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Doppler assessment of the fetus in pregnant women recovered from COVID-19

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Abstract

Objective: The aim of this study was to evaluate the maternal-fetal Doppler patterns in pregnant women recovered from COVID-19.

Methods: This prospective case–control study was conducted in Ankara City Hospital between July 1, 2020 and August 30, 2020. Thirty pregnant women who were diagnosed with COVID-19 and completed the quarantine process were compared with 40 healthy pregnant women in terms of the fetal Doppler parameters. All pregnant women diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were followed up in our clinic and their diagnoses have been confirmed in nasopharyngeal and oropharyngeal samples by quantitative real time reverse transcriptase polymerase chain reaction (RT-PCR) method. Doppler ultrasonographic assessment of the uterine arteries (UtA) and middle cerebral artery (MCA) were used in addition to umbilical artery (UA) Doppler between 23 and 40 weeks of gestation. Also, cerebroplacental ratio (CPR) was calculated according to gestational age.

Results: The pulsatility and resistance indices of umbilical and UtA showed a significant increase in pregnant women in the study group compared to the control group ($p < 0.05$). Multivariable logistic regression analysis revealed that pulsatility and resistance indices of the mean UtA were independently associated with disease (OR > 1000, 95%CI 9.77 to >1000, p = 0.009; OR 0,000 95%CI 0,000-0,944, p = 0,049), respectively. Medical treatment was given to 16/30 (53%) of pregnant women diagnosed with COVID-19.

Conclusion: In conclusion, uterine artery Doppler indices in the third trimester may have clinical value in pregnant women recovered from COVID-19.

Key words: COVID-19, fetal Doppler ultrasound, pregnancy, SARS-CoV-2.

Introduction

As of October 5, 2020, more than 35 million people infected and over 1 million died worldwide, the 2019 coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a crucial global health problem.[1] In parallel with the increasing mortality rates, more patients are admitted to the intensive care unit.[2] Additionally, new findings suggest that pregnant women with COVID-19 who develop severe disease in the same reproductive age are more likely to need intensive care treatment than nonpregnant women with COVID-19.[3]

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Even the frequency and molecular mechanisms of intrauterine vertical transmission of SARS-CoV-2 have not been determined yet, fetal vascular malperfusion is the most common finding in placental pathology.[4, 5]

It is clear that maternal-fetal morbidity and mortality increase in cases with severe course of pneumonia. On the other hand, with the ease of accessibility to polymerase chain reaction (PCR) tests, an increase in the number of asymptomatic cases has been observed. However, increased antenatal follow-up frequency of pregnant women in high risk group and more contact with the hospital setting explain the high positive rates seen in these pregnant women.[6]

SARS-CoV-2 infection can cause a broad spectrum of adverse pregnancy outcomes such as miscarriage, premature delivery, intrauterine growth restriction, preeclampsia, and maternal death. Therefore, it is strongly recommended that fetal growth should be monitored by ultrasound and Doppler assessments in terms of intrauterine growth restriction and other obstetric complications in pregnant women recovered from COVID-19.[7]

Instead of a single ultrasound parameter, biometric and biophysical parameters such as EFW (estimated fetal weight), cerebroplacental ratio (CPR), middle cerebral artery (MCA), umbilical artery (UA), and UtA parameters together with maternal characteristics can help predict adverse pregnancy outcomes.[8] Abnormal results on MCA Doppler ultrasonography were found associated with composite adverse neonatal outcomes for Zika virus in a recent study.[9] Raised UtA resistance was found in early pregnancy malaria parasitemia as in preeclampsia.[10] On the other hand, uterine and fetal placental Doppler indices are associated significantly with maternal cardiovascular function. In fact, the conventional description of uterine and fetal Doppler changes being initiated by placental insufficiency is a less plausible explanation for the pathogenesis of the conditions than that relating to maternal cardiovascular changes.[11] Acute changes in the maternal-fetal circulation in the presence of infection can be evaluated in this perspective.

The aim of this study was to evaluate the maternal-fetal Doppler patterns with ultrasound in pregnant women recovered from COVID-19.

Materials and Methods

This prospective case–control study was conducted in Ankara City Hospital between July 1, 2020 and August 30, 2020. Thirty pregnant women who were diagnosed with COVID-19 and completed the quarantine process were compared with 40 healthy pregnant women in terms of the fetal effects of this disease using Doppler ultrasound. Each participant provided informed written consent. The study was approved by our Institutional Ethical Committee (E1-20-602).

All pregnant women diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were followed up in our clinic and their diagnoses have been confirmed in nasopharyngeal and oropharyngeal samples by quantitative real time reverse transcriptase polymerase chain reaction (RT-PCR) method. The quarantine period was 14 days for patients who were discharged from hospital, and also for the patients who were followed up at home because they did not need to be hospitalized (provided that the symptoms recovered in both cases).[12] All patients diagnosed with COVID-19 were evaluated in outpatient clinic of our institution after the quarantine period. The cases in the control group were selected prospectively as in the COVID-19 group. Patients with chronic hypertension, diabetes, and high body mass index were not included from prospective patient selection in both groups. However, RT-PCR test was not performed in the control group. Fetal Doppler assessment was performed together with fetal biometric measurements.

All ultrasound examinations were performed transabdominally by three obstetricians (A.T.A, F.D.Y.Y, and G.B), all of whom were blinded to the clinical histories. With 2–4 MHz, C1-5-RS wide-band, convex transducer, Voluson S10 (GE Medical Systems, Zipf, Austria) ultrasound machine was used.

Doppler ultrasonographic assessment of the UA, MCA, and uterine arteries (UtA) was performed according to the Society of Maternal-Fetal Medicine (SMFM) Clinical Guideline.[13] Doppler ultrasonography measurements included pulsatility and resistance indices. The CPR was calculated by gestational age based on the analysis of data derived from routine second and third trimester screening studies conducted by the Fetal Medicine Foundation (FMF).[14] In addition, biometric measurements have been assessed such as biparietal diameter, abdominal circumference, and femur length. Amniotic fluid index has been measured for each patient.

Inclusion criteria for the study were the following: singleton pregnancy, age range between 18 and 40 years, gestational age range between 23 and 40 weeks and RT-PCR confirmation of SARS-CoV-2 infection.

Pregestational and gestational diabetes mellitus, chronic hypertension, intrauterin fetal demise, twin pregnancy, placental abruption (partial and complete), autoimmune diseases, clinical hypothyroidism or hyperthyroidism were exclusion criteria for both groups.

Maternal characteristics and obstetrical histories were recorded. In addition, body mass index, gestational age at diagnosis and birth, vaginal delivery and cesarean-section rates, birth weights, first and fifth minute Apgar scores were also recorded. Additionally, oxygen saturation on admission, medical treatment, time interval between Doppler measurement and COVID-19 diagnosis were recorded for COVID-19 patients.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22; IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA). Visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov test) were used to determine the normality of distribution. When comparing between the groups, we used the Mann–Whitney *U* test for non-normally distributed variables. Categorical data were presented as percentages. For delivery and cesarean section rates, we compared the groups by using the chi-square test. In addition, the effect level was investigated by univariate and multivariate logistic regression as an advanced analysis method for Doppler parameters.

Results

A total of 70 patients were included in this study. Thirty pregnant women who were diagnosed with COVID-19 and completed the quarantine period were compared with 40 healthy pregnant women in terms of the fetal Doppler parameters and biometric measurements. Median maternal age, body mass index, gravidity, and parity were not different between groups ($p > 0.05$) (Table 1). On the other hand, the pulsatility and resistance indices of umbilical and UtA showed a significant increase in pregnant women recovered from COVID-19 compared to the control group ($p < 0.05$) (Table 2). Multivariable logistic regression analysis revealed that pulsatility and resistance indices of the mean uterine artery were independently associated with disease (OR > 1000, 95%CI 9.77–>1.000, $p = 0.009$; OR 0.000, 95%CI 0.000-0.944, $p = 0.049$), respectively (Table 3). However, no significant changes were observed in MCA pulsatility index and CPR between two groups ($p > 0.05$) (Table 2).

Birth data of all patients were obtained in both groups. The cesarean section rates were significantly higher in the COVID-19 group than in the control group, 74% versus 42% ($p = 0.02$) (Table 1). When we compare the cesarean indications of both groups, the rates of cephalopelvic disproportion and fetal distress were higher in the COVID-19 group, additionally, severe preeclampsia was observed in the study group (Table 4). Intrauterine growth restriction (IUGR) and small for gestational age (SGA) fetus were seen in one case each in the COVID-19 group. Also, fetal outcome was poor in one of the fetuses delivered in the COVID-19 group. Preeclampsia was observed in two of the cases in the COVID-19 group. The rate of preterm delivery was nonsignificantly higher in pregnant women with previous COVID-19 than in the control group (20% vs 17%) ($p = 0.8$) (Table 1).

Doppler ultrasound assessment in pregnant women recovered from COVID-19 was performed approximately 3 weeks after the confirmation of this disease. At the same time, the median value of oxygen saturation of these patients was 96 on admission to hospital for COVID-19. Medical treatment was given to 16/30 (53%) of pregnant women diagnosed with COVID-19. Drugs in the treated group included low-molecular-weight-heparin (all 16 patients), azithromycin (one patient) and lopinavir/ritonavir (two patients). Isolation was considered adequate for the other 14 patients that did not receive medical treatment. There was no need for an intensive care unit admission for pregnant women diagnosed with COVID-19.

Discussion

To the best of our knowledge, this is the first report to present fetal Doppler changes in pregnant women with recovered from COVID-19 infection. We demonstrated that pulsatility and resistance indices of umbilical and UtA increased in pregnant women recovered from COVID-19 infection than in healthy pregnant women.

Conventionally, fetal Doppler ultrasound is used to evaluate UA and other fetal vessels for fetal well-being in the third trimester of pregnancy.[15] The pulsatility and resistance indices represent downstream vascular resistance by measuring the differences between peak systolic and end diastolic velocity

Table 1 Demographic features and pregnancy outcomes of the pregnant women recovered from COVID-19 and control groups

Variables	Pregnant women recovered from COVID-19 (n = 30)	Pregnant women without any defined risk factor (n = 40)	p-Values
Maternal age (years) (median, IQR)[a]	30 (10)	29 (8)	0.32
BMI (kg/m^2)[a]	27.6 (4.2)	28.5 (6.2)	0.79
Gravidity (median, IQR)[a]	2 (1)	2 (2)	0.43
Parity (median, IQR)[a]	1 (2)	0.5 (2)	0.57
Gestational age at Doppler ultrasound assessment (weeks) (median, IQR)[a]	31.5 (6.75)	31.5 (4.75)	0.89
CS rate (n, %)[b]	22 (74%)	17 (42%)	0.02
Preterm delivery rate (n, %)[b]	6 (20%)	7 (17%)	0.8
Gestational age at birth (week) (median, IQR)[a]	38 (3)	39 (3)	0.76
Birth weight (g) (median, IQR)[a]	3280 (788)	3375(955)	0.51
Apgar 1st minute (median, IQR)[a]	7.5 (1)	8 (1)	0.02
Apgar 5th minute (median, IQR)[a]	9 (1)	9 (1)	0.6

Note: Significance level is $p < 0.05$. Abbreviations: BMI, body mass index; CPR, cerebroplacental ratio; CS, cesarean section; IQR, inter quartile range; MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index.; [a]Statistical analysis was performed by Mann–Whitney U test. and [b]Statistical analysis was performed by chi-square test.

Table 2 Maternal-fetal Doppler parameters of the pregnant women recovered from COVID-19 and control groups

Variables	Pregnant women recovered from COVID-19 (n = 30)	Pregnant women without any defined risk factor (n = 40)	p-Values
Mean uterine artery PI (median, IQR)[a]	1 (1)	0.7 (0.2)	0.001
Mean uterine artery RI (median, IQR)[a]	0.6 (0.2)	0.5 (0.1)	0.02
Umbilical artery PI (median, IQR)[a]	1 (0.2)	0.9 (0.3)	0.04
Umbilical artery RI (median, IQR)[a]	0.6 (0.1)	0.5 (0.1)	0.008
MCA PI (median, IQR)[a]	1.7 (0.6)	1.8 (0.5)	0.41
MCA RI (median, IQR)[a]	0.8 (0.1)	0.7 (0.1)	0.03
CPR (median, IQR)[a]	1.8 (0.5)	1.9 (0.8)	0.47

Note: Significance level is $p < 0.05$. Abbreviations: CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index.

within the blood vessels in each cardiac cycle.[16] In the presence of high resistance to blood flow, Doppler ultrasound examination might also be useful to predict IUGR and preeclampsia.[17] Routine UA Doppler screening in a low-risk population has not been demonstrated to be effective in predicting IUGR.[11]

Favre et al. reported that pregnant women with laboratory-confirmed SARS-CoV-2 infection who are asymptomatic and those recovering from mild illness should be assessed with ultrasound and Doppler for intrauterine growth restriction.[9]

In current practice, UtA Doppler is measured in the first and second trimester of pregnancy for prediction of later pregnancy complications. Increased resistance may associated with placental dysfunction such as preeclampsia and fetal growth restriction. Also, recent studies showed that third trimester uterine artery Doppler was significantly associated with the risk of stillbirth and perinatal death.[8, 18–20] In addition, increased uterine artery mean PI is associated with significantly lower birthweight and fetal CPR in the third trimester.[18] Khalil et al. compared the stillbirth

Table 3 Logistic regression analysis of maternal-fetal Doppler parameters of the pregnant women recovered from COVID-19 and control groups

	Univariate model			Multivariate model		
	OR	% 95 CI	*p*-Values	OR	% 95 CI	*p*-Values
Gestational age at Doppler US assessment	0.99	0.88–1.13	0.933			
Mean uterine artery PI	23.00	3.25–162.55	0.002	> 1000	9.77–>1000	0.009
Mean uterine artery RI	327.68	3.85–>1000	0.011	0.000	0.000–0.944	0.049
Umbilical artery PI	15.39	1.04–226.85	0.046			
Umbilical artery RI	> 1000	11.79–>1000	0.007			
Middle cerebral artery PI	2.08	0.56–7.78	0.275			
Middle cerebral artery RI	3.57	0.12–110.07	0.467			
Cerebroplacental ratio	0.60	0.23–1.57	0.295			

Note: Logistic regression (forward LR). Significance level is $p < 0.05$. Abbreviations: CI, confidence interval, Presented OR with 95% CIs; OR, odds ratio; PI, pulsatility index; RI, resistance index; US, ultrasound.

Table 4 Comparison of cesarean indications between pregnant women recovered from COVID-19 and healthy pregnant women

Cesarean indications	Pregnant women recovered from COVID-19 (*n* = 30)	Pregnant women without any defined risk factor (*n* = 40)
Cephalopelvic disproportion	5	2
Previous cesarean	7	10
Fetal distress	5	3
Severe preeclampsia	2	-
Breech presentation	2	-
Macrosomia	1	1
Maternal congenital cataract	-	1

rates between the pandemic and prepandemic period and found that the incidence of stillbirth was significantly higher during the pandemic.[21] According to the recent studies, concomitant diseases such as diabetes, chronic hypertension, advanced age or increased body mass index in pregnant women with COVID-19 cause the effects of the disease to become more severe.[4] In our study, there was no concomitant disease in both groups due to the study design. Preeclampsia was seen in two cases in pregnant women recovered from COVID-19 infection.

Also, CPR is reported to be low in growth restricted fetuses as a result of increased UA PI and reduced MCA PI. CPR calculation may be of particular importance in late fetal growth restriction.[22] However, no significant changes were observed in MCA pulsatility index and CPR between two groups in our study. IUGR and SGA were seen in one case each in the COVID-19 group.

Coronavirus is a pro-inflammatory disease. The first and third trimesters of pregnancy include pro-inflammatory phases which may ease the development of the disease. However, intrauterine vertical transmission of SARS-CoV-2 has not been determined with detailed pathogenesis because of more complex protective mechanisms of the placenta.[23] Todros et al. noted the similarity of high proinflammatory cytokine levels (IL-6, TNF-*alpha*, IFN-*gamma*, etc.) in the mesenchymal stromal cells of the placenta in the most severe forms of COVID-19 and pre-eclampsia.[24] Pathological examinations have showed that syncytiotrophoblasts are often infected with SARS-CoV-2, however, transmission in the fetus has not always been detected. Mulvey et al. demonstrated fetal vascular malperfusion with multiple thromboses in placentas from COVID-19 patients who delivered at term.[6] Nevertheless, there have been on-going arguments about the vertical transmission of COVID-19 and this issue has not been clarified, yet. In our opinion, apart from the vertical transmission of the disease, excessive inflammation, vascular injury and impaired perfusion may lead to pregnancy loss in pregnant women with COVID-19. In our study, maternal cardiovascular changes may affect the maternal-fetal circulation in the presence of infection.

Both groups had good maternal and fetal clinical outcomes in our study. The time interval between diagnosis and Doppler measurements in pregnant women with previous COVID-19 infection was approximately 3 weeks. Although preterm delivery rate was higher in the study group, this difference could not reach statistical significance most probably due to the relatively low number of patients and the high frequency of mild cases. There was no stillbirth in either group.

The strengths of this study were prospective design, information about the long-term follow up of the cases, novelty and unique study design. Limitations of the study were single center experience and relatively low number of patients.

Although the pathophysiology of COVID-19 in pregnancy has not been fully elucidated, third trimester uterine artery measurement which is important in predicting the risk of late-onset FGR and stillbirth, can contribute to prediction of adverse outcomes when evaluated with serial biometric measurements and maternal demographics. In conclusion, uterine artery Doppler indices in the third trimester may have clinical value in pregnant women recovered from COVID-19. In studies to be conducted with larger populations, the relationship between SARS-CoV-2 infection and pregnancy outcomes will be examined in more detail and the effects of the infection on maternal and fetal circulation will be better understood.

Conflict of Interest

None declared.

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