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Original Article

The influence of COVID-19 pandemic on intrauterine fetal demise and possible vertical transmission of SARS-CoV-2

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ABSTRACT

Objective: The impact of COVID-19 on intrauterine fetal demise (IUFD) and vertical transmission of the SARS-CoV-2 from the mother to the fetus are crucial issues of the COVID-19 pandemic. In the current study, we aimed to detect the pandemic's influence on the IUFD and evaluate the vertical transmission of the SARS-CoV-2 through analysis of placental tissues collected from PCR positive women with IUFD above 20 weeks of gestation.

Materials and methods: The pregnant women above 20 weeks of gestation and had a fetus intrauterine demised during pandemic were included in the study. The pregnant women screened for COVID-19. Vertical transmission searched from placental tissues of COVID-19 positive women by RT-PCR tests for the presence of SARS-CoV-2 RNA. The number of IUFD before the pandemic and during the pandemic compared to assess the influence of the COVID-19 pandemic on the IUFD ratio.

Results: Among 138 pregnant women with IUFD, 100 of them could screen for COVID-19 status. RT-PCR test results of 6 of the screened pregnant women were positive for SARS-CoV-2. Placental tissues of these six women were analyzed, and one test result was positive for SARS-CoV-2 RNA. The IUFD ratio was significantly increased during the pandemic.

Conclusion: It is clear that COVID-19 increases the IUFD ratio. Previous data for vertical transmission of SARS-CoV-2 during the second trimester is limited. We present the third case of literature that has positive placental results for SARS-CoV-2 RNA in the second trimester of pregnancy.

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Introduction

A novel coronavirus, first detected in Wuhan, China, was named 2019-nCoV (for 2019 novel coronavirus) on January 7, 2020 [1,2]. On February 11, 2020, World Health Organization (WHO) officially called the disease Coronavirus Disease 19 (COVID-19). Etiologic virus of the COVID-19 disease was named Severe Acute Respiratory Syndrome (SARS)-CoV-2 by the International Committee on Taxonomy of Viruses [3]. On March 11, 2020, WHO declared the disease as a pandemic [4].

Pregnant women are classified as a vulnerable group, and in the light of previous experiences, more precautions were taken for them with COVID-19 [5,6]. It has been reported that poor obstetric outcomes, including preterm birth and fetal distress increase with COVID-19 [5,6].

The physiologic nature of pregnancy increases the risk of respiratory infections. The lung capacity and immunologic response decrease during pregnancy, making the mother prone to severe respiratory viral infections [7].

Since its initial identification, it is indicated that pregnancy may increase the severity of COVID-19. However, the knowledge on the influence of COVID-19 on pregnancy and obstetric outcomes is still limited.

In the present study, we aimed to evaluate the impact of COVID-19 on intrauterine fetal demise (IUFD) and search for the possible vertical transmission of SARS-CoV-2.

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Material and methods

Participants

This prospective study was performed in Ankara City Hospital, Department of Perinatology, Ankara, Turkey, between August 1, 2020, and February 1, 2021. Our hospital is one of the leading national pandemic centers which handles above 10.000 deliveries yearly, and our department has extensive experience dealing with COVID-19 infected pregnant women [8].

Before initiating the study, the Ministry of Health of Turkey's approval and ethical board approval from Ankara City Hospital Ethical Committee was obtained. The study protocol was performed according to the Declaration of Helsinki principles, and the written informed consent containing the details of the study was obtained from all the participants.

During the COVID-19 pandemic, pregnant women at or greater than 20 gestational weeks (gw) of pregnancy and had an intrauterine ex fetus were included in the study. The demographic characteristics including maternal age, gravidity, parity, number of the living children, number of miscarriages, co-morbid diseases, gestational age at diagnosis, pregnancy trimester at admission, symptoms of COVID-19, medications for COVID-19, the severity of illness, laboratory test results, mode of delivery were recorded. COVID-19 medications were edited according to the national guidelines at the time of admission [9].

COVID-19 infection screening tests were performed with RT-PCR kit. The pregnant women whose SARS-CoV-2 test results were positive, were screened for vertical transmission. After the delivery, samples were taken from the umbilical cord, amniotic membrane and placenta of the women with positive test results were evaluated for COVID-19 positivity.

Cases with IUFD before the pandemic and the total number of admissions during the study period were screened from the electronically recorded data of the hospital. Intrauterine fetal demise was defined as the intrauterine death of a fetus at any time during pregnancy [10].

Maternal and placental sampling

Nasopharyngeal and oropharyngeal swabs were used to screen the COVID-19 infection. To correctly perform the nasopharyngeal and oropharyngeal swab, pregnant women were seated with the back of their head against the headrest. An oropharyngeal sample was obtained by the swab. Subsequently, the same swab was inserted in the nose until reaching the nasopharynx's posterior wall and rotated swab for a few seconds. After taking the samples, swabs were transported to the laboratory in a transport medium within 2 h and tested.

Placental samples were taken after delivery of the placenta immediately. Utmost care to keep sterility was taken to prevent contamination of the tissues. Approximately 5 cm tissue, including the umbilical cord, amniochorionic membrane and the placenta was taken. The sterile cover samples were transferred to the molecular virology laboratory in PBS [phosphate buffer saline] solution within 30 min.

Tissue analysis for COVID-19

In the molecular virology laboratory, approximately 2–3 mm^3 of placental, amniochorionic membrane, and umbilical cord samples were taken and digested by 1000 microL of Buffer ATL [Qiagen, Hilden, Germany] and 50 microL of proteinase K [Qiagen Hilden, Germany] on a 65 °C heat block approximately for 3–4 h. After denaturation, for 10 min at 95 °C, vortex and spin processes were performed before dissolving 100 μL of the sample in 100 μL of Viral Nucleic Acid Extraction buffer [various manufacturers] and vortexing for 15 min before Polymerase Chain Reaction (PCR).

SARS-CoV2 tissues were detected by Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) method. Target genes were Orf1ab and N genes of SARS-CoV-2.

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 five 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] in a thermal cycler device [Rotor-Gene Q, Qiagen, Germany] with a program; 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. Cycle threshold [Ct] values of less than 35 were defined as positive.

Statistical analyses

The statistical analyses were made by using IBM SPSS Statistics version 21.0 (IBM Corp. Armonk, NY). Descriptive data were expressed as mean ± standard deviation and minimum, median, maximum values after evaluating the normality of variables by using the Kolmogorov–Smirnov test. For comparison of the total numbers of admissions and IUFDs, Pearson-χ test was used. An Independent sample t-test was used to compare the rates of IUFD before and during the pandemic. $P < 0.05$ values were defined as statistically significant.

Results

The perinatology clinic's total hospital admission number before pandemic (August 2019–January 2020) was 15.722, and during pandemic (August 2020–January 2021) was 13.037. There was a significant decrease in hospital admission during the pandemic ($p = 0.000$). Table 1 shows the total hospital admission and IUFD numbers during the pandemic and before the pandemic. Despite the total number of hospital admissions significantly decreased, the total IUFD number increased during the pandemic. IUFD ratio [IUFD/Total admission number] was considerably higher during the pandemic period than during the period before the pandemic (1.1 vs. 0.79, $p < 0.05$).

There were 138 pregnant women with a fetus at or above 20 gw intrauterine demised. Thirty-eight of them could not be screened for COVID-19. Among the 100 women tested for COVID-19 with RT-PCR, six of them had positive results for SARS-CoV-2. Additionally, four women had positive SARS-CoV-2 results at the earlier gestational weeks of pregnancy.

The demographic properties and clinical characteristics of the women and the newborns are presented in Table 2. Sixteen (16%) women had at least one preexisting gestational or chronic condition, including diabetes, thrombophilia, leukemia, lymphoma, breast ca, epilepsy, hypertension, familial Mediterranean Fever (FMF), goiter, preeclampsia, myoma uteri. Sixteen women had additional obstetric pathology (16%). There was a balanced distribution among the fetuses for gender.

There were 63 women in the second trimester, while the number of women in the third trimester was 37.

Clinical features and laboratory results of the PCR-positive women are presented in Table 3. Among 6 SARS-CoV-2 positive tested women, 5 of them were in the second trimester.

4 women had no symptoms. Half of the symptomatic women had symptoms as fever, cough, and fatigue, while the other half had myalgia and fatigue. Two women received medications for COVID-19.

Table 1
Total hospital admission and IUFD number during and before pandemic.

Years	Before pandemic 2019	During pandemic 2020	p[a]
	n	n	
IUFD	125	138	0.624
Total hospital admission	15722	13037	**0.030**
IUFD/total admission	0.79	1.1	**0.000**

[a] Independent t-test.

None of the women had severe pneumonia, and there was no maternal mortality. SARS-CoV-2 test result of placental tissue was positive only in 1 woman. In the present case, the Rt-PCR results for SARS-CoV-2 in the umbilical cord and membrane were negative.

The case with positive placental SARS-CoV-2 test result was at 23 years old. The gravidity of the woman was 3 with two previous cesarean sections. The gestational age was 26 weeks. The woman was symptomatic for COVID-19, having fever, cough, and fatigue. Lopinavir-ritonavir, corticosteroid, IL-1 receptor antagonist were initiated for the patient. The fetus's biometric measurements were compatible with the gestational age: 900 gr, ex-female fetus delivered by cesarean section.

Discussion

In the current study, we aimed to investigate the influence of COVID-19 on intrauterine fetal demise. The study results demonstrated a statistically significant increase in the rate of the IUFD during the pandemic according to the time before the COVID-19 pandemic. There was only one positive result of placental tissues among the pregnant women positive for SARS-CoV-2 who was in her second trimester of pregnancy.

The COVID-19 pandemic is not the first outbreak that humankind has ever faced. However, it is quite a challenging experience for the whole world. Based on the experience so far, we can say that older people are more vulnerable to COVID-19 with significant mortality risk. Pregnant patients, females, and children are less affected [11–13]. A systematic review reported that most of the COVID-19 positive pregnant women survived illness mildly [95.6% of 385 cases]. Previously, Sahin et al. presented the obstetric outcome of 533 COVID-19 positive pregnant women. Among 533 cases, COVID-19 was mild in 509 of them [95.5], while 2 pregnant women [0.4%] died [8].

Although COVID-19 progresses well in pregnant women, the mother and fetus's risks are still not fully known. Two early meta-analyses reported high rates of poor obstetric outcomes of COVID-19 positive pregnant women [14,15]. A recent meta-analysis involving 1100 patients from 24 studies and searching the impact of COVID-19 on pregnancy outcomes, five maternal death cases, and three stillbirths out of 779 pregnancies reported. One of the three stillbirths was not related to COVID-19, while the influence of COVID-19 was unclear on the other two cases [16]. The same review emphasized that COVID-19 related fetal and neonatal mortality risk was shallow [17]. Abbas M et al. reported that COVID-19 may cause IUFD, anemia, respiratory failure, fetal infections, and thromboembolism in infected pregnant women [18].

In our previous study, the positivity rate of SARS-CoV-2 among the asymptomatic pregnant women admitted to the hospital for delivery was 1.4%. In the current study, the ratio of SARS-CoV-2 positivity among the pregnant women who have a dead fetus is 10%. The IUFD ratio increased during the pandemic. There may be several causes of this increase. During the pandemic, the vast majority of pregnant women avoided going to the hospitals because of

Table 2
The demographic characteristics of the participants.

Variable	n
Maternal COVID-19	
Negative	94
Positive	6
Gravidity	
1	32
2	19
3	22
4 and above	27
Parity	
none	39
1	24
2	25
3 and above	12
Living child	
none	42
1	25
2	22
3 and above	11
Abortus	
none	66
1	23
2	9
3 and above	2
Gestational period	
2nd trimester	63
3rd trimester	37
Fetal gender[a]	
Female	51
Male	50
Obstetric findings	
Ablatio Placenta	6
Hydrops	6
IUGR	1
PPROM	2
Multiple fetal anomalies	8
Associated disease	
GDM/DM	2
Preeclampsia	1
Thrombophilia	3
Lymphoma	1
Guatr	1
Breast cancer	1
Epilepsy	1
FMF	1
HT	3
Leukemia	1
Myoma uteri	1
Mode of delivery	
Cesarean	37
Vaginal Delivery	63

	Mean ± SD	Median	Min–Max.
Maternal age	29.14 ± 6.09	29	[18–43]
Gestational week	27.61 ± 5.75	25.5	[20–40]
Birth weight	1137.29 ± 971.49	720	[190–3940]

IUGR: Intrauterine growth retardation.
PPROM: Premature rupture of membranes.
GDM/DM: Gestational diabetes mellitus/Diabetes mellitus.
FMF: Familial Mediterranean fever.
HT: Hypertension.
[a] There was one twin pregnancy.

Table 3
Clinical features and laboratory results of the PCR-positive women.

Case no.	Age [year]	Gestational week	COVID-19 Status	COVID-19 Symptom	Lymphocyte [10^3/mm^3]	CRP [mg/dL]	IL-6 [pg/mL]	COVID-19 treatment	Rt-PCR result of the placenta/cord/ membrans	Delivery mode	Gender	Birth weight
1	30	30	Asymptomatic	None	1240	29	38.6	None	Negative	cs	Male	1160
2	23	26	Mild	Fewer, cough, fatigue	450	24	–	Lopinavir-ritonavir, corticostreroid, IL-1 receptor antagonist	Positive	cs	Female	900
3	42	25	Asymptomatic	Asymptomatic	2060	4	10.2	None	Negative	cs	Female	720
4	29	27-twin	Mild	Cough, malasia	1060	98	44.2	Hydroxychloroquine, ertapenem, seftriaxon	Negative	Cs	F/M	1150/1190
5	21	21	Asymptomatic	Asymptomatic	920	71	–	None	Negative	ND	F	440
6	35	22	Asymptomatic		1460	27		None	Negative	ND	M	170
7	33	24	Asymptomatic	Asymptomatic	1940	18	5.2	None	None	nd	M	540
8	38	36	Asymptomatic	Asymptomatic	1610	46	–	None	None	nd	M	3310
9	43	38	Asymptomatic	Asymptomatic	1220	72	6.46	None	None	cs	F	2960
10	29	25	Asymptomatic	Asymptomatic	2120	5	–	None	None	nd	M	660

the fear of contracting the infection. Therefore, the optimal antenatal care could not be provided.

Secondly, COVID-19 causes pathological changes in many systems in the human body. Previously published six cohort or case series studies assessed the placentas of COVID-19 positive mothers. Although the placentas were not directly evaluated for SARS-CoV-2, the vast majority of the placentas demonstrated common pathology like villous infarctions, fibrin deposition, chronic villitis, intramural fibrin deposition [19,20]. In another study evaluating the placentas for SARS-CoV-2 of 5 COVID-19 positive women, none of the placentas was positive for SARS-CoV-2. However, similar malperfusion findings were obtained from the pathologic assessment.

Moreover, COVID-19 causes severe viral pneumonia among pregnant women. Maternal pneumonia is associated with adverse obstetric consequences as PPROM, IUFD, IUGR, PTL, miscarriage. COVID-19 induces microangiopathy and thrombus formation [21], one of the underlying pathologies of the IUFD. Pregnancy is an already hypercoagulable period.

In addition to the direct effect of the virus, an increased maternal inflammatory response can affect fetal tissues, leading to structural abnormalities and adverse obstetric outcomes such as perinatal death, fetal growth restriction, and preterm birth [22,23].

It is wondered that whether the SARS-CoV-2 virus effects the fetus by vertical transmission. Various mechanisms were suggested for vertical transmission of viruses; directly damaging the villouses, spread from maternal face to trophoblasts, transporting the infected maternal immune cells to the fetal capillaries, and ascending transmission from the vagina. Theoretically, SARS-CoV-2 may transmit to the fetus via the placenta. SARS-CoV-2 enters a cell by angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in the placenta (in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular muscle of the villi) [24,25]. This receptor is also expressed in the vagina [26], which may cause an ascendant infection of the fetus.

In the current study, we searched vertical transmission of SARS-CoV-2 by evaluating the placenta, umbilical cord, and amniotic membranes with the RT-PCR method. The major limitation of this study is the placental tissues were not evaluated pathologically. Among six placental tissues, one of them was positive for the SARS-CoV-2 test.

Previously positive test results of placental tissues for SARS-CoV-2 were reported.

In a systematic review and meta-analysis identifying eight cohorts or case series, it is reported 7.7% positivity of COVID-19 in the placentas of the women with COVID-19 [4]. Among 4 case reports which have COVID-19 positive placentas, two cases were in their second trimester [27,28].

A more recent systematic review and meta-analysis that including 69 studies, claimed that vertical transmission of Sars-Cov-2 is possible during the third trimester of pregnancy [29].

Most of the previous studies include pregnant women in their third trimester; only 2 cases report women's obstetric outcomes in their second trimester [27–59]. The reports belong to earlier gestational weeks are few. In our previous study, we reported results of placenta or abortion material from the first trimester. All of the RT-PCR results for SARS-CoV-2 of abortion material were negative in that study [60].

The second trimester is the period in which the immune response reaches the lowest. Pregnant women should maintain the pregnancy despite a semi-allogenic fetus; therefore, the human organism responds to altering immune response [61].

This is the first study searching the influence of COVID-19 on intrauterine fetal demise above 20 weeks. Also, we report the third case with placental positivity for SARS-CoV-19 during the second trimester in the literature to the best of our knowledge.

Fetal demise is the fifth cause of death in the World, and 76% of cases are unexplained [62,63]. The infection rate among the reasons is varying from 5% to 22% [64].

Although we cannot establish a direct relationship between COVID-19 and IUFD, we cannot completely exclude the role of COVID-19 on IUFD. We screened the women for SARS- Co V-2 positivity at the admission to the hospital for IUFD. Therefore, we could not evaluate the previous status of the women for COVID-19. We were blind to the women who had asymptomatic COVID-19 during pregnancy, and we could not interpret the exact association between the COVID-19 and IUFD. Also, none of the placentas of the women with COVID-19 were pathologically evaluated. We did not know whether the placentas include any changes which may be attributed to COVID-19 or not. None of the pregnant women in our study had severe viral pneumonia, a pathologic condition associated with adverse obstetric outcomes.

In conclusion, we can exactly say that the COVID-19 pandemic has directly or indirectly increased IUFD rates. However, the vertical transmission of the virus still remains a mystery.

Future studies involving the pathologic examination of the placentas will shed light on this issue.

Disclosure of conflict of interest

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