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Counseling in maternal-fetal medicine: SARS-CoV-2 infection in pregnancy

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Abstract

SARS-CoV-2 is a zoonotic Coronavirus that crossed species to infect humans, causing a disease called COVID-19. Despite a potentially higher risk of acquiring SARS-CoV-2 infection compared to the non-pregnant population, no additional specific recommendations to avoid exposure are needed in pregnancy. Fever, cough, lymphopenia and raised C reactive protein levels are the most common clinical symptoms and laboratory signs of SARS-CoV-2 infection in pregnancy. Pregnancy carries a higher risk of severe SARS-CoV-2 infection compared to the non-pregnant population, including pneumonia, admission to ICU and death, mostly after adjusting for potential risk factors for severe outcomes. The risk of miscarriage does not appear to be increased in women with SARS-CoV-2. Evidence is conflicting when focusing on PTB and perinatal mortality, but these risks are generally higher only in symptomatic, hospitalized women. The risk of vertical transmission, defined as the transmission of SARS-CoV-2 from the mother to the fetus or the newborn, is generally low. Fetal invasive procedures are generally safe in women with SARS-CoV-2 infection although the evidence is still limited. Steroids should not be avoided if clinically indicated, preferring dexamethasone and then methylprednisolone for a total of 10-day course. NSAIDs might be used if there are no other contraindications. Pregnant women hospitalized with severe course of SARS-CoV-2 disease should undergo prophylactic thromboprophylaxis throughout the time of hospitalization and at least until discharge, preferably LMWH. Hospitalized women who have recovered from a period of serious or critical illness with COVID-19 should be offered at least a fetal growth scan about 14 days after recovery from their illness. In asymptomatic or mildly symptomatic women tested positive for SARS-CoV-2 infection at full term (i.e. ≥39 weeks of gestation), induction of labor might be reasonable. To date, there is no clear consensus on a proper timing of delivery for critically ill women. In women with no or few symptoms, management of labor should follow routine, evidence-based guidelines. Regardless of COVID-19, mothers and infants should remain together, breastfeed, practice skin-to-skin contact and kangaroo mother care, and rooming-in day and night while applying necessary infection prevention and control measures.

Due to the absence of long-term evidence-based data, the possibility of undergoing vaccination should be offered after an extensive counselling on both the potential risk of a severe course of the disease and the unknown risk of fetal exposure to the vaccine.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has been a major Public Health concern since the beginning of 2020, with new cases of infection, hospitalization, admission to Intensive Care Unit (ICU) and deaths increasing on a daily basis worldwide.[1-2]

Since the beginning of the pandemic, pregnancy was thought to be associated with a higher burden of maternal mortality and morbidity compared to the general population, due to the physiologic cardiovascular, respiratory and immunological adaptations.[3-4]

Although several cohort studies and systematic reviews evaluating the impact of SARS-COV-2 infection on maternal and perinatal outcomes have been published,[5-11] the evidence on several aspects of the prenatal management of these pregnancies remains conflicting, including the type and frequency of fetal monitoring, potential risk associated with invasive prenatal diagnosis, timing at delivery and intra-partum monitoring.

The aim of this review is to provide an up-to-date of the literature and to review the quality of evidence on the management of pregnancies complicated by SARS-CoV-2 infection, as also summarized in Table 1.

CLINICAL QUESTIONS

What is SARS-CoV-2 infection and how can it be diagnosed?

In 2020 a novel Coronavirus, labelled as SARS-CoV-2 (previously called 2019-nCoV) was first identified in Wuhan, China, in patients exposed to a seafood or wet market as a responsible of a cluster of pneumonia.[1]

Coronaviruses are enveloped RNA viruses belonging to the Nidovirales order and broadly circulating among humans, other mammals, and birds that cause mainly respiratory disorders.[12]

Like two other zoonotic Coronaviruses did before — severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) — SARS-CoV-2 crossed species to infect humans, causing a disease called COVID-19.

A confirmed case of SARS-COV-2 infection is defined as a positive result on nucleic acid amplification testing (NAAT), obtained by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimen, that is currently the gold standard for the diagnosis of SARS-COV-2 infection. Antigen testing might also be used as an alternative to NAAT, with the advantage of a faster time to results, at expense of a lower sensitivity.[13]

Bottom line: *SARS-CoV-2 is a zoonotic Coronavirus that crossed species to infect humans, causing a disease called COVID-19. The gold standard for the diagnosis of SARS-CoV-2 infection is RT-PCR assay of nasal and pharyngeal swab specimens.*

Are pregnant women more likely to get SARS-COV-2 infection?

The contagiousness of a viral disease is commonly reported using the basic reproduction number (R0), which is an epidemiologic metric used which describes the transmissibility of infectious agents. R0 is affected by several biological, socio-behavioral, and environmental factors that govern pathogen transmission. The potential size of an outbreak or epidemic often is based on the magnitude of the R0 value for that event, which has been estimated to be around 2 in the early SARS-CoV-2 outbreak in China. Despite this, the R0 value only captures the average dynamics of transmission; a crucial question for control is whether specific situations and settings might be driving the outbreak. A better measure of the actual risk of transmission in different settings is provided by the secondary attack rate (SAR), defined as the probability that an infection occurs among susceptible people within a specific group which provides an estimation of how social interactions can relate to transmission risk.[14-16]

A recent systematic review assessing the SARS-CoV-2 SAR in household and healthcare settings according by symptom status and patients' age reported a pooled SAR of 18.1%, with large heterogeneity among the included studies. SAR of symptomatic index cases was higher than asymptomatic cases (RR: 3.23). Adults showed higher susceptibility to infection than children (RR: 1.71), while spouses of index cases were more likely to be infected compared to other household contacts (RR: 2.39). Finally, in healthcare settings, SAR was estimated at 0.7%.[17]

Although no specific study on SAR in pregnancy, there is no consistent data showing that pregnant women are more susceptible to SARS-COV-2 infection compared to the general population.

However, a recent study from Washington State showed that the SARS-CoV-2 infection rate was significantly higher in pregnant patients than in similarly-aged adults, and these data were confirmed also higher after excluding pregnant patients whose SARS-CoV-2 infections was detected through asymptomatic screening strategies, mostly when focusing on non-white ethnic groups.[18] Similarly, a report released by the Center for Disease Control and Prevention in the United States reported that, among pregnant women infected by SARS-CoV-2, 46.2% were Hispanic, 23.0% were non-Hispanic white, 22.1% were non-Hispanic black, and 3.8% were non-Hispanic Asian compared with 38.1%, 29.4%, 25.4%, and 3.2%, respectively, among nonpregnant women. To date, it is not clear whether this relatively higher occurrence of SARS-CoV-2 infection in Hispanic and non-Hispanic black people may be secondary to a spurious association rather than the result of a higher susceptibility of these ethnics groups to SARS-CoV-2 infection.[19]

On this basis, there is no specific indication to avoid the infection among pregnant women who should follow the same recommendations as nonpregnant people for avoiding exposure to the virus.

Bottom line: *Despite a potentially higher risk of acquiring SARS-CoV-2 infection compared to the non-pregnant population, no additional specific recommendations to avoid exposure are needed in pregnancy.*

Which are the most common signs and symptoms of SARS-CoV-2 infection in pregnancy?

There are no specific symptoms related to SARS-CoV-2 infection in pregnancy. The course of the infection has been reported to be asymptomatic in the large majority of cases (75-90% in the largest cohorts), although few series reported lower rates of asymptomatic pregnant women. The frequency of either the presence and the type of symptoms related to SARS-CoV-2 infection in pregnancy is difficult to estimate because the large majority of published studies pool together unselected and selected cohorts of women (i.e. those presenting to the hospital with clinical symptoms).

Cough and fever occur in about 40% of symptomatic pregnant women affected by SARS-CoV-2 infection, while lymphopenia (35%) and raised C reactive protein levels (49%) are the most common laboratory findings. When compared to the non-pregnant population, the likelihood of developing fever is lower in pregnancy, thus partially explaining the relatively high rate of asymptomatic cases reported in some series.[20]

Bottom line: *Fever, cough, lymphopenia and raised C reactive protein levels are the most common clinical symptoms and laboratory signs of SARS-CoV-2 infection in pregnancy.*

Are pregnant women more likely to develop severe SARS-CoV-2 infection compared to the non-pregnant population?

In non-pregnant patients, the severity of SARS-CoV-2 infection is graded according to different illness categories mostly based upon the degree of hypoxia into:

- Asymptomatic or pre-symptomatic infection, including individuals tested positive for SARS-CoV-2 but showing no symptom consistent with the disease.
- Mild illness, including individuals who have any of the various signs and symptoms of COVID-19 but who have no dyspnea, or abnormal chest imaging.
- Moderate illness: individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO2) ≥94% on room air at sea level.
- Severe illness: individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.
- Critical illness: individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

These criteria are not fixed, and the clinical presentation of a patient affected by SARS-CoV-2 infection may change over time.

The large majority of pregnant women acquiring SARS-CoV-2 infection do not develop critical symptoms related to COVID-19 and the course of the infection is asymptomatic in approximately 90% of the obstetric population.

However, in a recent propensity-scoring matched analysis including 5183 pregnant and 175905 non-pregnant women with SARS-CoV-2 infection, pregnant women had a higher risk of death (OR: 1.84, 95% CI: 1.26-2.69), pneumonia (OR: 1.86; 95% CI: 1.60-2.16) and ICU admission (OR: 1.86; 95% CI 1.41-2.45) after adjusting for background demographic and medical factors.[7]

Similarly, a recent systematic review including 11,580 pregnancies complicated by suspected or confirmed COVID-19, pregnant women had a higher risk of admission to an intensive care unit (OR: 1.62, 95% CI: 1.33-1.96) and invasive ventilation (OR: 1.88, 95% CI: 1.36-2.60). Advanced maternal age, increased BMI, chronic hypertension and pre-existing diabetes were associated with severe course of the disease in pregnancy. The presence of pre-existing maternal comorbidities was a risk factor for admission to ICU and invasive ventilation. The occurrence of death for any cause in the overall population was 0.1% (73/11580).[20] These figures were confirmed by a recent report from The Centers for Disease Control and Prevention (CDC) from the United States that included over 23,000 pregnant women and over 386,000 non-pregnant women in reproductive age with

symptomatic laboratory-confirmed SARS-CoV-2 infection, showing a higher risk of admission to ICU, need for invasive ventilation, ECMO and death in hospitalized pregnant women with SARS-CoV-2 infection.[21]

These findings highlight the need for a thorough follow-up of pregnant women with SARS-CoV-2 infection in order to identify those cases at higher risk of developing the most severe spectrum of the disease.

Bottom line: *Pregnancy carries a higher risk of severe SARS-CoV-2 infection compared to the non-pregnant population, including pneumonia, admission to ICU and death, mostly after adjusting for potential risk factors for severe outcomes. These risks seems to be higher in hospitalized women.*

Which are the fetal risks of SARS-CoV-2 infection?

From the beginning of the pandemic, several studies have been published to ascertain whether SARS-CoV-2 infection during pregnancy was associated with a higher risk of adverse perinatal outcome compared to unaffected pregnancies.

There is no evidence that SARS-CoV-2 infection during the first trimester of pregnancy increases the risk of early pregnancy loss.[22] Furthermore, SARS-CoV-2 infection does not alter the nuchal translucency or any of the other ultrasound signs used to screen for Trisomy 21 in the first trimester of pregnancy.[23-24] Although encouraging, data from early pregnancy are still limited and mostly refer to non-hospitalized and/or asymptomatic women. Finally, no specific anomaly has been reported to be associated with the infection.

The rates of preterm birth (PTB) have been reported to be higher in the majority of the studies published so far, with an incidence ranging between 15% and 20%. However, most of the data came from both selectively screened symptomatic patients and a smaller number of universally screened, test-positive asymptomatic women, and most of the studies do not specify whether the rate of PTB includes both iatrogenic and spontaneous PTB, thus leading to an overestimation of the role of SARS-CoV-2 infection in the incidence of PTB.[4,6,20] Indeed, reports from both European and American Institutions,[25-27] showed a decrease in the odds of PTB during the pandemic period compared with a similar pre-pandemic time, particularly when focusing on early PTB.

The difference between hospitalized women with COVID-19 and asymptomatic tested-positive women is also important when considering the association between SARS-CoV-2 infection and perinatal mortality. While early data demonstrated a significantly higher risk of perinatal death in women affected by COVID-19,[4,28] in a recent report from the overall population of pregnant patients with laboratory-confirmed SARS-CoV-2 infection stillbirth occurred in 0.4% of cases, that is not higher than the background risk.[29] These data were also confirmed in a recent systematic

meta-analysis comparing adverse pregnancy outcomes in pregnant women with and without SARS-CoV-2 infection that showed that the incidences of intrauterine fetal demise and neonatal death were similar among individuals who tested positive versus negative for SARS-CoV-2, when admitted to labor and delivery.[30]

Bottom line: *The risk of miscarriage does not appear to be increased in women with SARS-CoV-2. Evidence is conflicting when focusing on PTB and perinatal death, but these risks are generally higher only in symptomatic, hospitalized women.*

What is the risk of vertical transmission of SARS-CoV-2 infection?

The risk of vertical transmission, defined as the transmission of SARS-CoV-2 from the mother to the fetus or the newborn, is generally low.

A recent systematic review of 39 cohort or case series studies including 936 newborns from mothers affected by COVID-19 showed that the pooled proportion of vertical transmission was 3.2%, with 27 neonates tested positive for SARS-CoV-2 infection by nasopharyngeal swab. A subgroup analysis based on the study location showed a similar rate of vertical transmission when comparing studies from China with those from outside China (2.0% vs 2.7%). Furthermore, SARS-CoV-2 RNA was found in 2.9% of neonatal cord blood samples, in 7.7% of placenta samples, and in 9.7% of fecal or rectal swabs, while no viral RNA was found in amniotic fluid or urine samples.[31]

Bottom line: *The risk of vertical transmission, defined as the transmission of SARS-CoV-2 from the mother to the fetus or the newborn, is generally low (about 3.2%).*

Are fetal invasive procedures safe in women with SARS-CoV-2 infection?

There is no consistent data yet indicating that pregnant women affected by SARS-CoV-2 infection undergoing invasive procedures for fetal diagnosis and therapy are at higher risk of vertical transmission or adverse fetal outcomes, compared to the background risk.[32-33] The largest body of evidence of the potential effect of invasive procedure in pregnancies complicated by infectious diseases come from the past experience with human immunodeficiency virus and hepatitis.[34] In such women, especially if under antiviral therapy, the risk of vertical transmission following amniocentesis does not appear to be higher compared to women not undergoing invasive testing, particularly if the viral load is undetectable, although this evidence is limited by the small number of cases reported in the published literature. In case a pregnant woman affected by SARS-CoV-2 infection who requires invasive testing for an increased risk of aneuploidy based upon the combined screening test, it is reasonable to postpone the test in the second trimester or until the patient is tested negative. In case an invasive procedure is needed, it is preferable to opt for an amniocentesis

rather than chorionic villus sampling in view of the theoretical lower risk of admixture of maternal and fetal blood. Conversely, invasive testing should not be postponed in case of severe fetal anomalies strongly associated with aneuploidies, increased nuchal translucency or positive results at the non-invasive prenatal diagnosis suggesting a major chromosomal anomaly. Likewise, there should be no delay in case of acute fetal conditions requiring prompt prenatal intervention, such as twin to twin transfusion syndrome, the parents should be reassured that the risk of adverse outcome due to the peculiar fetal condition significantly exceeds that from maternal to fetal transmission of the virus.

Bottom line: *Fetal invasive procedures are generally safe in women with SARS-CoV-2 infection although the evidence is still limited. If required, amniocentesis is the most reasonable option. No delay should be undertaken in case of major structural anomalies or if a fetal therapeutic procedure is needed.*

What is the optimal therapeutic strategy in symptomatic women with SARS-CoV-2 infection?

The main symptoms of COVID-19 in pregnant women are similar to those observed in non-pregnant women with COVID-19 and in the general population.

In case of pregnant women suffering from COVID-19, drugs should be selected by interdisciplinary medical personnel, taking into account the safety of the drug for the pregnant woman and the fetus. A recent review focusing on the use of steroids in the management of pregnant women with COVID-19 concluded that only pregnant patients with an appropriate indication for oxygen therapy (such as persistent SpO2 values below 94%) should be considered for steroid therapy,[35] as the use of steroids was unsuccessful in patients not on oxygen therapy in the RECOVERY trial.[36]

In this scenario, the authors suggest a course of dexamethasone over 2 days (6 mg intramuscularly every 12 hours for four doses) when steroids are required for both fetal lung maturity and COVID-19, and then dexamethasone should be replaced with methylprednisolone (a total of 32 mg/d of methylprednisolone orally or intravenously, once a day or in divided doses) to complete a 10-day course.[35]

For women who are mildly symptomatic, or moderately symptomatic who require analgesic medication other than acetaminophen, nonsteroid anti-inflammatory drugs (NSAIDs) might be used if there are no other contraindications, according to the Society of Maternal Fetal Medicine (SMFM),[37] well aware that the inhibition of prostaglandin synthesis by NSAIDs in the third trimester may be related to a premature closure of the ductus arteriosus.

Data from non-pregnant adult patients showed that Tocilizumab reduced the chance of progression to the composite outcome of mechanical ventilation or death in hospitalized patients with Covid-19

pneumonia who were not receiving mechanical ventilation.[38] Furthermore, based on encouraging data coming from RCTs on the safety and effectiveness of Remdesivir in patients with severe course of COVID-19, the Food and Drug Administration (FDA) approved Remdesivir for hospitalized children ≥12 years and adults with COVID-19, regardless of disease severity.[39]

However, few studies have explored the role of antiviral drugs, such as Remdesivir, or other medications, such as monoclonal antibody therapies, in treating pregnant women infected with SARS-CoV-2, but due to the paucity of data, these drugs should not be broadly used as first line treatments, in the absence of specific clinical indications.

Depending on the severity of the disease, oxygen supplementation may be performed through the nasal cannula; however, intubation, mechanical ventilation, or extra-corporal membrane oxygenation may also be necessary in order to maintain SpO2 at or above 94/95%.

Bottom line: *Steroids should not be avoided if clinically indicated, preferring dexamethasone (6 mg intramuscularly every 12 hours for four doses) and then methylprednisolone (a total of 32 mg/d of methylprednisolone orally or intravenously, once a day or in divided doses) for a total of 10-day course. NSAIDs might be used if there are no other contraindications. Other drugs should not be considered as first line treatments, due to the paucity of data. Oxygen supplementation should aim at maintaining SpO2 at or above 94/95%.*

Should pregnant women affected by SARS-CoV-2 infection receive prophylactic anticoagulation?

There is an ongoing evidence suggesting a higher risk of thromboembolism in pregnant compared to non-pregnant women affected by SARS-CoV-2 infection.[40] Clinical data published in the early stages of the pandemic had shown elevated D-dimer levels (0.5 mg/L or higher) in 4.2% of patients with non-severe disease and in 59.5% of patients with severe disease,[41] in addition to the presence of other signs of activation of the clotting system, including a mild thrombocytopenia and a moderately prolonged time of prothrombin. A recent systematic review including 1063 pregnant women with a confirmed diagnosis of SARS-CoV-2 infection reported that arterial and/or venous thrombosis occurred in 0.28%, while disseminated intravascular coagulation in 0.66% of cases.[42]

Severe infection seems to represent the major risk factor for the occurrence of thromboembolic disorders. In a series including 1219 pregnant women affected by SARS CoV-2 infection, the occurrence of venous thromboembolism was 6.0% in severe, 0.2% in mild to moderate and 0% in asymptomatic cases, respectively.[43]

Although the pathophysiology of thromboembolism in patients affected by SARS-CoV-2 infection has not been completely elucidated yet, platelet hyperreactivity related to viral mediated endothelial inflammation, in addition to hypercoagulability associated with increased concentrations of coagulation factors, acquired antiphospholipid antibodies, and decreased concentrations of endogenous anticoagulant proteins seem to play a major role.[44]

Since pregnancy itself carries an increased risk of thrombosis, thromboprophylaxis is an important issue to deal with in the management of pregnant women with SARS-CoV-2. The decision to undertake prophylactic thromboprophylaxis in these patients should be take into account several factors including hospitalization, comorbidities, severity of the disease and the timing of delivery.

Asymptomatic or mildly symptomatic patients, those who do not warrant hospitalization for the infection or those who are hospitalized for reasons other than COVID-19 do not require anticoagulation.

Pregnant women hospitalized with severe SARS-CoV-2 disease have all three Virchow risk factors for venous thromboembolism: hypomobility, endothelial activation associated to the inflammation and the prothrombotic status that is typical of pregnancy. This subset of women should therefore undergo thromboprophylaxis throughout the time of hospitalization and at least until discharge. Low molecular weight heparin (LMWH) at prophylactic dosage (i.e. Enoxaparin 40 mg subcutaneously once daily) is the drug of choice for thromboprophylaxis in pregnant women with SARS-CoV-2 infection, unless delivery is expected within 12 hours. If the woman was already on heparin for other reasons, this should not be discontinued.[45]

Bottom line: *Asymptomatic or mildly symptomatic patients, those who do not warrant hospitalization for the infection or those who are hospitalized for reasons other than* SARS-CoV-2 *do not require anticoagulation. Pregnant women hospitalized with severe course of* SARS-CoV-2 *disease should undergo prophylactic thromboprophylaxis throughout the time of hospitalization and at least until discharge, preferably LMWH.*

What is the optimal follow-up of women after SARS-CoV-2 infection?

Even during the infection period, repeated elective ultrasound examinations should be used prudently and only when this use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient.

To date, there are no evidence-based data to guide antenatal care following SARS-CoV-2 infection. The optimal follow-up of these women is mainly based on gestational age at infection, maternal clinical and biochemical symptoms and signs and the presence of risk factors and/or comorbidities other than SARS-CoV-2 infection.

RCOG recommends that women recovering from mild or moderate symptoms of COVID-19 should be encouraged to attend antenatal, scheduled appointments with no specific, additional care based only of the previous infection. As fetal growth restriction (FGR) has been reported in few studies, it would be reasonable to perform an ultrasound scan to rule out any growth disorder.[45]

For women who have recovered from a period of serious or critical illness with COVID-19 and have been hospitalized for supportive therapy, the follow-up should be similar to that provided to any similarly ill pregnant woman and the ongoing antenatal care should be planned together with a maternal fetal specialist before the discharge, offering at least a fetal growth scan about 14 days after recovery from their illness (or >21 days from prior biometry ultrasound), unless there is a pre-existing clinical reason for an earlier scan.[45-46]

However, a recent study assessing the growth and Doppler's trend in pregnancies complicated by SARS-CoV-2 infection did not report a higher risk of FGR due to impaired placental function or Dopplers anomalies in these women.[47]

In those settings where is feasible, telehealth could be a reasonable choice for follow-up visits.[48]

Bottom line: *Women recovering from mild or moderate symptoms of COVID-19 should be encouraged to attend antenatal, scheduled appointments, undergoing ultrasound scan to rule out fetal growth disorder. Hospitalized women who have recovered from a period of serious or critical illness with COVID-19 should be offered at least a fetal growth scan about 14 days after recovery from their illness (or >21 days from prior biometry ultrasound) and scheduling other appointments with a maternal fetal medicine specialist before discharge. Telehealth is reasonable, when feasible.*

What is the optimal time of delivery of women with SARS-CoV-2 infection?

SARS-CoV-2 infection in an otherwise well woman is not an indication to expedite birth, in the absence of any other obstetric indications, and therefore timing of delivery should be dictated only by maternal and fetal conditions, as well as by gestational age and the presence of other maternal and fetal condition complicating pregnancy that represents an indication for earlier, planned delivery regardless of SARS-CoV-2 infection.[45-46,49]

In asymptomatic or mildly symptomatic women tested positive for SARS-CoV-2 infection at full term (i.e. ≥39 weeks of gestation), the choice of the timing of delivery should be planned balancing the possibility of worsening clinical conditions with expectant management, and therefore it might be reasonable to consider delivery in this scenario.[46]

Although there is no robust data on which type of cervical ripening agent (mechanical vs pharmacological) should be preferred in those women requiring induction of labor, using two

methods (i.e. mechanical and misoprostol or mechanical and oxytocin) may decrease the time from induction to delivery, compared with using one agent only.

In case of severe course of disease, timing of delivery is a delicate management decision that should be individualized mainly according to maternal symptoms.

To date, there is no clear consensus on a proper timing of delivery for critically ill women, but the general opinion is that preterm delivery might be considered if this could putatively improve maternal conditions.[46]

Pregnant women with COVID-19 related pneumonia might benefit from early delivery (i.e. around 34 weeks) in order to avoid the deterioration of maternal condition and the subsequent fetal exposure to maternal hypoxia, as well as to facilitate respiratory support (i.e. prone position).

Finally, in women admitted to ICU and in particular those requiring mechanical ventilation, 32-to-34-week range have been claimed by several experts as an adequate timing of delivery, balancing risks and benefits for both the mother and the fetus.

The high burden of complications due to prematurity in preterm deliveries before 32 weeks of gestation is a relative contraindication to expeditious delivery, unless strictly required by maternal and/or obstetric complications.

Bottom line: *In asymptomatic or mildly symptomatic women tested positive for SARS-CoV-2 infection at full term (i.e. ≥39 weeks of gestation), induction of labor might be reasonable. To date, there is no clear consensus on the timing of delivery of critically ill women; some authors suggest earlier delivery in pregnant women with COVID-19 related pneumonia (i.e. 34 weeks) or in women admitted to ICU and requiring mechanical ventilation (i.e. around 32-34 weeks) to avoid deterioration of maternal condition and the fetal exposure to maternal hypoxia.*

What is the optimal mode of delivery of women with SARS-CoV-2 infection?

SARS-CoV-2 infection is not an indication for cesarean delivery (CD), and therefore mode of delivery should not be influenced by the presence of COVID-19, unless a critical maternal condition requires an urgent intervention for birth.[45,49-50]

In a systematic review of 49 studies including information on mode of delivery and infant infection status of 655 women and 666 neonates, 2.7% of babies born vaginally were tested positive, compared with 5.3% of those born by CD, thus reaffirming the evidence that CD does not reduce the already low risk for intrapartum vertical transmission.[51]

Although some authors described successful induction of labor in intubated women or during extracorporeal membrane oxygenation (ECMO), the majority of patients with severe and critical

course of the disease undergo CD in a multidisciplinary setting involving at least maternal-fetal medicine specialists, neonatologists and intensivists.[52-53]

Data on perinatal transmission available to date do not preclude the use of forceps or vacuum when indicated.[37]

COVID-19 is not a contraindication to neuraxial anesthesia. Early epidural analgesia for labor should be considered to mitigate risks associated with general anesthesia and to reduce cardiopulmonary stress.[37]

Bottom line: *SARS-CoV-2 infection is not an indication for CD, and mode of delivery should not be influenced by the presence of COVID-19. If CD is needed in patients with severe and critical course of the disease, it should be performed in a multidisciplinary setting. Operative delivery with forceps or vacuum is allowed, in presence of obstetrical indication. COVID-19 is not a contraindication to neuraxial anesthesia.*

What is the optimal type of monitoring in women with SARS-CoV-2 infection in labor?

In women with no or few symptoms, management of labor should follow routine, evidence-based guidelines for both first and second stage of labor.[54-55]

SMFM suggests that amniotomy may still be utilized for labor management as clinically indicated, given the reassuring (but limited) data on vertical transmission, since SARS-CoV-2 has rarely been detected in vaginal secretions or amniotic fluid.[37]

Since few reports described fetal heart rate changes in women with SARS-CoV-2 infection, it is reasonable to consider women with SARS-CoV-2 infection as "high-risk pregnancies" and as such to be managed with continuous electronic fetal heart rate monitoring, as suggested by the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE).[56-57]

Shortening the second stage of labor has been suggested by a few authors in order to reduce the risk of respiratory secretion exposures to accompanying partner and medical personnel and it might be intuitively achieved by immediate pushing in the second stage,[58] although deep breathing and maternal expulsive efforts may increase exposure to the patient's respiratory secretions, too.[59]

Bottom line: *In women with no or few symptoms, management of labor should follow routine, evidence-based guidelines. Amniotomy may be utilized. Continuous electronic fetal heart rate monitoring might be reasonable, as well as shortening the second stage of labor.*

Are skin-to-skin, rooming-in and breastfeeding allowed for women with SARS-CoV-2?

Skin to skin (when the naked infant is prone on the mother's bare chest immediately after delivery) and rooming in (allowing mothers and infants to remain together 24 hours a day) policies are usually encouraged to create a baby-friendly environment in the healthcare setting and mostly to increase breastfeeding rates and duration.[60]

At the beginning of pandemic, many centers did not allowed these policies, as well as the presence of a birth partner during labor.

To date, data shows no difference in risk of SARS-CoV-2 infection to the neonate whether a neonate is cared for in a separate room or remains in the mother's room, and therefore ACOG recommends rooming-in combined with safety measures to minimize the risk of transmission, such as wearing a mask and practicing hand hygiene before any contact with the newborn.[61]

SARS-CoV-2 infection is not a contraindication to breastfeeding. As evidence from observational studies showed that breastfeeding is associated with short- and long-term health benefits both for the mother and the child, breastfeeding should be encouraged also for mother with COVID-19, taking all possible precautions to avoid spreading the virus to the infant, including hand hygiene and wearing a mask or cloth face covering, if possible, while breastfeeding.[61]

In a recent update on newborn care, the WHO has recommended that, regardless of COVID-19, mothers and infants should remain together, breastfeed, practice skin-to-skin contact and kangaroo mother care, and rooming-in day and night while applying necessary infection prevention and control measures.[62]

Bottom line: *Regardless of COVID-19, mothers and infants should remain together, breastfeed, practice skin-to-skin contact and kangaroo mother care, and rooming-in day and night while applying necessary infection prevention and control measures.*

Can pregnant women undergo vaccination for SARS-CoV-2?

The vaccination to prevent SARS-CoV-2 infection during pregnancy is currently a "hot topic". Pregnant women are often underrepresented in clinical research and excluded from trials solely for their pregnancy status, and have been excluded from the trials for vaccination against SARS-CoV-2 infection.

Two types of vaccines have been currently approved by both the Food and Drug Administration and the European Medicines Agency (Pfizer-BioNtech mRNA vaccine and Moderna mRNA-1273 vaccine).

In a recent Practice Advisory, ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on Advisory Committee on Immunization Practices (ACIP)-recommended priority groups,[63] and therefore several pregnant women have already undergone vaccination in the United States.

Conversely in United Kingdom, based on the Joint Committee on Vaccination and Immunisation recommendations, RCOG does not advocate for routine use of COVID-19 vaccines during pregnancy in the absence of safety data - although specifying that the available data do not indicate any safety concern or harm to pregnancy - while considers as reasonable the option of vaccination for pregnant woman defined as clinically extremely vulnerable, as well as for those who are frontline health or social care workers.[64]

At the time of writing, about 20000 pregnant women in the United States received Pfizer-BioNTech vaccine and no-severe acute flag was reported, and therefore also the International Federation of Gynecology and Obstetrics (FIGO) has recently declared that there are no risks – actual or theoretical – that would outweigh the potential benefits of vaccination for pregnant women, thus supporting COVID-19 vaccination to pregnant and breastfeeding women.[65]

Finally, CDC has just released the first, reassuring data coming from the "V-safe" pregnancy registry which show no significant difference in pregnancy outcomes such as miscarriage, perinatal mortality or congenital anomalies, in pregnant women undergoing vaccination, compared with the background risk.

Thus, despite the small sample size of data on safety of COVID-19 vaccine in pregnancy, it seems reasonable to offer the possibility of the vaccine after an accurate counselling on both the potential risk of a severe course of the disease and the unknown risk of fetal exposure to the vaccine.

Bottom line: *Several pregnant women have already undergone vaccination, mostly in the United States where ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination. First reports from the United States show no significant difference in pregnancy outcomes in pregnant women receiving SARS-CoV-2 vaccination during pregnancy, compared with the background risk. RCOG suggests more caution, as safety data are lacking. Based on the small sample size of data on safety of COVID-19 vaccine in pregnancy, it seems reasonable to offer the possibility of the vaccine after an accurate counselling on both the potential risk of a severe course of the disease and the unknown risk of fetal exposure to the vaccine.*

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67. **Table 1. Summary of evidence-based answers**

CLINICAL QUESTION	*UP-TO-DATE ANSWER*	*QUALITY OF EVIDENCE**
What is SARS-CoV-2 infection and how can it be diagnosed?	SARS-CoV-2 is a zoonotic Coronavirus that crossed species to infect humans, causing a disease called COVID-19. The gold standard for the diagnosis of SARS-CoV-2 infection is RT-PCR assay of nasal and pharyngeal swab specimens.	High
Are pregnant women more likely to get SARS-COV-2 infection?	Despite a potentially higher risk of acquiring SARS-CoV-2 infection compared to the non-pregnant population, no additional specific recommendations to avoid exposure are needed in pregnancy.	Moderate
Which are the most common signs and symptoms of SARS-CoV-2 infection in pregnancy?	Fever, cough, lymphopenia and raised C reactive protein levels are the most common clinical symptoms and laboratory signs of SARS-CoV-2 infection in pregnancy.	Moderate
Are pregnant women more likely to develop severe SARS-CoV-2 infection compared to the non-pregnant population?	Pregnancy carries a higher risk of severe SARS-CoV-2 infection compared to the non-pregnant population, including pneumonia, admission to ICU and death, mostly after adjusting for potential risk factors for severe outcomes. These risks seems to be higher in hospitalized women.	Moderate
Which are the fetal risks of SARS-CoV-2 infection?	The risk of miscarriage does not appear to be increased in women with SARS-CoV-2. Evidence is conflicting when focusing on PTB and perinatal death, but these risks are generally higher only in symptomatic, hospitalized women. Perinatal mortality is slightly increased, mostly in hospitalized women.	Low to moderate
What is the risk of vertical transmission of SARS-CoV-2 infection?	The risk of vertical transmission, defined as the transmission of SARS-CoV-2 from the mother to the fetus or the newborn, is generally low (about 3.2%).	Low to moderate
Are fetal invasive procedures safe in women with SARS-CoV-2 infection?	Fetal invasive procedures are generally safe in women with SARS-CoV-2 infection although the evidence is still limited. If required, amniocentesis is the most reasonable option. No delay should be undertaken in case of major structural anomalies or if a fetal therapeutic procedure is needed.	Very low to low
What is the optimal therapeutic strategy in symptomatic women with SARS-CoV-2 infection?	Steroids should not be avoided if clinically indicated, preferring dexamethasone (6 mg intramuscularly every 12 hours for four doses) and then methylprednisolone (a total of 32 mg/d of methylprednisolone orally or intravenously, once a day or in divided doses) for a total of 10-day course. NSAIDs might be used if there are no other contraindications. Other drugs should not be considered as first line treatments, due to the paucity of data. Oxygen supplementation should aim at maintaining SpO2 at or above 94/95%.	Low
Should pregnant women affected by SARS-CoV-2 infection receive prophylactic anticoagulation?	Asymptomatic or mildly symptomatic patients, those who do not warrant hospitalization for the infection or those who are hospitalized for reasons other than SARS-CoV-2 do not require anticoagulation. Pregnant women hospitalized with severe course of SARS-CoV-2 disease should undergo prophylactic thromboprophylaxis throughout the time of hospitalization and at least until discharge, preferably LMWH.	Low
What is the optimal follow-up of women with SARS-CoV-2 infection?	Women recovering from mild or moderate symptoms of COVID-19 should be encouraged to attend antenatal, scheduled appointments, undergoing ultrasound scan to rule out fetal growth disorder. Hospitalized women who have recovered from a period of serious or critical illness with COVID-19 should be offered at least a fetal growth scan about 14 days after recovery from their illness (or >21 days from prior biometry ultrasound), scheduling other appointments with a maternal fetal medicine specialist before discharge. Telehealth is reasonable, when feasible.	Low
What is the optimal time of delivery of women with SARS-CoV-2 infection?	In asymptomatic or mildly symptomatic women tested positive for SARS-CoV-2 infection at full term (i.e. ≥39 weeks of gestation), induction of labor might be reasonable. To date, there is no clear consensus on a proper timing of delivery for critically ill women; some authors suggest earlier delivery in pregnant women with COVID-19 related pneumonia (i.e. 34 weeks) or in women admitted to	Low

	ICU and requiring mechanical ventilation (i.e. around 32-34 weeks) to avoid deterioration of maternal condition and the fetal exposition to maternal hypoxia.	
What is the optimal mode of delivery of women with SARS-CoV-2 infection?	SARS-CoV-2 infection is not an indication for CD, and mode of delivery should not be influenced by the presence of COVID-19. If CD is needed in patients with severe and critical course of the disease, it should be performed in a multidisciplinary setting. Operative delivery with forceps or vacuum is allowed, in presence of obstetrical indication. COVID-19 is not a contraindication to neuraxial anesthesia	Moderate
What is the optimal type of monitoring in women with SARS-CoV-2 infection in labor?	In women with no or few symptoms, management of labor should follow routine, evidence-based guidelines. Amniotomy may be utilized. Continuous electronic fetal heart rate monitoring might be reasonable, as well as shortening the second stage of labor.	Low to moderate
Are skin-to-skin, rooming-in and breastfeeding allowed for women with SARS-CoV-2?	Regardless of COVID-19, mothers and infants should remain together, breastfeed, practice skin-to-skin contact and kangaroo mother care, and rooming-in day and night while applying necessary infection prevention and control measures.	Low
Can pregnant women undergo vaccination for SARS-CoV-2?	Several pregnant women have already undergone vaccination, mostly in the United States where ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination. First reports from the United States show no significant difference in pregnancy outcomes in pregnant women receiving SARS-CoV-2 vaccination during pregnancy, compared with the background risk. RCOG suggests more caution, as safety data are lacking. Based on the small sample size of data on safety of COVID-19 vaccine in pregnancy, it seems reasonable to offer the possibility of the vaccine after an accurate counselling on both the potential risk of a severe course of the disease and the unknown risk of fetal exposure to the vaccine.	Low

* Quality of the evidence was assessed with the use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines. This system classifies the quality of evidence in one of four levels: high (further research is very unlikely to change our confidence in the estimate of effect); moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate); and very low (any estimate of effect is very uncertain).[66]