

ISIDOG recommendations concerning COVID-19 and pregnancy.

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Abstract

Providing guidelines to health care workers during a period of rapidly evolving viral pandemic infections is not an easy task, but extremely necessary to coordinate appropriate action so all patients get the best possible care given the circumstances they are in.

With these ISIDOG guidelines we aim to provide detailed information how to diagnose and manage a pregnant women living in a pandemic of COVID-19.

Pregnant women need to be considered as high risk for COVID-19 infection, and if suspected or proven infected with the virus, they require special care in order to increase their survival rate and the wellbeing of their babies.

Protection of healthcare workers in such specific care situations as well as maximal protection of mother and child are envisioned.

1. Introduction.

These recommendations are based on currently available published or in press peer reviewed case series for COVID-19 and pregnancy (English only) and based on the following guidelines: [Centre for Disease Control \(CDC\) guidelines](#) (1), [Royal College of Obstetrics and Gynaecology \(RCOG\) guidelines](#) (2) and [Australian and New Zealand Intensive Care Society \(ANZICS\) guidelines](#) (3).

Currently little is known about the exact management of pregnant women in COVID-19 endemic settings. Based on an extensive literature review, the ISIDOG (International Society of Infectious Disease in Obstetrics and Gynecology) provides herewith recommendations to provide guidance for health care professionals dealing with pregnant patients and those implemented in writing national health policies. We provide an international approach, but every country will need to adopt and follow their own country specific guidelines. The recommendations are written with the current available knowledge, this might change with evolving research.

The term 'COVID-19' will be used to refer to both SARS-CoV-2, the corona-virus itself, and to the disease it causes. SARS-CoV-2 is a non-segmented, positive sense RNA virus. It is part of the family of coronaviruses (CoV) composed of 4 viruses that cause 'common cold', the Severe Acute Respiratory Syndrome (SARS) CoV and Middle East Respiratory syndrome (MERS) CoV. The latter 2 previously caused epidemics with high morbidity and mortality, especially in pregnant women (4-9). COVID-19 is most closely related to SARS. It binds via the angiotensin-converting enzyme 2 (ACE2) receptor located on type II alveolar cells and intestinal epithelia (10).

The incubation time of COVID-19 virus is at a median of 4 days (interquartile range of 2-7 days), with a range up to 14 days (11). Generally it causes a flu-like illness with constitutional signs and symptoms like myalgia and fever, and typical upper and, less frequently, lower respiratory symptoms (viral pneumonia). The latter usually presents with cough, dyspnea and fever (12-16). About 10% of

cases present initially with gastro-intestinal symptoms only (nausea, diarrhea) (17). Anosmia is reported to be an early symptom (18). However asymptomatic transmission has also been reported (11).

In the general population hospitalization occurs in about 23% of known COVID-19 positive cases (might be an overestimation since the amount of screening varies within each country) and among these the mortality rate is around 1-2% (higher in Italy due to lack of resources and lower in Germany and South Korea, though depending on country specific reporting). Most fatalities are due to acute respiratory distress syndrome (ARDS) and multi-organ failure. High morbidity and mortality is seen in elderly (>65 years of age) and patients with (multiple) co-morbidities (13, 16), see **Table 1** for an overview of high risk profiles. Since first cases were reported in November 2019 from the outbreak in the Hubei province in China, a worldwide pandemic emerged with a high disease burden and an increasing death toll, paralyzing the economy, and pressuring social security networks as well as health care systems.

2. Susceptibility of pregnant women to COVID-19: Are pregnant women more likely to get infected?

Although pregnant women are not immune-compromised in the classic sense, immunologic changes of pregnancy may induce a state of increased susceptibility to certain intracellular pathogens, especially viruses, intracellular bacteria, and parasites (19, 20). Measles, primary varicella, influenza, variola (small pox), lassa fever, ebola and SARS are all examples of viral infections, where pregnant women are more susceptible to be infected and develop more severe complications of the disease and higher mortality compared to the non-pregnant population. (4, 5, 19, 21-25).

As for COVID-19, the average number of people that an infected person transmits the virus to is between 2 and 3 (range 2,5-2,9), which is somewhat higher than seasonal influenza (26). This number is a reflection of both the virus' characteristics and infection potential, as well as the human behavior (e.g. social distancing or not). The virus is transmitted by droplet-infection as well as surface-contact (face-to-fomite), certain data describing persistence of viable virus on surfaces up to four days (11, 27). Airborne transmission is still controversial and estimated possible (especially in aerosol generating procedures) until further evidence is available (28, 29). Asymptomatic people can also transmit the disease, for that reason, in China, all pregnant women are advised to wear face masks whenever going out of their homes (11).

Guideline 1. Every pregnant woman is considered high risk, as their susceptibility due to altered immune response may be higher, disease course is more severe and delivering critical care is more difficult (see later). All pregnant women, in order to prevent infection, should take extensive preventative measures: hand hygiene and disinfecting surfaces with >60% ethanol and strictly adhere to measures of social distancing when interacting with other people (30). This also accounts for their (house)partners.

Guideline 2. As for pregnant women working in high risk exposure settings (labor and delivery, operating theatres, respiratory wards, intensive care or high dependency units), work removal or re-orientation to low risk exposure settings is preferred. The exposure risk assessment should be done by every professional group individually and depending on the local endemic statistics.

3. Maternal outcomes: are pregnant women once infected with COVID-19 at risk for developing more severe disease?

Limited data is available of maternal outcomes in COVID-19 infection in pregnancy. Pregnant women are suspected to be more vulnerable for viral pneumonitis and have more severe course of the disease when reviewing data from viral illnesses causing epidemics such as influenza, 'severe acute respiratory syndrome' (SARS) and 'Middle East respiratory syndrome' (MERS) (4-6, 19, 22, 31-33). Compared to non-pregnant women, these illnesses significantly increased maternal morbidity and mortality, especially in the second and third trimesters of gestation. Several explanations have been suggested such as physiological altered cellular immune response in pregnancy, and changes in pulmonary functions (19, 20). We would like to add to this the difficulty of managing severe pneumonia in pregnancy, such as intubation and mechanical ventilation, especially in 3rd trimester where often (premature) delivery is imminent (34, 35). Also ventral position during ventilation, which is often required in severe COVID-19 cases, is not easy or not at all feasible in late pregnancy.

Current data available on second and third trimester pregnancies with confirmed SARS-Cov-2/COVID-19 positivity (review of total 32 cases in four case report series) have not reported maternal deaths (36-39). In one case, a 31 year old woman at gestational age (GA) of 34 weeks, multi-organ failure and need for mechanical intubation was diagnosed, ultimately leading to extra-corporeal membranous oxygenation (ECMO) (37). One patient in Chen et al. series had concomitant pre-eclampsia at 36 weeks and was delivered by cesarean section without need for intensive care hospitalization.

Current data suggest lower morbidity and mortality for pregnant women in COVID-19 than during the SARS epidemic: for 6,3% (2/32) intensive care admissions versus 83% (5/6) and no mortality (0/32) versus 33% (2/6), respectively. The disease course tends to be rather mild and similar to non-pregnant peers, generally presenting with flu-like constitutional symptoms (fever, fatigue, myalgia), cough and occasionally dyspnea (17, 36, 37). Some pregnant patients present with laboratory abnormalities such as lymphopenia, thrombocytopenia and elevated liver enzymes (17, 36, 37). Based on these limited data, we find pregnant women infected with COVID-19, to have similar rates of developing critical illness with need for intensive care admissions (6,3%) as the general population (5%) (40).

There are no reports of maternal outcomes in first trimester pregnancies, but it may be too early since the start of the outbreak.

Guideline 3. With the limited evidence available at present, pregnant women seem to have a similar course of the disease, compared to the general population. However, previous outbreaks with similar respiratory viruses have taught us that pregnant women were not only more vulnerable, but also had a more severe course of the disease. Critical care management of pregnant patients is more difficult (airway management etc.). Therefore, until further data are available, pregnant patients above 24 weeks gestational age (GA), should be strictly protected from becoming infected (see above). Also, we advise pregnant women to be isolated from high risk exposure jobs (such as certain health care workers) until further evidence is available.

4. Pregnancy complications: what are the risks for the pregnancy?

Limited data is available of pregnancy outcomes in COVID-19 infection cases.

During the SARS epidemics an increased risk of miscarriage was reported during the first trimester in 7 proven infected cases (4/7 miscarriages). When evaluating the data in detail, three of the four were as early as 3-4 weeks of gestation (4, 32). So far, for COVID-19 no first trimester cases have been described, but further follow-up and research is awaited.

For second and third trimester outcomes we summarized the literature review of 31 singleton pregnancies at GA 25-39 weeks (**Table 2**)(36-39). One third of COVID-19 positive patients (10/31) presented with preterm premature rupture of membranes (PPROM) and preterm labor and in 35,4% (11/32) fetal distress was reported. It is unclear how much of this is directly related to COVID-19 infection, as in proven cases of a new infection, alertness should be increased. Maternal hypoxemia is suggested to be a possible cause of these complications. On the other hand fever could also explain the increased risk of PPRM and preterm labor. One case of intra-uterine fetal death is reported, in a case where the mother developed multi-organ failure, requiring intensive care hospitalization and extra-corporeal membranous oxygenation (ECMO). When reviewing the data we note a preterm birth rate of 53,6% (15/28). In COVID-19 positive patients, a cesarean section rate of 96,4% was seen, possibly indicating that iatrogenic reasons (obstetrician's fear) can also be a factor contributing to prematurity.

Intra-uterine fetal growth restriction (IUGR) has so far not been reported associated with COVID-19 infection. Although IUGR is a known consequence of chronic maternal hypoxia, the effects of short and transient hypoxia in COVID-19 are unknown (41). During the SARS-epidemic, small for gestational age neonates were reported in 2 women contracting the infection at 28 and 30 weeks GA and delivering at 33 and 37 weeks respectively (4). In the reported COVID-19 patients, delivery generally occurred within one week of diagnosis, so long term effects of maternal hypoxemia on fetal growth can hardly be assessed (36-39).

Guideline 4. Preterm delivery, PPRM and intra-uterine fetal distress are possible complications of maternal COVID-19 infection, possibly caused by maternal hypoxemia. Cesarean section rates are vastly higher than in the general population, partly iatrogenic due to obstetricians insecurity. Further evidence is needed for confirming a causal relation.

Guideline 5. Timing of delivery should be determined by a multidisciplinary team, on a case by case basis, considering maternal and fetal clinical presentation. The prevalence of admissions of COVID-19 positive pregnant patients to an intensive care unit is similar to the general population (around 5%), but high care management >24 weeks pregnancy is more difficult (airway management problems, fetal monitoring etc.). Data currently are too limited to draw definite conclusions.

Guideline 6. Intra-uterine growth restriction could be a possible long term complication in patients recovering from COVID-19 infection, when reviewing information obtained during the SARS epidemic. Information from COVID-19 patients is lacking. Therefore, fetal growth follow-up in COVID-19 infected pregnant patients is warranted. Additional ultrasound evaluation at gestational age 24-28-32-36 weeks with biometry, amniotic fluid measurement and assessment of uterine artery Doppler

pulsatility index and mid-cerebral artery Doppler in case of IUGR <10th percentile) is indicated, unless maternal condition does not allow further expectant management (42, 43).

5. Fetal risk: does vertical transmission occur?

When testing amniotic fluid, cord blood and neonatal throat swabs after 6 deliveries of COVID-19 infected patients, Chen H et al. showed no prove of intra-uterine vertical transmission (36). Additionally Liu et al. showed no 'serological' evidence of vertical transmission in 10 neonates born in their facility. However, the method used for performing serological testing was not described (37). Also Zhu et al. describe 10 neonates (8 singleton, 1 twin) with negative throat swabs for COVID 19, tested with PCR (39). One case report based on positive IgM serology in one neonate suggested intra-uterine infection of the neonate, since maternal IgM does not cross the placenta (44). The neonate was born by cesarean section to an COVID-19 positive mother with positive IgM and IgG antibodies (107.89 AU/mL and 279.72 AU/mL respectively; normal values IgM and IgG <10 AU/mL). The neonate was isolated immediately from the mother and 2 hours post-birth, IgM and IgG titers respectively were 45.83 AU/mL an 140.32 AU/mL. However 5 throat-swabs of the neonate for PCR from 2 hours until 16 days post-birth were performed to prove infection and could not detect COVID-19 virus. No PCR was performed on amniotic fluid, cord blood or placenta . We suspect, based on these findings that intra-uterine infection was unlikely and that the IgG anti-bodies were probably maternal. The IgM could be explained by false positive result, as described before in cases of cytomegalovirus infection(45).

Pathologic review of 3 placentas confirmed positive for COVID-19 patients after delivery by cesarean section showed no signs of villitis and chorioamnionitis, and all three placental samples were negative for the nucleic acid of COVID-19 (46).

Based on these reports, no evidence for intra-uterine vertical transmission for COVID-19 in second and third trimester has been confirmed. These findings in accordance to the findings in SARS-virus infections(47). The expression of angiotensin converting enzyme 2 (ACE-2) receptor, necessary for the viral intra-cellular integration of COVID-19, seems to be weak in all cells of the fetal-maternal interface. This feature is suggested to be a possible explanation for the absence of maternal-fetal transmission across the placenta (10, 48).

Guideline 7. Intra-uterine vertical transmission so far has not been reported with COVID-19, at least when infection occurs between 25-39 weeks of pregnancy. First trimester complications and data on teratology are so far lacking. Based on the assumption that cells on the fetal-maternal interface are less susceptible to COVID-19 infection, we estimate the risk of first trimester complications to be low, but this has to be confirmed. Therefore we advise pregnant patients should be informed about low or non- existent risks for intra-uterine infection by the COVID-19 virus.

6. Mode of delivery and perinatal transmission risk: is vaginal birth safe?

Certain generalized viral infections, such as HIV, predispose to intra-partum neonatal transmission (36, 49). For COVID-19 data are limited. In one case series three neonates were born vaginally (one singleton, one set of twins) and throat swabs for PCR at day one of birth were negative for COVID-19 in all three cases (37). In another report all nine patients underwent cesarean section, vaginal swabs have not been performed (36). One report had vaginal swab testing at birth of a COVID-19 positive patient performed, showing a negative result (50). Data are limited, but do not show an increased risk of perinatal vertical infection when passing through the birth canal.

All indications for cesarean section in the nine cases reported above were maternal, i.e. fear of deterioration of COVID-19 pneumonia (36). Only one case had an additional obstetrical indication for cesarean section (history of two previous cesarean sections) and two others had additional relative risk factors (one with pre-eclampsia and one with history of two intra-uterine fetal deaths). Two cesarean sections were performed for intra-uterine fetal distress, suggested to be related to maternal hypoxemia. In another case report cesarean section was performed at GA 30 weeks for a combination of maternal deterioration and fetal distress (38).

Of the reported neonates of COVID-19 positive mothers, half (4/8) were born preterm. Clinical outcomes in neonates reported seemed to be merely related to prematurity (mostly respiratory distress). One neonate died probably due to severe asphyxia following severe maternal disease with intensive care admission for multiple organ failure (39).

Guideline 8. Vertical transmission from passing through the birth canal is unlikely, but data are limited. Hence, if maternal condition allows this and good fetal surveillance can be assured, vaginal delivery is preferred.

7. Neonatal risks: Can neonates get COVID-19 after birth? Is breastfeeding safe?

7.1 Postpartum transmission to neonates.

According to a Chinese expert consensus paper, two neonates tested positive for COVID-19, the youngest 36 hours old, details on clinical outcomes and follow-up were lacking (51). Another review reported, that three neonates infected with COVID-19 showed fever, cough, vomiting of milk and in two cases dyspnea and otherwise stable vital signs (52). According to the official Xinhua news agency, a neonate tested positive for COVID-19, 30 hours after delivery to a COVID-19 positive mother. This infant had stable vital signs, no fever or cough, but shortness of breath together with abnormal chest radiographs and abnormalities of liver function (53). Considering that vertical intra-uterine infection is unlikely, post-partum droplet and/or contact transmission from parents or care takers to the neonate is the most plausible explanation (11, 27, 54). Whether or not airborne transmission occurs is still controversial (28, 29).

Guideline 9. Postnatal transmission from parents or care takers to the neonate is possible, hence strict hygienic measures, including masks, hand hygiene and social distancing (as far as possible) is advised.

7.2. Breast feeding

Breast milk samples of six COVID-19 positive mothers after giving birth showed negative PCR results (36). Samples of breast milk of two women during the SARS-epidemic were also negative for the virus, although these women had most likely already recovered from the infection at time of birth (31, 32). Guidelines disagree, although breastfeeding is allowed with precaution measures (RCOG). Alternatively isolation of the neonate for 14 days is required in a separate neonatology ward until maternal clinical illness resolves to protect the neonate against postpartum vertical transmission (CDC and Chinese guidelines)(1, 2, 51, 55, 56).

Guideline 10. Vertical transmission via breast milk seems unlikely. Neonates could be more vulnerable for developing (severe) complications of COVID-19 considering their immature immune system. Based on limited data.

Two different approaches are proposed. A: the advantages of mother-child bonding and breastfeeding (with preventative measures such as wearing a surgical mask, hand-hygiene and disinfecting the nipples before breastfeeding) outweigh the possible risk of neonatal infection (with the current limited data suggesting rather mild disease course in neonates) (2). B: partially based on guidelines written after SARS and MERS-epidemics. The neonate is isolated on a neonatal ward for 10-14 days for surveillance, and remains separated from their mother until clinical illness resolves and precaution measures are lifted, preventing breastfeeding. Since transmission through breast milk seems unlikely (see above), pumping milk and bottle-feed can be considered (1, 55, 57). Depending on the availability of further evidence, risks and benefits of both approaches should be offered and explained to the parents for a joint decision.

8. Diagnostics: how to diagnose COVID-19 in pregnancy? Can/should CT-scan be performed?

There appears no reason, that diagnosis of COVID-19 in pregnancy should be different from the general population. The threshold for testing pregnant patients presenting with suspicious symptoms should be low, considering the possibility to provide more close follow up for fetal and maternal complications. Hypoxia does not correlate with auscultation nor with chest imaging. Therefore, pulse oxygen saturation, tachypnea and dyspnea are important clinical signs.

8.1 Polymerase chain reaction (PCR) testing

Ideally, the diagnosis of COVID-19 infection is made by performing nasopharyngeal swabs for PCR testing in people presenting with suspicious symptoms. It is important to note, that while the specificity of this PCR is near 100% (few false positive cases), sensitivity is rather low between 66-80% (58). This could partly be due to sampling error, as deep intranasal and throat swabs are required, but not always easy to obtain. It is estimated that people with more severe disease may have higher viral burden. Likewise sampling early in the disease course may have lower sensitivity than later sampling. Therefore, if the PCR is negative but suspicion for COVID-19 remains, ongoing isolation and re-sampling 24 hours to several days later is imperative. In general two subsequent negative samples, rules out the diagnosis. There is no difference in swabbing or test result accuracy in pregnant versus non-pregnant women.

Guideline 11. The final diagnosis of COVID-19 infection in pregnant women is a deep nasal and/or throat swab for PCR. As sensitivity of PCR is estimated around 75% and thus 25% are false negative, in a suspicious case who tested negative, continued precaution measures should stay in place and a repeat swab after (minimum) 24 hours is imperative. As both maternal and fetal complications can occur, we advise a very low threshold for testing pregnant women.

8.2 Computed Tomography (CT) scanning

There have been reports about high sensitivities when conducting CT scanning for early diagnosis of COVID-19, even surpassing the PCR tests (59). In one study CT scanning was performed in 15 healthcare workers who were exposed to COVID-19 *before* they became symptomatic. Ground glass opacification on CT scan was seen in 14/15 patients. Guan et al. and Ali et al. found that in patients with a confirmed positive COVID-19 PCR, CT-scan was positive in 840/975 cases and 580/601 cases respectively, and thus resulting in sensitivity of 86% and 97% (14, 58). However several problems arise: 1 –Currently precise definition of what constitutes a “positive” CT scan is lacking. 2 – Findings are non specific, as any viral pneumonia can show similar images on CT. 3 – Among patients with constitutional symptoms only (fever, myalgia, malaise etc. but without respiratory symptoms), a CT scan may be less sensitive (around 50%)(60). 4 – Although radiation exposure of CT scanning is low enough not to be harmful for the fetus, especially when protected by lead protection covering the abdomen, the exposure of breast tissue of young women to radiation is known to be harmful, increasing future breast cancer risk (61, 62). A single chest x-ray, mammogram and CT-scan expose the patient to about 0.1 mSv, 0.4mSv and 10mSv respectively. This corresponds to the natural background radiation exposure of 10 days, 7 weeks or more than 3 years respectively (63). When using low dose chest CT the mean effective radiation dose is 1.4 mSv (standard deviation=0.5) and is thus estimated acceptable (64). Several centers are now applying routine low dose chest CT scanning for COVID-19 screening of all patients being admitted to the hospital. This allows detection of COVID-19 positive patients with higher sensitivity (including asymptomatic), and allows faster triage.

Guideline 12. Diagnosis of COVID-19 patients is similar as in non pregnant patients. PCR testing of nasopharyngeal swabs is standard. However, due to low sensitivity of this test, re-testing after minimum 24 hours is advised in case of negative result with suspicious clinical findings. Low dose CT-scanning can also be used as a screening test. Dosages are relatively safe for the pregnancy when abdominal shielding is used. Also, the risks of radiation on the breast tissue are to be balanced against the benefits of higher sensitivity and possibility of early triage of COVID-19 positive patients upon admission in the health care facility.

8.3 Serology testing

Currently no commercial antibody tests are available and approved, and several laboratories are working to develop reliable serology testing. Preliminary results of newly developed ELISA-tests and humoral response have been reported in China and the United States but further research is needed to generalize their findings (65, 66). Using an ELISA-assay with in suspected COVID-19 cases with initial negative qPCR, IgM and IgA antibodies were detected after a median of 5 days (interquartile range IQR 3-6), IgG was detected after 14 days (IQR 10-18). The detection efficiency by IgM ELISA is higher than that of qPCR method after 5.5 days of symptom onset. The positive detection rate is

significantly increased (98.6%) when combining IgM ELISA assay with PCR for each patient as compared with compare with a single qPCR test (51.9%) (65).

As it is currently unknown how long antibodies against COVID-19 last after primo-infection, repetitive antibody testing will be crucial to assess long term immunity in order to develop future vaccines. In addition, several strains with different virulence of COVID-19 have been reported (67, 68). It is not yet known, how fast the virus mutates, creating strains for which previously infected (or vaccinated) people would no longer be immune for. It will be important to include pregnant woman in these future vaccine studies since they are considered a high risk population (47).

Guideline 13. As soon as serology tests for immunity will be available, pregnant women should be tested primarily, and if these tests will be used for assessing vaccine efficacy in future studies, maternal vaccination should be considered early in the design of these studies (provide monoclonal dead vaccines are used).

9. Hospitalization: when to hospitalize a pregnant patient with suspected or confirmed COVID-19?

All pregnant patients with suspected symptoms should undergo testing. Clinical assessment will determine the need for hospitalization while awaiting the test results.

We proposed the following criteria for hospitalization in pregnant women based on Modified Early Obstetric Warning Score (MEOWS), see **addendum 1**, and proposed care for COVID 19 pregnant patients by Peyronnet et al. and Liang H et al. (69-73):

9.1. No hospitalization

Pregnant with **mild disease/no co-morbidities (cfr table 1)** : symptomatic but absence of dyspnea and stable vital signs.

Patient follow up of daily parameters at home: fever, respiratory rate, blood pressure, fetal movements.

Contact by phone with obstetric health care provider every 48 hours for reporting signs and symptoms or earlier in case of subjective deterioration or abnormal parameters based on MEOWS score (**Addendum 1**) .

9.2. Hospitalization on obstetric ward (referral to tertiary centre depending on gestational age, depending on local policy):

Pregnant with **moderate disease or mild disease with comorbidities (Table 1)**

- A) Acute community acquired pneumonia with oxygen requirement*:
 - desaturation <96% O₂ on ambient air.
 - or tachypnea ≥21 respirations/minute on ambient air.
 - or clinical evident signs dyspnea.

OR

- B) Signs of lower respiratory infection without oxygen requirement but with comorbidities (**Table 1**)

Isolation and infection prevention measures to be taken as described below.

9.3. Hospitalization on intensive care ward with consulting obstetric support (refer to tertiary centre depending on gestational age, depending on local policy):

- A) Pregnant with **severe disease**: respiration rate ≥ 30 /min, resting SaO₂ $\leq 93\%$, arterial blood oxygen partial pressure (PaO₂)/ oxygen concentration (FiO₂) ≤ 300 mmHg.

OR

- B) Pregnant with oxygen requirement (cfr supra) and comorbidities. (**Table 1**)

OR

- C) Pregnant with **critical disease**: shock with organ failure, respiratory failure requiring mechanical ventilation or refractory hypoxemia requiring extra-corporal membrane oxygenation.

To be determined and managed on a case by case basis by multidisciplinary team (senior obstetrician, internal medicine specialist/pulmonologist, intensive care specialist, infectious disease specialist).

Guideline 14. Pregnant patients need to be assessed according to their respiratory symptoms severity score and potential presence of co-morbidities. In severe/critical cases, immediate referral to a tertiary centre is indicated.

10. Treatment options: which medications for COVID-19 infection are safe to use when attempting treatment in pregnant patients?

10.1 Corticoids.

Clinical evidence does not support the use of corticoid treatment for COVID-19 related lung injury (74). However short term administration of corticoids (either betamethasone or dexamethasone as per local protocol) intramuscularly to improve fetal lung maturity when preterm delivery is imminent should be considered and is not harmful (73).

10.2 Anti-retrovirals.

Application of antiviral treatment should be implemented by per region specific protocols. All protocols are experimental. Current knowledge about antiviral treatment in pregnancy is summarized below and based on the Belgian interim guidelines consensus paper (75):

10.2.1. Chloroquine and Hydroxychloroquine.

Chloroquine has good in vitro activity against COVID-19 and seems to reduce the duration of viral shedding. This does not mean that this will be translated in clinical efficacy (many previous experiences were disappointing). Results of ongoing clinical trials are awaited eagerly. However, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages.

A very recent article suggests that hydroxychloroquine is more potent than chloroquine in vitro, so that lower dosages (than initially recommended) could be used (76). Results of Gautret's study have been just released and confirm that viral positivity in respiratory secretions (measured by PCR) is significantly decreased at day 6 in hydroxychloroquine-treated COVID-19 patients (n=26) versus those with supportive care (n=16 controls): 30% positivity versus 87.5%, $p < 0.001$ (77). The study has several limitations, acknowledged by the authors, and in particular some differences between the compared groups (no initial randomization). This observation however strongly supports the current choice of hydroxychloroquine as first-line treatment.

General precautions of hydroxychloroquine and chloroquine are: lengthening of QTc-interval, known drug interactions (check at <http://www.covid19-druginteractions.org>). Contra-indicated in patients with myasthenia gravis, porphyria, retinal pathology, epilepsy.

Chloroquine has been used for decades (at a total of 25 mg/kg within 3 days) for malaria treatment without any monitoring and side effects, including in pregnant women. However exposure to high dosages is limited (78). Long term daily use of hydroxychloroquine in pregnancy has not resulted in increased teratogenicity. The literature describes over 1100 pregnancies, all based on small case series, thus low level evidence (78).

Dosage: Chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) twice daily up to day 5, OR Chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 300mg twice daily up to day 5.

Hydroxychloroquine 400 mg at diagnosis and 400 mg 12 h later, followed by 200 mg twice daily up to day 5.

10.2.2. Lopinavir/ritonavir.

Lopinavir/ritonavir is an anti-retroviral protease inhibitor used in the treatment of HIV. It has been recently shown not to provide clinical benefit in hospitalized patients with COVID-19. Importantly, there was also no impact on viral excretion. This is in line with in vitro experiments with SARS-CoV2 but also SARS-CoV1. Lopinavir/ritonavir can still be therefore considered a second choice for the moment, when hydroxychloroquine is contraindicated.

Lopinavir/ritonavir are known to have potential severe side effects like pancreatitis, arrhythmia, severe allergic reactions, hepatotoxicity and drug interactions.

Lopinavir/ritonavir associated regimens for HIV treatment in pregnancy seem to have an higher rate of adverse birth outcomes. After adjustment for maternal age, gravida, and educational attainment, singleton infants exposed to tenofovir disoproxil -emtricitabine-efavirenz (TDF-FTC-EFV) from

conception were less likely to have any adverse birth outcome or any severe adverse birth outcome compared with infants exposed to tenofovir disoproxil -emtricitabine-lopinavir/ritonavir (TDF-FTC-LPV-R) (Adjusted Relative Risk ARR, 1.31; 95% CI, 1.13-1.52). Significant outcome difference: small for gestational age <10th percentile (ARR, 1.56; 95% CI, 1.25-1.97)(79). Use in pregnancy due to low evidence of efficacy for this indication therefore is not advised. If considered, advice of infectious disease and obstetric specialist is needed.

Dosage: lopinavir/ritonavir 400/100 mg (= 2 tablets of 200/50 mg) twice daily for 14 days

10.2.3. Remdesivir.

Current use only within the scope of clinical trials, safety profile and efficacy to be further determined. No data available in pregnancy.

Guideline 14. As no treatment for COVID-19 is established yet, all drug trials have to be considered experimental, and such has to be explained to patients and partner. Corticosteroids only have a place in prevention of neonatal lung hypoplasia, necrotic enterocolitis and interventricular hemorrhage due to prematurity. (Hydro)chloroquine have a reasonable safety profile in pregnancy but general precautions have to be taken into consideration. Antiretrovirals are tested now and have no place in pregnancy unless no other treatment options are present to safe maternal life.

11. Organization of health care facility: How to organize in and outpatient clinics? Which isolation precautions to take? Which protective equipment for health care personnel is needed?

11.1. Ambulatory obstetric care.

Guideline 15. During an epidemic routine obstetric follow-up consultations should be limited to the strict minimum in order to provide minimal exposure risk for both patients and health care providers (social distancing). We summarized our recommendations in **Table 3**.

Obstetric patients presenting with alarm symptoms for emergency consultation should contact their obstetric care provider by telephone to determine whether assessment in the hospital is necessary.

Guideline 16. All pregnant patients contacting a health care provider with symptoms suspected for COVID-19, should be directed by telephone to a specific COVID-19 triage unit (as per regional protocol) to get clinically evaluated and tested for COVID-19, and depending on clinical presentation either hospitalized with isolation measures or put in home isolation while awaiting the results.

11.2. Hygiene preventative measures.

International guidelines (CDC, ANZICS, WHO, RCOG) disagree on preventative measures to prevent airborne infection, whether or not to use FFP2/N95 ultra-filtration masks for health care providers in all contact with (possible) COVID-19 positive patients or only in aerosol producing procedures (2, 3, 27-29, 54, 80, 81). In our opinion, health care providers working in close and intensive contact with COVID-19 suspected or positive patients should always wear full personal protective equipment independent on performing 'aerosol producing' procedures (waterproof gown, gloves, glasses or face shield) with FFP2 or N95 masks instead of surgical masks. Examples for close contact are daily nutritional assistance, bathing, surgical procedures, on labor and delivery wards or in airway care, s. Implementation depends on country-specific guidelines and availability of FFP2/N95 masks.

Guideline 17. All health care providers should apply extensive hand hygiene and surface hygiene protocols, wear gloves when in contact with patients or medical material, and consider to wear a surgical mask to limit infection transmission to the patient, especially if coughing (health care personnel could be asymptomatic carriers). In case of any potential signs of illness related to COVID-19, even if minor, the care giver should stay home until the symptoms disappear and tested negative or for a minimum of 14 days in case no testing can be performed. These measures are extremely important, especially when in contact with pregnant patients.

Guideline 18. People working in close contact with COVID-19 suspected or proven positive patients, should always wear full personal protective equipment (waterproof gown, gloves, glasses or face shield and FFP2 or N95 masks). Implementation depends on country-specific guidelines and availability of FFP2/N95 masks. This includes all (health) care providers and to a more broad extend than in officially recognized 'aerosol' producing procedures: all nutritional and bathing care, all surgical procedures, during labor and especially during delivery or when performing airway manipulation or care. In all these circumstances airborne transmission could be more likely.

11.3. Assessing obstetric emergency in a potential COVID-19 infected patient.

Guideline 19. All patients should be asked to call the health care facility prior to visit. The obstetric health care provider should determine the level of 'obstetric emergency' (as by clinical expertise) and ask the patient for symptoms and possible risk contacts (close contact with people presenting with COVID-19 related symptoms or tested positive in the last 14 days). This triage determines the level of precautions taken during hospitalization or delivery.

Table 4: Action plan according to obstetric risk and Covid-19 infection status : Triage.

11.4. Management of COVID-19: Hospitalization on obstetric ward.

Table 5.1: Management of hospitalization on obstetric ward in COVID-19 endemic.

11.5. Labor and delivery ward.

Table 5.2: Management of hospitalization on obstetric ward in COVID-19 endemic.

12. Care in labor of COVID-19 positive women.

12.1. Initial assessment:

For all in patients with suspicion of COVID-19 upon admission on labor and delivery ward screening tests for COVID-19 are indicated as per local protocol (PCR swab and/or CT scan, maybe serology in the future). Clinical maternal parameters need to be assessed hourly, based on MEOWS score systems (**Addendum 1**). Especially need for monitoring peripheral oxygen saturation (aim to keep O₂ sat >94%) and respiratory rate (<20/min) , fever (aim to keep temperature <38,5°C) and blood pressure. Healthy pregnant woman tend to compensate long with normal oxygen saturations, thus respiratory rate should be monitored closely.

Even if the COVID-19 infection seems to be the most important finding, care has to be taken to rule out underlying pathology, such as pre-eclampsia, cardiac pathology, pulmonary embolism.... Screening for co-infection with influenza is also recommended. If indicated, other infections such as respiratory syncytial virus, mycoplasma, *Streptococcus pneumoniae* and legionella should be tested for. Bacterial blood cultures should be performed in patients presenting with lower respiratory symptoms and fever.

Complete blood count with differential, kidney function with electrolytes including calcium and magnesium levels, liver function tests (lactate dehydrogenase) and coagulation tests (INR, PTT, fibrinogen), C-reactive protein and procalcitonine, NT-proBNP, troponine should be done at admission (82). D-dimers are generally elevated in pregnancy and thus not reliable (83).

Lymphopenia is common in COVID-19, but when presenting with increased neutrophile count , bacterial sur-infection is likely and should be treated accordingly.

Arterial blood gas should be performed in severe cases presenting with desaturation <94%.

Pregnancy related adaptations (respiratory alkalosis with a normal p_aCO₂ of 28-32mmHg) should be taken into account when interpreting as shown in **table 6** (84, 85).

Guideline 20. Take care of pulmonary function and assessment of general condition of your patient with COVID-19 infection without losing underlying pathology out of sight. Account for pregnancy adaptation when oxygen saturation is decreased, in consultation with your pulmonologist.

12.2. Management during labor:

12.2.1. Position patient in a left lateral tilt or upright positions to minimize vena cava compression

12.2.2. Oxygen with nasal canula or face mask for maternal indications only, as it shows no intrapartum fetal benefit (86).

12.2.3. Fluid restriction is advised especially in oxygen dependent patients, avoid fluid boluses and even maintenance infusion (3). Close monitoring of fluid balance is advised and should be close to zero.

12.2.4. Antibiotic prophylaxis:

- GBS-prophylaxis with penicillin G or ampicillin as per local protocol.
- Additional prophylaxis for bacterial surinfection in case of COVID-19 pneumonia. Generally ceftriaxone 2g I.V. once daily during 5-7 days. Benefit of additional azithromycin (atypical bacteria) was proposed but is controversial (azithromycin 500mg loading dose, then 250mg once daily for four days) (75, 77, 82).

12.2.5. Antiviral treatment:

Based on local protocol. For (hydroxy)chloroquine, toxicity should be closely monitored with daily electrocardiogram (QTc-prolongation), glucose monitoring every 4 hours and daily laboratory tests (complete blood count, liver and kidney function, electrolytes)(75, 82).

Guideline 21. As a symptomatic COVID-19 infected patients is considered high risk, care should be taken to provide oxygen therapy, fluid restriction, and antibiotic and antiviral prophylaxis where possible.

12.2.6. Obstetric medications and safety profiles: see **Table 7** (87)88.

Guideline 22. In delivering specific obstetric medication, specific interactions may occur. This requires special caution and close observation.

12.3. Induction of labor.

Inductions of labor for medical indications should NOT be postponed. In case of indication for induction of labor, all COVID-19 suspected patients should be screened according to their level of emergency upon admission, as discussed in former chapter. If the patient is stable, she will be asked to go home and return for induction when test results are known. If obstetric emergency: admission on ward in isolation and treat as possible COVID-19 positive until screening results are known.

If COVID-19 is diagnosed early in the disease course in a term pregnancy, induction of labor is indicated to avoid complications. Considering the severity of the disease generally peaks in the second week (87). So immediate induction of delivery is warranted if maternal condition is (becoming) critical; even fetal lung maturation can in such cases not be awaited.

Prostaglandins and **Foley catheters** can be used according to the local protocol (87). **Oxytocin**, however, has to be used with care, as it is associated with risk of fluid overload in bolus/high dosages, which can worsen critical cases of COVID-19 (88-91).

Guideline 23. Induction of labor is indicated in suspected COVID-19 positive cases for any other obstetric reason, but if patient is not critical or obstetric reason is not urgent, test results should be awaited. Induction tools can be used as per protocol, but extreme care is warranted not to use high dose or boluses of oxytocin due to the risk of overfilling an cardiovascular decompensation in critically ill patients.

12.4. Delivery care.

Limit the number of people in the room

Everybody should be trained in and adapt donning and doffing of personal protective equipment (PPE) (see above) (28, 29, 80).

Every 'isolation' delivery room should have a basic provision of the following equipment that stays in the room until after delivery: a delivery set, CTG or Doppler monitor, a monitor for maternal vital signs including saturation, material for vacuum extraction and/or forceps, suturing material, provision for intravenous access and fluid administration, urinary single use and Foley catheters, oxygen masks, nasal canula, a Bakri-balloon (depending on availability and local protocol), a stethoscope and an adult ventilation balloon with mask. It should also dispose of a basic medication set containing oxytocin, prostaglandins (when used in treatment of post-partum hemorrhage), tranexamic acid, penicillin, magnesium sulfate bolus dose, glucose 50%, lidocaine or related medications for local anesthesia, epinephrine and crystalloid and colloid fluids.

Neonatologist should be present at birth because neonatal complications are possible and should be called largely ahead of time to allow time to put on PPE.

Guideline 24. Limit the people at delivery as much as possible and make sure everyone present is adherent to PPE application. Invitee neonatologist.

12.5. Third stage of labor and postpartum

Prostaglandins are safe to use in COVID-19 patients, but further evidence is needed to confirm.

Oxytocin can be used with care in COVID-19 patients (see above). A bolus of 5 international units (IU) at time of delivery of the first shoulder for active management of labor can be safely used. A second slow bolus of 10IU oxytocin can be applied and continuous oxytocin infusion of 10IU/hour until a maximum of 60IU/24 hours in case of uterine atony should also be safe to use.

Methylergometrine should not be used in COVID-19 patients, since cases of acute respiratory failure following the administration have been reported (92, 93).

Tranexamic acid is safe in COVID-19 patients, based on medication characteristics. Further evidence is needed to confirm.

Delayed cord clamping is not advised until more research confirms the finding of absent vertical transmission.

A separate 'isolation room' for the evaluation and resuscitation of neonates born to COVID-19 positive mothers should be installed. Depending on local policy the neonate will be isolated in the neonatology ward or remain with the mother after birth (as discussed earlier).

Guideline 25. During postpartum, be careful with oxytocin and don't use methylergomethrine. Take care of neonate in isolation room.

12.6. Analgesia in labor.

12.6.1. Peridural/spinal (neuraxial) anesthesia

- Is not contra-indicated in COVID-19 (2).
- Occasional thrombocytopenia due to COVID-19 should be ruled out.
- Decide in time for neuraxial anesthesia to minimize (the more frequent) need for general anesthesia in the event of emergency cesarean section.

12.6.2. Inhalation sedatives (nitric oxide etc.)

- Should be avoided in COVID-19 since it increases the risk of forming aerosols, potentially increasing the risk of exposure for health care providers.

12.6.3. Opioid pump analgesia (morphine pumps etc.)

- Should be avoided in COVID-19 since respiratory suppression can occur.

12.6.4. General anesthesia

- To be avoided when possible since intubation increases the risk of creating aerosols, potentially increasing the risk of exposure for health care providers.

Guideline 26. Peridural/spinal analgesia is preferred. Inhalation or general anesthesia should be avoided.

13. Partners of suspected or confirmed COVID-19 positive woman: Can a partner be present at birth? Can a partner visit the patient?

(Household) partners of patients presenting with symptoms, or patients with a possible risk contact (as described in section 10), or patients confirmed COVID-19 positive will be considered and treated as COVID-19 positive.

Guideline 27. A partner of a COVID-19 positive woman will be considered as COVID-19 positive. Whether a partner can be present at birth should depend on local policy and availability of personal protective equipment. We need to minimize the risk exposure of the health personnel.

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Table 1 : Criteria for people at high-risk for severe illness with COVID-19.

Table 1. Criteria for people at high-risk for severe illness with COVID-19	
People aged 65 years and older	
People who live in a nursing home or long-term care facility	
Other high-risk conditions could include:	
➤ People with underlying end organ dysfunction	
	Chronic lung disease (mucocoviscidose, chronic obstructive lung disease, moderate to severe asthma or any other lung disease wich could deteriorate with viral infection)
	Serious heart conditions (New York Heart Association classification NYHA 3-4, heart valve disease, history of cardiac surgery or coronary artery disease)
	Severe renal insufficiency (requiring hemodialysis)
	Severe hepatic disease (liver cirrhosis ≥Stadium 4)
	Diabetes mellitus (poorly controlled insuline-dependent or with complications such as micro-and macro-angiopathy)
	Severe obesity (body mass index [BMI] >40)
	Metastasized cancer
➤ People who are immunocompromised	
	Drug-induced (chronic steroid use or other agents that supress immunity)
	Organ transplant patients under immunosuppression
	Hemathological malignancies
	Cancer therapies (chemotherapy etc.)
	Poorly controlled HIV-infected with CD4<200/mm
➤ People who are pregnant	
Based on CDC COVID-19 guidelines, Belgian COVID-19 guidelines, CNGOF COVID-19 and pregnancy guidelines.	© ISIDOG COVID-19 2020 guidelines

Table 2 : Second and third trimester singleton pregnancy outcomes in 31 confirmed COVID-19 positive patients.

Table 2. Second and third trimester singleton pregnancy outcomes in 31 confirmed COVID-19 positive patients.					
	Chen H et al. (Lancet)	Liu et al. (J of infection, pre-press)	Zhu et al. (Transl Pediatr)	Wang X et al. (Clin Infect Dis)	Total %
	n=9	n=13	n=8	n=1	
Median maternal age (years; range)	28;24-40	30; 22-36	30; 25-35	30	
Median gestational age at diagnosis (weeks; range)	37;36-39	35; 25-39	35; 33-39	30	
Intensive care hospitalisation	0/9	1/13	0/8	1/1	6,3%
Mechanical ventilation	0/9	1/13	0/8	0/1	3,2%
Maternal mortality	0/9	0/12*	0/8	0/1	0%
Delivery within 1 week after diagnosis	9/9	NA**	8/8	1/1	100%*
Intra-uterine fetal distress during hospitalisation	2/9	3/13	5/8	1/1	35,4%
PPROM/preterm labour	1/9	7/13	2/8	0/1	32,3%
Premature delivery (<37 weeks)	4/9	6/10 **	4/8	1/1	53,6%
Extreme premature delivery (<34 weeks)	0/9	NA**	1/8	1/1	11,1%
Mors in utero	0/9	1/13	0/8	0/1	3,2%
Neonatal vertical transmission	0/6***	0/10**	0/7***	0/1	0%
Cesarean section	9/9	10/10 **	7/8	1/1	96,4%
<p>* The patient intensive care on extra-corporeal membrane circulation at time of publication, outcome unknown. ** Gestational age at time of delivery not reported, 3 patients were discharged home after clinical remission delivery data on these patients are lacking. Thus 100% delivery within 1 week of infection is an overestimation. *** Data of throat swabs in 6/9 neonates Chen et al. and 7/8 Zhu et al.</p>					
<p>PPROM= <i>preterm premature rupture of membranes</i></p>					
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Table 3: Proposed out-patient pregnancy follow-up schedule in COVID-19 epidemic.

Proposed follow-up schedule to continue for pregnant patients in COVID-19 epidemic.	
11+0 – 13+6 weeks	intake consultation documentation and risk stratification + blood type, complete blood count and serological testing (as per standard protocol) + clinical parameters + structural ultrasound scan (+/- trisomy screening)
20-22 weeks	clinical parameters + structural ultrasound scan + arranging appointment for glucose challenge test if indicated (as per country specific protocol) + instructions for alarm symptoms + at home follow up of blood pressure (BP) at 24 and 28 weeks
24-28 weeks	glucose challenge test ambulatory (without consultation) as per country specific protocol (general screening or risk selection)
30-32 weeks	clinical parameters + fetal biometry ultrasound scan + instructions for alarm symptoms + at home follow up of BP 2-weekly
34-36 weeks	clinical parameters + Group B streptococcal sampling (as per country specific protocol) + delivery planning + instructions for alarm symptoms + at home follow up of BP weekly

If a pregnant patient is positive for COVID-19 - routine consultations should be postponed by 14 days.
 If a pregnant patient is assessed high risk and needs additional follow-up this needs to be assessed case by case.
 We advise partners to be absent for routine consultations, to limit the exposure risk for health care providers.

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Table 4: Triage and outpatient action plan according to obstetric risk and COVID-19 infection status.

Table 4. Action plan according to obstetric risk and Covid-19 infection status		
Obstetric emergency	LOW	HIGH
COVID-19 symptoms	COVID-19 triage unit + testing	Admission in special isolated room in obstetrical ward
	Postpone obstetric visit until test result is known	All isolation and protection measures in place (see below)
Contact COVID-19 only	Outpatient visit possible	Restricted visit
	Patient wears mask and gloves	
No contact/no symptoms	Outpatient visit possible	Normal obstetric ward admission
	Hand hygiene + social distance	

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Table 5.1 : Management of hospitalization on obstetric ward in COVID-19 endemic.

Table 5.1 Management of hospitalization on obstetric ward in COVID-19 endemic.	
NO COVID-19 symptoms or contact	Normal room on obstetric ward.
	Instruction to patient of hygienic measures.
	Health care workers: hand hygiene, gloves, surgical mask.
Contact COVID-19 and/ or symptoms	Designated isolation room in obstetric ward (negative pressure if available and at distance from other obstetric patient's rooms).
	All personnel entering the room wearing full personal protective equipment (PPE): waterproof gown, goggles of eye-shield, surgical mask, gloves.
	If symptomatic, patient wears surgical mask + hand hygiene.
	Cardiotocographic (CTG) monitor and medical material should not leave the patient's room.

	Limited personnel, PPE trained, who does not care of other pregnant patients.
	No visitors.
	All precaution isolation and infection prevention measures stay in place until COVID-19 test result is known.
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Table 5.2 : Management of labor and delivery ward in COVID-19 endemic.

Table 5.2. Management of labor and delivery ward in COVID-19 endemic.	
All patients upon admission.	All referred to a designated triage 'isolation room' on the labor and delivery ward where risk stratification should be done.
NO COVID-19 symptoms or contact	Normal labour/delivery room.
	Instructions to patient of hygienic measures.
	Health care workers: hand hygiene, surface hygiene, gloves, surgical mask.
Contact COVID-19 and/ or symptoms	Designated isolation room in obstetric ward (negative pressure if available and at distance from other obstetric patient's rooms).
	All personnel entering the room wearing full personal protective equipment (PPE): waterproof gown, goggles of eye-shield, surgical mask, gloves.
	If symptoms, patient wears surgical mask + hand hygiene
	Cardiotocographic (CTG) monitor and medical material should not leave the patient's room.
	Health care providers present at delivery wear full PPE, with FFP2 or N95 mask (depending on availability).
	Same precautions for cesarean section, whether or not general anesthesia is applied.
	No 'gentle sectio', as this requires extra personnel and complicates social distancing and extra use of PPE.
	Limited personnel, PPE trained, who does not care of other pregnant patients
	One partner at birth (see below)
	All precaution isolation and infection prevention measures stay in place until COVID-19 test result is known.
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Table 6 : Normal values for arterial blood gases in pregnant and non-pregnant women.

Table 6. Normal values for arterial blood gases in pregnant and non pregnant women			
	Normal values	Values in pregnancy	
pH	7.34-7.44	7.40-7.46	Increased
Arterial oxygen partial pressure (PaO₂)	10-13 kPa		Unchanged
	75-100 mmHg		
Arterial carbon dioxide partial pressure (PaCO₂)	4.7-6.0 kPa	3.7-4.2 kPa	Decreased
	35-45 mmHg	28-32 mmHg	
HCO₃⁻	22-26 mEq/L		
SBCe (standardized bicarbonate)	21-27 mmol/L	18-21mmol/L	Decreased
Base excess	-2 to +2 mmol/L		Unchanged
<i>kPa = kilopascal, mmHg= millimeters of mercury, mmol = millimol, L = liter, mEq= milliequivalent</i>			

Table 7 : Recommendations for use of obstetric medication in COVID-19 patients.

Table 7. Recommendations for use of obstetric medication in COVID-19 patients				
Indication	Medication Class	Examples	Use in COVID-19	Pre-cautions/Remarks
Fetal maturation				
	Corticoids	Betamethasone, Dexamethasone	Yes	Viral clearance of COVID19 may be delayed, though short term treatment is assumed to be safe.
Neuroprotection				
	Membrane stabilising salt	Magnesium sulfate	Yes	Toxicity should be monitored (therapeutic range of 4.8 to 8.4 mg/dL OR 2.0 to 3.5 mmol/L). Magnesium is known to cause respiratory suppression. One of the first sign of toxicity is hyporeflexia.
Tocolytic drugs				
	Non-steroidal anti-inflammatory	Indomethacine	No	NSAIDS increase the expression of ACE-2 receptors and are therefore not advised in COVID19
	Calcium-antagonists	Nifedipine	Yes	No contra-indications based on medication characteristics have been reported.
	Beta2-agonists	Salbutamol, Ritodrine	Preferably No	Risk of fluid overload by causing hypotension and fluid resuscitation
	Oxytocin antagonist	Atosiban	Yes	No contra-indications based on medication characteristics have been reported.
Uterotonic drugs				
	Prostaglandins	Prostaglandin E2, Misoprostol, Sulproston	Yes	No contra-indications based on medication characteristics have been reported.
	Oxytocin receptor agonists	Oxytocin, Carbetocine	Yes	Risk of fluid overload because of inducing cardiovascular changes and ADH-like properties, especially when high doses or boluses. *
	Serotonergic, dopaminergic, α -adrenergic (ant)agonist	Methyl-ergometrine	No	Risk of pulmonary edema has been reported, therefore use in COVID-19 patients is not advised.
Hemostatic drugs				
	Inhibitor of trombolysis	Tranexamic acid	Yes	No contra-indications based on medication characteristics have been reported.
<p>* Oxytocin dosages estimated to be safe: Active third stage of labour: A bolus of 5 international units (IU) at time of delivery of the first shoulder. Uterine atony: A second slow bolus of 10IU oxytocin after 15 minutes or continuous oxytocin infusion of 10IU/hour in case (maximum of 60IU/24 hours).</p>				
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Addendum 1 : Modified early obstetric warning score (MEOWS).

Addendum 1. Modified early obstetric warning score.							
MEO W Score	3	2	1	0	1	2	3
O2 saturation (%)	≤85	86-89	90-95	≥96			
Respiratory Rate (breaths/min)		<10		10-14	15-20	21-29	≥30
Heart Rate (beats/minute)		<40	41-50	51-100	101-110	110-129	≥130
Systolic blood pressure (mmHg)	≤70	71-80	81-100	101-139	140-149	150-159	≥160
Diastolic blood pressure (mmHg)			≤49	50-89	90-99	100-109	≥110
Diuresis (ml/hour)	0	≤20	≤35	35-200	≥200		
Central nervous system level			Agitated	Alert/awake	Response only to verbal stimuli	Response only to pain stimuli	Unresponsive
Temperature (°C)		≤35	35-36	36-37,4	37,5-38,4	≥38,5	
MEO WS 0-1	Normal						
MEO WS 2-3	Abnormal but stable, report findings to health care provider the same day.						
MEO WS 4-5	Abnormal and unstable, to be evaluated by medical doctor within 30 minutes.						
MEO WS ≥6	Abnormal and critical, to be evaluated by medical doctor within 10 minutes.						

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