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Investigating the risk of maternal-fetal transmission of SARS-CoV-2 in early pregnancy

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ABSTRACT

Introduction: The possibility of vertical transmission of SARS-CoV-2 from the mother to the fetus is one of the most crucial issues regarding the COVID-19 effects on pregnancy. In this study, we aimed to explore the risk of maternal-fetal transmission before 24 weeks of gestation, through analysis of abortion materials collected from PCR-positive women with pregnancy loss. To the best of our knowledge, apart from case reports, this study is the first prospective work on the vertical transmission of SARS-CoV-2 in early pregnancy.

Methods: The patients who had attended our clinic with the diagnosis of pregnancy loss before 24 weeks of gestation were screened for COVİD-19. Vertical transmission in PCR-positive women was assessed through the presence of SARS-CoV-2 RNA in fetal-placental tissues by rt-PCR test.

Results: 24 of 210 (%11,4) pregnant women participating in the study had positive rt-PCR results. Placenta and curettage material samples of these PCR-positive patients were analyzed and all valid test results (21 samples) were negative for SARS CoV-2 RNA. In three cases, the rt-PCR results were invalid due to failed internal controls.

Discussion: In the literature, the possibility of intrauterine vertical transmission of SARS-CoV-2 is still controversial. The findings of the present study did not reveal any evidence of vertical transmission of SARS-CoV-2 in early pregnancy.

1. Introduction

2019 coronavirus disease pandemic (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an important concern for pregnant women and obstetricians [1]. Numerous studies highlighted the relationship between COVID-19 infection and adverse pregnancy outcomes such as preterm birth, low birth weight, high neonatal intensive care unit admission and stillbirth [2,3].

One of the most crucial questions about the effects of COVID-19 on pregnant women is whether the virus is passed from the mother to the fetus. The answer is still unclear, although some studies based on molecular, serological and histopathological tests on fetal-placental and neonatal tissues suggest that vertical transmission is possible [4–6].

Despite intense interest in this topic since the beginning of the pandemic, there are still some research gaps. The vast majority of the studies addressing maternal-fetal vertical transmission of SARS-CoV-2 focused on the third trimester of pregnancy. Our knowledge about the transmission in early pregnancy is very limited. This is a very delicate period where the fetus is more vulnerable and viral transmissions can potentially cause adverse effects on prenatal development. Therefore, it is important to clarify the vertical transmission in early pregnancy [7].

In this study, we aimed to investigate the risk of maternal-fetal transmission of SARS-CoV-2 in early pregnancy (<24 weeks of gestation). Since the diagnosis of COVID-19 in fetus or placenta during pregnancy requires invasive procedures, we examined the possibility of vertical transmission through abortion materials collected from PCR-positive women with pregnancy loss.

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2. Material and methods

2.1. Participants

This is a prospective study investigating women with early pregnancy loss (<24 weeks of gestation) who had attended the perinatology clinic at Ankara City Hospital (Turkey) between September 1, 2020 and December 1, 2020. Since the beginning of the COVID-19 pandemic, this tertiary reference hospital serves as one of the main national pandemic centers with an extensive experience dealing with COVID-19 infected pregnant women [8].

Pregnancy loss was diagnosed when observed an intrauterine empty gestational sac or an embryo or fetus without cardiac activity in the ultrasound examination [9]. During the study period, all patients with a diagnosis of pregnancy loss before 24 weeks of gestation and who hospitalized for medical or surgical abortion procedure in our center were assessed for participation to the study. 13 patients who needed emergency intervention due to vaginal bleeding were not included in the study. A total of 210 patients participated in the study (Fig. 1). The patients were informed about the study and the written informed consent was obtained.

All patients were screened for SARS-CoV-2 infection before medical or surgical abortion procedure. Abortion material of patients with positive results was sampled for SARS-CoV-2 RNA analysis.

2.2. Sample collection and processing methods

2.2.1. Maternal samples

Maternal samples were collected by nasopharyngeal and oropharyngeal swabs and transported to the laboratory with viral transport medium (VTM, various manufacturer) within 12 h and tested on arrival.

2.2.2. Placental samples

In pregnancies later than 12 weeks, within minutes of removal of the placenta after medically induced abortion, placental biopsy was taken from the fetal surface of the placenta. Due to the difficulty of obtaining separate placental tissue in early pregnancies, samples were taken from the abortion material consisting of decidua, trophoblastic and fetal tissue mixture obtained by aspiration curettage. During the material collection and transfer to the laboratory, care was taken to comply with the sterility rules and to prevent contamination. The samples were transferred to the hospital's molecular virology laboratory within 30–60 min after collection.

2.2.3. Tissue lysis

An approximately 2–3 mm^3 of placental samples or abortion material was sectioned, and digested on a 65 °C heat block with 1000 μl of Buffer ATL (Qiagen, Hilden, Germany) and 50 μl of proteinase K (Qiagen, Hilden, Germany) for min 3 h.

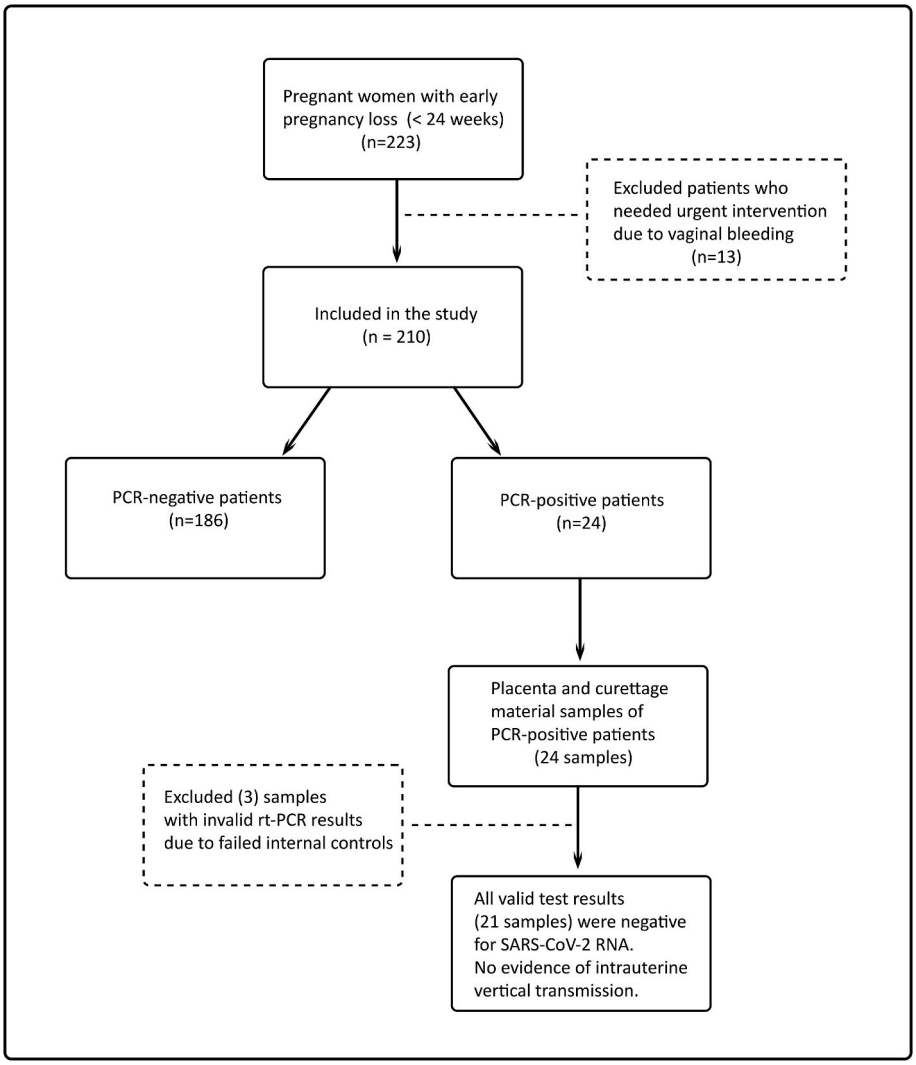

Fig. 1. Flow chart of the study participants.

2.2.4. Nucleic acid extraction

After denaturing for 10 min at 95 °C, vortex and spin processes were performed. 100 μl of this sample was then dissolved in 100 μl of Viral Nucleic Acid Extraction buffer (various manufacturers) and vortexed for 15 min before Polymerase Chain Reaction (PCR).

2.2.5. Real Time Reverse Transcriptase Polymerase Chain Reaction

SARS-CoV-2 in placental tissues and abortion material were detected by Real Time Reverse Transcriptase Polymerase Chain Reaction (rt-PCR) method targeting Orf1ab and N genes.

Real-time reverse-transcription PCR was performed by using Coronex COVID-19 rt-qPCR Detection Kit (DS Bio and Nano Technology, Ankara, Turkey) with 20 μL reaction containing 5 μL of RNA, 12,5 μL of CORONEX-Covid 19 DS Mix E (rt-qPCR Master mix) and 2,5 μL of CORONEX-Covid 19 DS PP1 (Orf1ab, N and RNP gene and primer-probe mix). Thermal cycling was performed at 48 °C for 20 min for reverse transcription, followed by 95 °C for 2 min and then 35 cycles of 95 °C for 5 s, 60 °C for 10 s, in Rotor-Gene Q device (Qiagen, Hilden, Germany). Cycle threshold (Ct) values of less than 35 were defined as positive.

2.3. Statistical analyses

Statistical analyses were carried out with IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). We used descriptive statistical methods. The mean and standard deviation were calculated for continuous and normally distributed variables. Categorical variables were presented as frequencies and percentages. To compare the differences between the PCR-positive and PCR negative patients' characteristics, we used Student t-test for continuous variables and Fisher's exact test for categorical variables.

2.4. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki principles. It was approved by the Ethics Review Committee of Ankara City Hospital (approval number: E1-20-1222).

3. Results

Twenty-four of 210 (11,4%) pregnant women participating in the study had positive rt-PCR results for SARS-CoV-2 RNA (Fig. 1). There was no significant difference between PCR-positive and PCR-negative patients in terms of maternal age, gestational week, gravida, parity, previous abortions and pre-pregnancy body mass index. In the vast majority of the study group (181 of 210 patients, 86,2%), pregnancy loss occurred during the first trimester. The demographic characteristics were presented in Table 1.

Among 24 PCR-positive pregnant women, 20 (83,3%) had no symptoms of COVID-19. Three patients had mild COVİD-19 disease with non-specific symptoms such as dry cough, sore throat, fatigue, diarrhea, and fewer. One patient with 19 weeks of gestation had critical COVİD-19 disease. Spontaneous abortion occurred while she was being treated in the intensive care unit, and after 4 days she died. Clinical and laboratory findings of the PCR-positive patients were presented in Table 2.

Abortion materials of 24 pregnant women infected with COVID-19 were analyzed for SARS-CoV-2 RNA by rt-PCR test. In three cases, the rt-PCR results were invalid due to failed internal controls. All valid test results (21 samples) were negative for SARS-CoV-2 RNA. In others words, the analysis of PCR-positive patients' abortion materials did not reveal any evidence of maternal-fetal vertical transmission of SARS-CoV-2.

Table 1
Demographic characteristics of the study group.

	COVID-19 Negative	COVID-19 Positive	*P*
	n = 186	*n* = 24	
Maternal age, years, mean ± SD	29,69 ± 6,61	30,58 ± 5,8	,528
Gestational age, weeks, *n* (%)			,113
<14	163 (87,6)	18 (75)	
≥14	23 (12,4)	6 (25)	
Gravida, *n* (%)			,58
1	43 (23,1)	5 (20,8)	
2	58 (31,2)	10 (41,7)	
≥3	85 (45,7)	9 (37,5)	
Parity, *n* (%)			,744
0	57 (30,7)	9 (37,5)	
1	62 (33,3)	9 (37,5)	
≥2	67 (36)	6 (25)	
Previous abortions, *n* (%)			,867
0	125 (67,2)	15 (62,5)	
1	45 (24,2)	7 (29,2)	
≥2	16 (8,6)	2 (8,3)	
Pre-pregnancy Body Mass Index, *n* (%)			,071
<30	159 (85,5)	17 (70,8)	
≥30	27 (14,5)	7 (29,2)	
Smoking status, *n* (%)			,227
Non-smokers	171 (91,9)	24 (100)	
Smokers	15 (8,1)	0	
Co-morbid diseases, *n* (%)			,747
Present	161 (86,6)	22 (91,7)	
Absent	25 (13,4)	2 (8,3)	

4. Discussion

Questions regarding transmission of SARS-CoV-2 from mothers to fetuses during pregnancy remains pending. Since angiotensin converting enzyme 2 (ACE2) receptor, which is estimated to be the primary receptor of SARS-CoV-2, is highly expressed in maternal-fetal interface cells, there is a theoretical risk of maternal-fetal vertical transmission and subsequent adverse perinatal outcomes such as fetal malformations, early pregnancy losses and stillbirth [1]. Increasing evidences from studies that highlighting the presence of viral RNA and proteins in fetal and neonatal tissues and detection of positive serology also support the possibility of vertical transmission of SARS-CoV-2 [10–15].

However, current available data from literature reviews showed that the evidence provided by the studies is poor and the vertical transmission of SARS-CoV-2 is still uncertain [4–6]. A meta-analysis, reviewing 38 studies, reported that viral transmission was mostly studied in neonatal nasopharyngeal swabs, and SARS-CoV-2 RNA positivity was 3,2% (22 out of 936 cases). In addition, SARS-CoV-2 RNA positivity was found to be 7,7% in placental samples (two of 26 cases), 3, 6% in umbilical cord blood (one of 28 cases), and 9,7% in anal/rectal swabs (three of 31 cases), and the serological tests were positive in three of 81 cases (3.7%). In amniotic fluid samples (51 cases), no positive result was reported [16].

In the current literature, most of the data on vertical transmission are about pregnant women in third trimester, and the data regarding the transmission in early pregnancy is very limited. To the best of our knowledge, apart from case reports, the present study is the first prospective work on the vertical transmission of SARS-CoV-2 in early pregnancy. Baud et al. reported a 19-week case of second trimester fetal loss in a COVİD-19 infected woman with documented SARS-CoV-2 PCR positivity on the fetal surface of the placenta [17]. In another case report on a pregnant woman in second trimester with COVID-19 infection, Hoiser et al. demonstrated the presence of SARS-CoV-2 RNA in placental tissues [18]. In the present study, as a result of analysis on the abortion materials of twenty-one COVİD-19 infected pregnant women, we could not find any evidence to vertical transmission in early pregnancy.

It has been shown that the expression of ACE-2 and transmembrane protease serine type 2 receptors, which are used by the virus to enter the host cell, increases in placental and fetal tissues as the gestational age progresses [19]. Future studies are needed to investigate whether low receptor levels are protective for SARS-CoV-2 vertical transmission in

Table 2
Clinical and laboratory findings of the PCR-positive patients.

Patient no.	Age, year	Gestational week	COVID-19 Status	COVİD-19 Symptom	Lymphocyte (10^3/mm^3)	CRP (mg/dL)	IL-6 (pg/mL)	COVID-19 Treatment	rt-PCR result of the abortion material
1	32	9	Mild	Cough, fatigue	1080	4,6	16,8	Hydroxychloroquine	Negative
2	33	16	Asymptomatic	None	1590	13,6	7,59	None	Negative
3	16	18	Asymptomatic	None	520	56	–	None	Negative
4	35	12	Asymptomatic	None	1250	9,3	7,79	None	Negative
5	34	8	Asymptomatic	None	1790	14,1	10,8	None	Invalid
6	38	10	Mild	Diarrhea, fatigue	1970	3,9	6,03	Favipiravir	Negative
7	33	6	Asymptomatic	None	790	103,7	126	None	Negative
8	33	9	Asymptomatic	None	1290	14,1	–	None	Negative
9	31	5	Asymptomatic	None	1700	11,7	5,8	None	Negative
10	27	19	Critical	Respiratory and multi-organ failure	820	156	23	Lopinavir-ritonavir, corticosteroid, IL-1 receptor antagonist	Invalid
11	35	17	Asymptomatic	None	1630	140,8	–	None	Negative
12	31	14	Asymptomatic	None	1180	–	–	None	Invalid
13	43	7	Mild	Sore throat	1400	32,4	10,2	Hydroxychloroquine	Negative
14	30	9	Asymptomatic	None	1030	33,8	–	None	Negative
15	28	7	Asymptomatic	None	1920	10,1	–	None	Negative
16	29	7	Asymptomatic	None	1520	5,7	–	None	Negative
17	37	10	Mild	Cough, fever	1940	118,6	6,51	Hydroxychloroquine	Negative
18	34	10	Asymptomatic	None	1420	13,8	–	None	Negative
19	28	8	Asymptomatic	None	2800	1,1	3,37	None	Negative
20	24	8	Asymptomatic	None	2130	3,8	7,02	None	Negative
21	28	9	Asymptomatic	None	1430	–	–	None	Negative
22	21	8	Asymptomatic	None	1240	1,6	–	None	Negative
23	31	7	Asymptomatic	None	1780	0,9	–	None	Negative
24	23	18	Asymptomatic	None	1110	24,2	–	None	Negative

early pregnancy.

In some studies, on pregnant women infected with SARS-CoV-2, non-pathognomonic histopathological changes such as decidual vasculopathy and intervillositis in the placenta have been reported [18,20]. These histopathological changes may be associated with fetal growth restriction, preterm delivery, miscarriage and stillbirth [20,21], and this raises concerns about COVID-19 related adverse pregnancy outcomes. Studies investigating the relationship between COVID-19 and pregnancy loss present controversial findings. While some studies suggested a higher risk of stillbirth among COVID-19 patients [3,22], others have not shown any increase in miscarriage and stillbirth during the pandemic [23,24].

In the present study, the COVİD-19 positivity rate was 11,4% among women with early pregnancy loss, and asymptomatic positive patient rate was 9,5%. In another study conducted in the same center between April and June 2020, asymptomatic positive patient rate among pregnant women was 1,4% [25]. Although it is not appropriate to make a comparison due to the fact that the two studies were not conducted in the same period, the difference in COVID 19 positivity rate between women with pregnancy loss and pregnant women is remarkable.

5. Conclusion

Previous studies reporting evidence of vertical transmission of SARS-CoV-2 mostly based on the third trimester of pregnancy. The results of this study focusing on early pregnancy do not support the possibility of intrauterine vertical transmission of SARS-CoV-2. More research is needed to reveal the risk of vertical transmission during pregnancy and whether the early pregnancy is less vulnerable.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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