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Evaluation of second trimester uterine artery doppler indices in women diagnosed with COVID-19 during the first trimester of their pregnancy

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Abstract. – OBJECTIVE: This study aimed at evaluating the hypothesis that 6-14 months pregnant women diagnosed with COVID-19 may have abnormal placental function detectable by increased uterine artery Doppler indices in the second trimester and whether these women could benefit from treatment.

PATIENTS AND METHODS: A total of 63 women were diagnosed with COVID-19 during the first trimester of their pregnancy and 68 healthy women were involved according to the exclusion criteria. In both groups, Doppler measurements were performed for the determination of high-risk pregnancy by increased uterine artery Doppler indices in the second trimester.

RESULTS: It was observed that uterine artery Doppler indices (PI and RI) were significantly increased in second trimester women with COVID-19 infection compared to those without COVID-19. Furthermore, the number of women with a PI value exceeding the 95th percentile and the number of patients with early diastolic notch were higher in the COVID group compared to the control group.

CONCLUSIONS: Doppler Ultrasound measurement may be a potential method for the management of high-risk pregnancies after asymptomatic/mild COVID-19 infection.

Key Words:
Pregnancy, Gynecology, COVID-19, Uterine Artery Doppler, Doppler indices.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic was caused by the acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), and millions of people lost their lives since beginning in 2019 in Wuhan, China[1]. The severity of the disease is defined as from flu-like symptoms to critical pneumonia and respiratory failure. Besides advanced age (≥50 years), male sex and having chronic comorbidities or pregnancy are important risk factors for severe COVID-19 disease[2].

SARS-CoV-2 is a single-stranded RNA virus belonging to the coronavirus family which uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell[3]. The viral spike (S) protein is activated by trans-membrane serine protease 2 (TMPRSS2), facilitating the entry of the virus into the cell[3]. Expression of ACE2 and TMPRSS have been demonstrated in the respiratory and intestinal tract, as well as the heart, liver, uterus, ovaries, placenta, and fetal cells[4]. Also, SARS-CoV-2 may cause immune system alterations such as overproduction of pro-inflammatory cytokines, abnormalities in the number and functional properties of T cells, and excessive antigen presentation activity[5,6]. Apart from the direct damage of virus replication, the placenta can be altered by dysregulated immune status during COVID-19 infection. This underlying effect has been supported by several trials[7,8] which have reported placental histopathological anomalies, such as decidual arteriopathy and increased peri- or inter-villous fibrin deposition in pregnant women with SARS-CoV-2 infection. Therefore, the frequency of obstetric consequences, such as miscarriage, preterm birth, premature rupture of membranes, and intrauterine growth retardation, is increased in women with severe COVID-19[9,10]. Also, it was reported that these women may manifest pre-eclampsia-like features including hypertension, low platelet count, thrombocytopenia, and immune dysregulation that indicate a possible placental pathology[11]. Although the pregnancy period in which the placenta is more sensitive to SARS-CoV-2-related damage is unknown, owing to the gradual decrease in ACE2 and TMPRSS2 expression from early to late pregnancy, it is feasible to suggest that risks are greater during early

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pregnancy[12-14]. Furthermore, polycystic ovarian syndrome and the use of multiple inositol before getting pregnant may be important factors in SARS-CoV-2 infection[15,16].

Uterine artery Doppler ultrasound provides significant information about uteroplacental function[17]. Pulsatility index (PI) and resistance index (RI) have been shown to enable the prediction of placenta-related diseases such as preeclampsia and intrauterine growth retardation[18,19].

In this study, we aimed to evaluate the hypothesis that women diagnosed with COVID-19 in early pregnancy (6-14th weeks) may have an abnormal placental function that can be detected by increased uterine artery Doppler indices in the second trimester, and to assess whether these women could benefit from a "High-Risk Pregnancy" follow-up program.

Patients and Methods

Study Design and Group

This is a multicenter and retrospective study performed at Izmir Private Can Hospital Izmir, Turkey, and Private Erciyes Kartal Hospital, Kayseri, Turkey, between September 2021 and April 2022. The initial cohort comprised 76 women who were diagnosed with COVID-19 in early pregnancy (6-14th weeks), and they were examined with second-trimester uterine artery Doppler indices as part of routine antenatal follow-up in the two hospitals. After applying the inclusion/exclusion criteria according to patient data, 63 patients were finally enrolled, regardless of COVID-19 severity, and were defined as the "COVID group". In control group, 68 healthy women were included who had been continuing antenatal follow-up at the same centers and had undergone Doppler ultrasound of the uterine artery in the second trimester.

Exclusion criteria for both groups were as follows: being aged older than 40 years or under 18 years, detection of a structural anomaly in the fetus, having multiple pregnancy, non-gestational diabetes, chronic hypertension, vascular disease, rheumatologic or autoimmune diseases, patients with a history of smoking, alcohol use, heparin or aspirin use, preeclampsia, intrauterine growth retardation, preterm birth, ablatio placenta, intrauterine fetal demise, and uterine surgery other than cesarean section.

Ethical approval was obtained from the non-interventional Clinical Research Ethics Committee of İzmir Bakircay University (Decision date: 17.05.2022, Approval number: 601). All protocols were conducted under the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in this study.

Data Collection

The following data were obtained and recorded from the electronic medical records of the patients in both groups: maternal demographics, obstetric history, gestational age at diagnosis of COVID-19 infection, the date of the last COVID-19 vaccination, history of previous uterine surgery, gestational age at second trimester antenatal follow-up, second-trimester uterine artery Doppler indices (Pulsatility, Resistive indices and S/D ratio), the number of patients whose PI values were above 95% percentile according to previously-determined uterine artery PI reference ranges based on gestational age, and placenta localization[20].

The diagnosis of COVID-19 was confirmed by oropharyngeal and/or nasopharyngeal swabs by quantitative real-time reverse-transcriptase polymerase chain reaction (qRT-PCR) (CTK Biotech, CA, USA). The quarantine period was applied as 14 days for patients after hospital discharge (if hospitalized) and for patients who were followed at home. All patients diagnosed with COVID-19 were evaluated at the obstetric clinics of the study hospitals after the completion of quarantine. Apart from scheduled follow-up visits missed due to quarantine, all women continued their routine schedule according to the antenatal program of the study hospitals. The last dose of COVID-19 vaccination was evaluated for the time interval from the last shot to the last menstruation.

The gestational age of the women was based on the last menstrual period, as verified by measurement of crown-rump length in the first trimester. Doppler measurements were performed between 18-22 weeks of gestation by two experienced obstetricians with fetal Doppler sonography training, using a Samsung HS40 Ultrasound Machine equipped with a VN4-8 convex probe (Seoul, Korea) (C.M.G) or a GE Voluson E6 Ultrasound device (Chicago, IL, USA) equipped with a with 5-9 MHz convex probe (Z.A. and B.S.F, respectively).

Uterine artery Doppler assessments of uterine arteries were performed according to the clinical guideline put forth by the Society of Maternal-Fetal Medicine (SMFM)21. After the identification of uterine arteries at the cervico-uterine junction, three measurements were performed from bilateral uterine arteries. The mean value of

six measurements from the right and left uterine arteries were calculated[22].

Diastolic notch was defined as a persistent decrease in blood flow velocity in the early diastole and was also recorded if detected. In both groups, fetal biometric calculations and fetal anatomic detailed examinations were also performed, according to the antenatal second-trimester follow-up programs of the obstetrics clinics of the hospitals.

Statistical Analysis

The normality of the distribution of continuous variables was tested by the Shapiro-Wilk test. The Student *t*-test (for normally-distributed data) or the Mann-Whitney U test (for non-normally distributed data) were used to compare continuous variables between the two groups. Chi-square tests were used to investigate differences between groups in terms of categorical variables. Mean ± standard deviation (mean ± SD) values were used for normally-distributed data and median (25-75% quartiles) values were used for non-normally-distributed data when summarizing descriptive data. Statistical analysis was performed with the SPSS software for Windows version 24.0 (IBM Corp., Armonk, NY, USA) and a p-value <0.05 was accepted to demonstrate statistical significance.

Results

A total of 131 patients (63 patients in the COVID group and 68 patients in the control group) were included in the final analyses. Demographic and other baseline characteristics of the patients were similar in two groups (Table I). However, the number of unvaccinated women was significantly higher in the COVID group compared to the control group.

The mean gestational age at diagnosis of COVID-19 infection was 8±3.2 weeks. Severe COVID-19 infection was not observed in any of the patients. Six patients in the COVID group were hospitalized for mild COVID-19 infection and received azithromycin (2 patients), lopinavir/ritonavir (4 patients), and low-molecular-weight heparin (6 patients) during hospitalization. Non-hospitalized patients were treated with paracetamol symptomatically.

The mean PI and RI indices of the uterine artery were significantly higher in the COVID group compared to the control group. The number of patients with increased PI (>95th percentile of the reference range) and the number of patients with diastolic notch were significantly higher in the COVID group. However, the mean SD values were similar in the two groups. Interestingly, all unvaccinated women demonstrated PI values over the 95% percentile. None of the women who had been vaccinated within six weeks from the last menstruation had PI values above the 95th percentile. A comparison of uterine artery Doppler indices between groups is shown in Table II.

Discussion

This study revealed that the uterine artery Doppler indices (PI and RI) measured in the second trimester were significantly increased in women with COVID-19 infection in their first trimester compared to women without COVID-19. The number of women with PI values exceeded the 95th percentile and the number of patients with early diastolic notch were significantly higher in the COVID group compared to the control group. However, the mean SD value did not significantly different between the groups.

The second-trimester uterine artery Doppler investigation has been used to predict poor antenatal and perinatal outcomes[18,19]. It was assumed that the increased PI and RI indices cause of fetal growth retardation, pre-eclampsia, and stillbirth due to abnormal trophoblast invasion and disturbed placental histology[18,23]. In addition, persistent early diastolic notch may predict an increased risk of pre-eclampsia, preterm birth, and intrauterine growth retardation[19]. Although the utility of uterine artery Doppler ultrasound in the evaluation of low-risk populations has been questioned, we routinely perform uterine artery Doppler ultrasound on all patients in the second trimester[17].

The association between COVID-19 infection and poor obstetric outcomes has been a matter of debate since the relatively early phase of COVID-19 spread. In a large-scale study, involving 3,527 women with COVID-19 infection at the time of delivery, fetal death, preterm birth, pre-eclampsia, and emergency cesarean delivery were significantly more common in women with infection compared to healthy women[24]. Also, a recent systematic review and meta-analysis[25] reported that COVID-19 infection during pregnancy was associated with a higher frequency of pre-eclampsia. Because placental insufficiency is directly related to the aforementioned obstetric problems, these findings inevitably brought to mind

Table I. Comparison of socio-demographic and baseline characteristics of patients.

Variables	COVID Group (n=63) Mean ± SD	Control (n=68) Mean ± SD	*p*-value
Age	28.45 ± 5.57	28.43 ± 4.77	0.985
	Median [25%–75%]	**Median [25%–75%]**	
BMI kg/m²	25.7 [19.7–24.1]	21.15 [20.2–24.75]	0.314
Gravida	2 [1–4]	2 [1–5]	0.481
Parity	2 [0–3]	2 [0–4]	0.836
GA at second-trimester follow-up	19 [18.5–21.2]	19.2 [18.6–21.3]	0.318
	134 [99–227]	189.5 [117.5–278.5]	0.171
	n (%)	**n (%)**	***p*-value**
Placenta localization			
Anterior	21 (33.3)	24 (35.2)	0.937
Posterior	19 (30)	20 (29.4)	0.879
Left lateral	11 (17.4)	13 (19.1)	0.732
Right lateral	12 (19)	11 (16.1)	0.546
Type of delivery in a prior pregnancy			
Cesarean section	28 (44.4)	33 (48.5)	0.673
Vaginal birth	21 (33.3)	24 (35.2)	0.978
Nullipar	12 (19)	11 (16.1)	0.897
Covid-19 vaccination			
Last dose within six weeks	40 (63.5)	52 (76.4)	0.325
Last dose beyond six weeks	12 (19)	15 (22)	0.834
No vaccination	11 (17.4)	1 (1.4)	**0.001***

*Significant at 0.05 level; Student *t*-test and Mann-Whitney U test for numerical variables, Chi-square test for categorical variables. BMI: Body Mass Index, GA: gestational age.

the idea that there may be an association between COVID-19 infection and placental pathology. In a systematic review[8], including 56 articles concerning placental pathologies in women with COVID-19 infection, which used many different laboratory techniques such as histopathological examination, PCR, and immunohistochemistry, it was reported that only 17.5% of placentas demonstrated normal placental histology. The placentas showed a range of abnormal histological findings, including central-peripheral villous infarction, fibrin deposition, decidual arteriopathy, and acute/chronic inflammatory changes, which caused maternal and fetal vascular malperfusion8,26. Although most of the studies[27,28] had included women with severe COVID-19 infection, it was also reported that having severe COVID-19 may not be mandatory for the occurrence of placental involvement or poor obstetric outcomes. However, Ayhan et al[29] performed fetal and uterine artery Doppler measurements and claimed that COVID-19 infection seemed to have no adverse effects on fetal/placental circulation in mildly- or moderately-ill patients during the acute phase of the infection. In our study, we performed Doppler measurements approximately 10 weeks after COVID-19 diagnosis instead of the acute phase. In our opinion, it takes time for placental

Table II. Comparison of uterine artery Doppler indices between groups. (Patients with increased uterine artery indices or diastolic notch were informed about their conditions and directed to a "High-Risk Pregnancy Follow-up Program" in the study hospitals. They have also prescribed 150 mg of aspirin.

Variables	COVID Group (n=63) Mean ± SD	Control (n=68) Mean ± SD	*p*
Mean UtA PI	1.55 ± 0.3	1.01 ± 0.2	**0.001***
Mean UtA RI	0.63 ± 0.03	0.51 ±0.01	**0.001***
Mean UtA S/D	2.77 ± 0.44	2.51 ± 0.37	0.341
	n (%)	**n (%)**	
PI elevation (>95th Percentile)	18 (28.5)	5 (7.3)	**0.001***
Diastolic notch	31 (49.2)	10 (14.7)	**0.001***

*Significant at 0.05 level, shown in bold; Mann-Whitney U test for numerical variables.

damage to disrupt Doppler indices and translate into observable changes in placental histology, and therefore, measurements performed in the acute phase of the infection might fail to reveal outcomes associated with COVID-19 exposure.

Consistent with our data, Anuk et al[30] showed significantly increased uterine and umbilical artery Doppler indices (PI and RI) in women who recovered from COVID-19 (during the third trimester) when compared to healthy pregnant women. In this study, the time interval between COVID-19 diagnosis and Doppler measurement was approximately 3 weeks.

The gestational period in which COVID-19 exposure causes greater risks for placental damage remains a debated topic[31]. It can be assumed that the risk is higher during early pregnancy because pro-inflammatory reactions are common in COVID-19 with elevated levels of mediators such as IL-6, TNF alpha, and IFN gamma (particularly in the first and third trimesters), and because ACE2 (5-6) and TMPRSS2 (12) expressions decrease from early to late pregnancy. However, some authors[32,33] reported that maternal disease severity and pregnancy loss rates were not increased in women who recovered from COVID-19 during their first trimester. Despite these outcomes, the major limitation of these studies was that they focused on acute obstetric problems in the early period after COVID-19 infection; however, it is possible to suggest that other potential complications could develop in the later period among patients exposed to COVID-19.

In a case-control study (including 225 pregnant women), Cosma et al[33] reported that although first-trimester COVID-19 infection did not increase abortion rates, due to a lack of data about possible pregnancy complications, patients had to be properly informed about the risk of inflammatory involvement of the placenta and its consequences, such as intrauterine fetal demise and preterm birth. In support of this conclusion, a secondary analysis of the WAPM study on COVID-19 reported that infection in the first trimester was associated with poor fetal outcomes, while there was no such association when infection occurred in the second or third trimester[34]. According to our results, it would be reasonable to assume that there is an increased risk of placental pathology and placental insufficiency in women who recovered from COVID -19 infection in the first trimester. Indeed, with respect to potential adverse effects, Favre et al[35] advised twice weekly Doppler ultrasound in women who recovered from COVID-19 infection even after asymptomatic disease. Our findings supported these recommendations in highlighting that Doppler indices may be altered after asymptomatic/mild COVID-19 infection. In our opinion, women with such findings should be included in "high-risk pregnancy management" with regular Doppler Ultrasound evaluation.

Limitations

This is the first study to evaluate the relationships between first trimester COVID-19 infection and increased uterine artery Doppler indices in the second trimester. However, the limitations of the study include the retrospective nature of research, lack of data about ongoing antenatal follow-up studies and perinatal outcomes of the study populations, and absence of analyses concerning the possible effects of vaccination.

Conclusions

In conclusion, second-trimester uterine artery Doppler indices, PI and RI, were significantly increased in women with COVID-19 infection in the first trimester of their pregnancy compared to those without COVID-19. The frequency of patients with elevated PI value (>95th percentile) and early diastolic notch was significantly higher in the COVID group compared to the control group. Further randomized trials comparing subgroups of pregnant women, such as vaccinated *vs.* unvaccinated women with COVID-19 infection, are necessary to assess the effects of COVID-19 and/or vaccinations in this context.

Availability of Data and Materials

Data may be provided on reasonable request to the corresponding author.

Funding

None.

Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

Ethics Approval

Ethical approval was obtained from the Non-interventional Clinical Research Ethics Committee of İzmir Bakircay University (Decision date: 17.05.2022, Approval number: 601).

Authors' Contribution

ZA and CMG designed the research; ZA, CMG, and BSY performed the research; ZA, CMG and ŞÖS wrote the paper. All authors read and approved the final manuscript.

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