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Maternal and neonatal outcomes of pregnant women with SARS-CoV-2 infection in our tertiary hospital

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Abstract

Objective: To evaluate clinical features, laboratory test results, and maternal and neonatal outcomes of pregnant patients with the Coronavirus disease (COVID-19).

Methods: We reviewed clinical data from pregnant women with a laboratory-confirmed SARS-CoV-2, who were admitted to our university hospital in Türkiye. Demographic and clinical characteristics, laboratory test results, and maternal and neonatal outcomes were collected.

Results: A total of 46 pregnant women were included in this study. The mean maternal age was 28 (min. 21 – max. 39) years and gestational age was 31 (min. 26 – max. 41) weeks. Two (4.37%) pregnant women were vaccinated with 1 dose of BioNTech® vaccine, and all other patients were unvaccinated. Shortness of breath was the most common symptom present in 15 cases (32.6%). Twenty-seven (58.69%) pregnant women gave birth in the preterm period, and 19 (41.30%) in the term period. Six (13.04%) pregnant women were followed up in the Anesthesia Intensive Care Unit. Two women with critical COVID-19 died in the postpartum period.

Conclusion: COVID-19 infection has negative consequences in terms of maternal and neonatal outcomes. The most common causes of adverse neonatal outcomes are iatrogenic or spontaneous preterm births, while the most common causes of adverse maternal outcomes are prolonged hospitalization time, increased likelihood of intensive care hospitalization, and maternal deaths. The most effective way to prevent this situation is to get vaccinated regardless of trimester.

Keywords: Coronavirus, COVID-19, pregnancy, SARS-Cov-2.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which was first reported from Wuhan, China in December 2019, has taken its toll on the whole world.[1] In March 2020, it was declared a pandemic due to the rapidly increasing number of cases in many parts of the world.[2] According to official figures, at the time of writing (30 March 2022), 485 million people were infected and 6.13 million died because of COVID-19. Every day, new cases, data, vaccine and treatment recommendations are reported to the literature regarding the COVID-19 outbreak.

The infection process of pregnant women infected with COVID-19 concerns both the pregnant woman and the fetus closely. In the natural course of pregnancy, in the first trimester, there is a pro-inflammatory environment due to trophoblast invasion, while in the third trimester, there is a pro-inflammatory environment to trigger delivery.[3] This pro-inflammatory environment creates a favorable environment for virus invasion dur-

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ing the first and third trimesters. In addition, progesterone, which is the predominant steroid hormone of pregnancy, has an immunosuppressive effect.[4] However, some physiological changes such as decreased functional residual volume, diaphragm elevation, edema in the respiratory mucosa, which occur within the framework of the physiological changes of pregnancy, also cause viral infections to progress more severely in pregnant women.[5] In many studies, it has been shown that there are both fetal and maternal adverse outcomes such as preterm birth, respiratory distress, fetal distress, and premature rupture of membrane in pregnant women who have had COVID-19.[1,6–8]

In this study, we evaluated the fetal and maternal outcomes in pregnant women infected with COVID-19 between April 2020 and December 2021 in our clinic, which is the only tertiary hospital in our city.

Methods

The research protocol used in this study was approved by Clinical Studies Ethics Committee of the Muğla Sıtkı Koçman University Training and Research Hospital (Date: 24.03.2022, Number: 18). It was conducted in accordance with the Principles of the Declaration of Helsinki. We conducted a retrospective cohort study of pregnant women who were confirmed to have COVID-19 by real-time quantitative reverse transcription PCR (qRT-PCR) and gave birth between April 2020 to December 2021.

Two authors (FM, HOY) evaluated the potentially eligible patients for concordance with the inclusion criteria for the study. Pregnant women who delivered while they were COVID-19 positive confirmed by nasopharyngeal and oropharyngeal swab specimens were included regardless of their symptoms.

The demographic and clinical data of the patients were obtained from the electronic medical records and archive files. The maternal age, gestational age at the time of birth, body mass index (BMI), symptoms, obstetric complications during pregnancy and neonatal outcomes were recorded. Laboratory tests included complete blood count, aspartate transaminase (AST), alanine transaminase (ALT), C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), urea, and creatinine. Fetal heart rate (FHR) monitoring via cardiotocography when pregnancy is >26–28 weeks of gestation and ultrasound assessment of fetal growth and amniotic fluid volume were performed. SARS-CoV-2 infection severity was categorized as severe and mild-moderate. Mild symptoms were described as upper respiratory congestion, headache, gastrointestinal symptoms, and myalgia. Severe symptoms were described as chest pain, dyspnea or low oxygen saturation (sO_2<92%)

Due to COVID-19 national guidelines issued by the Scientific Committee of the Turkish Ministry of Health, patients were followed up and treated.[9] When the women were stable, did not have shortness of breath or did not require oxygen, they were discharged and self-isolation at home was considered.

Statistical analysis was performed with SPSS version 23 (IBM Corp., Armonk, NY, USA). Descriptive statistical analysis was made. The normal distribution was evaluated by the Sharipo-Wilk test.

Results

A total of 46 pregnant women were included in this study. All pregnancies were singleton gestations. When the co-morbid diseases were evaluated, it was detected that 4 (8.69%) pregnant women had hypertension, 3 (6.52%) pregnant women had gestational diabetes mellitus (GDM), 2 (4.34%) pregnant women had DM and beta-thalassemia, 1 (2.17%) pregnant woman had hypothyroidism, F11 deficiency, and asthma. The demographic characteristics of the participants were shown in **Table 1**.

The mean number of admission days was 7.50±4.13. The patients who had severe symptoms (dyspnea, low oxygen saturation) were hospitalized (39 patients, 39.1%). The evaluation of complaints of pregnant women was as follows: dyspnea in 15 (32.6%), fever in 8 (17.39%), cough in 6 (13.04%), visual impairment in 2 (4.34%), and respiratory failure and tachypnea in 1 (2.17%). Eighteen (39.13%) pregnant women were

Table 1. Demographic characteristics of the participants.

	Mean	Range
Age (years)	28	21–39
Gravida (n)	2	1–7
Parity (n)	1	0–3
BMI (kg/m²)	26	19–35

asymptomatic. Laboratory findings of the participants were shown in **Table 2**. Bilateral diffuse lung involvement was present in 5 (10.86%) pregnant women, and viral pneumonia was present in the right and middle lobes in 1 (2.17%) pregnant woman. Two (4.37%) pregnant women had 1 dose of BioNTech® vaccine and all other patients were unvaccinated.

Six (13.04%) pregnant women were followed up in the Anesthesia Intensive Care Unit (ICU). All of them were unvaccinated. Two (4.34%) of them died. A pregnant woman who died at the age of 28 was unvaccinated, and a Cesarean section (CS) was performed at the 27 weeks of gestation with the diagnosis of preeclampsia and fetal distress. Diabetes mellitus (DM), hypertension and hyperlipidemia were present among the co-morbid diseases. Seven days after her symptoms started, she was admitted to ICU because of dyspnea, hypoxemia and widespread pulmonary lesions. She was given lopinavir+ritonavir (10 days), intravenous immunoglobulin 0.4 mg/kg/day (5 days), methylprednisolone 250 mg/day for 3 days proceeded by 1 mg/kg, antibiotherapy, magnesium infusion for preeclampsia and vitamin D supplementation. She was intubated on the 2nd day of her admission. At the 7th day, CS was performed due to persistent hypoxia and hypertension. She was extubated on day 10. However, she had critical illness with motor neuropathy, pericarditis, and severe pneumonia during the ICU course, and ultimately died due to septic shock after being followed up in our ICU for approximately 1 month.

The other pregnant woman who died was 29 years old, unvaccinated and at 28 weeks of gestation. After she was delivered by CS with the diagnosis of respiratory failure and fetal distress, she died while being followed up with an extra corporeal membrane oxygenation (ECMO) device on the postpartum 38th day. She was given antibiotherapy, dexamethasone 8 mg/day, favipravir 3200 mg for first day and 1200 mg/day (4 days), and intravenous immunoglobulin 0.4 mg/kg/day (5 days). Her lung compliance was very low and standard measures such as lung protective ventilation, prone positioning and muscle relaxants did not improve oxygenation and ventilation. Thus, she was placed on veno-venous ECMO on 5th day. However, her lung compliance never restored and she died due to complications related to hypoxemia.

Of the COVID-positive pregnant women delivered in our clinic, 43 (93.47%) had CS and 3 (6.52%) had vaginal delivery. When the timing of delivery was evaluated, 27 (58.69%) pregnant women delivered in the preterm period, and 19 (41.30%) in the term period. Indications for CS were as follows: previous CS history in 19 (30.23%) pregnant women, hypertensive disorders of pregnancy such as preeclampsia and eclampsia in 10 (23.25%) pregnant women, uteroplacental insufficiency in 6 (13.95%) pregnant women, fetal distress in 3 (6.97%) pregnant women, maternal disseminated intravascular coagulation disorder (DIC), BPU and maternal pneumonia in 2 (4.65%) pregnant women, and maternal hypoxia and maternal sepsis in 1 (2.32%) pregnant woman. Obstetrician's and pregnant women's negative attitude towards vaginal birth is another reason for the high CS rate. There were 4 fetuses with fetal intrauterine exitus. None of them accepted fetal autopsy. In the maternal evaluation of these fetuses, 2 (4.65%) pregnant women developed DIC and 2 (4.65%) pregnant women developed severe preeclampsia. Seven (15.21%) babies with APGAR score >7 were born. Of these pregnant women, 2 (4.34%) had eclampsia, 1 (2.17%) had pneumonia, sepsis and bilateral lung involvement. The neonatal outcomes of the participants are shown in **Table 3**.

Table 2. Laboratory findings of pregnant women included in the study.

	Mean	Range
WBC (mcL) *10^3	11	4.39–20.6
Lymphocyte (mcL)	1750	240–16,830
Neutrophil (mcL)	7790	410–19,310
CRP (mg/L)	16	0.75–287
AST (unit/L)	24	6–1136
ALT (unit/L)	12	5–346
Urea (mg/dl)	15	3.2–125
Creatinine (mg/dl)	0.6	0.34–1.7
D-dimer (ng/mL)	1096	469–6986
Platelet (cell/mL) *10^3	226	24–488

Table 3. Neonatal outcomes of the participants.

	Mean	Range
Week of gestation (w)	36	23–40
Birth weight (g)	2600	610–3600
Apgar score* (n)	8	2–10

*IU dead fetuses are not included.

Discussion

The number of studies in the literature on pregnant women infected with COVID-19 is increasing day by day. We gain experience in the disease process and management thanks to these studies. In the present study, our purpose is to contribute to the literature by sharing the follow-up process of pregnant women infected with COVID-19 that we follow in our tertiary hospital.

One of the milestones of the battle against COVID-19 is vaccination. After an effective vaccination process, the pandemic was brought under control. The possibility of transmission to vaccinated people has decreased, while individuals infected with COVID have started to have mild symptoms.[10] In the process, there were beliefs that the fertility of vaccinated women would be adversely affected, and that there would be a teratogenic effect on the fetus in pregnant women.[11,12] However, with the increase in information about the vaccine, it has been proven that there is no such result. Currently, many associations, especially the Centers for Disease Control and Prevention (CDC) mention that it is possible to be vaccinated at any time of pregnancy.[13] Only 1 (2.17%) of the patients in our study had 1 dose of the BioNTech® vaccine, all the other patients were unvaccinated. But it is not possible to draw direct conclusions about the effects of the vaccine in this study. Today, WHO and American College of Obstetricians and Gynecologists (ACOG) recommends Coronavirus vaccine for all pregnant and postpartum women.[14]

Symptomatology has an important place in the follow-up and treatment of both pregnant and non-pregnant patients infected with COVID-19.[15] In the study of Yüksel et al. conducted in our country, pregnant women infected with COVID-19 were divided into two groups according to their symptoms as mild-moderate symptoms and severe symptoms. According to these groups, the symptoms were respectively as follows; fever 28.6% and 9.5%, myalgia 64.5% and 66.7%, cough 60.7% and 61.9%, loss of taste 41.9% and 14.3%, and dyspnea 3.2% and 19.0%.[14] In the study of Şahin et al., the symptoms were as follows: fever 27.6%, cough 58.6%, dyspnea 34.5%, chest pain 3.4%, myalgia 51.7%, nasal congestion 13.8%, sore throat 37.9%, anosmia 31%, ageusia 20.7%, headache 24.1%, nausea/vomiting 20.7%, and diarrhea 3.4%.[1] In our study, the symptoms were as follows: dyspnea 32.6%, fever 17.39%, cough 13.04%, visual impairment 4.34%, and respiratory failure and tachypnea 2.17%.

In a study conducted in the United States, it was shown that advanced age and co-morbid diseases such as obesity, chronic lung diseases, chronic hypertension, and pregestational DM cause COVID infection to be more severe in pregnant women.[16] In the study of Takemoto et al., it was stated that the most common co-morbid disease associated with maternal mortality was asthma.[17] In the study conducted by Şahin et al. in our country, co-morbid diseases were detected in 34.5% of pregnant women infected with COVID-19.[18] These diseases are obesity (50%), hypothyroidism (40%), and asthma (10%). Of the 46 pregnant women included in our study, 4 (8.69%) had chronic hypertension, 3 (6.52%) had GDM, and 2 (4.34%) had pregestational DM, hyperthyroidism, asthma, and Factor 11 deficiency. There were no obese pregnant women and pregnant women at an advanced age.

A recent systematic review of 1630 COVID-positive pregnant women reported that 15 women were diagnosed with coagulopathy, thromboembolic disease, deep vein thrombosis, or DIC, suggesting that COVID-19 increases the risk for these pathologies.[19] Tendency to thromboembolic conditions during pregnancy can be triggered by the intervention of COVID to the process. Extensive bilateral lungs involvement was observed in 10% of pregnant women, and lobar pneumonia was observed in 2%. In addition, DIC development was observed in 2 (4.34%) pregnant women, and sepsis in 1 (2.17%). As can be seen in our study, DIC is one of the factors that cause worsening of the picture and fetal deaths in this process.

Compared with non-pregnant women infected with COVID, pregnant women were found to be more likely to be admitted to ICU (10.5 vs. 3.9 per 1000 cases), 2.9 times more likely to require invasive ventilation (2.9 vs. 1.1 per 1000 cases), 2.4 times more likely to require extracorporeal membrane oxygenation (0.7 vs. 0.3 per 1000 cases), and 1.7 times more likely to die (1.5 vs. 1.2 per 1000 cases).[20] In the study conducted by Yüksel et al. conducted in our country, the rate of hospitalization in ICU and pregnant women with severe symptoms were 12.9% and 14.3%, respectively.[14] Follow-up of 6 (13.04%) pregnant women who had a severe course of the disease and needed additional treatment was performed in the Anesthesia ICU.

The entry of SARS-CoV-2 into the body is mediated by angiotensin-converting enzyme 2 (ACE2). ACE2

expression increases during pregnancy, which may predispose to SARS-CoV2 infection. In the period when COVID-19 is especially "severe"; Its pathogenesis causes systemic inflammation, ARDS, multi-organ failure. This causes the uncontrolled release of proinflammatory cytokines which leads to death.[21] In our study, there were two (4.34%) cases of pregnant women which resulted in maternal death. Clinical information about these pregnant women was given in the Results section of our article.

In the literature, it is known that pregnant women infected with SARS-CoV-2 have an increased risk of preeclampsia, preterm birth and stillbirth compared to those who are not infected with SARS-CoV-2.[1] In the study of Özsürmeli et al. conducted in our country, preeclampsia was found 8.3%.[22] At the time of publication of the study by Şahin et al., 34.5% of the pregnancies were terminated. Preeclampsia was detected in 1 (10%) of 10 pregnant women who gave birth.[18] In our study, we observed preeclampsia in 2 (4.34%) patients and eclampsia in 2 (4.34%) patients.

A UK Obstetric Surveillance System (UKOSS) study confirmed that preterm birth is more common in women infected with COVID-19. Nineteen percent of symptomatic pregnant women and 9% of asymptomatic pregnant women delivered before 37 weeks gestation. Wei et al. found that the probability of preterm birth increased by 1.82 times (OR) in pregnant women with COVID-19 in the meta-analysis.[1] In the study of Şahin et al., the rate of preterm birth was 6.9%.[18] In the study of Erol Koç et al., the mean week of delivery of pregnant women infected with COVID-19 was 35.6±3.6.[23] In our study, when we evaluated the timing of delivery, 27 (58.69%) pregnant women delivered in the preterm period, and 19 (41.30%) in the term period. We need to optimize maternal treatment in our COVID-19 management or to avoid fetal deaths in fetal distress, which we frequently encountered.

Maternal COVID-19 is associated with an increased rate of CS delivery. A study in Wuhan, China comparing COVID-19-positive pregnant women and COVID-19-negative pregnant women reported an increased risk of CS in those with COVID-19 (OR 3.34 and 95% CI 1.60–7.00). Indications for CS included worsening COVID-19 symptoms such as shortness of breath in the mother.[24] In the study of Şahin et al., the CS rate was 50%.[18] The reasons for CS indications is the deterioration of the maternal condition in 40%, and fetal reasons in 60%. Similarly, in our study, CS rates seem to have increased in COVID-positive pregnant women. In the study of Erol Koç et al., the CS rate was 71.8%.[23] Forty-three (93.47%) in the COVID-positive group of patients delivered in our clinic had CS and 3 (6.52%) had a vaginal delivery. The most common indication is CS history with 30%, followed by hypertensive diseases of pregnancy (23.25%), uteroplacental insufficiency (13.95%), fetal distress (6.97%), maternal hypoxia (4.65%), and maternal sepsis (2.32%).

There may be an increased rate of fetal distress during labor in women with COVID-19. In the study conducted by Özsürmeli et al., the infants' mean 1-minute and 5-minute Apgar scores were 7.11±2.13 and 8.55±1.33, respectively. One neonatal death was detected in the same study.[22] In the study conducted by Şahin et al., the mean 1-minute and 5-minute Apgar scores were 8 (1.25, 6–9), and 9 (1.8–10), respectively. In the same study, 30% of the infants were hospitalized in the neonatal ICU.[18] Three of the pregnant women in our study underwent CS due to fetal distress. When we evaluated all of the deliveries, mean 5-minute Apgar score was 8 (2–10). In addition, we observed 4 (8.69%) intrauterine deaths in our study.

In addition to the direct impact of COVID-19 on pregnancy outcomes, there is evidence that the pandemic and its effects on health systems have adverse effects on pregnancy outcomes, even among those not infected with SARS-CoV-2.[25] The ongoing curfews at the beginning of the COVID-19 pandemic may have indirectly made it difficult for pregnant women to access health services due to reasons such as the increase in the need for intensive care and the lack of health personnel, and may have caused secondary consequences by resulting in delays in follow-up.

Limitations

The conduction of our study in a single hospital with a small number of patients is a limitation of our study. The lack of information about treatment modalities and options is another limitation of our study.

Conclusion

According to the results of our study, COVID-19 infection has negative consequences in terms of maternal and neonatal outcomes. The most common causes of adverse

neonatal outcomes are iatrogenic or spontaneous preterm births, while the most common causes of adverse maternal outcomes are prolonged hospitalization time, increased likelihood of intensive care hospitalization, and maternal deaths. It is noteworthy that the majority of our patients who were followed up were unvaccinated, and a few of them were partially vaccinated. Therefore, vaccination should be recommended to women who are planning a pregnancy or are pregnant.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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