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Original Article

Perinatal outcomes of pregnant women having SARS-CoV-2 infection

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ABSTRACT

Objectives: Aim of this study is to evaluate the prognosis of pregnant women having SARS-CoV-2 infection and investigate whether there was a difference in perinatal outcomes between pregnant women who had SARS-CoV-2 infection and those who did not.

Materials and methods: This prospective observational study was conducted with 116 singleton pregnancies. Cases enrolling in the study were divided into two groups. While those in the first group had a history of SARS-CoV-2 infection ($n = 46$) the second group consisted of healthy pregnant women ($n = 70$).

Results: Emergency Cesarean section was performed on three SARS-CoV-2 infected pregnancies (30, 33 and 34 gestational weeks). Intensive care unit admission was required for all three cases after delivery and two of them died. Among the pregnancies that had an infection in the third trimester, 71.4% ($n = 20$) of them had delivery in 14 days after diagnosis and 17.4% ($n = 8$) of their newborns were followed up at newborn intensive care unit. Overall, only one newborn had a positive swab test result for SARS-CoV-2. There was no statistically significant difference between groups regarding their delivery week (37.02 ± 5.85 vs 38.5 ± 2.33). Similarly, there was no significant difference between groups, concerning mean age, parity, and birth weight ($P = 0.707$, $P = 0.092$, $P = 0.334$; $P < 0.05$). Furthermore, the difference between SARS-CoV-2 infected pregnancies that were followed up as inpatient or outpatient with respect to the delivery week and birth weight was not significant ($p > 0.05$). Also, APGAR 5 scores of hospitalized women (9.3 ± 1.1) were found to be lower than the outpatient group (9.8 ± 0.8) ($P = 0.043$; $p < 0.05$).

Conclusion: No significant difference was detected between groups in terms of the delivery week, birth weight, and APGAR scores. The inpatient group was found to have lower APGAR 5 scores.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019, and has infected millions of people around the world causing thousands of deaths. This major public health problem affected pregnancies, as well. The pregnancy rate of 15–44 aged women with laboratory-confirmed SARS-CoV-2 infection was reported as 9% [1]. It is suggested that SARS-CoV-2 infects the host cell by using a similar receptor such as angiotensin-converting enzyme 2 (ACE2). Expression in endometrium tissue and placenta was reported, too [2]. Regarding the outcome of such an expression, it can be argued that the expression of viral receptors increases vulnerability to infection theoretically. Yet, so far, pregnancy has been known not to be a condition that adversely affects the SARS-CoV-2 infection course [3,4]. In the literature, some studies have pointed the association between SARS-CoV-2 infection and preterm birth and increased maternal intensive care unit (ICU) need. However, adverse fetal and maternal outcomes in patients infected during pregnancy are still the subject of research.

In this study, we, primarily, aimed to evaluate the prognosis of pregnant women who were treated for SARS-CoV-2 infection. Secondly, study also focused on determining whether there was a difference in perinatal outcomes between pregnant women who had SARS-CoV-2 infection during their pregnancies and those who did not.

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Material and methods

This prospective observational study was conducted at the Department of Obstetrics and Gynecology, Umraniye Research and Training Hospital, Turkey which was a tertiary care referral center for COVID-19 between June 2020 and January 2021. A total of 116 pregnancies that were delivered in our hospital were included in the study. Cases included in the study were divided into two groups. Those in the first group had a history of SARS-CoV-2 infection and the second group consisted of healthy pregnant women.

Pregnancies who were followed up at the pandemic clinic and giving birth at our hospital were included in the study group. Healthy pregnant women giving birth at our hospital were included in the control group. A reverse transcription-polymerase chain reaction (RT-PCR) test of a nasopharyngeal swab was used to confirm the diagnosis [5].

Demographic and obstetric characteristics of all the pregnancies were also reviewed. Additionally, study also reviewed parameters such as the gestational week that the mother was infected, symptoms, drugs administered for the treatment of SARS-CoV-2 infection, gestational week of birth, route of delivery, APGAR scores, and need for neonatal intensive care unit (NICU). During the study, neonatal testing for SARS-CoV-2 was performed on infants born within 3 weeks of maternal infection or when it was clinically indicated within 24 h subsequent to the delivery. Regarding the infants born to symptomatic mothers, routine isolation from mothers was applied [3].

The study was approved by the Local Ethics and Clinical Investigation Committee on 21.05.2020 (Approval Record Number is 215). Informed consent was taken from all patients. The Statistical Package for the Social Sciences (SPSS v21, Chicago, IL, USA) was used for statistical analyses. Descriptive statistics are presented as mean ± standard deviation for normally distributed data. The relationship between the categorical variables was examined using the chi-square test. The Kolmogorov–Smirnov test was used for the assessment of the normality of the data. The Mann–Whitney U test was used for the data that were not normally distributed. The results were evaluated against a confidence interval of 95%, and P-value < 0.05 for statistical significance.

Results

This study was conducted with 116 pregnancies between June 2020 and January 2021. General characteristics of groups are shown in Table 1. There was no significant difference with respect to the delivery week between pregnant women who had SARS-CoV-2 infection and those who did not (37.02 ± 5.85 vs 38.5 ± 2.33) ($P = 0.206$; $P > 0.05$). Also, there was no significant difference between groups after controlling mean age, parity, and birth weight ($P = 0.707$, $P = 0.092$, $P = 0.334$; $P > 0.05$).

Among 51 SARS-CoV-2 infected pregnancies, 46 women were included in the study (3 of them have not delivered yet and two of them gave birth at a different hospital). Amongst the infected cases, 10.9% ($n = 5$) had infection in the first trimester, 28.3% ($n = 13$) in the second trimester and 60.8% ($n = 28$) in the third trimester. SARS-CoV-2 infected cases were admitted to emergency service with complaints of cough (41.3%), dyspnea (26.1%), myalgia (15.2%), loss of taste (2.2%), fever (8.7%), fatigue, and diarrhea (2.2%). The mean duration from admission to symptom onset was 2.85 ± 2.28 days. In this study, we should also note that, 67.4% ($n = 31$) of the infected cases were hospitalized. Leucocyte and lymphocyte count at admission ranged from 1221 to 21,330 cells/mm^3 and from 590 to 5050 cells/mm^3 respectively. Relevant blood test results at admission are shown in Table 2. As for the treatment process, all hospitalized SARS-CoV-2 infected pregnant women received low molecular weight heparin therapy. Overall, 32.6% ($n = 15$) received hydroxychloroquine, 13.3% ($n = 6$) were given favipiravir, 17% ($n = 8$) were administered Kaletra (50 mg ritonavir plus 200 mg lopinavir) and 39.1% ($n = 18$) did not receive any treatment. One patient was given both hydroxychloroquine and favipiravir treatment. O_2 supplementation was required for five patients (10.9%). There was no significant difference between SARS-CoV-2 infected pregnancies that were followed up as inpatient or outpatient regarding their delivery week (36.9 vs 37.1 gestational weeks) ($P = 0.211$; $P > 0.05$). Moreover, there was no significant difference in terms of birth weight and APGAR 1 scores ($P = 0.265$, $P = 0.214$; $P > 0.05$). However, APGAR 5 scores of hospitalized women (9.3 ± 1.1) were found to be lower than the outpatient group (9.8 ± 0.8) ($P = 0.043$; $P < 0.05$) (Table 3).

All deliveries of symptomatic cases were performed without delayed cord clamping and skin-to-skin contact. All newborns were isolated immediately after the delivery. Emergency CS was performed on three pregnancies (at 30, 33 and 34 gestational weeks) when they were being followed up in the SARS-CoV-2 inpatient clinic. All these women needed ICU admission after their delivery and two of them died due to of SARS-CoV-2 complications (Table 4). Among the pregnancies who had an infection in the third trimester, 71.4% ($n = 20$) had delivery in 14 days after diagnosis and 17.4% ($n = 8$) of newborns were followed up at NICU. Only one newborn had a positive result for SARS-CoV-2. The swab test results of newborns whose mothers died because of the complications stemming from the infection were negative (Table 4).

The preterm delivery ratio was 13.04% ($n = 6$) among pregnant women having SARS-CoV-2 infection. As for the cases who had an infection in the first trimester, two of them had abortions in 7 and 18 gestational weeks, and none of the newborns were reported to have a fetal anomaly.

Discussion

The SARS-CoV-2 infection has spread quickly and become a major health problem in the world. During this pandemic period,

Table 1
General characteristics of pregnant women.

	SARS-CoV-2 infected group ($n = 46$)	Control group ($n = 70$)	P
	Mean ± SD	Mean ± SD	
Age (year)	28.87 ± 4.74	28.67 ± 5.95	0.707
Parity	1.09 ± 0.79	1.51 ± 1.26	0.092
Delivery week	37.02 ± 5.85	38.5 ± 2.33	0.206
Birth weight (gram)	3165 ± 724	3113 ± 619	0.334
APGAR 1	8.25 ± 1.43	8.27 ± 1.71	0.462
APGAR 5	9.48 ± 1.05	9.47 ± 1.54	0.302

Mann Whitney U Test, $p < 0.05$.

Table 2
Blood test results of SARS-CoV-2 patients at admission.

	Minimum-Maximum	Mean ± SD
Temperature (Celcius)	35.7–38.6	36.58 ± 0.52
WBC (cells/mm^3)	1221–21330	10,487 ± 3658
Lymphocyte (cells/mm^3)	590–5050	1903 ± 683
Neutrophil (cells/mm^3)	1277–23000	6894 ± 3940
CRP (mg/dL)	0.10–34	2.1 ± 4.72
LDH (IU/L)	140–909	308 ± 118
Fibrinogen (mg/dL)	169–776	455 ± 137
D dimer (μg FEU/mL)	640-10 000	2012 ± 1693
Duration from admission to symptom onset (day)	0–7	2.85 ± 2.28

WBC:white blood cell, CRP:C-reactive protein, LDH:Lactate dehydrogenase.

Table 3
Comparison of outcomes between outpatient and hospitalized SARS-CoV-2 infected pregnancies.

	Inpatient group ($n = 20$)	Outpatient group ($n = 26$)	
	Mean ± SD	Mean ± SD	
Delivery week (week)	37.1 ± 4.4	36.9 ± 8.3	0.211
Birth weight (gram)	3079 ± 781	3341 ± 576	0.265
APGAR 1	8.1 ± 1.6	8.6 ± 1.1	0.214
APGAR 5	9.3 ± 1.1	9.8 ± 0.8	0.043*

Mann Whitney U Test, *$p < 0.05$.

pregnant women without comorbidities are reported to have developed similar clinical features with nonpregnant patients. In a cohort study including 252 SARS-CoV-2 positive and 3122 negative pregnant women, adverse pregnancy outcomes were found to be similar. It has been concluded that SARS-CoV-2 infection in pregnancy did not lead to adverse outcomes [4]. The neonatal infection rate was reported as 3% [4]. However, adverse fetal and neonatal outcomes are yet to be investigated. This study aimed to investigate and determine whether there is an association between SARS-CoV-2 infection and perinatal outcomes.

The risk of vertical transmission during pregnancy is yet to be identified since there is limited data available about the vertical transmission. However, it is suggested that in utero transmission can occur at a rate of 3% [6]. Ozturk et al., analyzed the abortus material of 21 pregnant women with laboratory-confirmed SARS-CoV-2 infection. Placenta and curettage samples were found to be negative for SARS-CoV-2 RNA [7]. Gao et al. investigated the association of clinical characteristics and placental pathological changes in SARS-CoV-2 infected pregnancies. They studied eight placentas of pregnant women in the third trimester. SARS-CoV-2 RNA and chronic histiocytic intervillositis were not detected in placenta samples [8]. In another study, a case of a pregnant woman with severe clinical features was reported whose delivery was performed by CS and the newborn was isolated immediately. A positive neonatal nasopharyngeal swab test was obtained 16 h after the delivery. As a result, authors mentioned the probability of in utero transmission of SARS-CoV-2 [9]. In the systematic review by Yang et al., neonates of 83 SARS-CoV-2 positive mothers were included in a relevant study. SARS-CoV-2 infection was confirmed in three neonates by nasopharyngeal swab RT-PCR test. In our study, the nasopharyngeal swab test results of two neonates were positive as well. The swab test results of two newborns whose mothers died because of complications caused by the infection were negative [10]. In the literature, the teratogenic effect of the infection on newborns has not been reported so far. In their case-control study, Cosma et al. reported that first trimester SARS-CoV-2 infection was not associated with early pregnancy loss [11]. In our study, on the other hand, two of five cases having infection in the first trimester had abortus in 7 and 18 weeks.

The outcome of 18 SARS-CoV-2 infected pregnancies during the late 3rd trimester were reported in a retrospective study from Wuhan, China. Swab tests of all newborns were detected to be negative. Although vertical transmission was not detected, the ratio of neonatal pneumonia was found to be higher [12]. While leucocyte count was increased in 7 women, there was a decrease in lymphocyte count in 8 women. Of the patients, 94% had CS and 17% had a premature birth. Also, authors reported neither maternal nor neonatal deaths [12]. Additionally, in another review, it is reported that pregnant women did not have an increased risk of SARS-CoV-2 infection but had a higher risk of ICU need. Also, preterm birth rates were found to be higher in pregnancies with COVID-19 infection [6,13]. The rate of ICU admission and mortality rates were reported as 4% and 0.2% among pregnant women, respectively [13]. Preexisting comorbidities (high BMI, diabetes, hypertension) increase ICU and invasive ventilation needs [11,13]. Newborn to SARS-CoV-2 infected mothers had a higher risk of neonatal unit admission rates [13] as well. In another large study, the outcomes of 598 hospitalized pregnant women with SARS-CoV-2 infection between March and August 2020, were reported. Overall, 45.5% ($n = 272$) were symptomatic at admission. The ratio of ICU needs among symptomatic patients was 16.2%. The maternal death ratio was detected as 1% ($n = 2$). It was also reported that pregnancies that had an infection during the first or second trimester were more frequently symptomatic. The ratio of preterm delivery was 23.1% in symptomatic women and 8% in asymptomatic women. In addition, premature rupture of membrane was 2.5% [14]. While cough, sore throat, and body aches were reported as the first symptoms leading

Table 4
Characteristics of pregnant women who were followed up at intensive care unit.

	Age	Gestational week at admission	Treatment	Admission to symptom onset	Neutrophil Count (cells/mm^3) at admission	Lymphocyte count (cells/mm^3) at admission	D-Dimer (μg FEU/mL) at admission	Fibrinogen (mg/dL) at admission	Maternal ICU	Delivery week	Delivery route	Apgar 1-5	NICU	Fetal swab
1	33	30	Kaletra	6 days	23,000	1600	1590	613	8th day-EX	31	CS	2–5	yes	Negative
2	32	33	Kaletra	3 days	11,910	1500	2100	776	10 days	34	CS	7–9	yes	None
3	35	34	Favipiravir	5 days	10,650	1140	5120	445	17th day-EX	34	CS	8–9	yes	Negative

pregnant women to be tested [15] fever and myalgia were reported less among pregnant women compared to non-pregnant patients [13]. Similarly, we detected fever less often at admission. In our study, the most common symptoms at admission were found to be cough (41.3%), dyspnea (26.1%), and myalgia (15.2%). The preterm delivery ratio was 13.04% ($n = 6$). The median resolution time of symptoms was reported as 37 days. However, symptoms persisted 8 weeks or more amongst the 25% of pregnant women [15]. In their prospective cohort study, Hcini et al. reported that only 25% of pregnant women were symptomatic at admission. Also, they did not detect an increased risk in terms of preterm birth and CS delivery. Their study reported that pregnant women with SARS-CoV-2 infection had increased risk in terms of postpartum hemorrhage, transfusion, and intrauterine fetal demise compared to those without infection [16]. In a cohort study from Spain, outcomes of asymptomatic SARS-CoV-2 positive ($n = 174$) and negative pregnant women ($n = 430$) were compared. Authors detected higher preterm rupture of membranes among term deliveries in the asymptomatic group compared to the SARS-CoV-2 negative group. Additionally, they detected no significant difference between groups in terms of maternal and fetal outcomes [17]. Similarly, we detected no statistically significant difference between groups concerning the delivery week, birth weight, and APGAR scores.

In a multinational retrospective cohort study, 887 singleton pregnancies confirmed with RT-PCR swab test were included. Three cases of maternal death were reported. Advanced maternal age was found to be associated with adverse perinatal outcome [18]. In our study, maternal death occurred in two cases (4.3%).

Main limitation of our study is the small number of cases at inpatient and outpatient groups. We detected a mortality rate of 4.3% and there was no significant difference between pregnant women having SARS-CoV-2 infection and those who did not, when considering the delivery week, birth weight, and APGAR scores. Also, no significant difference was observed in terms of the delivery week, birth weight, and APGAR 1 scores between SARS-CoV-2 infected pregnant women who were followed up as inpatient and those who were outpatient. However, APGAR 5 scores were found to be lower in the inpatient group. Additionally, the swab test results of newborns whose mothers died due to the complications caused by infection were negative. The vertical transmission of infection is still unclear. New studies including large cases among pregnant women having severe diseases might be conducted in order to better identify vertical transmission.

Declaration of competing interest

The authors declare no conflict of interest.

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