HEALTH SCIENCES

Does being infected with SARS-CoV-2 in the first-trimester increase the risk of miscarriage?

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Abstract: Aim of this study is to investigate whether the risk of miscarriage increases in pregnant women who had COVID-19 in first trimester. Our study included 52 patients with SARS-CoV-2 infection detected by RT-PCR and 53 patients with negative RT-PCR test in samples taken with nasopharyngeal swab in the first trimester between March 1 and December 31, 2020. Complete abortion, incomplete abortion, blighted ovum, intrauterine exitus, biochemical pregnancies were accepted as in the miscarriage group (MG). Pregnant women with COVID-19 and control group were compared in terms of demographic data, miscarriage rate and laboratory results. Patients were divided into MG and ongoing pregnancy groups (OPG) and compared in terms of the diagnosed weeks, clinical findings, laboratory results, treatments, and hospitalization. While miscarriage was observed in 15 (28.8%) of pregnant women infected with SARS-CoV-2 in the first trimester, this number was 7 (13.2%) in the control group. While the common symptoms in the MG were cough (60%), fever (53.3%), shortness of breath (53.3%), and fatigue (46.7%) (p<0.05); asymptomatic patients (51.4%) were higher in the OPG (p<0.001). Hospitalized patients were 33.3% in the MG and 8.1% in the OPG (p=0.02). According to the results of our study, the risk of miscarriage increases in pregnant women infected with SARS-CoV-2 (especially in severe infection) in the first trimester.

Key words: Abortus, First trimester, COVID-19, Miscarriage, Pregnancy loss, SARS-CoV-2.

INTRODUCTION

Coronavirus-disease-2019 (COVID-19) is caused by severe-acute-respiratory-syndrome coronavirus-2 (SARS-CoV-2). COVID-19 was first identified in Wuhan, China in November 2019, and within months it spread rapidly to the whole world and was recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020 (WHO 2020).

Pregnancy may trigger important changes in respiratory functions, both anatomical and physiological, making pregnant women susceptible to respiratory disease (Jamieson et al. 2009). Management of pregnant women with COVID-19 pneumonia are more difficult than nonpregnant patients, because drug therapy and intrapartum risks should also need to be considered (Wong et al. 2004).

Maternal and perinatal consequences of COVID-19 are not known yet. No maternal and perinatal complications have been reported in limited publications in the literature (Chen et al. 2020, Li et al. 2020b). A recent study has reported that the mortality rates of pregnant women with COVID-19 were similar to those of non-pregnant women, while the rate of hospitalization was higher in pregnant patients (Ellington et al. 2020).

In a meta-analysis, the most common pregnancy complication due to coronavirus [severe-acute-respiratory-syndrome-coronavirus (SARS-CoV), SARS-CoV-2 and middle-east-respiratory-syndrome-coronavirus (MERS-CoV)] was reported as preterm delivery (Di Mascio et al. 2020). In addition, increased cesarean rate and pre-eclampsia have been reported in COVID-19 (Li et al. 2020a, Mendoza et al. 2020)

Maternal infections in the first trimester may have serious and permanent effects on the fetus compared to advanced gestational weeks (because implantation and organogenesis are occur in 1st trimester) (Silasi et al. 2015). Previous coronavirus epidemics such as SARS, MERS and seasonal influenza have been associated with increased pregnancy losses and miscarriage (Wong et al. 2004, Schwartz & Graham 2020, Dorélien 2019). However, there are very few studies in the literature regarding the results of COVID - 19 in the first trimester.

Cytokines are central to the pathophysiology of COVID-19; while some of them are beneficial (type-I interferon, interleukin-7), others appear detrimental (interleukin-1β, interleukin-6, and TNF-α) particularly in the context of the so-called cytokine storm (Jamilloux et al. 2020). Embryo orientation, apposition, docking, and implantation are critical, any excessive pro- or anti-inflammatory signal is detrimental to pregnancy development and maintenance (van Mourik et al. 2009). The increase in neutrophil-lymphocyte ratio (NLR), which is an indicator of an increased inflammatory response, is also accepted as a poor prognosis indicator for COVID-19 (Shang et al. 2020).

COVID-19 is known to cause systemic microvascular thrombosis. It has been reported that increased d-dimer and decreased platelet levels due to coagulopathy are associated with mortality and morbidity (Zhang et al. 2020, Liu et al. 2020c). It is known that hypercoagulopathy has a place in early pregnancy loss etiology (Kutteh & Triplett 2006). In the light of this information, we thought that the inflammatory condition secondary to COVID-19, the effect of hypercoagulopathy and/or virus may cause an increase in miscarriage rates.

The aim of this study is; to determine the pregnancy course and miscarriage rate of patients diagnosed with COVID-19 by real-time reverse transcription-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab specimens in the first trimester; to compare the week of diagnosis, clinical symptoms, and laboratory results in patients with and without miscarriage; to show whether being infected with SARS-CoV-2 in the first trimester increases the risk of miscarriage (comparing with the control group), and if so, in which patient group this increase is greater.

MATERIALS AND METHODS

To determine the effects (especially in terms of whether it increases miscarriage) of COVID-19 in 1st trimester pregnant patients, we conducted a single-center, retrospective observational study between March 1, 2020, and December 31, 2020, in a tertiary level hospital in Erzincan, Turkey. This study was conducted following the principles of the Declaration of Helsinki. The study was approved on 22.03.2021 by the Erzincan Binali Yildirim University local ethics committee and by the Ministry of Health. Clinical Research Ethics Committee no: 05/09.

Our study included 52 SARS-CoV-2 infected patients and 53 control groups, whose diagnosis was proven by RT-PCR in nasopharyngeal swab samples in the first trimester. The patients in the control group consisted of the patients who applied to the pregnant outpatient clinic for the first time, and those who did not infected

by SARS-CoV-2 during their follow-up. The demographic characteristics of the patients, at what gestational week they were diagnosed, clinical findings at the time of diagnosis, laboratory results, treatments, and the needs of hospitalization were recorded. The gestational week of the patients was calculated according to the first day of the last menstrual period (LMP). Ultrasonography was performed on the day of diagnosis for all patients, and the gestational age of the pregnant women who could be seen ultrasonographically was confirmed. Ultrasound measurements were considered as correct in case of LMP did not match the ultrasound measurement. The patients were followed up in terms of pregnancy loss and complications until the 20th gestational week.

Complete abortion (removal of all pregnancy material with contraction and vaginal bleeding), incomplete abortion (removal of some of the pregnancy material with contraction and vaginal bleeding), blighted ovum (gestational sac without a fetal pole via transvaginal ultrasound by 7 weeks gestational age), intrauterine fetal heartbeat loss, biochemical pregnancies (transient rise in β-hCG without evidence of a gestational sac in-utero, and a subsequent fall in serum β- hCG levels) were accepted as miscarriage. Fifteen patients with pregnancy loss were included in the miscarriage group (MG), and the other 37 patients were included in the ongoing pregnancy group (OPG). Ectopic pregnancy (1 patient) was not included in the MG.

Complete blood count was measured on the Sysmex XN-1000 Hematology System (Sysmex Corporation, Kobe, Japan) automated blood counter. C-reactive protein (CRP) was measured in the BN™ II System device by the nephelometric method (Siemens, Munich, Germany). D-dimer was measured from whole blood on the AQT90 flex Radiometer® (Bronshoj, Denmark) device.

IBM SPSS ver. 21 (IBM Corp., Armonk, N.Y., USA) was used for the analysis of data. The compliance of the data to normal distribution was tested with the Shapiro-Wilk test. Normally distributed data were compared using Student's t-test and presented as means±standard deviations. The Mann–Whitney U test was used for non-normally distributed data and presented as median (minimum-maximum) value. Categorical data were compared using the Chi-squared test and presented as a number of exposed cases and percentages of the total number of cases. A p-value<0.05 was considered statistically significant.

RESULTS

The demographic data of COVID and control group are shown in Table I. While miscarriage was observed in 15 (28.8%) of pregnant women infected by SARS-CoV-2 in the first trimester, this number was 7 (13.2%) in the control group. The median value of the abortion week was 8 weeks 6/7 days (5-19w). The median value between diagnosis and pregnancy loss was 7 (1-43) days. The earliest abortion was observed in 5 weeks and 4/7 days, and the latest in the 19th gestational week. In this patient who had an abortion at the 19th gestational week, oligohydramnios was detected at the 17th week, the patient did not want to be evacuated, spontaneous abortion occurred in the 19th week. Miscarriages were mostly seen ≤10 weeks. The number of miscarriage by gestational week is shown in Figure 1.

A total of 20 patients in both groups were asymptomatic, the most common symptom was fatigue (36.5%). Common symptoms in MG were cough (60%), fever (53.3%), and shortness of breath (53.3%) (p<0.01). The number of asymptomatic patients (51.4%) was statistically

Table I. Demografic variables and charasterictics.

	Miscarriage Group (n=15)	Ongoing Pregnancy Group (n=37)	All COVID patients (n=52)	Control Group (n=53)	p[1] value	p[2] value
Age	31.3 ± 4.35	28.65 ± 5.67	29.42 ± 5.42	28.39 ± 4.42	0.14[*]	0.10[*]
BMI	24.14 ± 3.4	23.95 ± 4.04	24.0 ± 3.8	24.47 ± 4.46	0.86[*]	0.43[*]
Gravidity	3 (1-7)	2 (1-5)	2 (1-7)	2 (1-6)	0.1[**]	0.11[**]
Parity	2 (0-3)	1 (0-3)	1 (0-3)	1 (0-4)	0.69[**]	0.34[**]
Week	7 ± 2.6[¥]	9.3 ± 3.1[¥]	8.6 ± 2.7[¥]	7 ± 1.03[Θ]	**0.03[*]**	**<0.01[*]**
Miscarriage	15 (100%)	0	15 (28.8%)	7 (13.2%)	<0.01[***]	0.04[***]

[¥]Diagnosis week of COVID. [Θ]Diagnosis week of pregnancy. BMI: Body mass index. Results were presented as mean±SD or Median (Min-Max). [*]Student's t test was performed. [**]Mann-Whitney U test was performed. [***]Chi-square test was performed. p[1]: Comparison of Miscarriage Group and Ongoing Pregnancy Group. p[2]: Comparison of COVID group and control group. Statistically significant p values are written in bold.

significantly higher in OPG (p <0.01). Other symptoms and signs are shown in Table II.

Lymphopenia (<1.1x10^{9} / L) was detected in 53.3% of patients in MG and 21.6% in OPG (p = 0.02). D-dimer > 500 μg / L was statistically significantly higher in MG (66.7% vs 32.4%, p = 0.02). NLR was 4.3 in MG and 2.5 in OPG (p = 0.01). Other laboratory findings are shown in Table III.

There was a statistically significant difference between the two groups in terms of low percutaneous oxygen saturation (SaO2, below 93%) (the lowest measured value was based on) (p <0.01). SaO2 < 93% was detected in 6 (40%) patients in MG and 3 (8.1%) patients in OPG. The number of patients hospitalized for COVID-19 pneumonia was 5 (33.3%) in the group with miscarriage and 3 (8.1%) in the group without pregnancy loss (p = 0.02) (Table II). Only 2 patients needed intensive care. One of these patients's pregnancy resulted in miscarriage, the pregnancy of the other patient continued without any problem in the follow-ups until the 20th gestational week. Maternal mortality was not observed in any group.

The pharmacological treatments applied to the patients were shown in Table IV, and no statistically significant difference was observed between the groups (p≥0.05).

DISCUSSION

Studies on COVID-19 are mostly concentrated in the second and third trimesters of pregnancy and the number of patients' are limited. This study is the first study in the literature in which patients infected with SARS-CoV-2 in the first trimester. The striking points of the study are that the rate of pregnancy loss in patients infected with SARS-CoV-2 in the first trimester is very high compared to uninfected patients, and the rate of miscarriage increases in earlier weeks of gestation.

It is known that viral infections have negative effects on pregnancy in the first trimester. A very high rate (57%) of miscarriage in the first trimester due to SARS-CoV has been documented during the 2002-2003 epidemic (Wong et al. 2004). During the MERS-CoV epidemic, the alarming rate of adverse pregnancy outcomes was
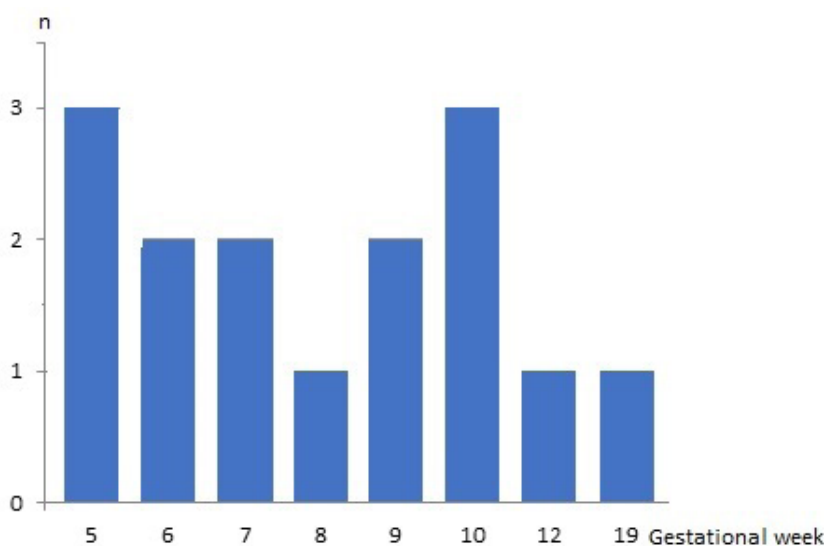
Figure 1. Number of miscarriage by gestational week.

reported previously (Favre et al. 2020). However, the effects of SARS-CoV-2 in first-trimester is not known yet. In the literature, there are a few studies examining the first trimester effects of SARS-CoV-2. A case with 10 weeks and 6 days of pregnancy reported had an abortion that could not be explained for any other reason 14 days after being diagnosed with COVID-19 (Rana et al. 2021). Rotshenker-Olshinka et al. (2021) found that early pregnancy loss rates were similar among asymptomatic patients before and after the pandemic (Rotshenker-Olshinka et al. 2021).

In the study of Cosma et al. (2021), pregnancy loss and pregnancy continuing patients were compared. No difference were found in terms of the previous infection between two groups. In their study results, they reported SARS-CoV-2 is not a predisposing factor for early pregnancy loss in the first trimester. However, they reported that the study group consisted only of patients who applied to the hospital for care. They stated that losses during early pregnancy may not need obstetric care, and therefore, the possibility of being overlooked is the limitation of the study (Cosma et al. 2021). In our study, we found the rate of pregnancy loss in patients infected with SARS-CoV-2 in the first trimester as 28.8%, and

this rate is high compared to uninfected patients (13.2%)(p=0.04). In addition, this rate is higher when compared with the rate of pregnancy loss (15%) reported in the literature and the spontaneous abortion rate (14%) reported by Turkish Population and Health studies between 2008-2013 (Quenby et al. 2021, Hacettepe University Institute of Population Studies 2013). Unlike the other two studies, the reason of the higher miscarriage rates in our study compared to the control group and the literature may be that our study included all symptomatic and asymptomatic pregnant patients diagnosed with COVID-19 in the first trimester in our city.

In a recent study, SARS-CoV-2 virions were identified in syncytiotrophoblast in placental villi of a pregnant woman infected with SARS-CoV-2 as a result of visualization performed by electron microscopy. In addition, it has been suggested in the literature that intrauterine nutrition of the fetus will be disrupted as a result of perivillous fibrin accumulation and villose infarctions in response to injury/inflammation in the placental tissue. At the end of this processes the rates of preterm delivery, intrauterine growth restriction, and miscarriage may increased (Algarroba et al. 2020, Liu et

Table II. Symptoms and signs.

	All patients (n=52)	Miscarriage Group (n=15)	Ongoing Pregnancy Group (n=37)	p
No symptoms	20 (38.5%)	1 (6.7%)	19 (51.4%)	**<0.01**
Fatigue	19 (36.5%)	7 (46.7%)	12 (32.4%)	0.33
Cough	17 (32.7%)	9 (60%)	8 (21.6%)	<0.01
Fever©	14 (26.9%)	8 (53.3%)	6 (16.6%)	**<0.01**
Myalgia	14 (26.9%)	5 (33.3%)	9 (24.3%)	0.5
Shorthness of breath	10 (19.2%)	8 (53.3%)	2 (5.4%)	**<0.01**
Nausea&vomiting	9 (17.3%)	2 (13.3%)	7 (18.9%)	0.6
$SaO_2 < 93\%$	9 (17.3%)	6 (%40)	3 (8.1%)	**<0.01**
Hospitalization	8 (15.4%)	5 (33.3%)	3 (8.1%)	**0.02**
Sore throat	8 (15.4%)	2 (13.3%)	6 (16.2%)	0.79
Anosmia	4 (7.7%)	2 (13.3%)	2 (5.4%)	0.3
Diarrhea	2 (3.8%)	1 (6.7%)	1 (2.7%)	0.5

©Body temperature measured at anytime (when infected with SARS-CoV-2) above 37.8°C was considered to be fever. Statistically significant p values are written in bold. Chi-square test was performed. p: Comparison of Miscarriage Group and Ongoing Pregnancy Group.

al. 2020a). The study by Patberg et al. (2021) is noteworthy in that increased abnormalities were observed in the histopathological examinations of placentas of mothers infected with COVID-19, even if the patients were asymptomatic (Patberg et al. 2021). The possible pathophysiology underlying the increased miscarriage rates in our study may be histopathological disorders in the placenta and/or uteroplacental disorder secondary to the SARS-CoV-2 infection.

In our study the number of symptomatic patients was higher in MG. The relationship between symptoms and high viral load has been reported in the literature (Liu et al. 2020d). We also think that the increased viral load may be associated with pregnancy loss. Viral load measurement cannot be made in our center. Further studies that will show the virus isolation and tissue reactions in response to inflammation

in the abortion material or placenta might make it more possible to explain the etiology.

The current balance between inflammatory and proinflammatory cytokines is reshaped as the protective balance of the fetus in pregnancy. But this immuntolerance that is formed to protect the fetus makes the mother more vulnerable to maternal infections during this period (Kraus et al. 2010). In addition cytokine increase that continued until the second week after diagnosis was detected in COVID-19 patients. In a study, increased cytokines, especially IL-6, was associated with the increased mortality in COVID-19 (Ruan et al. 2020). Any excessive pro- or anti-inflammatory signal can be harmful to pregnancy outcomes (van Mourik et al. 2009). This supports the hypothesis of our study.

In their modeling studies, Sills and Wood argued that there may be early pregnancy losses and implantation failure secondary to COVID-19.

Table III. Laboratory Findings.

	Miscarriage Group (n=15)	Ongoing Pregnancy Group (n=37)	All COVID patients (n=52)	Control Group (n =53)	p[1]	p[2]
Leucocytes (x10^9/L)*	5.2 (2.7-11.7)	7.3 (2.9-16.3)	7.2 (2.7-16.3)	8.6 (4.8-15.4)	0.16	0.07
<5.7x10^9/L	7 (46.7%)	8 (21.6%)	15 (28.8%)	3 (5.7%)	0.07***	**0.02***
> 13.6x10^9/L	1 (6.7%)	4 (10.8%)	5 (9.6%)	3 (5.7%)	0.6***	0.44***
Lymphocytes (x10^9/L)**	1.2 (0.8-3.2)	1.9 (0.5-3.5)	1.8 (0.5-3.5)	2.2 (1-4.9)	0.16	**<0.01**
<1.1x10^9/L	8 (53.3%)	8 (21.6%)	16 (30.8%)	2 (3.8%)	**0.02***	**<0.01***
CRP	4.6 (3-152)	7 (3-56)	6.5 (3-152)	3.05 (1-34)	0.2	**0.01**
>10 mg/L	5 (33.3)	20 (54.1)	25 (48.1%)	4 (7.8 %)	0.22***	**<0.01***
Platelets (x10^9 per mm^3)	160.5 (110-285)	224 (123-442)	196.5 (110-442)	237.5 (117-473)	0.01	**0.01**
<150x10^{9}per mm^3	5 (33.3%)	2 (5.4%)	7 (13.5%)	2 (3.8 %)	**<0.01***	0.07***
D-dimer (µg/L)	680 (150-1986)	415 (179-1400)	477 (150-1986)	395 (157-425)	**0.01**	**0.03**
>500 µg/L	10 (66.7%)	12 (32.4%)	22 (42.3%)	5 (9.5%)	**0.02***	**<0.01***
Hemoglobin (g/L)	12.5 (9-14.4)	12.7 (8.7-14.8)	12.6 (8.7-14.8)	12.7 (10.4-16.9)	0.53	0.2
Neutrophil (x10^3 µL)	5.86 (2.64-10.6)	5.25 (1.53-11.8)	5.2 (1.5-11.8)	5.4 (2.4-11)	0.07	0.3
NLR	4.3 (0.8-11.2)	2.5 (1.1-7.6)	3.1 (0.8-11.2)	2.6 (1-6.2)	0.01	0.04

*Leucocytes reference range in first trimester, 5.7–13.6 x10^9/L (Williams Obstetrics 25th Edition). **Lymphocytes reference range: 1.1–3.2 x10^9/L. ***Chi-square test was performed. NLR: Neutrophil Lymphocyte Ratio. p[1]: Comparison of Miscarriage Group and Ongoing Pregnancy Group. p[2]: Comparison of COVID group and control group. Statistically significant p values are written in bold. Chi-square test was performed. CRP: C-reactive protein.

They suggested that, after SARS-CoV-2 infection in early pregnancy, the supraphysiological cytokine signal would disrupt the decidualization, implantation, and fetal nutrition continuing through the placenta (Sills & Wood 2020).

NLR is one of the important markers showing the inflammatory process. In recent studies, severe COVID-19 cases were reported to have high NLR and were found to be an independent risk factor for hospitalization (Qin et al. 2020, Liu et al. 2020b). The inflammatory response can stimulate neutrophil production and accelerate the apoptosis of lymphocytes. This causes an increase in NLR. It is believed that irregular immune cell responses and thus immunological abnormalities play

Table IV. Pharmacologic Treatments.

	All COVID patients	**Miscarriage Group**	**Ongoing Pregnancy Group**	**p**
No pharmacologic treatment	24 (46.2%)	5 (33.3%)	19 (51.4%)	0.2
Hydroxychloroquine	2 (3.8%)	2 (13.3%)	0	0.02
Any antibiotics	11 (21.6%)	3 (21.4%)	8 (21.6%)	0.98
LMWH	16 (30.8%)	4 (26.7%)	12 (32.4%)	0.68
Favipiravir	1 (1.9%)	1 (6.7%)	0	0.1
Lopinavir	3 (5.8%)	1 (6.7%)	2 (5.4%)	0.86

LMWH: Low molecular weight heparin. Chi-square test was performed. p: Comparison of Miscarriage Group and Ongoing Pregnancy Group.

significant roles in the severity of viral diseases (Channappanavar & Perlman 2017). In our study, a higher rate of NLR in MG compared to OPG supports the relationship of the inflammatory process with the risk of miscarriage. High fever, an indicator of the inflammatory response, was observed more in patients with pregnancy loss. The number of patients with SaO2 <93%, which is another indicator of severe disease, and the rate of hospitalization was observed more in the group with pregnancy loss. Especially in the patient group in which COVID-19 progresses more seriously and the inflammatory balance is impaired, the increasing abortion rate supports the negative effects of inflammatory response and cytokine balance on pregnancy. We think that the increased inflammatory response and disturbed cytokine balance are one of the underlying mechanisms of pregnancy loss in the first trimester (balanced work of multiple and complex mechanisms is important for implantation and the continuation of pregnancy in first trimester).

It is known that coagulation disorders occur and increased hypercoagulability is important in COVID-19 (Levi et al. 2020). The increase in d-dimer levels, which is used as an indicator of increased coagulation disorder, has been associated with mortality and morbidity of COVID-19 (Zhang et al. 2020). Thrombocytopenia, which is an indicator of systemic microvascular thrombosis, has been accepted as an indicator of coagulopathy associated with COVID-19 and has been reported to increase the risk of mortality related to the disease by 4.24 times (Liu et al. 2020c, Wool & Miller 2021). In our study, d-dimer >500 µg/L and trombocytopenia were found more in MG than OPG (p=0.008, p=0.02 respectively). Therefore, we think that in addition to the susceptibility to hypercoagulability caused by pregnancy, microvascular thrombosis caused by COVID-19 is also associated with increased abortion rates. D-dimer levels in patients infected with SARS-CoV-2 in the first trimester may have a place in predicting miscarriage and perhaps early anticoagulant therapy may be critical in terms of healthy pregnancy maintenance.

In addition to direct effects, the COVID-19 pandemic created a environment dominated by intense stress such as economic instability, fear, and uncertainty. Chronic stress has been reported to be associated with poor obstetric outcomes and increasing miscarriage rates (Keasley et al. 2017). High pregnancy loss rates (which are thought to be the result of increased cortisol and negative immune system effects) was observed in pregnant women under the threat of war (Wainstock et al. 2013). In our study,

a scale was not used that can evaluate the anxiety levels of the patients. However, it was observed that pregnant women suffer from the restricted environment, concerns about reaching the hospital, and the uncertainty of the effects of the pandemic on the fetus. We thought that increased miscarriage rates may also be related to this chronic stress.

The limited number of patients and the fact that the study group represents a single ethnic race are the limitations of the study. Since there was no clear protocol for the treatment of pregnant patients enfected with SARS-CoV-2, the treatments applied varied. Because of this not enough patients were given anti-coagulant therapy. So we could not investigate the efficacy of anticoagulant therapy in the prevention of miscarriages.

In conclusion; according to the results of our study, the risk of miscarriage increases in pregnant women infected with SARS-CoV-2 in the first trimester. This situation is more common in symptomatic patients with high NLR and d-dimer levels and low platelet counts. Increased inflammatory response, cytokine storm, hypercoagulability, and exposure to chronic stress appear to be possible underlying mechanisms. Negative effects of COVID-19 should not be ignored in first trimester pregnancies, for which less studies have been conducted compared to other trimesters. More studies are needed, especially with a larger number of patients, to shed light on the etiopathogenesis of mechanisms.

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