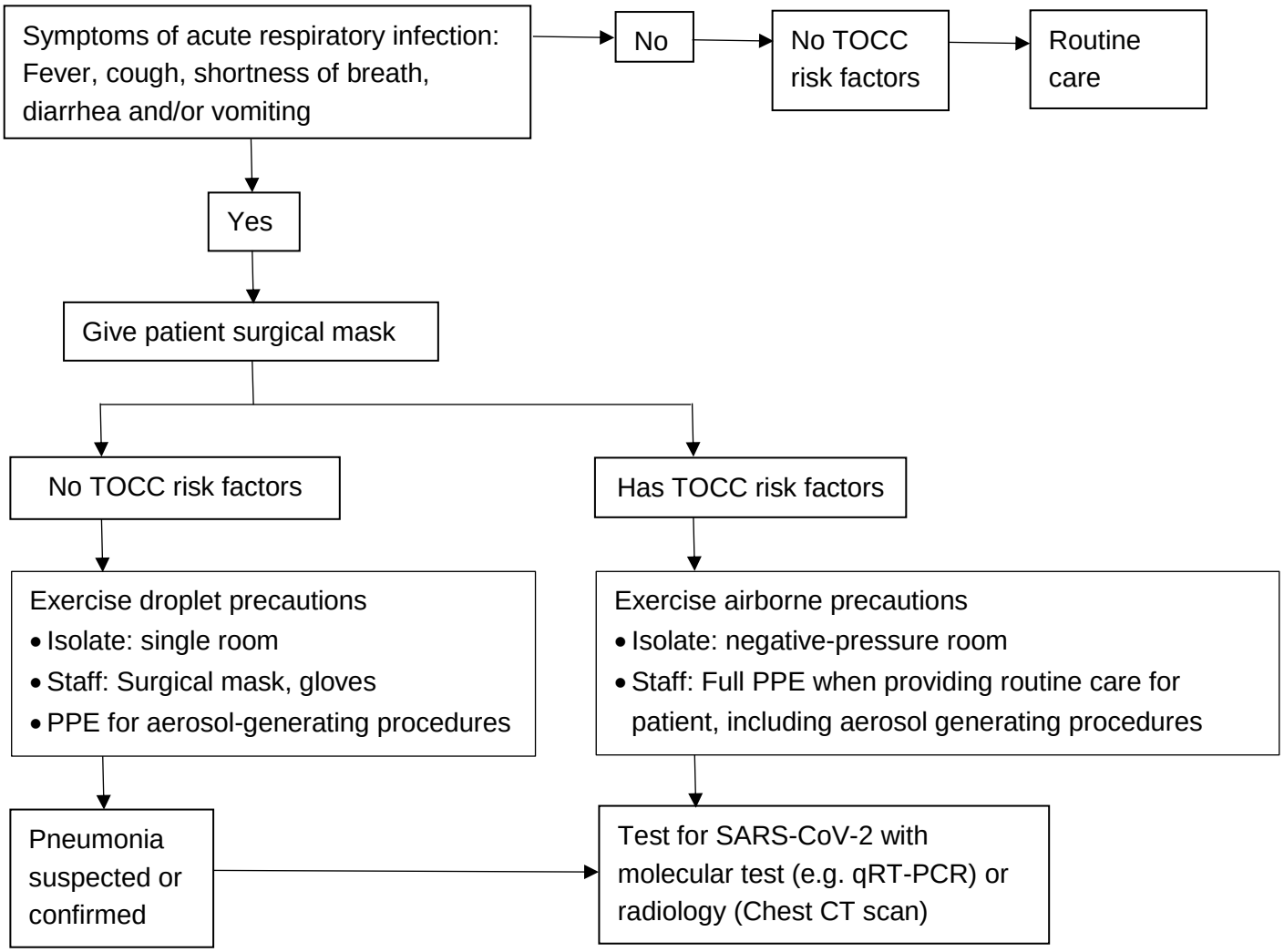


Appendix 1 Flowchart to assess coronavirus disease 2019 (COVID-19) risk in obstetric-unit attendees. CT, computed tomography; PPE, personal protective equipment; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TOCC, travel, occupation, contact and cluster.

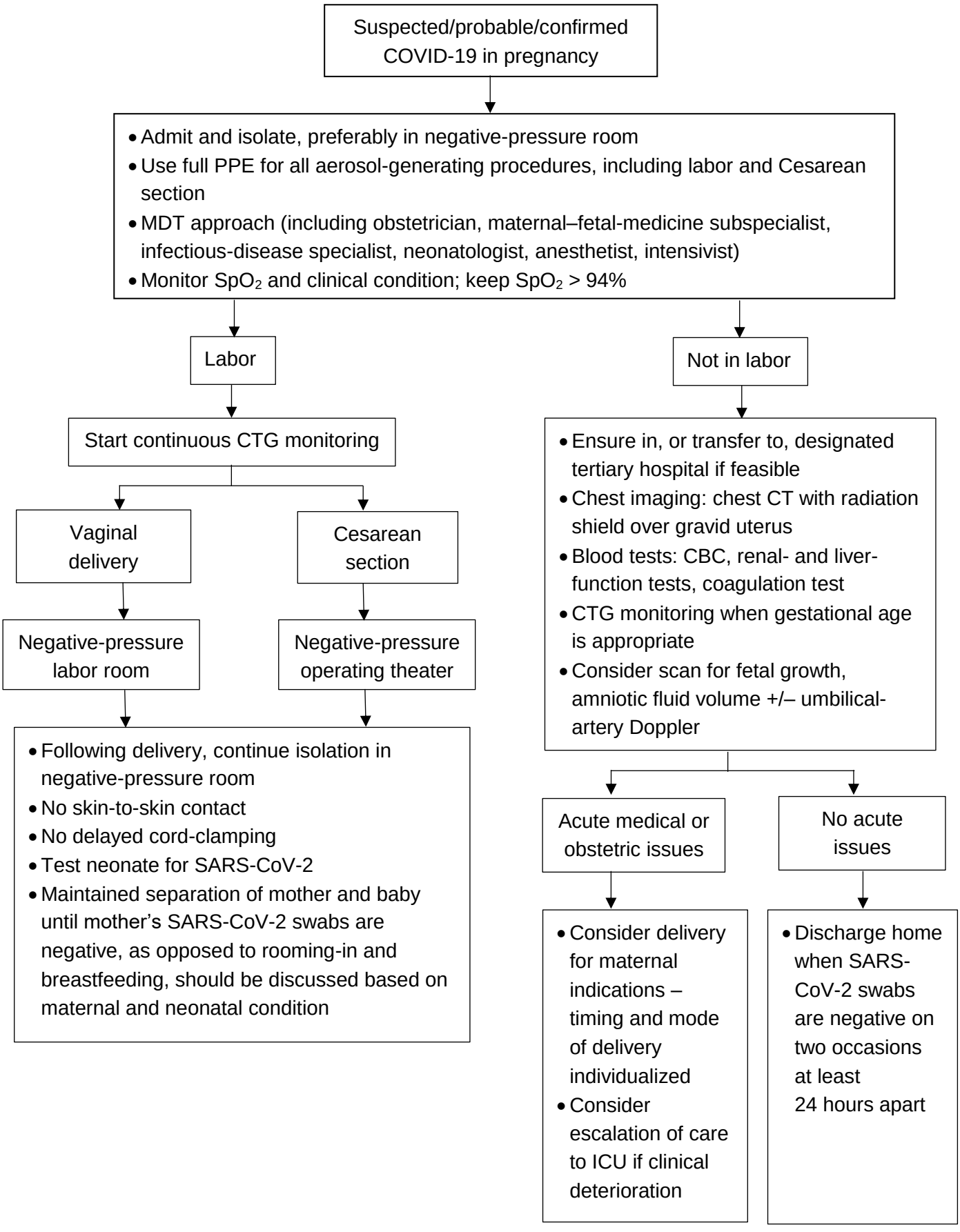
Appendix 2 Example of symptoms and TOCC (significant travel history, occupation, contact and cluster) checklist

Checklist for Symptoms and TOCC

1	**Influenza-like illness symptoms**	
☐	Fever	→ **Airborne precautions** for patient with respiratory symptoms
☐	Cough	
☐	Sore throat	
☐	Shortness of breath	
☐	Diarrhea and/or vomiting	→ **Contact precautions**
☐	None of above	
☐	Information cannot be obtained	
2	**TOCC: 14 days before onset of symptoms**	
☐	History of recent **T**ravel Date of travel: from _____ to _____ Area: _____	*If influenza-like-illness symptoms +ve plus TOCC +ve ➔ **Prompt isolation** ➔ **Airborne, droplet & contact precautions**
☐	High-risk **O**ccupation (e.g. laboratory workers, healthcare workers, wild-animal-related work)	
☐	History of unprotected **C**ontact with a person with confirmed COVID-19	
☐	**C**lustering of influenza-like illness / pneumonia (≥ 2 affected persons)	
☐	None of above	
☐	Information cannot be obtained	
3	**Types of Isolation Precautions required:**	
☐ Droplet precautions	☐ Contact precautions	☐ Airborne precautions Nil ☐
Date:		
Name & Signature:		
Designation:		

Droplet precautions: put surgical mask on patient; single room; healthcare worker uses PPE appropriately, including wearing mask, upon entry to room[33,88].
Contact precautions: single room; healthcare worker uses PPE appropriately, including wearing gloves and gown, upon entry to room; use disposable equipment[33,88].
Airborne precautions: put surgical mask on patient; negative-pressure isolation room; healthcare worker uses PPE appropriately, including wearing fit-tested N95, FFP2 or equivalent standard respirator, eye protection (goggles and/or face shield), disposal fluid-resistant and impermeable protective gown and double gloves, upon entry to room; negative-pressure isolation room; restrict susceptible healthcare workers from entering room; use disposable equipment[33,88].

Appendix 3 Flowchart to manage suspected/probable/confirmed COVID-19 in obstetric-unit attendees. CBC, complete blood count; CT, computed tomography; CTG, cardiotocography; ICU, intensive care unit; MDT, multidisciplinary team; PPE, personal protective equipment; SpO_2, peripheral capillary oxygen saturation.



Appendix 4 Modified early obstetric warning score (MEOWS)
Adapted with permission from Irish Maternity Early Warning System (IMEWS) Version 2[89].

Vital sign	Normal	Light zone	Dark zone
Respiratory rate	11–19/min	20–24/min	≤ 10/min ≥ 25/min
Oxygen saturation, only if respiratory rate triggers	96–100%		≤ 95%
Temperature	36.0–37.4°C	35.1–35.9°C 37.5–37.9°C	≤ 35.0°C ≥ 38.0°C
Maternal heart rate	60–99/min	50–59/min 100–119/min	≤ 49/min ≥ 120/min
Systolic blood pressure	100–139 mmHg	90–99 mmHg 140–159 mmHg	≤ 89 mmHg ≥ 160 mmHg
Diastolic blood pressure	50–89 mmHg	40–49 mmHg 90–99 mmHg	≤ 39 mmHg ≥ 100 mmHg
AVPU neurological response	A: Alert		V: Voice P: Pain U: Unresponsive

Threshold for intervention

1 light gray	2 light OR 1 dark gray	> 2 light on 1 dark gray
Repeat full set of observations on IMEWS after 30 and before 60 minutes.	Call obstetrician to review. Repeat full set of observations after 30 minutes.	Call obstetrician and request immediate review. Repeat full set of observations within 15 minutes or monitor continuously.

NB If concerned about woman, escalate care regardless of vital signs.

SUPPORTING INFORMATION ON THE INTERNET

Appendix S1 Summary of changes from previous Interim Guidance[1]

Area	Details
Background	Added information about viability of SARS-CoV-2 and new information concerning mortality rate. Added reference about the prevalence of asymptomatic infection in pregnancy
Diagnosis of infection and clinical classification	Updated WHO case definitions
Computer tomography (CT)	Added information about CT pulmonary angiogram and chest X-ray
Ultrasound	Added information regarding how to perform ultrasound evaluation of lungs
Triage of patients	Added information regarding triage of patients
Place of care	Further specified negative-pressure ventilation and appropriate personal protective equipment Added Appendix 3: Flowchart to manage suspected/probable/confirmed COVID-19 in obstetric-unit attendees
Referral to intensive care unit	Added information regarding referral to intensive care unit Added Appendix 4: Modified early obstetric warning score (MEOWS)
Non-severe disease	Advised conservative fluid administration Added a section regarding antiviral treatment, including Appendix S2: Potential drugs for treatment of COVID-19 in pregnant women[90–115] Added a section concerning comorbidities
Severe and critical disease	Advised conservative fluid administration Referred to Hour-1 Surviving Sepsis Campaign bundle of care, added Appendix S4: Hour-1 Surviving Sepsis Campaign bundle of care[59] Added some key points for oxygen therapy and general therapy
Management during pregnancy	Added recommendation not to perform cervical-length screening
Outpatient antenatal care	Added information regarding outpatient antenatal care
Inpatient antenatal care	Added information regarding inpatient antenatal care
Fetal monitoring and ultrasound	Reorganized and added a subsection on fetal monitoring and ultrasound
Management during childbirth	Advised continuous fetal monitoring, and avoidance of water birth Added advice concerning oxytocin administration Added warning concerning category-1 Cesarean delivery Added section concerning anesthesia and birth-partner Added advice concerning antenatal steroids and tocolysis Added Appendix 3: Flowchart to manage suspected/probable/confirmed COVID-19 in obstetric-unit attendees

Risk of vertical transmission	Added information regarding risk of vertical transmission
Neonatal management	Added advice concerning breast pumps and risk of cross-contamination
General precautions	Recommendation to wear surgical mask Recommendation to reduce the number of visitors Recommendation to separate medical staff treating COVID-19 patients and those treating non-COVID-19 patients
Key points for consideration	Recommendation to use MEOWS chart Recommendation to use regional anesthesia over general anesthesia Recommendation to submit data to COVID-19 registries
Appendix 1	Flowchart to assess coronavirus disease 2019 (COVID-19) risk in obstetric-unit attendees
Appendix 2	Example of symptoms and TOCC (significant travel history, occupation, contact and cluster) checklist
Appendix 3	Flowchart to manage suspected/probable/confirmed COVID-19 in obstetric-unit attendees
Appendix 4	Modified early obstetric warning score (MEOWS)
Appendix S2	Potential drugs for treatment of COVID-19 in pregnant women[90–115]
Appendix S4	Hour-1 Surviving Sepsis Campaign bundle of care

Appendix S2 Potential drugs for treatment of COVID-19 in pregnant women[90–115]

Hydroxychloroquine[90–93]

- Pregnancy: There are some data in pregnant women (data between 300-1,000 pregnancies) indicating that hydroxychloroquine does not cause malformations or fetal / neonatal toxicity. Hydroxychloroquine crosses the placental barrier and accumulates in the melanin cells of the fetus where it remains for prolonged periods. As a precautionary measure, it is preferable to avoid its use during pregnancy. However, during the acute attack of malaria the risk-benefit ratio derived from its use may be favorable (since malaria is more severe during pregnancy). Likewise, in patients with lupus erythematosus, the withdrawal of hydroxychloroquine before or during pregnancy has been associated with an increase in the activity of the disease. It can be used in pregnancy if it is clinically beneficial.
- Lactation: Hydroxychloroquine is excreted in breast milk (range 0.0005 - 2% of the daily maternal dose), but at therapeutic doses, no effects are expected in breastfed children. It can be used in lactation.

Lopinavir / ritonavir[94–97]

- Pregnancy: Lopinavir / ritonavir has been evaluated in more than 3,000 women during pregnancy, including more than 1,000 in the first trimester. Post-marketing surveillance by the Antiretroviral Pregnancy Registry has not reported an increased risk of birth defects from exposure to lopinavir / ritonavir in more than 1,000 women after being exposed during the first trimester. It can be used in pregnancy if it is clinically beneficial.
- Lactation: Lopinavir / ritonavir is excreted in human breast milk. No severe adverse outcomes have been reported although caution is needed in premature neonates. Assess individual risk / benefit of treatment and breastfeeding and decide accordingly.

Interferon β-1b[98–101]

- Pregnancy: Outcomes of more than 1,000 pregnancies from registries, national registries, and post-marketing experience with interferon β-1b indicate that there is no increased risk of major congenital abnormalities after preconception exposure or during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, as data was collected when the use of interferon β-1b was contraindicated during pregnancy and treatment was probably discontinued upon detection and / or confirmation of pregnancy. Experience with exposure during the second and third trimesters of pregnancy is very limited. Based on animal data, a possible increased risk of miscarriage was reported. However, a recently published reporting pregnancy outcomes from the global pharmacovigilance database on interferon β-1b exposure suggest no increase in risk of spontaneous abortion or congenital anomalies in women exposed during pregnancy.
- Lactation: The limited information available on the transfer of interferon β-1b in breast milk, together with the chemical / physiological characteristics of interferon β-1b, suggests that the levels of interferon β-1b excreted in breast milk are negligible. It can be used in lactation.

Tocilizumab[102–104]
- Pregnancy: There is insufficient data about its use in pregnancy. An animal study has shown an increased risk of miscarriage / embryo-fetal death at a high dose. It is preferred to avoid during pregnancy, unless clearly necessary.
- Lactation: There is little information about tocilizumab during breastfeeding, but small amounts of tocilizumab have been detected in breastmilk after intravenous doses in several mothers with no reported adverse effects. Assess individual risk / benefit of treatment and breastfeeding and decide accordingly.

Azithromycin[105–112]
- Pregnancy: Azithromycin is a commonly used drug during pregnancy. In animal studies azithromycin has been shown to cross the placenta but there is no evidence of harm or teratogenic effects to the fetus. In human, no increase in the frequency of malformation or other direct or indirect harmful effects on the fetus have been observed. There are, however, no adequate and well-controlled studies in pregnant women. A recent population-based cohort study has shown an increased risk of major malformations when macrolide antibiotics (mainly clarithromycin) are administered in the first trimester and an increased risk of genital malformations when prescribed at any trimester. Additionally, warnings have been issued in regard to a possible increased risk of miscarriage, cerebral palsy and epilepsy. However, studies show contradictory results and most drug agencies currently state that azithromycin should only be used during pregnancy if the benefit outweighs the risk.
- Lactation: Azithromycin is excreted in human milk and breastfed infants should be monitored for gastrointestinal side effects. Assess individual risk / benefit of treatment and breastfeeding and decide accordingly.

Remdesivir[113–115]
- Pregnancy: Remdesivir is a broad-spectrum direct-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[113]. Its use appears to be safe in human pregnancies and phase 3 trials evaluating efficacy in COVID-19 are currently underway in the United States (ClinicalTrials.gov number NCT04280705) and China (ClinicalTrials.gov number NCT04252664 and NCT04257656)[114]. Assess individual risk / benefit of treatment and compassionate use and decide accordingly.
- Lactation: There is no data on whether remdesivir is present in breast milk, but one newborn infant with Ebola treated with remdesivir experienced no adverse effects and was virus free on day 20 of life[115]. Assess individual risk / benefit of treatment and breastfeeding and decide accordingly.

Appendix S3 2007 Infectious Diseases Society of America/American Thoracic Society criteria for defining severe community-acquired pneumonia[55,56]

Validated definition includes either one major criterion or three or more minor criteria

Minor criteria

Respiratory rate ≥ 30 breaths/min

Pa_{O2}/FI_{O2} ratio ≤ 250

Multilobar infiltrates

Confusion/disorientation

Uremia (blood urea nitrogen level ≥ 20 mg/dL)

Leukopenia* (white blood cell count < 4000 cells/mL)

Thrombocytopenia (platelet count < 100 000/mL)

Hypothermia (core temperature < 36°C)

Hypotension requiring aggressive fluid resuscitation

Major criteria

Septic shock with need for vasopressors

Respiratory failure requiring mechanical ventilation

*Due to infection alone (i.e. not chemotherapy-induced).

Appendix S4 Hour-1 Surviving Sepsis Campaign bundle of care[59]

- Measure lactate level. Remeasure if initial lactate is > 2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure ≥ 65 mmHg.