The Impact of Coronavirus Disease-19 on Pregnancy Outcomes, A Case Series

Bilge CETINKAYA DEMIR¹, Ozge ALBAYRAK¹, Kiper ASLAN¹
Bursa, Türkiye

ABSTRACT

OBJECTIVE: To investigate the impact of Corona Virus Disease 19 (COVID-19) infection on pregnancy outcomes.

STUDY DESIGN: This retrospective study was conducted at a tertiary university hospital between the years of October 2020-October 2021. All the pregnant women with COVID-19 diagnoses were enrolled in the study during this period. Demographic parameters, a history of Favipiravir use, COVID-19 symptoms, treatment approaches, hospitalization, intensive care unit admission, and obstetric and neonatal outcomes were recorded.

RESULTS: A total of 92 patients were enrolled in the study. The mean age was 30+5 years. Forty-seven of the patients were asymptomatic (51%). The most common symptoms were respectively; fatigue (37.8%), fever (27.6%), dyspnea (22%), cough (17.8%), headache (11%), anosmia (4.4%), hyperemesis (4.4%), diarrhea (2.2%). There were 20 patients (21.7%) who were hospitalized. Eight of these women (8.6%) required intensive care unit admission due to COVID pneumonia-related acute respiratory distress syndrome. Five of the patients treated in the intensive care unit died due to respiratory failure. Two patients had a miscarriage before the 20th week. There were four stillbirths. The gestational weeks at which fetal death occurred were 24, 26, 28, and 38 weeks of gestation. There were 19 patients with a history of favipiravir use. There was not any other congenital abnormality due to Favipiravir usage.

CONCLUSION: Our study showed that COVID-19 disease has similar symptoms in pregnant women to non-pregnant women, according to the literature data. However, COVID-19 infection increases the rates of pregnancy complications and maternal mortality.

Keywords: Corona virus disease, COVID-19, Favipiravir, Pregnancy

Introduction

Since the first case of Coronavirus Disease 19 (COVID-19) was reported in Wuhan City, China (1), there have been over five million deaths with nearly 500 million cases due to COVID-19 infection (2). The COVID-19 pandemic is one of the most devastating pandemics of our times regarding this actual number. Although it has been over three years, health providers still could not find an exact treatment for the disease. Symptomatic treatments and vaccines have been developed, but the curative treatment is still waiting to be explored. Beyond the treatment, there are too many unknowns about COVID-19. The disease can react differently in different patient populations, such as pregnant women. Pregnant women may be risky of developing more severe conditions after infection due to physiological changes in the immune and cardiopulmonary systems during pregnancy (3). Small case series was published at the first stages of the pandemic and those studies reported increased fatality and more severe complications during pregnancy (4-6). However, COVID-19 pneumonia in pregnant women has been reported to be similar to that in non-pregnant women (7,8). The exact relationship between COVID-19 and pregnancy is not very clear. Furthermore, there is still no evidence of vertical transmission of COVID-19 (9). Therefore, the intrauterine and neonatal effects of the disease due to maternal infection are also unclear.

The present study aimed to investigate the association between COVID-19 and pregnancy. We studied the maternal
and neonatal outcomes of COVID-19-positive pregnant women.

**Material and Method**

**Study Design, Ethical Approval:** This retrospective study was conducted at Bursa Uludag University School of Medicine, Dept. of Obstetrics and Gynecology. The study protocol was approved by Bursa Uludag University Faculty of Medicine, Clinical Trials Ethical Committee with the number; 2022-1/10.

**Patient Selection:** The study period was from 1 October 2020-1 October 2021. The women who were admitted to the perinatology clinic were investigated. Pregnant women whose COVID-19 PCR test was positive and who had a history of favipiravir usage during pregnancy or before pregnancy (<8 weeks) were included in the study. Since the study was conducted in a perinatology clinic, a control group consisting of non-pregnant women with COVID-19 could not be formed.

**Interventions and Statistical Analysis:** Demographic parameters, obstetric history, maternal and fetal risk factors, gestational age at the COVID-19 diagnosis, symptoms, treatment approaches, favipiravir usage, the need for hospitalization or intensive care unit (ICU), and obstetric & neonatal outcomes of all patients were recorded from the electronic database. To investigate whether there is any adverse effect of COVID-19 disease on the placenta, the placentas of all patients with stillbirth were evaluated by the pathology department.

Depending on the distribution, continuous variables are defined as mean ± standard deviation (SD) or median (25th-75th percentile). Categorical variables are defined as percentages.

**Results**

Eighty-nine patients with COVID-19 PCR positive test and three with Favipiravir usage due to COVID before pregnancy (<8 weeks) were included in the study. The obstetric outcomes of the six patients were missing. Four patients were diagnosed in the first trimester, and the other two were diagnosed at the 34th and 35th weeks of pregnancy. They gave birth elsewhere due to their clinical well-being. Therefore, a total of 86 patients’ records were included in the analysis (Figure 1).

Five patients were health providers (one pediatrician-intubated, one internal medicine resident, one clinic staff, one operation room staff, and one wife of the operation room staff). The incidence of COVID-19 in health providers was found as 5.4%.

The mean age was 30±5 yrs. The median gestational week at COVID-19 diagnosis was 14 (25-75 Percentiles; 5-25) weeks. Forty-seven of the patients were asymptomatic (51%) (Figure 2). The most common symptoms were respectively: fatigue (37.8%), fever (27.6), dyspnea (22%), cough (17.8%), headache (11%), anosmia (4.4%), hyperemesis (4.4%), diarrhea (2.2%) (Figure 3).
There were 20 hospitalized patients (21.7%). Eight of these women (8.6%) required ICU admission due to COVID pneumonia-related acute respiratory distress syndrome. Five patients in the ICU died due to respiratory failure. One of these patients had 20 weeks of pregnancy. Therefore, we did not plan the birth, but the others had viable pregnancies. Cesarean section (CS) was performed for these patients after intubation. Details are given in table I.

### Table I: Maternal and neonatal outcomes of the patients who required ICU admission

<table>
<thead>
<tr>
<th>Age</th>
<th>Gravida</th>
<th>Parity</th>
<th>Symptom</th>
<th>Gestational Week at COVID-19 Diagnosis</th>
<th>Treatments</th>
<th>Intubation</th>
<th>Maternal Outcome</th>
<th>Birth Week</th>
<th>Birth Indication</th>
<th>Way of the birth</th>
<th>Fetal Weight</th>
<th>APGAR Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>2</td>
<td>1</td>
<td>Fatigue</td>
<td>25</td>
<td>Favipiravir Remdesivir Meropenem LMWH</td>
<td>Yes</td>
<td>Ex (Myocarditis)</td>
<td>28</td>
<td>Fetal Demise</td>
<td>Vaginal Birth</td>
<td>600</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>4</td>
<td>3</td>
<td>Fatigue Dyspnea</td>
<td>34</td>
<td>Ritonavir Lopinavir LMWH</td>
<td>Yes</td>
<td>Ex (Respiratory Failure)</td>
<td>34</td>
<td>Previous CS</td>
<td>CS</td>
<td>2290</td>
<td>8-9</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>1</td>
<td>Dyspnea Fatigue</td>
<td>28</td>
<td>Remdesivir Prednisolone LMWH</td>
<td>Yes</td>
<td>Discharged</td>
<td>28</td>
<td>Fetal Distress</td>
<td>CS</td>
<td>1260</td>
<td>1-4-5-6 Intubated</td>
</tr>
<tr>
<td>36</td>
<td>1</td>
<td>0</td>
<td>Dyspnea Fatigue</td>
<td>25</td>
<td>Remdesivir Prednisolone LMWH</td>
<td>Yes</td>
<td>Discharged (ECMO for 3 Months)</td>
<td>25</td>
<td>Maternal Indication</td>
<td>CS</td>
<td>845</td>
<td>1-5-7 Intubated</td>
</tr>
<tr>
<td>36</td>
<td>1</td>
<td>0</td>
<td>Dyspnea Fever</td>
<td>24</td>
<td>Remdesivir Prednisolone LMWH</td>
<td>Yes</td>
<td>Discharged at 27th pregnancy week</td>
<td>38</td>
<td>Elective</td>
<td>CS</td>
<td>3500</td>
<td>9-10</td>
</tr>
<tr>
<td>23</td>
<td>1</td>
<td>0</td>
<td>Dyspnea Fatigue</td>
<td>27</td>
<td>Steroid Remdesivir Ceftriaxone Ritonavir Anakinra</td>
<td>Yes</td>
<td>Ex (Respiratory Failure)</td>
<td>28</td>
<td>Fetal Distress</td>
<td>CS</td>
<td>1070</td>
<td>1-4-5-5 Intubated</td>
</tr>
<tr>
<td>31</td>
<td>4</td>
<td>3</td>
<td>Dyspnea Fatigue</td>
<td>19</td>
<td>Lonipavir Prednisolone LMWH</td>
<td>Yes</td>
<td>Ex (Respiratory Failure)</td>
<td>21</td>
<td>Preterm Birth</td>
<td>Vaginal Birth</td>
<td>400</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>2</td>
<td>1</td>
<td>Dyspnea Fatigue</td>
<td>26</td>
<td>Lonipavir Steroid LMWH Ceftriaxone</td>
<td>Yes</td>
<td>Ex (Respiratory Failure)</td>
<td>28</td>
<td>Twin/Preterm Birth</td>
<td>CS</td>
<td>1080/1035</td>
<td>7-8/7-8</td>
</tr>
</tbody>
</table>
Nineteen patients had favipiravir usage (preconceptionally eight weeks or early pregnancy <8 weeks). Eight of these patients underwent pregnancy termination due to favipiravir’s teratogenicity. One of the patients with ongoing pregnancy after favipiravir usage had preterm labor due to PPROM (21st pregnancy week). The remaining 10 pregnancies resulted in live births. The routine audiometry test was abnormal in one of the newborns. There was another neonate with unexplained neonatal seizures & abnormal electroencephalogram (EEG). There was not any other congenital abnormality due to favipiravir usage.

Two patients had a miscarriage before the 20th week. There were four stillbirths. These patients had no favipiravir usage. The gestational weeks at which fetal death occurred were 24th, 26th, 28th, and 38th weeks. Pathological examination of placentas taken from these patients was reported as placental infarct. Details are given in table II.

Mean birth week was 354±5 weeks, mean birth weight was 2934±898 gr. Fifty-six patients gave birth by CS and 15 patients by vaginal delivery.

The median APGAR1 score was 7 (25-75 Percentiles; 8-9), and the median APGAR5 was 8 (25-75 Percentiles; 8-9).

All the neonates were tested for COVID-19 by PCR test on the first day, and none of the tests was positive.

**Discussion**

This study presented the pregnancy outcomes of COVID-19 positive-women. While 51% of the women were asymptomatic, 21.7% required hospitalization, and 8.6% needed ICU admission. The maternal mortality rate due to COVID-19 was 5.4%. The overall mortality rate is approximately 1.2% according to the World Health Organization (WHO) Coronavirus database (2). These results show that pregnancy complicates the progress of the COVID-19 disease. Furthermore, the maternal mortality rate is nearly 30 times higher than the healthy population. The increased mortality rate of COVID-19-positive pregnancies is thought to be related to physiological changes due to pregnancy conditions. A widespread multinational study by Villar et al. showed that COVID-19 in pregnancy is associated with consistent and substantial increases in severe maternal morbidity and mortality (10). Another reason for the high mortality rate in our study may be related to the fact that our hospital is a referral center. The main reason for our deaths was respiratory failure due to COVID-19 pneumonia, except for one patient who died because of myocarditis (Table II).

Beyond the increased maternal mortality, there is enough evidence about the relationship between adverse pregnancy outcomes and COVID-19 (4). We demonstrated relatively high miscarriage (4.3%) and stillbirth (4.3%) than the healthy population. These results are also similar to the previously published studies about COVID-19 pregnancies. Kumari et al. reported a stillbirth rate of 2.7% (11), and another study investigating the pregnancy results of low-income countries found a 2.8% stillbirth rate during the COVID-19 pandemic (12). A prospective comparative study demonstrated the 5.1% stillbirth rate in COVID-19-infected mothers (13). The possible etiology for fetal loss is mainly related to the effects of the virus on the fetoplacental unit, notably with coagulopathy (14,15). In our study, pathological examination of placentas taken from patients with stillbirth was reported as infarct. Therefore, the exact reason for the fetal loss is probably placental coagulopathy due to COVID-19 infection.

<table>
<thead>
<tr>
<th>No</th>
<th>Age (years)</th>
<th>Risk Factors</th>
<th>Gestational Week at COVID-19 Diagnosis</th>
<th>Estimated Week of Fetal Demise</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>Hydrops Fetalis</td>
<td>28</td>
<td>29</td>
<td>The etiology of hydrops fetalis could not be determined in the pregnancy follow-up, it was found to be positive for COVID-19 during the routine checks after fetal death.</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>Trisomy 21</td>
<td>14</td>
<td>38</td>
<td>The fetus had serious cardiac malformations due to Trisomy 21.</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>Chronic Hypertension</td>
<td>15</td>
<td>24</td>
<td>The patient had regular visits during pregnancy without hypertension until COVID-19 infection. During the infection, fetal growth restriction and superimposed pre-eclampsia developed. Pathologic investigation of the placenta resulted in an infarct.</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>IVF Twin Pregnancy</td>
<td>25</td>
<td>27</td>
<td>The patient had COVID-19 pneumonia and pulmonary embolism. One of the fetuses died in utero. CS was performed and APGAR 6-7 940 gr healthy fetus was born. Pathologic investigation of the placenta resulted in infarct, bleeding, and chorioamnionitis.</td>
</tr>
</tbody>
</table>
preterm delivery rate in our study was 27%. The main reason was preterm labor. A meta-analysis of COVID-19 pregnancies reported a preterm birth rate of 29.7% in case reports and 16% in observational studies (16).

The cesarean rate in our study was 75%. The most common indications for CS were previous CS - almost half, fetal distress 19%, and malpresentation 11%. At the beginning of the pandemic, there was a trend toward CS for all suspected infectious mothers to avoid intrapartum transmission (17). Novel case series show high rates of CS than expected numbers (over 80%) (17,18). Our results are consistent with the published data.

None of the fetuses had a positive COVID-PCR test. These results support that COVID-19 infection has no vertical transmission during pregnancy. There is still no evidence of vertical transmission. A systematic review that included 43 articles with 1300 neonates born from pregnant women confirmed for COVID-19 reported that only 93 (7%) of the newborns’ tests were positive, which may be due to perinatal or postnatal transmission (19).

Another issue about COVID-19 and pregnancy is favipiravir usage. Favipiravir is an antiviral drug that is one of the treatment options for COVID-19 (21). Favipiravir use has been shown to increase congenital malformations and fetal loss in animal studies (22). Therefore, it is contraindicated to use it preconceptionally and during pregnancy. Moreover, it has adverse effects on sperm (23). There were 19 women with a history of favipiravir use (preconceptionally or during pregnancy). Eight of these patients decided to terminate the pregnancy in the first trimester due to the high risk of teratogenicity. Other women (12/19) who wished to continue pregnancy were followed up.

One patient had preterm labor due to amniotic fluid leakage at the 21st gestational week. The only observed congenital malformations were ventriculomegaly and nasal bone hypoplasia. The ventriculomegaly spontaneously regressed before birth. We performed chorionic villus sampling for the fetus with nasal bone hypoplasia, and the result was reported as 46 XX. The patient gave a healthy 3460 gr girl by CS. There were two neonatal abnormalities; one fetus had an abnormal audiometry test, and one had unexplained seizures with abnormal EEG. We do not know whether these abnormalities are related to favipiravir use. A novel publication that assessed favipiravir and pregnancy outcomes showed that favipiravir is unlikely to be a major human teratogen (24). The data is still limited for a well-grounded assessment of favipiravir. United States Food and Drug Administration (FDA) has only approved Remdesivir as an antiviral drug for COVID-19 (25).

Our study has some limitations; Firstly, we tried to compare our results with the published literature data, lack of a control group limits the interpretation of our results. Secondly, since our hospital is a referral center, the high number of risky patients may have affected the results.

Conclusion

In this study, we reported the outcomes of COVID-19-positive pregnancies. Our results showed that COVID-19 has similar symptoms in pregnant women to non-pregnant women according to the literature data. However, COVID-19 infection increases fetal loss rates (miscarriage or stillbirth), preterm birth, CS, and, maternal mortality.

Declarations

Ethics Approval and Consent for Using Data: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Bursa Uludag University (2022-1/10).

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Author Contributions: All authors contributed to the study’s conception and design. BCD designed and reviewed the study. Material preparation, data collection, and analysis were performed by OA. The first draft of the manuscript was written by KA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials: The data underlying this article can be shared on reasonable request to the corresponding author.

References


