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Clinical Management of Coronavirus Disease 2019 (COVID-19) in pregnancy: Recommendations of WAPM-World Association of Perinatal Medicine

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Recommendations and Guidelines for Perinatal Practice

Clinical management of coronavirus disease 2019 (COVID-19) in pregnancy: Recommendations of WAPM-World Association of Perinatal Medicine

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Introduction

The novel coronavirus, SARS-CoV-2 is a new strain of coronavirus that has not previously been identified in humans. An outbreak of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China in December 2019 with increasing global transmission. Although single case reports and case series of COVID-19 infection in pregnant women, have been reported, the evidence currently available to guide clinical management in this specific situation has been limited. The World Association of Perinatal Medicine (WAPM) has developed COVID-19 in pregnancy study databases with an aim to guide clinical management of pregnancy when the pregnant woman is infected with SARS-CoV-2. On the 10th of April, 2020, the World Association of Perinatal Medicine (WAPM) launched a multinational, multicentre collaborative effort and study group on COVID-19 in pregnancy and created a joint database from perinatal centers around the world. Further information can be found at http://www.worldperinatal.org/covid-19/. The first data analysis was completed on the 1st of May and large cohort of COVID-19 infection during pregnancy including 388 pregnant women from 72 different centers in 22 countries in Europe, Asia, America and Oceania. The details of this study regarding the burden of COVID-19 infection on maternal mortality and morbidity will be utilized in the guidelines which follow. These guidelines follow the mission of the WAPM, which brings together groups and individuals throughout the world with the goal of improving outcomes of maternal, fetal and neonatal (perinatal) patients. Guidelines for auditing, evaluation, and clinical care in perinatal medicine enable physicians diagnose, treat and follow-up of COVID-19-exposed pregnant women. These guidelines are based on quality evidence in the peer review literature as well as the experience of perinatal expert throughout the world. Physicians are advised to apply these guidelines to the local realities which they face. We plan to update these guidelines as new evidence become available.

1) How is COVID-19 diagnosed in symptomatic pregnant women? (chest CT ? RT -PCR ? IgM and IgG antibody testing?)

Diagnosis of acute COVID-19 in pregnant women is made using clinical, laboratory and radiological features, as in the general population. However, the symptoms and radiological findings of COVID-19 are non-specific. The most common symptoms for COVID-19 is fever and dry cough, tiredness, smell and taste disturbance in the general population (1). Among these, fever is the most common symptom occuring at the beginning or sometimes during the course of the infection (98.6%) followed by fatigue (69.6%) and then dry cough (59.4%) in the general population (2). Smell and taste disturbance is also among the predominant symptoms with 64.4% prevalence (1). Case-series and a limited number of systematic reviews of pregnant women indicate that majority of pregnant women experience only mild or moderate cold/flu-like symptoms. Cough, fever, headache, and smell and taste disturbance are among the other most common symptoms in pregnant women whereas shortness of breath, myalgia, sore throat and diarrhoea are among the less common symptoms (3). Pregnant women living in an outbreak area who present with one or a combination of more than one of the symptoms should be tested for SARS-CoV-2.

We do not currently recommend using chest CT scans or X-rays as a first-line test for diagnosing COVID-19 in symptomatic pregnant women since radiologic findings in COVID-

19 are not specific and overlap with other infections (4,5). Most radiology societies have similarly commented against using CT as a screening test for or as a first-line test to diagnose COVID-19 (4). Typical features of most viral pneumonias on CT at initial presentation are bilateral multilobar ground-glass opacities with a peripheral or posterior distribution (2). Crazy paving, subpleural dominance and consolidation are other radiological signs which may develop at later stages (5,6). A chest CT scan or X-ray may be necessary for patients with respiratory difficulty such as reduced SpO2 or increased respiratory rate in order to document the pulmonary parenchymal involvement and categorize the severity of the disease. CT scan of the chest can be safely performed in pregnancy as the dosage of ionizing radiation is not believed to be teratogenic. (7,8) However, the role of the CT scan of the chest is limited.

We need more specific tests to diagnose COVID-19, namely tests which identify the SARS-CoV-2 virus antigen or antibodies produced in the host's body in response to infection. However, these types of tests have variable detection rates for SARS-CoV-2. The clinical sensitivity of RT-PCR analyses ranges from 66% to 80% predominantly due to improper sample collection (due to improper technique and quality of sampling, improper time of sample collection such as too late or too early, improper sample storage, variation in viral presence in nasopharyngeal secretions, etc) (9,10). ***Despite the accuracy of the RT-PCR testing for most viruses is far from perfect, reverse-transcription polymerase chain reaction test (RT-PCR) is considered the gold standard of diagnosis for COVID-19 and other viral infections (9).***

Therefore, when a pregnant woman presents with classic symptoms of COVID-19 and is in an outbreak area, it is suggested to diagnose a person with the disease in spite of a negative RT-PCR test due to its low accuracy. Due to the relative low sensitivity of RT-PCR testing, serological tests showing specific IgM appearing about a week post-infection and IgG produced two to four weeks post-infection, have been rapidly produced by manufacturers for diagnosing COVID-19, with the hope of yielding quicker and more accurate test results. It is unfortunate that the U.S. Food and Drug Administration (FDA) allowed manufacturers to sell their tests without first having appropriate data evaluation and with the relaxed requirements to allow rapid development of antibody tests. Although companies declare above 90% sensitivity and 80-95% specificity, the scientific evidence on the sensitivity and specificity of these tests is poorly documented. On the other hand, the current antibody tests may cross-react with other human coronaviruses, resulting in false positives. Furthermore, these serological tests might accurately detect antibodies in severely ill patients with less accuracy in patients with fewer antibodies (such as asymptomatic infection, mild infection, infection in immunocompromised people with no antibody production) which may lead false negatives. Additionally, IgG sensitivity is known to increase with time and symptoms. Similarly, some studies have also shown that most people with SARS-CoV-2 do not seroconvert until at least 11 to 12 days after symptom onset (11). Thus, testing a woman with recent onset of symptoms for SARS-CoV-2 IgM antibodies would yield false-negative results. The only appropriate use of antibody testing for active infection may be for people who have had symptoms for over a week but are PCR negative (11). ***Therefore, we do not recommend routine serological testing to diagnose active COVID-19 in symptomatic pregnant women with negative RT-PCR.***

2) Should we screen all pregnant women admitted for labour for SARS-CoV-2?

Several studies have documented SARS-CoV-2 infection in asymptomatic patients and pre-symptomatic patients. The presence of asymptomatic infection with SARS-CoV-2 has been documented in 13% of children and in 50 % of health-care workers in 2 different studies (12). Since asymptomatic persons are not routinely tested in the general population, the prevalence of asymptomatic infection and detection of pre-symptomatic infection is not well understood.

Since pregnant women are continuing to deliver and will be delivering during this pandemic period, they are frequently being admitted to the hospital for labour during these challenging times. Asymptomatic and pre-symptomatic pregnant women might contribute to SARS-CoV-2 transmission to their neonates, other patients and health care teams. Studies from pregnant women have reported striking prevalence of asymptomatic infection amoung pregnant women. A study from New York, one of the hot spots of the pandemics, has reported 32.6% of their pregnant population had no COVID-19 associated symptoms at initial presentation, 71.4% developed symptoms or signs of COVID-19 infection over the course of their delivery admission or early after postpartum discharge and 85% of these initially asymptomatic patients were identified upon universal screening (13). Another study from New York similarly reported their results of universal screening in pregnant women (14). In this study, nasopharyngeal swabs were obtained from 210 of the 211 women who did not have symptoms of COVID-19; of these women, 13.7% were found to be positive for SARS-CoV-2 and 87.9% of these SARS-CoV-2 positive patients had no symptoms of COVID-19 at presentation. Similar to these reports, the analysis of our WAPM COVID-19 registry revealed a rate of 24.2% COVID-19 in asymptomatic pregnant women (15). These studies underscore the risk of COVID-19 among asymptomatic obstetrical patients. The potential benefits of a universal testing approach may provide an important opportunity to protect mothers, babies, and health care teams. However, these prevalences might have limited generalizability to geographic regions with lower rates of infection. ***Therefore, we recommend all health care teams to be aware of the asymptomatic infection risk in pregnant women and the institutions in high prevalence areas may opt for universal screening of SARS-CoV-2 for their obstetrical patients admitted for labor if they have accessible test facilities. This recommendation might not be applicable for health care systems in areas of low prevalences or low resources.***

3) Is the clinical course of COVID-19 different in pregnant women when compared with the general population?

The largest cohort of >44,000 patients with COVID-19 from China showed that illness severity is mild to moderate with mild symptoms up to mild pneumonia in 81% whereas it is severe with dyspnea, hypoxia, or >50% lung involvement on imaging in 14% of the population. The disease course is classified as critical with respiratory failure, shock, or multiorgan system dysfunction in 5% of the population (16). The previous serious experiences with pregnant women during influenza, H1N1, SARS and MERS pandemics have raised important concerns regarding the course of COVID-19 in obstetrical patients. These infections led to more severe disease courses with increased rates of intensive care unit admissions and case-fatality rates in the pregnant women when compared to the general population (17-21).

Although the data from the pregnant population is not as extensive as the data from the general population, some convincing data has started to emerge and COVID-19 disease severity in pregnancy seems to be similar to the non-pregnant population (13, 15, 22, 23). ***Most of the women (85 - 86%) contracting SARS-CoV-2 will exhibit mild disease characteristics and the rates of severe disease varies between 9.3 - 11.1% and the rates of critical disease varies between 2 - 6.9%, which are just as similar to the general population*** (13, 15, 22-24). Our COVID-19 Registry results have shown that the most important parameters associated with composite adverse maternal outcome were earlier gestational age at infection, the presence of shortening of breath, bilateral CT abnormalities and increased LDH levels (15). Awareness of such risk factors associated with severe or critical disease would help the health care teams to manage these women better. ***Since our registry is a large cohort of pregnant women with COVID-19, women with these risk factors may be categorized as high-risk women for developing severe or critical disease and managed accordingly until new supporting or opposing data emerges.***

On the other hand, most studies have suggested that maternal mortality rates are not increased in COVID-19 in contrast to previous pandemics of H1N1 and SARS. Most studies witha limited number of pregnant women have reported almost zero maternal deaths (22-25). The maternal mortality rate of the largest cohort of WAPM COVID-19 Registry was calculated as 0.8% (15). Among the three maternal deaths, only one had a co-morbidity (pregestational DM Type II) and one had preeclampsia with the last one having no co-morbidities or pregnancy-related disorders. A recent multi-institution case series from Iran reported the characteristics of 9 critically ill pregnant women infected with SARS-CoV-2 (26). At the time of their reporting, 7 of 9 died, 1 remained critically ill and ventilator-dependent, and only one recovered after a prolonged hospitalization. The maternal outcomes were more found to be more severe when compared to other high and low-risk family members. Although this study was not a surveillance cohort and did not report any mortality rate, the fatal cases reported in this study demonstrate it is not zero as shown also in our large cohort (15,26). As a summary, ***maternal mortality rates seem to be not increased extensively in COVID-19 in contrast to previous pandemics of H1N1 and SARS but we recommend caution in calculating estimates of attributable risk with pregnancy. Obstetrical patients and healthcare teams should not be reassured for the absolute absence of death among pregnant women until more comprehensive pregnancy data is collected.***

4) Is the rate of perinatal complications increased due to maternal COVID-19?

Complications of other respiratory viral illnesses including H1N1, SARS and MERS include spontaneous abortion, preterm labor, premature rupture of membranes, intrauterine growth restriction, intrauterine fetal death and neonatal death (27). Elevated temperature in early pregnancy might be associated with an increased rate of birth defects such as neural tube defects, cleft lip and limb reduction defects (28, 29). Therefore, similar complications would be expected in pregnancies infected with SARS-CoV-2 however increased rates of miscarriage, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) have not been reported for COVID-19 up to now (22-26). This may be due to the fact that most case-series of pregnant women with COVID-19 include pregnancies at their third trimesters, almost all of which are delivered shortly after the diagnosis of the infection most probably due to obstetricians' fear of maternal clinical deterioration in respect to previous experience other

respiratory viral infections (22-26). Since the SARS-CoV-2 is a very young virus of 5 months of age, the long-term perinatal consequences such as fetal organ malformations, IUGR, IUFD in recovering pregnant women when infected in their first or second trimester are not known for this time being, but close surveillance of these women till the end of their pregnancies will be able to answer this. Eight percent of women in WAPM COVID-19 registry including 388 patients were diagnosed in the first, 22.2% in the second and 69.8% in the third trimester of pregnancy (15). The results of the continuing pregnancies will let us gain more information about the effect of COVID-19 in the first and second trimesters. On the other hand, the miscarriage rate was 2.3%, intrauterine fetal demise 2.3% and neonatal death rate was 2%, with an overall rate of perinatal death of 4.2% in the WAPM COVID-19 registry (15). All neonatal mortality in the registry were considered as prematurity-related adverse events.

The placental viral infection with SARS-CoV has been previously shown to cause thrombotic vasculopathy resulting impaired fetal vascular perfusion (30). A small study of three placentas from mothers infected with SARS-CoV-2 infection in the 1st and 2nd trimester of pregnancy has similarly reported increased amount of fibrin deposition and one case of placental infarction which might be clinically relevant (31). Therefore, ***there is an urgent need for perinatal results of women infected in early and mid-pregnancy in order to manage these pregnancies better and the upcoming analysis of the registries will be able to answer this difficult question.***

On the other hand, there exists more extensive data on the perinatal effects of COVID-19 in the third trimester. ***The most remarkable effect of COVID-19 infection in the third trimester is preterm delivery.*** Studies have reported preterm birth rates (before 37 weeks) as 5%, 21.2%, 39% and 41% (13, 23, 24, 32). WAPM COVID-19 registry analysis also yielded a higher rate of preterm birth in pregnant women infected with SARS-CoV-2 compared to the general population (15). It should be emphasized that this observed increase in the rate of preterm birth in obstetrical patients is not related to spontaneous onset of uterine contractions, but mostly due to elective induction of labor or cesarean section before term with the indication of maternal COVID-19. This increased interventional approach of the obstetricians is understandable given the sudden emergence of a pandemic with a novel virus responsible for a respiratory syndrome potentially worse in the pregnant population than the general population, as previously observed with H1N1, SARS and MERS. The delivery of pregnant women with severe or critically ill disease was most probably thought to reduce the burden of the fetus on the pulmonary system and the diaphragm. ***The rate of spontaneous preterm labor in pregnant with COVID-19 may be lower when the indications leading to preterm birth is scrutinized.*** This rate may be as low as 5-6.1% and the most common indication is the preterm rupture of membranes (13, 24). Preterm rupture of membranes (PPROM) is a frequent finding in pregnant women with COVID-19, with rates of 6.1%, 20.7% and 26.5% (23, 24, 32). The increased cytokine release due to maternal inflammation, hypoxia, and pro-thrombotic state in COVID-19 might be the causative factors for PPROM leading to spontaneous preterm labor.

Finally, the rates of stillbirth and neonatal death in maternal COVID-19 do not seem to be increased above the baseline risk. However, neonatal death or stillbirth may be occasionally encountered especially in case of with severe or critical disease (23,25, 26,34). Furthermore, the perinatal mortality may be expected to be higher in COVID-19 leading to maternal death,

however this data needs to be confirmed (32). The pathophysiology behind fetal or neonatal death may be due to the organ injuries in the offspring caused by transplacental passage of those maternal inflammatory cytokines causing the critical disease.

5) Is there any risk of vertical transmission?

Definitive evidence that SARS-CoV-2 crosses the placenta and infects the fetus is lacking; although, a few cases of possible in utero infection have been reported. Most studies which tested vaginal secretions, amniotic fluid, cord blood, breast milk for SARS-CoV-2 did not document vertical transmission (13, 22, 33)

Three of 33 infants born to mothers with COVID-19, developed early-onset infection. However, amniotic fluid, cord blood, and breast milk, were negative for SARS-CoV-2 in these three cases. Clinical symptoms from these infants infected with COVID-19 were mild and outcomes were favourable (34). A paper from China reported possible vertical transmission which documented IgM positivity in a neonate of a mother with COVID-19 at 2 hours of life without other exposure. The early time period of detection coupled with knowledge that IgM does not cross the placenta has called into question the possibility of vertical transmission in this case (35). Besides from this paper, IgM positivity has been reported in 2 neonates in a retrospective review of 6 pregnant women with COVID-19 (36). Similarly, WAPM COVID-19 registry also reported one case of suspected vertical transmission, with a neonate tested positive soon after birth at RT-PCR test on nasopharyngeal swab, but no IgM positivity (15). The newborn was asymptomatic and had negative RT-PCR test after 14 days of life. Amniotic fluid was not tested, and specimens from placenta were not obtained, thus questioning whether the infection occurred in utero or immediately prior or after birth could not be answered. A very recent interesting case-report described how a 22 week's COVID-19 pregnant woman with severe hypertension, coagulopathy, preeclampsia and placental abruption, delivered a pre-viable fetus by cesarean section (37). The analysis for the presence of SARS-CoV-2 through molecular, immunohistochemical assays and by electron microscopy has revealed presence of SARS-CoV-2 within the placenta but no evidence of the virus within the fetal heart and lungs. Therefore, one might think that the placenta might have played a barrier-role for the vertical transmission of the virus or since the fetus was immediately delivered, the virus might have not found sufficient time to get into the fetal circulation. The virus was predominantly found in the syncytiotrophoblast cells at the maternal-fetal interface of the placenta and histological examination revealed a dense macrophage infiltrate, but no evidence for decidual vasculopathy explaining the occurrence of preeclampsia. However, the intervillositis within the placenta suggest that COVID-19 might have contributed to placental inflammation that consequently resulted in early-onset preeclampsia. Finally, a recent research has studied 11 placental or membrane swabs collected immediately after delivery from 32 COVID-19 positive pregnant patients and three of these came as positive. However, none of the infants tested positive for SARS-CoV2 in days 1-5 of life and none demo
nstrated symptoms of COVID-19 infection (38). Given the mixing of maternal and fetal fluid and tissue at time of delivery whether vaginally or by cesarean section (most deliveries by cesarean), the origin of the detected SARS-CoV-2 RNA in this series remained unidentified. Nevertheless, decreased length of exposure to these tissues during cesarean may be the explanation for no vertical transmission and for vaginal deliveries, the virus may require a

more extended incubation period before the swabs convert to positive. Placenta's barrier-role for prevention of vertical transmission of the virus should also be discussed.

Further data is needed to understand the vertical transmission risk of maternal COVID-19. Therefore, we recommend neonatal RT-PCR tests on nasopharyngeal swab, amniotic fluid, breast milk and placenta in maternal COVID-19, if possible. This would help for further accumulation of more data regarding perinatal vertical transmission and may help early management and isolation of neonates if infection is detected.

6) What is the optimal mode and time of delivery in pregnant women with COVID-19?

COVID-19 itself is not an indication for delivery. Mode and timing of delivery should be tailored according to the clinical status of the patient, gestational age and fetal well-being. However, according to the existing evidence, most of the pregnant women with COVID-19 in their third trimester have been delivered by caesarean section immediately following the diagnosis of COVID-19 (22-25). The possible explanations for this effect of COVID-19 on the time and mode of delivery was most probably to protect the mother, the fetus and the caring health care personnel. Immediate cesarean delivery of a woman with COVID-19 would have been expected to reduce the burden of the pregnancy on the infected maternal lungs before progression of the disease to severe or critical stages requiring intensive care support or mechanical ventilation, to reduce the risk of fetal demise and to reduce the transmission of the virus to the obstetric team by reducing the length of exposure in active labor management and eliminating the need for aggressive pushing which would cause aerosolization of the virus particles. However, the role of cesarean for reducing these risks is not evidence based. Furthermore, emergent cesarean delivery of a woman with COVID-19 would increase her odds for premature delivery as has been shown in WAPM COVID-19 registry and many other small cohorts or case-series (22-25). This would in turn lead to an increased risk of neonatal complications. ***Nevertheless, other than obstetric contraindications, vaginal delivery in a COVID-19 pregnant woman is not contraindicated unless her medical condition would cause fetal hypoxia or fetal distress due to her lowered oxygen saturation or would interfere with her pushing.*** An operative vaginal delivery may be considered to shorten the second stage since active pushing while wearing a surgical mask or N-95 mask may be difficult for the patient. ***If there is an indication for cesarean, delivery should be performed in an operating room with negative pressure (if available) and with obstetric team properly donned with personal protective equipment (PPE) (respirator, goggle, face protective shield, surgical gown and gloves). Regional anesthesia is superior to general anesthesia*** both for maternal benefit and prevention of exposure to the healthcare team given the aerosolizing effect of intubation. ***Since there is insufficient evidence regarding delayed cord clamping and the possibly related the risk of infection to the newborn via direct contact, we do not recommend delayed cord clamping in neonates of mothers with COVID-19. Since the presence of SARS-CoV-2 has been demonstrated within the placenta and the membranes, placental tissue should be treated as infectious tissues and disposed of or sent to the pathological and microbiological examination appropriately (37, 38)***.

7) How are pregnant women with COVID-19 and their neonates cared for? Is breastfeeding contraindicated?

Pregnant women with mild COVID-19 with normal vital signs, no difficulty or shortness of breath, no clinical indication for imaging or treatment which is the case in around 85% of cases, ***the patient can be managed at home.*** However, any abnormal vital signs or difficulty in breathing requiring oxygen therapy or pulmonary CT may require hospital admission. ***COVID-19 is not an indication for preterm delivery***, In particular, delivery should not be planned in the first 14 days following the diagnosis of infection. Since the course of COVID-19 is mostly mild, obstetricians should not rush to deliver their pregnant patients unless there are any maternal or fetal indications. When pregnant women with COVID-19 are admitted for labor, routine care should be given to asymptomatic women. If negative-pressure isolation rooms are not available, patients should be isolated in single rooms, or grouped together once COVID-19 infection has been confirmed. The woman should wear at least a surgical mask or N95 mask in case of sufficient facility and all staff and physicians in the room during the second stage of labor or cesarean delivery should be wearing full PPE including gown, gloves, eye protection, and N95 mask. However most health authorities have stated the opinion that second stage is not considered an aerosol-generating procedure (39). When features of severe illness such as dyspnea, hypoxia, >50% lung involvement, respiratory failure, shock, or multiorgan system dysfunction develop, transfer to the intensive care unit may be required. The woman may be transferred back to the postpartum unit with continuous O2 monitoring when an improvement of clinical condition is observed, with milder symptoms of the disease, decreased oxygen requirement and stable conditions for at least 24 hours. COVID-19 mothers should not be separated from their neonates unless the mother's poor condition to care for her baby. If the mother is unable to take care of her baby, another family caregiver may be identified. The recommendation of not separating the mother and her newborn is based on the fact that the neonatal risk of COVID-19 is low and if infection occurs, it is typically mild or asymptomatic. Furthermore, the existing evidence suggests that SARS CoV-2 is not detectable in the human milk of mothers with COVID-19. On the other hand, breastfeeding provides protection to newborn infants against many illnesses during early life and is the best source of nutrition for most infants. The mother should be advised to perform frequent hand hygiene with soap and water or alcohol-based disinfectant, especially before contact with her child and to wear a surgical or N95 mask until 14 days of symptoms resolution or at least two negative RT-PCR results of nasopharyngeal swab or occurrence of SARS-CoV-2 IgG antibodies in the maternal serum.

Treatment for mild illness is focused on symptoms, no antiviral treatment is currently recommended for mild cases of COVID-19. Acetaminophen and adequate hydration should be used to control fever because the antiviral treatment has a close association with congenital defects especially in the first trimester exposure. Patient should self-isolate in the home for 14 days after the diagnosis and they should be checked every 24-48 hours by the local health system. They should be instructed to give information to the hospital if they experience worsening dyspnea, fever resistant to anti-pyretics, intolerance to oral hydration and other obstetric complaints. Any pregnant patient with respiratory symptoms should be admitted as an inpatient. As with other non-pregnant patients symptoms compatible with severe COVID-19 may be listed as follows (40):

- SpO2 ≤ 93% on room air at sea level (However, since pregnant population's oxygenation targets are higher due to need for fetal perfusion, ***a higher cut-off for SpO2 such as < 95% may be suggested in the pregnant population***)
- ***Respiratory rate > 30/m***
- ***PaO2/FiO2 < 300***
- ***Lung infiltrates > 50%***
- ***Maternal tachycardia > 120 not improved with fluids***
- ***Hypertension defined by systolic blood pressure > 140mmHg or diastolic blood pressure > 90mmHg on two separate measurements at reasonably spaced intervals in the absence of chronic hypertension or hypotension with systolic blood pressure < 90 or diastolic blood pressure < 50mmHg***
- ***Persistent fever***
- ***Elevated creatinine or new thrombocytopenia***

If hospitalization is indicated, ideally the care should be provided in a facility that has the capability to conduct close perinatal monitoring. Since severe disease slightly increases the risk of perinatal complications such as fetal distress, intrauterine fetal loss, premature rupture of membranes, close fetal surveillance is required in these patients when admitted to the hospital.

A low threshold in pregnant women evaluation is encouraged and suggested criteria indicating the opportunity of ICU transfer include increased work of breathing, increasing tachypnea, increasing oxygen need, PCO2 > 40 or pH < 7.35, hypotension or oliguria despite adequate fluids, chest pain, worsening tachycardia and altered mental status.

8) Which medication are effective? Treatment for COVID-19 is evolving rapidly. It is important to emphasize that ***none of the anti-viral medications has been approved by the FDA for the treatment of COVID-19.***

Anti-viral medications are usually not used in patients with mild symptoms of COVID-19. However, they have been frequently used in study and hospital protocols in patients requiring hospitalization in order to decrease viral replication and maternal inflammatory response.

Chloroquine that has been used in Covid-19 treatment worldwide is an antimalarial drug. ***Hydroxychloroquine*** is an analog of chloroquine used to treat autoimmune diseases, like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Hydroxychloroquine has the advantage of having fewer less severe toxicities and fewer drug-drug interactions than chloroquine.

Hydroxychloroquine (HCQ) is an investigational agent for the treatment of COVID-19 and has not yet been demonstrated to be effective in pregnancy (13). HCQ is considered safe to continue for the management of rheumatologic diseases, such as systemic lupus erythematosus (SLE), in pregnancy. Several studies of women in whom HCQ therapy was continued in pregnancy revealed no adverse fetal outcomes (41). Additionally, HCQ is considered safe to use in lactating mothers because of low levels detected in breast milk. Women with severe disease, or with other risk factors for progression of moderate disease are usually prescribed HCQ despite the fact that insufficient clinical data is present to

recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19 (40).

Reports have documented serious arrhythmias in patients with COVID-19 treated with chloroquine or hydroxychloroquine, often in combination with azithromycin and other medicines that prolong the QTc interval, therefore Food and Drug Administration (FDA) recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside of the setting of a hospital or clinical trial. When chloroquine or hydroxychloroquine is used, the QTc interval should be monitorized (42). High-dose chloroquine (600 mg twice daily for 10 days) has been compared with lower-dose chloroquine (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days) where in addition, all of the participants received azithromycin and 89% of the participants received oseltamivir. This study was abandoned early when preliminary results showed higher rates of mortality and QTc prolongation in the high-dose chloroquine group (40). Therefore, the high-doses are not recommended in the treatment of moderate-severe COVID-10 pregnant women. The combination of azithromycin with HCQ should not be recommended unless there is a secondary bacterial infection requiring antibiotherapy.

HIV protease inhibitors (Lopinavir/ritonavir) are inhibitors of SARS-CoV 3CLpro in vitro, and this protease appears highly conserved in SARS-CoV-2 (43). Although lopinavir/ritonavir has in vitro activity against SARS-CoV, higher than tolerable levels of the drug are probably required to achieve significant inhibition in vivo (44). There is wide experience with the use of lopinavir/ritonavir in pregnant women with HIV, and no teratogenicity has been shown due to its low placental transfer (40). However, the data showing the efficacy of lopinavir/ritonavir in patients with COVID-19 is very limited and most probably higher doses than HIV treatment is required for SARS-CoV-2 treatment.

Remdesivir is an investigational antiviral agent that has not yet been studied in pregnant women. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. Remdesivir is not approved by the Food and Drug Administration (FDA), Still it is available through an FDA emergency use authorization (EUA) for the treatment of hospitalized adults, children and pregnant women with COVID-19 and is currently being investigated in clinical trials (40). Some preliminary data from a multinational, randomized, placebo-controlled trial (Adaptive COVID-19 Treatment Trial [ACTT]) of hospitalized patients with COVID-19 showed that patients who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo. However, the clinical trial data assessing the role of remdesivir for patients with mild to moderate COVID-19 is very limited. Therefore, remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease may be recommended but not in mild-moderate disease.

Immunomodulators are among the investigational therapies in patients with COVID-19. However, for now, ***there are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19*** (40). ***The data regarding the use of Interleukin-1 inhibitors (e.g., anakinra) and Interleukin-6 inhibitors (e.g., sarilumab, siltuximab, tocilizumab) is also very insufficient to recommend either for or against the use of the following agents for the treatment of COVID-19.*** Therefore, their routine use in COVID-19 or pregnancy unless part of a clinical trial is not

advised. Among these, ***only Tocilizumab may be considered for off-label use in pregnant women who have severe or critical COVID-19 with the suspicion of cytokine activation syndrome with elevated IL-6 levels as a last resort or based on a clinical research protocol.***

Favipiravir, also known as T-705 or Avigan, is a pyrazine derivative that acts as an inhibitor of viral RNA-dependent RNA polymerase, causing chain termination and preventing RNA elongation. Favipiravir has demonstrated activity against influenza viruses, especially for those that are oseltamivir-resistant, and has been approved in Japan and China for the treatment of novel influenza virus infections (45). A prospective, multi-center, randomized trial in China comparing favipiravir with umifenovir but not published in a peer-review journal, demonstrated a higher clinical recovery rate at day 7 in those receiving favipiravir among moderately ill patients but not among mildly or severely ill patients (46). This antiviral has been used in many hospitalized COVID-19 patients with moderate disease progressing to severe disease in many hospital or national protocols but the data still remains very limited to recommend its routine use in patients with COVID-19. ***On the other hand, favipiravir is a mutagen and has the potential for both teratogenicity and embryotoxicity in humans. Therefore, its use in pregnancy is contraindicated.***

Conclusions

The COVID-19 pandemic has rapidly emerged as a serious threat to maternal, fetal and neonatal patients throughout the world. The WAPM through the efforts of perinatalogists around the world has endeavored to provide clinical guidance to assist practitioners in their individual locals. It is essential that management be based on the best evidence available as it emerges. With conscientious attention and diligence the war against the COVID-19 pandemic will be managed effectively and eventually won.

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