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CLINICAL ARTICLE

Obstetrics

Fetal pulmonary artery Doppler evaluation in pregnant women after recovery from COVID-19

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Abstract

Objective: To evaluate fetal lung development using pulmonary artery Doppler in pregnant women who had recovered from COVID-19.

Methods: The prospective case–control study included 41 pregnant women who had recovered from COVID-19 and 43 healthy pregnant women (control group). All the women in the study group had been diagnosed with COVID-19 and had completed a quarantine period.

Results: The demographic data of patients were similar in the groups ($P > 0.05$). Main pulmonary artery peak systolic velocity was higher and pulsatility indices were lower in pregnant women who recovered from COVID-19 compared to the controls ($P < 0.001$, $P = 0.001$). Acceleration time, ejection time, and acceleration/ejection time ratio (PATET) of the fetal MPA Doppler were significantly decreased in pregnant women who recovered from COVID-19 ($P < 0.001$, $P = 0.036$, and $P = 0.002$, respectively). The patients who had recovered from COVID-19 were divided into two groups: those treated with expectant management and those treated in hospital. The pulmonary artery acceleration time and PATET ratio were significantly lower in the group treated in the hospital ($P = 0.023$ and $P = 0.045$, respectively).

Conclusion: Detailed Doppler evaluations of the pulmonary artery may help in evaluating the fetal adverse effects of COVID-19 disease.

KEYWORDS
COVID-19, fetal Doppler ultrasound, pregnancy, pulmonary artery Doppler

1 | INTRODUCTION

Inadequate lung development leads to neonatal complications, with high mortality and morbidity, especially respiratory distress syndrome (RDS) in newborns.[1] In contrast to amniotic fluid testing, a Doppler exam is a non-invasive method to assess fetal lung maturation.[2–4] Determining fetal pulmonary artery blood flow acceleration time, ejection time, and acceleration/ejection time ratio (PATET) is a new approach for monitoring pulmonary artery pressure.[2,3] Previous studies showed that the acceleration time was negatively correlated with pulmonary artery systolic pressure.[5,6]

The COVID-19 pandemic has spread rapidly worldwide, with adverse pregnancy outcomes, including maternal multisystemic organ damage, with hypercoagulation, hypoxia, and an excessive inflammatory response, reported in infected individuals.[7–10] The aforementioned adverse effects can explain reported complications, such as early pregnancy loss and fetal growth retardation, caused by COVID-19.[11–13] Although the mechanisms underlying

placental transmission of COVID-19 and its associated effects on fetal organs are not clear, fetal vascular malperfusion is the most common finding in placental pathology.[14,15] Fetal vascular malperfusion may lead to incomplete maturation of fetal lungs and increased pulmonary artery pressure. The aim of the present study was to evaluate the development of fetal lungs using pulmonary artery Doppler in pregnant women who had recovered from COVID-19.

2 | MATERIALS AND METHODS

The present study was conducted at Ankara City Hospital between February 1, 2021, and June 30, 2021. The prospective case–control study included 41 pregnant women who had recovered from COVID-19 and 43 healthy pregnant women (control group). All the women in the study group had been diagnosed with COVID-19 by a reverse transcription polymerase chain reaction test and had completed a quarantine period. The quarantine period was 14 days for those discharged from the hospital and patients who were followed up at home. Women with a history of multifetal pregnancies, fetal structural anomalies, and maternal systemic diseases were excluded. In the control group, pregnant women with symptoms associated with COVID-19 infection (e.g. a fever, cough, sore throat, or myalgia) were not included.

Written informed consent was obtained from all participants. Approval for the study was obtained from the Turkish Ministry of Health and Medical Research Ethics Department of the hospital (decision number E2-21-380).

Gestational age was determined by the last menstrual period or first trimester crown–rump length. All Doppler measurements were performed at 28–40 weeks of gestation by the same maternal fetal medicine specialist using a Voluson S10 ultrasound machine C1-5-RS convex probe (1.75–4.95 MHz; General Electric Healthcare). The fetal cardiac four-chamber view was obtained first and then the fetal main pulmonary artery (MPA) was visualized. The pulmonary valves and the bifurcation of the right and left branches of the pulmonary artery were identified. The measurements were obtained by placing the cursor between the valve and the bifurcation of pulmonary artery. When a specific MPA Doppler pattern was obtained,[4] systolic/diastolic (S/D) ratio, resistance index (RI), pulsatility index, and peak systolic velocity (PSV) values were measured by manual or automatic tracing.[16] Acceleration time and ejection time were measured by a manual trace. Acceleration time is the time from the onset of flow to the maximum flow of the PSV and ejection time is the time from the beginning to the end of ventricular systole. The PATET ratio was calculated.[16,17]

In the Doppler measurements, the mean values of three consecutive cardiac cycles were used.

Statistical analysis was enforced using IBM SPSS Statistics 17.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median and minimum–maximum values for numerical data that do not follow a normal distribution. The normality of the variables was tested with both Shapiro–Wilk and Kolmogorov–Smirnov tests. Groups were compared with the Student *t*-test and Mann–Whitney *U*-test. A type-1 error less than 0.05 was considered statistically significant.

3 | RESULTS

The present study included 41 patients who recovered from COVID-19 and 43 control cases. Table 1 shows the demographics of the study population. The maternal baseline characteristics of the two groups were similar. The clinical features of COVID-19 are shown in Table 2. The mean gestational age at the time of the COVID-19 diagnosis was 16.1 weeks (range 5–30 weeks), and 12 (29%) of the patients had been hospitalized. All the hospitalized patients received treatment with low-molecular weight heparin. Only one patient received lopinavir-ritonavir therapy.

TABLE 1 Baseline data and characteristics of the groups[a]

	Controls ($n = 43$)	Recovered from COVID-19 ($n = 41$)	*P* value
Maternal age (years)	27.4 ± 4.8	28.6 ± 5.5	0.342
BMI (kg/m^2)	28.5 ± 7.0	27.8 ± 4.1	0.477
Nulliparity	19 (44.2)	16 (39)	0.230
Gestational age at ultrasound assessment (weeks)	32.0 ± 0.7	32.3 ± 4.3	0.823
BPD (weeks)	32.9 ± 3.9	32.7 ± 4.1	0.903
AC (weeks)	31.6 ± 5.9	31.3 ± 6.1	0.801
FL (weeks)	32.0 ± 3.9	31.8 ± 4.1	0.854
EFW (g)	2053 ± 785	2015 ± 814	0.872
DVP (mm)	50.9 ± 11.7	50.6 ± 10.8	0.907

Abbreviations: AC, abdominal circumference; BMI, body mass index; BPD, biparietal diameter; DVP, deepest vertical pocket; EFT, estimated fetal weight; FL, femur length.

[a]Values are given as as number (percentage) or mean ± SD.

TABLE 2 Clinical characteristics of COVID-19[a]

Variables	Values
Gestational age at diagnosis (weeks)	16.1 (5–30)
Admission to hospital	12 (29)
COVID-19 therapy	12 (29)
Low-molecular weight heparin	12 (29)
Lopinavir-ritonavir	1 (2)

[a]Values are given as number (percentage) or median (interquartile range).

TABLE 3 Fetal Doppler assesment[a]

	Controls ($n = 43$)	Recovered from COVID-19 ($n = 41$)	*P* value
PA PSV	53.5 ± 11.8	66.8 ± 16.7	**<0.001**
PA S/D	7.1 ± 1.1	6.6 ± 1.6	0.082
PA PI	2.2 ± 0.2	1.8 ± 0.5	**0.001**
PA RI	0.8 ± 0.01	1.0 ± 0.4	0.565
PA AT	57.2 ± 9.8	44.9 ± 13.4	**<0.001**
PA ET	215.0 ± 35.8	198.9 ± 40.5	**0.036**
PATET	0.27 ± 0.06	0.23 ± 0.07	**0.002**

Abbreviations: AT, acceleration time; ET, ejection time; PA, pulmonary artery; PATET, acceleration/ejection time ratio; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic ratio.

[a]Values are given as mean ± SD. Statistically significant data ($P < 0.05$) is written in bold.

The findings of the Doppler assessments are shown in Table 3. The MPA-PSV was higher and the pulsatility index was lower in the pregnant women who had recovered from COVID-19 compared to the controls ($P < 0.001$ and $P = 0.001$, respectively). The acceleration time, ejection time, and PATET ratio of the fetal MPA were significantly decreased in the pregnant women who had recovered from COVID-19 ($P < 0.001$, $P = 0.036$, and $P = 0.002$, respectively). The patients who had recovered from COVID-19 were divided into two groups: those treated with expectant management and those treated in hospital. When the pulmonary artery Doppler data in these groups were compared, the pulmonary artery S/D ratio, acceleration time, and PATET ratio were significantly lower in the group treated in the hospital ($P = 0.049$, $P = 0.023$, and $P = 0.045$).

4 | DISCUSSION

In the present study, low MPA pulsatility index, acceleration time, and ejection time values and low PATET ratios were found in the pregnant women who had recovered from COVID-19 compared to the values in the control group. In addition, the pulmonary artery S/D ratio, acceleration time, and PATET ratio were significantly lower in the group treated in the hospital.

During fetal lung maturation, pulmonary impedance decreases, and pulmonary artery flow increases, with the ejection flow reaching a peak in mid-systole. In contrast, the ejection flow peaks earlier in patients with high pulmonary impedance. As a result, the acceleration time and PATET ratio decrease, as reported in earlier studies.[5,6,18] A study that investigated the relationship between the PATET ratio and surfactant/albumin ratio revealed an inverse relationship between the PATET ratio and neonatal respiratory distress.[18] In another study, the PATET ratio was lower in infants diagnosed with RDS.[5] Büke et al.[2] investigated the relationship between the fetal PATET ratio and neonatal transient tachypnea. In their study, the PATET ratio had a negative predictive value of 96%, sensitivity of 83.3%, and specificity of 82.7% in detecting transient tachypnea. In the present study, both the PATET ratio and acceleration time were decreased in the patients who had recovered from COVID-19. The PATET ratio and acceleration time were significantly lower in the symptomatic patients who required hospitalization. It is believed that these findings might be a reflection of the adverse effects of maternal COVID-19 infection on the fetal lung.

In a study on 756 fetuses that used fetal MPA Doppler to predict neonatal RDS, the PATET ratio was decreased in fetuses that developed RDS. In contrast to the present findings, they reported that the MPA pulsatility index was increased, and the PSV was decreased, in fetuses that developed RDS. Importantly, in the present study, the ability of the pulsatility index and RI to predict the development of RDS appeared to have lower sensitivity and specificity compared to that of the PATET ratio.[16] On the other hand, Lindsley et al.[19] observed no differences in fetal pulmonary artery PSV, S/D ratio, pulsatility index, and RI value of preterm newborns with RDS versus those without RDS. Further studies are needed to shed light on the importance of the PSV, S/D ratio, pulsatility index, and RI in fetal lung maturation (Table 4).

Fetal distress and preterm birth are common obstetrical complications of COVID-19. Fetal pulmonary status has become an

TABLE 4 Comparison of fetal pulmonary artery Doppler data according to treatment approach of patients recovered from COVID-19[a]

	Expectant management ($n = 29$)	Treatment in hospital ($n = 12$)	*P* value
PA PSV	68.5 ± 18.6	62.8 ± 10.7	0.436
PA S/D	7.1 ± 1.1	6.6 ± 1.6	**0.049**
PA PI	1.7 ± 0.6	2.0 ± 0.4	0.185
PA RI	1.06 ± 0.5	0.95 ± 0.4	0.488
PA AT	48.1 ± 13.4	37.1 ± 10.3	**0.023**
PA ET	203.3 ± 38.6	188.2 ± 44.6	0.250
PATET	0.24 ± 0.07	0.20 ± 0.07	**0.045**

Abbreviations: AT, acceleration time; ET, ejection time; PA, pulmonary artery; PATET, acceleration/ejection time ratio; PI, pulsatility index; PSV, peak systolic velocity; S/D, systolic/diastolic ratio.

[a]Values are given as mean ± SD. Statistically significant data ($P < 0.05$) is written in bold.

important issue.[11–13,20,21] In a review on neonatal complications in newborns (n = 67), RDS or pneumonia was observed in 18% (n = 12), low birth weight in 13% (n = 9), asphyxia in 2% (n = 1), and perinatal death in 3% (n = 2) of the newborns. Despite strict infection control and prevention procedures during the birth and separation of the mother and newborn, four newborns, three of whom had pneumonia, were positive for COVID-19, and vertical transmission could not be excluded.[22] However, there is insufficient evidence to support vertical transmission of COVİD-19.[23] Previous research showed that the virus disrupted fetomaternal perfusion by causing placental injury, including villitis, inflammation, and arteriopathy.[24,25] It was therefore hypothesized that COVID-19 infection-related events, such as increased levels of cytokines, maternal hypoxia, and impaired coagulation cascades, may have negative effects on fetal pulmonary circulation, including placental malperfusion.[7,11,13]

The present study has strengths and weaknesses. It was a prospective single-center study, with a standard follow-up protocol. However, the cases were not evaluated with respect to vertical transmission. In addition, neonatal outcomes could not be presented as they were delivered at different centers.

In conclusion, COVID-19 causes more severe disease in pregnant women compared with non-pregnant women.[20,21] Many studies have been conducted on fetal adverse effects,[14,15,20,21] but many questions about fetal consequences remain unanswered. COVID-19 infection can have a negative impact on placental tissues and fetal organs.[24,25] Further studies are needed to clarify the impact of maternal COVID-19 infection on fetal lung development.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

ET, SGA, and DS conceived the study. ET, EOT, and DO performed the statistical analysis. The management of the trial was overseen by ET, SGA, DS, and OMT. ET drafted the manuscript. All authors contributed to the approved the final manuscript.

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REFERENCES

1. Liu J, Sorantin E. Neonatal respiratory distress syndrome. In: *Neonatal Lung Ultrasonography*. Springer; 2019:17-39. doi:10.1007/978-94-024-1549-0_3.
2. Büke B, Akkaya H. A non-invasive method to rule out transient tachypnea of the newborn (TTN): fetal pulmonary artery acceleration to ejection time ratio. *J Perinat Med*. 2018;46:219-224. doi:10.1515/jpm-2016-0380.
3. Zhan HY, Xu FQ, Liu CX, Zhao G. Clinical applicability of monitoring pulmonary artery blood flow acceleration time variations in monitoring fetal pulmonary artery pressure. *Adv Clin Exp Med*. 2018;27:1723-1727. doi:10.17219/acem/75686.
4. Azpurua H, Norwitz ER, Campbell KH, et al. Acceleration/ejection time ratio in the fetal pulmonary artery predicts fetal lung maturity. *Am J Obstet Gynecol*. 2010;203:40.e1-40.e8. doi:10.1016/j.ajog.2010.01.075.
5. Guan Y, Li S, Luo G, et al. The role of doppler waveforms in the fetal main pulmonary artery in the prediction of neonatal respiratory distress syndrome. *J Clin Ultrasound*. 2015;43:375-383. doi:10.1002/jcu.22219.
6. Büke B, Destegül E, Akkaya H, Şimşek D, Kazandi M. Prediction of neonatal respiratory distress syndrome via pulmonary artery Doppler examination. *J Matern Fetal Neonatal Med*. 2019;32:1640-1645. doi:10.1080/14767058.2017.1413549.
7. Gotsch F, Romero R, Kusanovic JP, et al. The fetal inflammatory response syndrome. *Clin Obstet Gynecol*. 2007;50:652-683. doi:10.1097/GRF.0b013e31811ebef6.
8. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol*. 2020;222:521-531. doi:10.1016/j.ajog.2020.03.021.
9. Sahin D, Tanacan A, Erol SA, et al. A pandemic center's experience of managing pregnant women with COVID-19 infection in Turkey: a prospective cohort study. *Int J Gynaecol Obstet*. 2020;151:74-82. doi:10.1002/ijgo.13318.
10. Sahin D, Tanacan A, Erol SA, et al. Updated experience of a tertiary pandemic center on 533 pregnant women with COVID-19 infection: a prospective cohort study from Turkey. *Int J Gynaecol Obstet*. 2021;152:328-334. doi:10.1002/ijgo.13460.
11. Bahadur G, Homburg R, Yoong W, et al. Adverse outcomes in SARS-CoV-2 (COVID-19) and SARS virus related pregnancies with probable vertical transmission. *J Bras Reprod Assist*. 2020;24:351-357. doi :10.5935/1518-0557.20200057.
12. Halici-Ozturk F, Ocal FD, Aydin S, et al. Investigating the risk of maternal-fetal transmission of SARS-CoV-2 in early pregnancy. *Placenta*. 2021;106:25-29. doi:10.1016/j.placenta.2021.02.006.
13. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. *Ultrasound Obstet Gynecol*. 2020;56:15-27. doi:10.1002/uog.22088.
14. Komine-Aizawa S, Takada K, Hayakawa S. Placental barrier against COVID-19. *Placenta*. 2020;99:45-49. doi:10.1016/j.placenta.2020.07.022.
15. Mulvey JJ, Magro CM, Ma LX, Nuovo GJ, Baergen RN. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. *Ann Diagn Pathol*. 2020;46:151530. doi:10.1016/j.anndiagpath.2020.151530.
16. Moety G, Gaafar HM, el Rifai N. Can fetal pulmonary artery Doppler indices predict neonatal respiratory distress syndrome? *J Perinatol*. 2015;35:1015-1019. doi:10.1038/jp.2015.128.
17. Peyvandi S, Rychik J, McCann M, Soffer D, Tian Z, Szwast A. Pulmonary artery blood flow patterns in fetuses with pulmonary outflow tract obstruction. *Ultrasound Obstet Gynecol*. 2014;43:297-302. doi:10.1002/uog.12472.
18. Schenone MH, Samson JE, Jenkins L, Suhag A, Mari G. Predicting fetal lung maturity using the fetal pulmonary artery Doppler wave acceleration/ejection time ratio. *Fetal Diagn Ther*. 2014;36:208-214. doi:10.1159/000358299.
19. Lindsley W, Hale R, Spear A, et al. Does corticosteroid therapy impact fetal pulmonary artery blood flow in women at risk for preterm birth? *Med Ultrason*. 2015;17:280-283. doi:10.11152/mu.2013.2066.173.wly.
20. Metz TD, Clifton RG, Hughes BL, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. 2021;137:571-580. doi:10.1097/AOG.0000000000004339.
21. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus

disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2019;2020:370. doi:10.1136/bmj.m3320.
22. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J*. 2020;39:469-477. doi:10.1097/INF.0000000000002700.
23. Sinaci S, Ocal DF, Seven B, et al. Vertical Transmission of SARS-CoV-2: a prospective cross-sectional study from a tertiary center. *J Med Virol*. 2021;93:5864–5872. doi:10.1002/jmv.27128.
24. Algarroba GN, Rekawek P, Vahanian SA, et al. Visualization of severe acute respiratory syndrome coronavirus 2 invading the human placenta using electron microscopy. *Am J Obstet Gynecol*. 2020;223:275-278. doi:10.1016/j.ajog.2020.05.023.
25. Gao L, Ren J, Xu L, et al. Placental pathology of the third trimester pregnant women from COVID-19. *Diagn Pathol*. 2021;16. doi:10.1186/s13000-021-01067-6.

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