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COVID-19 infection in pregnancy: A single-center experience in Rize in the Eastern Black Sea Region

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Abstract
Aim: In this study, it was aimed to share the clinical experiences of mothers and their babies (perinatal, natal) who encountered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy.
Material and Methods: The study was carried out retrospectively, 62 pregnant individuals were diagnosed with the 2019 coronavirus disease (COVID-19). Demographic characteristics, clinical course, laboratory and radiological findings and clinical results of the baby were evaluated by examining electronic and file records.
Results: The average age of the 62 pregnant women included in the study was 29.8±4.7 (19-42) years, and the average gestational week at the time of admission was 28.5±10.4 (5-40) weeks. More than half of the patients (80,6%) on admission were in their third trimester. The most common initial symptoms were cough (45.2%), myalgia (43.5%),) fever (21%). In total, 15 of the pregnant women had evidence of COVID-19 pneumonia in lung involvement. The PCR test results of all pregnant women were positive. There were three cases admitted to the intensive care unit, one of whom was due to gestational diabetes. No maternal mortality was recorded. One gestation ended in a miscarriage and two women gave birth prematurely. One stillbirth occurred at the 33h week of gestation. Among 22 neonates, two were admitted to the neonatal intensive care unit. Neonatal mortality, congenital malformation, and mother- to- child transmission were not observed in newborns.
Discussion: The results of our study suggest that the clinical course of COVID-19 infection in pregnant women was mostly asymptomatic/mild.

Keywords
COVID-19, Maternal Outcome, Pregnancy, Perinatal Outcome, SARS-CoV-2

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Introduction

The 2019 coronavirus infection (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV 2) started as an epidemic and soon caused a pandemic all over the world and spread rapidly. Even though the COVID-19 virus usually causes non-symptomatic or mild, self-limited respiratory tract infection, it is more prominent in the immunocompromised patient group, including pregnancy. It causes more serious disorders such as viral pneumonia, acute respiratory distress syndrome (ARDS) and multisystem organ involvement, including gastrointestinal, cardiovascular and neurological (World Health Organization. Coronavirus Disease 2019 (Covid-19) Situation Report – 88. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation reports/. Accessed October 7, 2020). Today, its epidemiology, physiopathology and what kind of effects it creates in which type of patients are still not fully clarified, and research continues [1-3].

Pregnant women are prone to infections, especially respiratory diseases, both due to anatomical and physiological changes during pregnancy and due to immunosuppression. In addition, immature immune systems in the fetus and newborn make pregnant women vulnerable to infections. Outbreaks of coronavirus experienced in previous years, "Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS)", have been associated with serious consequences such as high mortality in pregnant women, their fetuses and newborns, and premature birth [4-9].

In the literature, the current COVID-19 outbreak is considered to pose a potential threat to pregnant women and their fetuses. However, data on the impact of COVID-19 infection on pregnancy are still limited, and clinical management algorithms and effective treatment of pregnant women infected with COVID-19 are not yet clear. Therefore, it seems that more data on the effect of the disease on pregnant women are needed. In this study it was aimed to share clinical experiences of mothers and their babies (perinatal, natal) who encountered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy.

Material and Methods

The study was conducted as a retrospective descriptive study. Patients who were followed up by the Department of Infectious Diseases and Clinical Microbiology of the XXXXXXXXXXX of Medicine with the diagnosis of COVID-19 in the first year of the pandemic and who had clinical symptoms and had compatible PCR positivity and tomography (CT) findings were included in the study. Demographic and clinical characteristics, laboratory and radiological findings and perinatal outcomes of the patients were analyzed with the data obtained from the patient follow-up and treatment form using the hospital registry system. Pregnant women were categorized according to the severity of the disease as asymptomatic, mild-moderate, severe-critical [10].

Pregnant women with mild to moderate pneumonia disease (fever, muscle, joint pain, cough, sore throat symptoms, respiratory rate<20/minute, SpO2>93%, lung involvement), pregnant women with severe-critical pneumonia disease (fever, muscle, joint pain, cough, sore throat symptoms and SpO2<90, respiratory rate ≥30/minute, diffuse lung involvement), pregnant women who are asymptomatic and who were followed up on an outpatient basis, pregnant women with clinical symptoms who did not accept treatment despite being offered treatment, and pregnant women diagnosed with respiratory tract pathogens other than COVID-19 were excluded from the study. The treatment protocol was chosen according to the Turkish Ministry of Health guidelines. Written consent was obtained from pregnant women for the examination and treatment protocols to be applied.

Ethical Approval

The study was approved by the Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine Training and Research Hospital (protocol no 2021/110).

Statistical Analysis

Statistical analyses were done using SPSS version 21.0 (Chicago IL, USA). Data are presented as mean ± standard deviation, median (minimum-maximum), n (%) or n/N (%), where N is the total number of patients with available data.

Results

Among the patients examined within the scope of the study, 20 out of 82 pregnant women with a history of exposure to COVID-19 infection were excluded because their clinic was asymptomatic or they did not accept treatment. The average age of the 62 pregnant women included in the preliminary study was 29.8±4.7 (19-42) years, and the average gestational week at the time of admission was 28.5±10.4 (5-40). Most of the pregnant women (n=50 and 80.6%) were found to be infected with SARS-CoV-2 in the third trimester. When the application complaints were examined, it was determined that 45.2% (n= 28) cough, 43.5% (n= 27) myalgia, and 21% (n=13) fever were the most common complaints. The oxygen saturation of the patients at the time of admission was 92.42±7.51 (85-99). Five pregnant women had a pre-existing chronic disease (rheumatoid arthritis, renal failure, hypothyroidism, two chronic hepatitis B (HBV), respectively), one pregnant had a history of gestational diabetes and one of them had a history of gestational hypertension. The clinical features of the pregnant women, disease severity and treatment included in the study are summarized in Table 1.

At the time of admission, lymphocytes of the patients were 1399±598 (360-3350), neutrophil-lymphocyte ratio was 5.5±3.7(1.3-18.7), D-dimer (ng/ml) was 1.3±0.7(0-3.5) and CRP values were found to be 21.4±23.6 (0.4-110). Laboratory data are summarized in Table 2. Eight patients (12.9%) who had respiratory distress (oxygen saturation SpO2<93, respiratory rate ≥30/min) on hospitalization were screened for PAAC radiographs after obtaining their consent. Local infiltration was detected in two patients (3.2%) and bilateral infiltration in six patients (9.6%). Protected lung tomography was performed in seven patients (9.7%), and more than 50% pneumonic involvement was observed in all of them. In total, 15 of the pregnant women had radiological findings of COVID-19 pneumonia in lung involvement. COVID-19 PCR test of all pregnant women was positive.

Antiviral treatment was given to 23 pregnants, treatment was started in 15 pregnants during pregnancy and eight pregnants

after birth. Hydroxychloroquine (HCQ) treatment was not applied to any of the pregnant women. Lopinavir-ritonavir treatment in 17.7% (n=11) of pregnant women (for a mean duration of 7.7±3.2 (2-10) days) and remdesivir treatment in 6.4% (n=4) of pregnant women (for five days). Favipiravir treatment was given to 14.5% (n=8) of the pregnant women followed immediately after birth (for five days for four, for ten days for four). Favipiravir treatment was administered in 75% (n=6) of the patients at 37 weeks and above, 25% (n=2) of them at a gestational age below 32 weeks after giving birth.

Table 1. Clinical features of the pregnant women, disease severity and treatment

Maternal characteristics	All patients (n=62)
Age	29.8±4.7 (19-42)
Gestational age at presentation, week	28.5±10.4 (5-40)
≤12 week (first trimester), n (%)	(n= 5)
13–24 week (second trimester), n (%)	(n= 7)
≥28 week (third trimester), n (%)	(n= 50)
Gravidity	(n= 62)
Parity	(n= 22)
Living children	(n= 22)
Comorbidities	
Gestational Diabetes and gestational hyppertansion, n (%)	(n=2) (3,2%)
Hypothyroidism, n (%)	(n=1) (1,6%)
Hepatitis B, n (%)	(n=2) (3,2%)
Rheumatoid Arthritis and renal failure, n (%)	(n=2) (3,2%)
Epidemiological contact history	
Yes, n/N (%)	(n=60) (96,7%)
No, n/N (%)	(n=2) (3,22%)
Symptoms on admission	
Fever, n/N (%)	(n=13)(21,0%)
Headache, n/N (%)	(n=17) (27,4 %)
Myalgia, n/N (%)	(n=27) (43,5%)
Sore throat, n/N (%)	(n=5) (8,1%)
Cough, n/N (%)	(n= 28) (45,2 %)
Dyspnea, n/N (%)	(n=18) (29,0%)
Chest pain, n/N (%)	(n=18) (29,0%)
Rhinorrhea/Nasal stuffiness, n/N (%)	(n=5) (8,1 %)
Anosmia, n/N (%)	(n=5) (8,1%)
Palpitation, n/N (%)	(n=5) (8,1%)
Nausea/Vomiting, n/N (%)	(n=13) (20,9%)
Diarrhea, n/N (%)	(n=2) (3,2%)
Weakness, n/N (%)	(n=23) (37,1%)
Disease Severity	
Asymptomatic, n (%)	(n=13) (20,9%)
Mild, Moderate, n (%)	(n=50) (80,6%)
Severe, Critical, n (%)	(n=12)(19,3%)
Intensive care, n (%)	(n=3) (4,8%)
Treatment	
Lopinavir/ritonavir, n (%)	(n=11) (17,7%)
Hydroxychloroquine, n (%)	(n=0) 0(%)
Remdesvir, n (%)	(n=4) (6,4%)
Favipravir, n (%)	(n=8) (12,9%)
Low molecular weight heparin, n (%)	(n=46) (74,1%)
Low-dose steroid, n (%)	(n=10) (16,%)

Note: Data are presented as median (minimum-maximum), n (%) or n/N (%), where N is the total number of patients with available data.

Low molecular weight heparin (LMWH) was administered to 73% (n=46) of the pregnant women (mean 17.1±11.9 (3-68) days) and followed up. During the follow-ups, 15.9% (n=10) of them were treated with steroids (on average 17.4±17.4 (2-60) days). Three pregnant women received 250 mg of pulse steroid for three days, followed by 6 days of low-dose steroid, and seven pregnants received low-dose steroids for five days. All pregnant women who were started on steroids received oxygen support. Diffuse bilateral infiltration and low Sat O2 (Sat O2 84 and 85) were present in CT scans of two pregnant women who had to perform premature labor.

Only three pregnants were followed up in the intensive care unit (ICU), two of them were intubated and connected to mechanical ventilation. One was followed up in the ICU for five days and the other for three days, and then she was taken to the service. Both pregnant women were discharged in good health, after 14 days and 70 days of hospitalization. Reservoir mask and continuous positive airway pressure (CPAP) treatment was applied to the other pregnant woman. The pregnant woman, who was hospitalized in the intensive care unit due to gestational diabetes complications, gave a stillbirth at 37 weeks of gestation. She was discharged after three days of follow-up in the ICU and seven days in the service. No maternal mortality was observed in any of the pregnant women.

During the research period, 23 (37.1%) of the pregnant women gave birth; 86.7% (n=20) of the deliveries resulted in cesarean section, 8.7% (n=2) were live births by vaginal route, and 4.3% (n=1) resulted in abortion. The mean gestational week of 22 live-born babies was 36.5±5.4 (28-40), mean birth weight was 3047±562 (1900-3940) gr, and the APGAR score was 8.1±1.3 (3-9). The number of births under 2500 g was four, and the APGAR

Table 2. Laboratory findings of pregnant women during their hospitalization

	Average	SD	Minimum	Maximum
Wbc (/ml)	8465	2726	3400	15880
Neutrophil (/ml)	6466	2394	1930	13480
Lymphocyte (/ml)	1399	598	360	3350
N/L ratio	5,5	3,7	1,3	18,7
Platelet (103/ml)	211	57	107	376
MPV	9,8	1,2	6,8	12,5
PDW	16,2	0,3	15,3	17,1
Hemoglobin (g/dl)	11,8	1	9,8	14,6
aPTT (sn)	30,7	6,8	22,4	62,9
PT (sn)	13,1	4	10,7	41,8
Creatinine (mg/dl)	0,5	0,1	0,3	1
AST (U/L)	22,8	8,8	10	48
ALT (U/L)	18,3	12,7	5	78
Albumin (g/dl)	35	3,5	29	46
BUN (mg/dl)	14,9	5,1	6	35
CPK (U/L)	63	41,9	17	188
CK-Mb (U/L)	1,1	1	0,2	4,9
Troponin (mg/L)	0,5	1,7	0	7,9
Fibrinogen (mg/dl)	427,4	93,4	221	617
D-dimer (ng/ml)	1,3	0,7	0	3,5
Ferritin (mg/L)	72,1	104	4	497
CRP (mg/L)	21,4	23,6	0,4	110

score of a baby was three at birth. Fetal distress symptoms occurred in two babies and hospitalization in the Neonatal Intensive Care Unit was required. Both babies were discharged from the ICU after one week of follow-up with CPAP treatment without the need for mechanical ventilation. Neonatal mortality and congenital malformations were not observed in any of the 22 infants with available data. The SARS-CoV-2 PCR test was performed on postnatal nasopharyngeal swab samples from only eight infants and the result was negative.

Discussion

Although it is thought that COVID-19 infection may pose a potential threat to pregnant women and their fetuses, this situation has not yet been clearly clarified. Data on this subject are limited and research is still ongoing [11-15]. In the study, the clinical course of COVID-19 was very severe in only three out of 62 pregnant women and needed ICU admission. However, none of the pregnant women died. Almost all live-born babies did not need ICU and were discharged in good health, except for two. These findings showed that the course of SARS-CoV-2 infection was not unfavorable for the followed-up pregnant women and their fetuses.

It has been observed that there are not enough studies on the effects of COVID-19 on pregnancy, maternal and perinatal outcomes, and the existing ones are mostly descriptive [13,15]. Similarly, in our study, it was carried out descriptively. It has been reported that pregnant women are susceptible to many viral infections, especially respiratory tract, due to a suppressed immune system during pregnancy. It has been observed in studies and in our own experience that infections in previous years (SARS-CoV, MERS-CoV and influenza) were more severe and even mortal in pregnant women [9,10]. However, studies on how the course of COVID-19 progresses or will progress during pregnancy are limited, and it is thought that it will become clear in time.

It has been observed that pregnant women may present with asymptomatic and different symptomatic pictures due to COVID-19 infection. In the study of Khalil A et al., it was reported that the complaints of pregnant women infected with COVID-19 were primarily cough and shortness of breath, while in the study of Akhtar H et al, fever was the most common and cough was the second most frequent complaint [14,15]. In our study, although cough was the most common reason for admission, it was found that pregnant women applied with the complaints of widespread myalgia and fatigue. This situation may be caused by many reasons such as regional and immunological.

In the literature, different maternal, fetal and perinatal outcomes have been reported in studies on the course of COVID-19 during pregnancy. While positive clinical experiences were reported in some of the studies, others emphasized that the results were not good [16-21]. It has been reported that the most common adverse outcome is iatrogenic preterm birth, however, there is no or very little intensive care transfer, and the mortality of both pregnant women and their babies is rare (<1%). However, in some studies, on the contrary, it has been determined that there are no positive developments. It has been reported that pregnant women have more concomitant maternal comorbidities, and the prevalence of COVID-19 is high in studies reported to be accompanied by adverse effects. In our study, it was observed that the maternal and perinatal clinical course was positive, and no maternal deaths or serious consequences were detected. There was no infant death except for the stillbirth of the mother with a history of gestational diabetes. However, the low number of infected pregnant women and the fact that there are not many comorbid and accompanying predisposing diseases may be related to the positive results. Also, the study is not generalized as it reflects a small population. It should be supported by more comprehensive studies more data.

Although different antiviral treatment regimens are recommended in various guidelines for the management of pregnant women infected with COVID-19, there is still no proven efficacy and safe treatment option. However, it has been observed that there is often antiviral treatment experience in the studies in the literature. In our country, the treatment of pregnant women begins in line with the recommendations of the COVID-19 Diagnosis and Treatment Guidelines, which were created and constantly updated by the Ministry of Health of the Republic of Turkey for the management of COVID-19 patients, and according to the severity of the infection. In our study, antiviral drugs were given to less than half of the pregnant women, and unlike other studies, fewer antiviral drugs were used. In addition, empirical antibacterial therapy was not initiated.

It is not yet clear whether there is direct transmission from mother to baby in COVID-19 infection. However, it was observed that there was no transition in most of the studies in the literature. In the review that evaluated 2567 pregnant women, it was stated that neonatal SARS-CoV-2 PCR positivity is rare, but the issue will become clearer as the information on this subject accumulates, but the lack of a universal test for SARS-CoV-2 (90% of pregnant women infected with SARS-CoV-2) being asymptomatic) has been reported as the non-standardization of prenatal surveillance, management, timing, and mode of delivery of women with COVID-19 [14,15]. The PCR test was performed in only eight of the newborns in our study, and the results were negative in all infants, suggesting that the possibility of transmission from mother to infant may be quite low, but this should be supported by studies with more data. The results of our study and other studies may be related to the direct effects of SARS-CoV-2, as well as indirect effects of COVID-19 (changes in maternal care, screening, maternity care delivery) with changes in the immune system caused by pregnancy. In addition, conditions such as an insufficient number of PCR tests and a lack of interlaboratory standardization may also cause different results in studies. Measuring and reporting outcomes may allow for more objective effects of COVID-19 on maternal and perinatal outcomes.

In our study examining the effects of COVID-19 infection on pregnancy, a significant portion of pregnant women were infected with COVID-19 in the third trimester or after birth. For this reason, no meaningful interpretation could be made about the results of viral exposure in the early stages of pregnancy and after. It is thought that these time-consuming situations will be better clarified as data are shared in the future. Exposure of

pregnant women to the virus in the late period may be effective in not worsening our maternal and perinatal outcomes.

Instudies in the literature, mother-to-child transmission could not be evaluated clearly with the available data. It is reported that more data and comprehensive studies are needed to answer questions about the possibility of vertical transmission, how often and how vertical transmission of the virus occurs [14-18,21-23]. In our study, it was not possible to say that there was no vertical transmission in a very small number of newborn babies, since the COVID-19 PCR test was not performed and direct testing was not performed for breast milk, cord blood or amniotic fluid to evaluate fetal transit. Today, information about the pregnancy and postpartum effects of COVID-19 infection is still not clear, and further studies are needed [21-23].

Limitations

Our study had important limitations such as being descriptive, single-center and not randomized. First of all, our data were small because we included only the patients we followed up and consulted, and there were missing data because the study was conducted retrospectively. In addition, there were ongoing pregnancies that precluded evaluating the outcome of all patients with COVID-19 infection. Another limitation of ours was that only eight newborns were tested for SARS-CoV-2, and no direct testing was performed for breast milk, cord blood, or amniotic fluid to assess possible maternal-to-fetal transmission.

Conclusions

In conclusion, most of the pregnant women in the study had a favorable clinical course of COVID-19 infection and no maternal death. We cannot rule out mother-to-child transmission with available data, therefore further studies are needed to answer the questions about possibility of vertical transmission. In the study, it was observed that clinical follow-up of the infection was positive in pregnant women and their babies infected with COVID-19. However, it is thought that the course will become clearer with studies in which more and standardized data are available and long-term follow-up results of infected mothers and their babies are shared.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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