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Can asymptomatic SARS-CoV-2 infection cause spontaneous abortion?

Rukiye Ada Bender[1], Renginar Akbulak[2], Ali Şengül[3]

[1]Department of Obstetrics and Gynecology, School of Medicine, Biruni University, İstanbul, Turkey
[2]Department of Obstetrics and Gynecology, İstanbul Esenler Women and Children Diseases Hospital, İstanbul, Turkey
[3]Department of Immunology, Medicana International İstanbul Hospital, İstanbul, Turkey

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ABSTRACT

Aim: The probability of spontaneous abortion is known to increase (15%) in the pregnant women who develop symptomatic and even "Severe Acute Respiratory Syndrome (SARS)" due to maternal infections. It is known that the SARS-CoV-2 virus, one of these infectious agents, enters host cells by binding to angiotensin-converting enzyme 2 (ACE2). New literature data have shown the increased ACE2 receptor in the endometrium during the decidualization phase and the ability of SARS-CoV-2 to enter endometrial stromal cells through ACE2 proteins. This shows that the COVID-19 infection can cause many pathologies such as early pregnancy loss. The aim of this study is to investigate the effects of SARS-CoV-2 virus which are positive in the uterine samples on pregnancy loss.

Material and Method: 13 women who had first trimester pregnancy loss were included in this cross-sectional study. None of these pregnant women had any known symptoms of SARS-CoV-2 infection. SARS-CoV-2 infection was screened in uterus and naso-oropharynx samples by real-time polymerase chain reaction (RT-PCR) test in these pregnant women. Women with positive RT-PCR results will be evaluated for pneumonia by lung tomography. It is planned to evaluate the sample taken from the naso-oropharynx in the partners of these women for SARS-CoV-2 infection by RT-PCR. In addition, in positive cases, RT-PCR was planned from the uterus and naso-oropharynx samples at 7-day intervals until the case turned negative.

Results: RT-PCR test for SARS-CoV-2 was positive only in a sample taken from the uterus of one woman (7.6%). The naso-oropharyngeal sample of the same patient was negative, and the patient had no symptoms of COVID-19. No COVID-19-related lesion was observed in the lung tomography of this patient. The results of the RT-PCR test performed 7 days later with samples taken from the uterus and naso-pharynx were also negative. After the patient's positive RT-PCR result, a naso-oropharyngeal sample was taken from his partner. The RT-PCR test result for SARS-CoV-2 in the patient's partner was negative.

Conclusion: The fact that the SARS-CoV-2 virus was negative in the naso-oropharyngeal sample and positive in the uterine sample in a pregnant woman who had a miscarriage suggests that the endometrium may be an entry route for the virus. These data suggest that the virus can lead to adverse pregnancy outcomes, including early pregnancy loss, even without known symptoms. A large number of studies are needed to evaluate the effects of common viruses on pregnancy beyond the expected and defined symptoms.

Keywords: Pregnancy loss, SARS-CoV-2, abortion, intrauterine, COVID-19

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INTRODUCTION

Pregnancy loss, also known as a miscarriage or spontaneous abortion, is generally defined as a nonviable intrauterine pregnancy up to 20 weeks of gestation (1,2). Common risk factors for abortion include advanced maternal age, medical conditions, drug and/or substance abuse, and environmental exposure.

Overall, approximately 15% of abortions are associated with an infectious etiology (3). The cumulative incidence of abortion due to parvovirus B19 infection during pregnancy is approximately 8%, and the risk of abortion due to an infection is 5.6 times higher in the first trimester than in the second trimester (4). Untreated syphilis leads to a 21% increased risk of abortion and stillbirth (5). Maternal cytomegalovirus (CMV) infection increases the abortion rate by 2.5 times (6). However, maternal infection with HIV or toxoplasmosis has not been shown to be associated with abortion risk (7,8).

Coronavirus disease 2019 (COVID-19) was first seen in Wuhan, China in December 2019 as a disease that can progress to acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) caused by the severe

Corresponding Author: Rukiye Ada Bender, r.adabender@gmail.com
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acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to the ongoing pandemic caused by the infection, new scientific data are rapidly added to the literature. However, the relationship between SARS-CoV-2 and abortion has not yet been clarified (9). On the other hand, there are data suggesting that infection may cause maternal vascular malperfusion and decidual arteriopathy in pregnant women (10-12). SARS-CoV-2 positivity has been shown in tissues such as the placenta or placental membranes of a small number of patients (10,13).

The SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) to enter the cell. For this reason, studies have shown that it can replicate not only in the respiratory system but also in other tissues where ACE2 is present (14). The fact that SARS-CoV-2 can enter endometrial stromal cells using ACE2 shows that it can also cause pregnancy loss (15,16).

The aim of this study was to investigate the effects of the SARS-CoV-2 virus on pregnancy loss by showing positivity in uterine samples.

MATERIAL AND METHOD

The study was approved by the Republic of Turkey, Ministry of Health, Scientific Research Studies Evaluation Commission (Date: 16.05.2020, Decision No: 2020-05-15T15_13_17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Women who were evaluated for pregnancy loss in the Department of Obstetrics and Gynaecology, Medicana International İstanbul Hospital, and Esenler Maternity and Children's Hospital between 15 April 2020 and 14 June 2020 were invited to participate in the study. The study included 13 women who agreed to participate. The presence of COVID-19 symptoms during pregnancy, smoking habits, obstetric history, and chronic diseases of these women were questioned.

Vacuum aspiration was planned to be performed under sedation and sterile operating room conditions as a treatment for pregnancy loss. The coagulation and hemogram parameters of all patients were evaluated preoperatively. Before starting the operation, samples were taken from the naso-oropharynx and uterus of all patients under sedation for RT-PCR test.

The RT-PCR method targeting the RdRp (RNA-dependent RNA polymerase) gene was used for the detection of SARS-CoV-2 in naso-oropharyngeal and uterine samples. Specimens were transported to the Molecular Virology Laboratory within 12 hours of collection and tested immediately upon acceptance.

RT-PCR was studied in the naso-oropharyngeal samples of the partners of women with a positive RT-PCR result for the SARS-CoV-2 virus to screen the virus. Chest computed tomography (CT) examinations of these women and their partners were evaluated for the presence of infiltrating areas. Their serum CRP, Ferritin, D-Dimer, LDH levels were also measured. In addition, in positive cases, RT-PCR was planned from the uterus and naso-oropharynx samples at 7-day intervals until the case turned negative.

Data were analyzed using the SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A p-value less than 0.05 was considered statistically significant.

RESULTS

The study consisted of a cross-sectional analysis of 13 pregnant women who had pregnancy loss during the SARS-CoV-2 pandemic. Age, gestational age, gravida, parity, abortion, the presence of COVID-19 symptoms during pregnancy, smoking habits, and chronic diseases were determined (**Table 1**).

Table 1: Demographic and laboratory data of 13 women, who had pregnancy loss

	Min	Max<	Mean	Standart Deviation
Age	20	38	29	5.29
Gestatational Age (day)	34	88	52.61	15.22
Gravida	1	5	2.38	1.44
Parite	0	3	1	0.91
Abort	0	2	0.3	0.63
WBC* Count (10^3/uL)	5.15	14.69	8.81	2.59
Hemoglobine Count (g/dL)	10.8	14	12.53	1.02
Platelet Count (10^3/uL)	158	405	260.46	77.96
Lymphocyte Count (10^3/uL)	1.3	4.3	2.28	0.74
aPTT* (second)	26.9	47.8	34.88	4.68
Prothrombin time (INR*)	0.92	1.29	1.04	0.98
	n		%	
Chronic Disease	1		7.6	
Smoking Habits	4		30.8	
COVID-19 Symptoms	0		0	

*WBC: White blood cell, aPTT: Activated partial thromboplastin time, INR: International Normalized Ratio

According to their gestational age, all patients were in the first trimester of pregnancy. None of the patients had symptoms that may be caused by COVID-19. Only one woman had controlled hypothyroidism as a chronic disease. The laboratory results of the patients showed no severe anemia, lymphopenia, or coagulation disorder.

Given the RT-PCR results, the SARS-CoV-2 virus was not detected in any of the naso-oropharyngeal samples. The RT-PCR test was positive for the SARS-CoV-2 virus in the uterine sample of only one 38-year-old woman, who was a smoker, pregnant for the first time, and had no additional chronic disease or symptoms (7.69 %) (**Table 2**).

Table 2. Demographic and laboratory data of women who were positive for SARS-CoV-2 in endometrial rt-PCR

Age	38
Gestational Age (day)	57
Gravida	1
Parite	0
Abort	0
WBC Count	8.48 10^3/uL
Hemoglobine Count	13.9 g/dL
Platelet Count	223 10^3/uL
Lymphocyte Count	2.27 10^3/uL
aPTT	26.9 second
Prothrombin time	0.92 INR*
Chronic Disease	no
Smoking Habits	10 cigarettes maximum per day
COVID-19 Symptoms	no
Naso-oropharynx rt-PCR*	negative
Endometrial rt-PCR	positive
LDH*	147 U/L
CRP*	1.3 mg/dL
Ferritin	27.52 ng/mL
D-Dimer	577 ng/mL
Thorax-CT*	no infiltrative lesion
Chromosomal abnormalities in abort material	no

*WBC: White blood cell, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, rt-PCR: Real-time reverse transcriptase-polymerase chain reaction, LDH: Lactate dehydrogenase, CRP: C-reactive protein CT: Computed tomography

The patient was evaluated based on the positive intrauterine RT-PCR result, which was reported four days after the surgical procedure. The asymptomatic patient was also examined for COVID-19 infection. Her chest CT showed no active infiltration. The laboratory evaluation showed normal lymphocyte count and LDH levels. Acute phase reactants (CRP, ferritin, D-dimer) were also studied. The CRP and D-Dimer levels were above the normal range but the ferritin level was normal.

The partner of the patient was considered a suspected COVID-19 patient and was evaluated with RT-PCR of the naso-oropharyngeal sample, which negative for SARS-CoV-2.

The treatment algorithm recommended by the Ministry of Health of the Republic of Turkey for asymptomatic patients was used for the treatment of the patient who was isolated and followed up at home. Seven days after the initiation of the patient's treatment, an intrauterine RT-PCR sample was taken for a follow-up examination and the result was reported negative for this sample. In the later period, the patient and her partner exhibited no symptoms associated with COVID-19.

Only in this case, genetic analysis was ordered for the abortion material upon the patient's own request. No chromosomal abnormalities was detected on the examination of the abortion material.

DISCUSSION

Although many studies have been conducted on the effects of SARS-CoV-2 on pregnancy and fetus, the long-term effects of SARS-CoV-2 are still unclear since it is a quite new infectious agent (17). Most studies have evaluated naso-oropharyngeal swab samples of pregnant women (18). However, the data at the molecular level have shown that the respiratory epithelium is not the only tissue through which the virus enters the cell and becomes effective (16). SARS-CoV-2, which enters the cell via ACE2, also involves other tissues including the lung, heart, intestine, kidney, and placenta (15).

The increased expression of ACE2 during the formation of the decidual endometrium also increases the probability of viral replication (15). It has been reported that SARS-CoV-2 is effective in the decidual endometrium in the early stage of pregnancy, while it is effective in the placental area with the formation of the placenta in the later stage of pregnancy (11, 19). The virus is believed to cause pregnancy complications due to maternal vascular malperfusion and decidual arteriopathy (19). A limited number of meta-analyses in the literature have reported cases of maternal death, neonatal death, preterm birth, preeclampsia, and early pregnancy loss (17,18,20). Among these data, there are only a few case reports evaluating the fetus, placenta, and placental appendages separately for SARS-CoV-2 (10). Despite the small sample size, this study is of importance in terms of filling this gap in the literature.

This study evaluating 13 cases of pregnancy loss demonstrated positive RT-PCR result for the virus in the uterine sample of only 1 patient. No virus was detected in the naso-oropharyngeal sample taken simultaneously from the same patient. Although this data does not provide clear evidence, it suggests sexual transmission of SARS-CoV-2. The absence of known symptoms of COVID-19 and infiltrative lesions on chest CT in the positive case strengthens the suspicion that the virus may also cause disease manifestations beyond the known.

Our study is a prospective study conducted with the special permission obtained by the COVID-19 Ethics Committee from the Ministry of Health at the beginning of the COVID-19 pandemic. Ethics Committee permission of the Ministry of Health, which was obtained at the beginning of the study, was granted for a period of 3 months. In this context, this time has been determined out of necessity for the study. However, studies have also reported that pregnant women increase their protective measures, and therefore, pregnant women are less infected (21). This situation reduces our sample size dramatically.

The long-term complications of the COVID-19 infection in pregnant patients and the asymptomatic illness are still mysterious (22). The indications for the SARS-CoV-2 test

include the presence of predetermined symptoms and a history of suspected contact. Accordingly, there is not sufficient knowledge on the role of SARS-CoV-2 positivity in obstetric complications. The investigation of the relationship between obstetric complications and SARS-CoV-2 positivity will help predict adverse reproductive outcomes. Therefore, there is a need for more comprehensive studies including intrauterine fetal deaths in the later stages of pregnancy.

CONCLUSION

A positive SARS-CoV-2 sample from the uterus indicates that the endometrium can serve as an entry route for the virus. The SARS-CoV-2 virus can enter through the endometrium in pregnant women, potentially leading to adverse pregnancy outcomes, including early pregnancy loss. While our study's sample size was small, it supported this finding. Large-scale studies are needed to investigate the effects of SARS-CoV-2 and other common viral infections during pregnancy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Republic of Turkey, Ministry of Health, Scientific Research Studies Evaluation Commission (Date: 16.05.2020, Decision No: 2020-05-15T15_13_17).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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