Pregnancy During the Covid-19 Pandemic: What an Obstetrician Needs to Know

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ABSTRACT

In February 2020, the World Health Organization identified the coronavirus disease 2019 (COVID-19). The virus that causes COVID-19 is known as severe acute respiratory syndrome coronavirus 2. Nations worldwide have reported high death tolls and are adopting measures, particularly in Turkey wherein efforts are made to ensure that pregnant women are minimally affected by this epidemic that has such terrible effects. To date, a total of 206,844 cases have been confirmed in Turkey in approximately 115 days. However, the exact number of pregnant COVID-19 patients in Turkey or worldwide is not yet known. There are no conclusive data that confirm whether pregnant women are at a higher risk of acquiring this infection compared to the rest of the population. It is also not yet known if or how fetuses will be affected by this infection. However, the body of research evidence concerning COVID-19 is rapidly growing, and multiple organizations are constantly updating and expanding resources for interim guidance. In this review, we aimed to summarize the latest available research on COVID-19 virology and epidemiology as well as the status of pregnant healthcare workers together with the reported data on pregnant women and other recent findings and to discuss COVID-19 during pregnancy based on the available data.

Keywords: COVID-19, SARS-CoV-2, pregnancy, pandemic

INTRODUCTION

Coronaviruses are important pathogens for humans and animals. In late 2019, a new coronavirus was found to be the cause of a subset of pneumonia cases in the Wuhan province of China. Since then, it has spread worldwide, resulting in a pandemic. The World Health Organization (WHO) coined the term coronavirus disease 2019 (COVID-19) (1). The virus that causes COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This severe acute respiratory syndrome seems to spread from one person to another mainly through the transmission of SARS-CoV-2 by respiratory droplets, Similar to the case of influenza (2). Authorities have recommended several infection control measures in order to reduce the transmission of COVID-19. These include controlling the major source of the infection (e.g., using physical barriers to cover the nose and mouth in order to contain respiratory secretions), the early identification and isolation of patients suspected of being infected, the use of adequate personal protective equipment while providing care to COVID-19 patients, and the disinfection of the environment. Limiting the transmission of SARS-CoV-2 is an important component in the management of patients with suspected or identified COVID-19. An early report of COVID-19 from China consisting of 138 patients estimated that 43% of them had contracted the infection in a hospital setting (3).

Most studies describing the clinical characteristics of COVID-19 were conducted among hospitalized patients. A report of COVID-19 pneumonia from Wuhan consisting of 138 patients, determined that the most frequent clinical findings at the onset of the disease were fever (99%), fatigue (70%), dry cough (59%), anorexia (40%), myalgia (35%), dyspnea (31%), and thick mucus from coughs (27%) (3).

Individuals of all ages can be infected with SARS-CoV-2, although middle-aged and especially elderly people with serious diseases are the most frequently affected. A report from the Chinese Center for Disease Control and Prevention (CDC) stated that of 44,500 confirmed COVID-19 patients, 87% were aged between 30 and 79 years (4).

Common laboratory findings of hospitalized COVID-19 patients include lymphopenia, elevated amino transaminase and lactate dehydrogenase levels, and increased inflammatory markers (e.g., ferritin, C-reactive protein, and erythrocyte sedimentation rate) (3).

Disease severity can range from mild common cold symptoms to pneumonia and even death. Currently, the virus has been detected in every continent except Antarctica, and there are serious outbreaks especially in China, Italy, and New York. Current findings

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show that the average incubation period is 5 days, but can vary from 2 to 14 days (5). The morbidity and mortality of COVID-19 have been largely associated with acute viral pneumonitis that evolves into acute respiratory distress syndrome (ARDS). Common complications of ARDS associated with COVID-19 include acute renal failure (ARF), elevated liver enzymes, and cardiac injury involving cardiomyopathy, pericarditis, pericardial effusion, arrhythmia, and sudden cardiac death. For example, a single-center retrospective cohort study from China assessed 52 COVID-19 patients who were in a critical condition and reported the following complications: ARF (29%), liver dysfunction (29%), and heart damage (23%) (6).

In this review, we will summarize the latest available research on COVID-19 virology and epidemiology, the status of pregnant healthcare workers together with the reported data on pregnant women and other recent findings, and we will discuss COVID-19 during pregnancy together with the available data.

Clinical and Research Consequences

Virology and Epidemiology

Full genome sequencing and phylogenetic analysis have revealed that the virus associated with COVID-19 is a betacoronavirus from the same subgenus as the severe acute respiratory syndrome (SARS) coronavirus (and also a few bat coronaviruses), but belongs to a different clade. The structure of the receptor-binding gene region of COVID-19 is quite similar to that of the SARS coronavirus, and both viruses use the same receptor (angiotensin-converting enzyme 2 for cellular entry (7). The International Committee on Taxonomy of Viruses Coronavirus Study Group recommended naming the virus as SARS-CoV-2 (8). A phylogenetic analysis of 103 SARS-CoV-2 strains from China defined two different strains of SARS-CoV-2 called type L (accounting for 70% of the strains) and Type S (accounting for 30%) (9).

More than three million confirmed COVID-19 cases have been reported worldwide. Since the first case was reported from the city of Wuhan in the Hubei province of China at the end of 2019, more than 80,000 cases of COVID-19 have been reported in China, most of which were from Hubei and the surrounding provinces. A joint WHO-China fact-finding mission estimated that the Chinese outbreak peaked between the end of January 2020 and the beginning of February 2020 (10), and the rate of new cases declined significantly in early March. In the United States (US), cases of COVID-19 have been reported in all the 50 states, Washington DC, and at least four territories (11).

Pregnancy and COVID-19

Guidelines suggest that pregnant women avoid exposure by following the same precautions recommended to non-pregnant

Main Points:

- The exact number of pregnant women affected by COVID-19 is not known.
- Vertical transmission and the fetal and maternal effects of COVID-19 are still not clearly understood.
- COVID-19 does not affect the mode of delivery.

individuals such as social distancing, hand hygiene, and disinfection of surfaces. Pregnant women with a history of epidemiological contact should be monitored.

Pregnant Healthcare Professionals

All pregnant women are considered to be at a high risk for COVID-19 because of their high sensitivity to changes in immune responses. These women should adopt comprehensive preventive measures, including practicing hand hygiene, disinfecting surfaces with >60% ethanol, and strictly following social distancing measures when interacting with other people (12). Accordingly, pregnant healthcare professionals have additional concerns, and there is no standard occupational guidance for them. Some human resources departments recommend that pregnant women in the third trimester, especially those at \geq 36 weeks of gestation, should suspend face-to-face patient consultations in order to help reduce their risk of acquiring the infection and its consequences. The International Society for Infectious Diseases in Obstetrics and Gynecology suggests that pregnant women at \geq 24 weeks of gestation who are working in settings with an increased risk of exposure (e.g., labor and delivery, operating rooms, intensive care, or high dependency units) should switch to positions where they would be subjected to a lower risk of exposure (12).

Clinical Characteristics

All pregnant women should be monitored for the development of COVID-19 signs and symptoms, especially if they were in close contact with a suspected or confirmed case. A systematic review of 33 studies that included 356 pregnant COVID-19 patients reported that the most common symptoms were fever (67%), cough (66%), dyspnea (7%), sore throat (7%), fatigue (7%), and myalgia (6%) (13). Other reported symptoms included rhinorrhea, nasal congestion, loss of appetite, nausea and vomiting, headache, and possibly abnormalities in the sense of smell and/ or taste. The most common laboratory findings included lymphopenia (14%), moderate liver enzyme elevation (5%), and thrombocytopenia (1%) (13).

Classification

The US National Institute of Health has provided the following system for the classification of COVID-19 according to severity (14):

- Asymptomatic or presymptomatic infection: Tested positive for SARS-CoV-2 but without symptoms.
- Mild disease: Any signs or symptoms (fever, cough, sore throat, fatigue, headache, myalgia) without shortness of breath or abnormal chest radiography.
- Moderate disease: Evidence of lower respiratory tract disease in the clinical evaluation or imaging and oxygen saturation (SaO₂) of >93% when breathing room air at sea level.
- Severe disease: Respiratory rate of >30/min and SaO₂ of \leq 93% when breathing room air at sea level, ratio of arterial oxygen over the fraction of inspired oxygen (PaO2/FiO₂) of <300.
- Critical disease: Respiratory failure, septic shock, and/or multiple organ dysfunction.

Pregnancy Complications and Vertical Transmission

Early data show similar intensive care unit (ICU) admissions for pregnant and non-pregnant individuals who develop COVID-19 pneumonia but an increased risk of preterm and cesarean deliveries (15).

A preliminary report from the US showed that 4 (2.8%) out of 143 pregnant COVID-19 patients were admitted to the ICU; however, it was indicated that the data were incomplete (16). The first US experience from New York that included 43 pregnant patients with confirmed COVID-19 reported that the course of the disease was mild in 37 patients (86%), severe in 4 patients (9.3%), and critical in 2 patients (4.7%) (17). A more extensive cohort study of 147 pregnant patients included in the WHO-China Joint Mission Report and a different report of 118 pregnant patients in Wuhan indicated that 8% of all subjects had severe disease and 1% were in a critical condition (18). Only one maternal death was reported in the medical literature, caused by multiorgan failure (19), but there are several anecdotal reports (20).

An early review of 51 well-documented pregnant COVID-19 patients have reported that 39% delivered before 37 weeks of gestation and 96% delivered by cesarean section (21); however, a larger systematic review including 252 pregnant COVID-19 patients indicated that 15% delivered before 37 weeks of gestation and 70% delivered by cesarean section (13). When we reviewed the limited available studies in the literature, we found that pregnancy was not an additional risk factor for severe COVID-19 prognosis. Therefore, follow-up without treatment should be considered first for pregnant women with uncomplicated COVID-19 infections. Testing positive for COVID-19 should not be considered as an indication for delivery. Delivery needs to be decided according to the patient's clinical condition and gestational age. In other words, premature birth should not be considered if the patient is asymptomatic or stable. The decision for the type of delivery should be based on the indications of pregnancy and not be influenced by COVID-19 positivity. There are currently no data on whether pregnancy delays recovery from the viral disease or causes treatment resistance.

The frequency of spontaneous abortions may not increase, but there are limited data regarding infections in the first trimester (13). As reported previously, fetal deaths were noted in two patients in critical conditions—one of whom died, whereas the other required extracorporeal membrane oxygenation (ECMO) (19).

More than 95% of newborns reportedly had a good overall condition at birth, and neonatal complications were thought to be largely associated with premature birth (13). The criteria for the definitive diagnosis of vertical SARS-CoV-2 transmission are unclear. Researchers have suggested various methods for this purpose, such as a SARS-CoV-2-positive neonatal nasopharyngeal swab within 1–2 hours of birth and before contact with an infected individual and an elevated SARS-CoV-2 IgM level in cord blood. To date, SARS-CoV-2 has not been detected in cord blood or amniotic fluid (22). However, there is at least one case where a confirmed COVID-19 patient had a second trimester miscarriage, and examinations revealed that the placental cotyledon and submembrane were positive for SARS-CoV-2, whereas all fetal, amniotic fluid, cord blood, maternal blood, and vaginal samples were negative (23). A review that included 51 pregnant women with COVID-19 did not report any cases of intrauterine transmission (21).

Diagnostic Method

A positive reverse transcription-polymerase chain reaction usually confirms the diagnosis of COVID-19, although it is possible to have false-positive results. False-negative results were common in the first tests (approximately one in four) (12) and were also reported in pregnant women (24). If the initial nasopharyngeal test is negative but COVID-19 is still suspected and the determination of the infection is important for management or infection control, the test should be repeated within 24 hours to several days. Infection control measures for COVID-19 should continue during reassessments. Two more consecutive negative results usually exclude infection (12). If COVID-19 infection is strongly suspected and the diagnosis is required for treatment, lower respiratory tract samples (sputum, bronchoalveolar lavage, etc.) can be tested due to their higher sensitivity (25). In most hospitalized COVID-19 patients, lung radiography is sufficient for the initial assessment of lung complications. The fetal radiation dose for a single lung radiograph is very low at 0.0005-0.01 mGy. Computed tomography (CT) should be performed if indicated because the fetal radiation dose is not associated with increased risk of fetal anomalies or miscarriage for a routine chest CT. Some authors advocate for pulmonary ultrasound in the rapid diagnosis of pneumonia in pregnant women and argue that this would be the fastest approach to detect COVID-19 infection in highly suspicious pregnant women (26).

Pregnancy Monitoring

There are many ways of reducing the duration of pregnancy follow-up consultations, especially for patients with high-risk pregnancies (27). For example, a clinician may utilize the 2-hour 75-gram glucose tolerance test (GTT) or the 3-hour 100-gram GTT (in patients with positive results); the cell-free DNA scanning can be used for Down syndrome (\geq 10 weeks). In patients without symptoms, ultrasonography should be performed within the first trimester and detailed ultrasonography should be performed between 18 and 22 weeks. Any further ultrasonographic examinations should not be done unless necessary.

The psychological impact of COVID-19 should also be recognized and addressed. One study reported that approximately one-third of all subjects indicated moderate-to-severe anxiety (28). Another longitudinal study found that there was no major change in anxiety, depression, and stress symptoms at baseline and four weeks into the COVID-19 pandemic (29). Psychological interventions include online cognitive behavior therapy and mindfulness-based therapies via smartphone applications will help to alleviate anxiety and depression in pregnant women during the COVID-19 pandemic (30). Most pregnant patients with known or suspected COVID-19 have mild disease that does not require hospital care if there are no associated obstetric problems. Pregnant COVID-19 patients in the third trimester should be mindful of the number of fetal movements and report to their physicians if they are reduced. Other than this, the home care and other relevant instructions are similar to those for non-pregnant individuals (12). The US Food and Drug Administration has expanded its approval for the use of non-invasive fetal and maternal monitoring devices at home among patients requiring fetal and/or maternal monitoring for non-COVID-19-related cases (31). This could help reduce patient and healthcare provider contact and potential COVID-19 exposure during the pandemic.

Pregnant women with mild disease and comorbidities and those with moderate to critical illness are hospitalized. Hospitalized pregnant patients with severe disease, ventilation requirements, and comorbidities or those who are in critical condition should be monitored by a multidisciplinary team (12). These patients should be monitored with fetal monitoring and for preterm labor while paying close attention to the maternal oxygen levels. There are limited data regarding the association between COVID-19 and the risk of thromboembolism, but the available data suggest an increased risk. The American Society of Hematology, the Society of Critical Care Medicine, and the International Society of Thrombosis and Hemostasis recommend routine pharmacological venous thromboembolism (VTE) prophylaxis for pregnant patients with COVID-19 if there are no contraindications (32).

Antiviral Therapy

Remdesivir is a novel nucleotide analogue that is effective against SARS-CoV-2 *in vitro* (33) and against other related coronaviruses *in vitro* and in animal studies (34). It has been used in pregnant women with Ebola and Marburg viral diseases without causing fetal toxicity (35) and has been used to treat pregnant patients with severe COVID-19. Pregnant and breastfeeding women were not included in randomized trials of the drug during the COVID-19 outbreak.

Both hydroxychloroquine and chloroquine have been reported to inhibit SARS-CoV-2 *in vitro*, but data from early randomized studies have shown that they were not generally beneficial. Hydroxychloroquine crosses the placenta. Animal studies have reported its accumulation in fetal ocular tissues; however, given that the drug is commonly used by pregnant women to treat systemic lupus erythematosus or to prevent malaria, it is not associated with fetal ocular toxicity in humans. Adverse maternal effects include abnormal heart rhythms (36, 37).

Studies have investigated various other drugs such as lopinavir/ ritonavir, which is used primarily for the treatment of HIV infection, including during pregnancy. It crosses the placenta, can increase the risk of premature birth, and has not been observed with an increased risk of teratogenic effects in humans (38).

Tocolysis

In patients with known or suspected COVID-19, the recommended tocolytic agent is nifedipine. It is a suitable alterative to indomethacin and beta sympathomimetics (39).

Corticosteroid Therapy

For the general population, the CDC recommends avoiding glucocorticoids in COVID-19 positive individuals. This is because it has been associated with increased risk of mortality in influenza patients and delayed viral clearance in patients with Middle East Respiratory Syndrome- Coronavirus infection. However, the CDC has not evaluated the use of antenatal glucocorticoids to reduce neonatal morbidity and mortality resulting from premature birth in pregnant COVID-19-positive patients. Due to the clear benefits of antenatal betamethasone administration between 24 + 0 and 33 + 6 weeks in patients at a high risk of early preterm birth within seven days, the American College of Obstetricians and Gynecologists (ACOG) continues to recommend its use for standard indications in suspected or confirmed COVID-19 patients (40). However, for pregnant patients with suspected or confirmed COVID-19 at 34 + 0 to 36 + 6 weeks of gestation and at risk of preterm birth within seven days, the benefits to the newborn are less clear, and the ACOG has advised that betamethasone should not be administered to these patients.

Low-dose Aspirin Therapy

For non-COVID-19-positive pregnant women, the ACOG has stated that low-dose aspirin should continue to be prescribed as medically indicated (e.g., the prevention of preeclampsia) (41). For pregnant patients with suspected or confirmed COVID-19 for whom low-dose aspirin is indicated, the decision to use the drug should be made at an individual level.

Timing of Birth

Delivery is not indicated for most women with preterm mild-to-moderate COVID-19 who do not have any medical or obstetric indications for an emergency delivery. Ideally, delivery is performed after a negative test result is obtained or isolation is no longer required. This aims to minimize the risk of transmission of the virus to the newborn after birth (42).

The timing of birth is difficult for pregnant women with COVID-19 who are intubated or in a critical condition. Some authors argue that delivery is indicated after 32 to 34 weeks of gestation if the patient is stable; however, this approach can worsen the mother's condition. Fetal monitoring and maternal support are recommended for patients between the viability limit and <32 weeks of gestation as long as the mother's condition remains stable or improves. In some cases, maternal ECMO may be required (43).

Type of Delivery

COVID-19 is not an indication for changing the mode of delivery, and birth by cesarean section should be performed only for standard obstetric indications (44).

Postpartum Period

Venous thromboembolism prophylaxis

VTE prophylaxis should be decided on a case-by-case basis after risk assessment for all postpartum women with COVID-19. The optimal duration of anticoagulant therapy after delivery is unclear. Some authors recommend the discontinuation of prophylaxis after discharge, and others recommend continued prophylaxis for up to 10 to 14 days (12, 45).

Postpartum analgesia

For the treatment of postpartum pain in patients with COVID-19

in whom pain cannot be control with acetaminophen, non steroidal anti-inflammatory drugs can be used as the alternative of opioids (46).

Newborn assessment

Babies born to mothers with COVID-19 are considered suspicious for COVID-19 and should be tested. They need to be isolated from other healthy infants and cared for according to infection control measures for confirmed or suspected COVID-19 patients (47).

It is recommended that newborns be temporarily separated from suspected or confirmed COVID-19-positive mothers to reduce the risk of mother-to-baby transmission, but this application may also have adverse consequences (48). The WHO recommends that mothers who are suspected, likely, or certain to have the COVID-19 infection should stay together with their babies and have skin-to-skin contact (44).

The CDC recommends that the decision on whether to separate the baby from their confirmed or suspected COVID-19-positive mother should be taken on a case-by-case basis through a decision process involving both the mother and the healthcare team (47).

The infectiousness of the virus through breast milk is unknown. Breast milk samples from 26 infected women tested negative for SARS-CoV-2 (13).

Discharge

To limit the risk associated with hospital stay, early post-delivery discharge is recommended: one day after vaginal delivery and no more than two days after cesarean delivery (49).

The Current State in Turkey

In Turkey, the respiratory tract samples of patients who meet the criteria of suspected COVID-19 are evaluated with polymerase chain reaction diagnostic tests for COVID-19 in the Microbiology Reference Laboratories of the Public Health General Directorate (50), and COVID-19 rapid diagnostic kits have been available in Turkey since March 23, 2020. Our review of the literature indicated that there are currently no studies that have reviewed COVID-19 in pregnancy cases in Turkey, although there are individual case reports.

CONCLUSION

With a rapid increase in the number of cases, deaths, and affected countries, the COVID-19 outbreak is spreading rapidly. However, the full effects of the virus are not clearly understood due to limited data. Particularly, vertical transmission and the fetal and maternal effects of COVID-19 are still not clearly understood. It is especially important to put in place measures for the protection of pregnant healthcare workers who are under increased risk of infection. In addition, considering that the outbreak may have a psychological impact on pregnant patients and pregnancy-related side effects, pregnant women should be educated, provided with psychological support, and informed about the subject. During the outbreak, data should be recorded and evaluated reliably and the effects of the disease on the mother and fetus should be investigated.

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