Received: 10 February 2021 | Revised: 12 May 2021 | Accepted: 11 June 2021

DOI: 10.1111/echo.15146

Echocardiography WILEY

ORIGINAL ARTICLE

Effects of SARS-COV-2 infection on fetal pulmonary artery Doppler parameters

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Abstract

Purpose: To determine the effect of SARS-CoV-2 infection on the fetal pulmonary system using the acceleration time (AT), ejection time (ET), and acceleration/ejection time ratio (PATET) of the fetal main pulmonary artery Doppler waveform.

Methods: We prospectively studied pregnant women attending our hospital with confirmed SARS-CoV-2 infection by RT-PCR test and an age-matched control group who admitted for routine prenatal care. An ultrasound examination that included measurements of the AT, ET, and AT/ET ratio (PATET) were performed and the results were compared.

Results: Fifty-five SARS-CoV-2-infected and 93 control group pregnant women were included in this study. AT found higher in the COVID-19 positive group when compared with controls. When the ET and PATET parameters were compared, no differences were detected between the groups. Eleven neonates had Neonatal Intensive Care Unit (NICU) requirement in the COVID-19 positive group while there were none in the control group. All fetal pulmonary artery Doppler values were decreased in NICU admitted fetuses. The mean gestational week of this group was lower than non-NICU COVID-19 positive group and the control group.

Conclusion: COVID-19 infection increases fetal pulmonary blood flow, which appears high AT values on Doppler parameters. NICU admission only occurred in the COVID-19 group and their Doppler values were found significantly lower than non-NICU COVID-19 group. The clinical significance of this result must be evaluated with further studies.

KEYWORDS
color Doppler, fetal echocardiography, pulmonary artery

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a procoagulant effect on the hematologic system that aggravates hypoxia in infected patients.[1] Pregnancy does not increase the risk of SARS-CoV-2 infection; however, it appears to worsen the clinical outcomes of coronavirus disease 2019 (COVID-19) compared with non-pregnant women of the same age.[2,3] Recent data show that obstetric complications such as preterm labor, fetal distress, and stillbirths increase with COVID-19.[2–4] Additionally, a higher rate of neonatal intensive care unit admissions has been identified in neonates born to SARS-CoV-2-infected mothers.[5,6] This situation is consistent with

a fetal inflammatory response syndrome due to maternal infection, which has been described in the literature previously.[7–9]

Pulmonary artery Doppler is a noninvasive tool that can be used to predict respiratory complications in preterm neonates.[10–16] In respiratory distress syndrome (RDS), due to incomplete maturation of the fetal lungs, pulmonary arterial pressure and impedance increase and are reflected in Doppler parameters. The hypercoagulapathy, hypoxia, and excessive inflammatory response of COVID-19 might affect fetal pulmonary circulation in the same way. In contrast, Thomas W. has shown that intrauterine infection and inflammation have positive effects on fetal lung function.[17]

In this study, our aim was to investigate fetal pulmonary artery Doppler parameters in COVID-19-infected pregnant women to determine the effect of infection on the fetal pulmonary system.

2 | MATERIALS AND METHODS

This is a prospective cohort study conducted between August 1, 2020 and October 1, 2020 in Turkish Ministry of Health Ankara City Hospital and pregnant women with confirmed SARS-CoV-2 infection. The RT-PCR test was used to confirm SARS-CoV-2. Pregnant women hospitalized for mild or moderate COVID-19 infections were compared with an age-matched control group of pregnant women monitored for routine prenatal care. Women known to have multifetal pregnancies, fetal structural anomalies, and maternal systemic diseases were excluded. Also, in the control group, pregnant women with symptoms associated with COVID-19 infection (fever, cough, sore throat, myalgia, etc.) were not included. Written informed consent was obtained from all participants. The applied protocol was approved by the Turkish Ministry of Health and Medical Research Ethics Department of the hospital.

The last menstrual period or first trimester crown–rump length was used to determine gestational age. Doppler measurements were performed between 32 and 39 weeks of gestation by the same maternal fetal medicine specialist using software of the GE Voluson S10 Ultrasound machine C1-5-RS convex probe (1.75–4.95 Mhz). Researchers used personal protective equipment during ultrasound exams of patients infected with COVID-19. Patients were examined in a semi-Fowler position to avoid orthostatic hypotension. The fetal cardiac four-chamber view was obtained first, then the fetal main pulmonary artery (MPA) was visualized by rotating the transducer from the four-chamber view to the short-axis view. At the proximal portion of the MPA, pulmonary valves and the bifurcation of the right and left branches of the pulmonary artery were identified. The sample volume gate was adjusted to 3 mm and positioned between the valves and the bifurcation. The blood flow waveform was displayed with a velocity range of 100 cm/s and a sweep speed of 200 mm/s. The shortest time interval that could be measured was 1 ms. When a specific MPA Doppler pattern[18] was obtained, acceleration time (AT) and ejection time (ET) measurements were done by manual trace. AT and ET were measured by averaging three cardiac cycles for each parameter. AT is the time interval from the onset of flow to the maximum flow of the peak systolic velocity and ET is the time interval from the beginning to the end of ventricular systole (Figure 1). The pulmonary artery AT/ET (PATET) ratio was calculated.

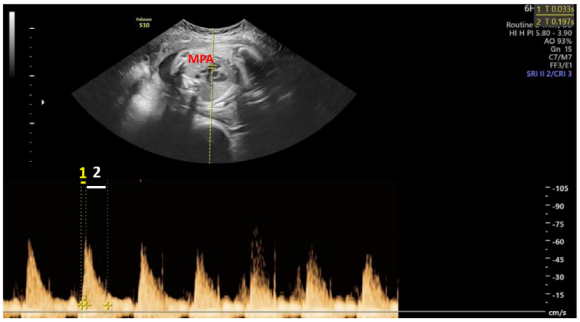

Figure 1 Main pulmonary artery (MPA) Doppler evaluation in the short axis view. 1: Acceleration time (AT), 1+2: Ejection time (ET)

All Doppler measurements were performed prior to betamethasone administration.

SPSS 17 was used for statistical analysis. The Shapiro- Wilk test, Kolmogorov–Smirnov test were used to determine the distribution of normality. The continuous variables were presented as mean and standard deviations. Groups were compared with The Student's t-test and Mann-Whitney U test. A type-1 error below .05 was considered statistically significant.

3 | RESULTS

Table 1 shows the demographic features of patients with COVID-19 (n = 55) and patients in the control group (n = 93). The two groups were homogenous, and no differences were noted in the demographic data. When the AT parameters were compared, the COVID-19 group displayed increased values compared to the controls. When the ET and PATET parameters were compared, no differences were detected between the groups. Table 2 provides a summary of all Doppler parameters.

Eleven neonates had Neonatal intensive care unit (NICU) requirement in COVID-19 positive group while there were none in control group. Table 3 shows relation between pulmonary artery Doppler parameters and NICU admission in COVID-19 positive pregnant women. AT, ET, and PATET values of fetuses who admitted to NICU were significantly decreased. Mean gestational week of NICU positive group was 31.2 ± 3.2 which was lower than NICU negative (34.9 ± 4.1) group.

4 | DISCUSSION

In the present study, we found high AT values and similar ET values and PATET ratios in the MPA of COVID-19-positive patients when compared to the control group. However, when COVID-19 positive group evaluated for pulmonary artery Doppler parameters we found significantly decreased values in NICU admitted group when compared not admitted fetuses.

TABLE 1 Demographic data

Variables	COVID-19 + group (n = 55)		Control group(n = 93)	*P* value
Age (years)(mean, SD)	28.4 ± 5.28		28.2 ± 5.5	.28
Gravidity (mean, SD)	1.76 ± 1.09		1.70 ± 1.15	.28
Parity (mean, SD)	.81 ± .8		.77 ± 1	.28
BW (mean, SD)	3257 ± 506		3182 ± 467	.39
APGAR 1. MIN (mean, SD)	7.51 ± .65		7.77 ± 071	.38
APGAR 5. MIN (mean, SD)	9.2 ± .64		9 ± .61	.39
Gestational Week (mean, SD)	33.9+/-3.8		34.1+/-2.9	.41
	NICU+(n = 11)	NICU- (n = 44)		
	31.2 ± 3.2	34.9 ± 4.1		

BW: birth weight, MIN: minute, NICU: newborn intensive care unit.

TABLE 2 Fetal Pulmonary Artery Doppler Parameters

Variables	COVID-19 + group (n = 55)	Control group(n = 93)	*P* value
AT (mean, SD)	54 ± 15,4	50 ± 14,9	**0,044***
ET (mean, SD)	223 ± 45,4	220 ± 41,3	0,960*
PATET (mean, SD)	0,25 ± 0,07	0,23 ± 0,07	0,191*

AT, acceleration time; ET, ejection time; PATET, AT/ET ratio.
*Mann Whitney U (MWU) test.

TABLE 3 COVID-19 positive group fetal pulmonary artery Doppler parameters

Variables	NICU + group (n = 11)	NICU − group (n = 44)	*P* value
AT (mean, SD)	39 ± 14,5	58 ± 13,1	.001**
ET (mean, SD)	192 ± 21,9	232 ± 46,4	.008*
PATET (mean, SD)	.21 ± .07	.26 ± .06	,039**

AT: acceleration time, ET: ejection time, PATET: AT/ET ratio.
*(MWU), ** Independent Sample T Test.

Pulmonary artery Doppler investigations have been used successfully in neonates to identify pulmonary hypertension. When mean pulmonary artery pressure increases, peak velocity is maximized at the early systole and AT time becomes shorter.[14] Some previous results have indicated that ET did not change throughout gestation.[13,15,17] To date, fetal pulmonary artery Doppler has been used in many studies to assess fetal lung maturity and as a predictor of neonatal RDS. Chaui et al. (1998) reported that the human fetus demonstrates a short AT with a significant lengthening throughout gestation, and a significant increase in the PATET ratio.[13] Schenone et al. (2014) found increasing PATET values with increasing gestational age, which correlates with testing of fetal lung maturity by amniocentesis.[19] These data indicate that increases occur in 1) angiogenesis during fetal lung maturity, 2) wall elasticity of the pulmonary artery, and 3) blood flow, which suggests that AT reaches peak values during an extended time period.

In another study, the AT values and PATET ratios were significantly lower in the RDS group than in the non-RDS group, even after controlling for gestational age 15.

SARS-CoV-2 causes multisystemic infectious disease that may also affect fetuses by vertical transmission. The virus can cause acute severe pneumonia, which results in serious hypoxia in the patients. Although vertical transmission to the fetus has not been proven, some data have indicated that the virus causes villitis, inflammation, and arteriopathy in the placenta. Virions have been identified on placental villi as well.[20,21]

Thus, fetal distress and preterm birth are common obstetrical complications of COVID-19, and fetal pulmonary status has become an important issue. We hypothesized that fetal pulmonary circulation may be affected negatively by COVID-19 infection-related events, such as increased cytokine levels, maternal hypoxia, and impaired coagulation cascades.[22–24] However, slightly increased fetal pulmonary blood flow has been observed in COVID-19-infected patients compared to controls. A recent case report has indicated that fetal inflammatory response syndrome is caused by SARS-CoV-2.[25] Several previous studies have shown that intrauterine infection and inflammation alter fetal lung development.[26,27] Microorganisms increase the production of surfactant lipids and improve lung compliance.[28] This inflammatory process may explain the increased blood flow toward fetal lungs.

Additionally, maternal hypoxia may lead to fetal hypoxia, and this is a stimulus for oxidative stress.[29] However, reports are inconsistent regarding lung maturation and respiratory outcomes following fetal hypoxemia in both clinical and animal studies.[30,31] These inconsistencies may relate to assessment of the severity and duration of fetal hypoxemia. In our study, all COVID-19 patients were in the mild or moderate infection category and hypoxemia was not evident, offering one explanation for the findings of the present study.

The presence of angiotensin-converting enzyme 2 (ACE2) on target cells is the key to SARS-CoV-2 entry.[32] With regard to fetal lung tissues, Goyal et al. showed significant overexpression of both ACE-2 mRNA and protein in fetal lungs as a consequence of maternal hypoxic stress; thus, we expected decreased fetal lung blood flow in infected pregnant women.[33]However, a recent study using

immunocytochemistry analysis revealed that ACE2 was barely detectable in human fetal lungs at 15 weeks and did not exist after that point in time.[34] Thus, fetal lungs do not appear to be a target for the virus, offering an explanation for the lack of negative effects of the virus on fetal lung circulation.

Smith et. al. showed that the incidence of NICU admission with COVID-19 infection was higher than the general population.[35] Supporting this, NICU was required only for our COVID-19 group. Moreover, all fetal pulmonary artery Doppler parameters were significantly decreased in our NICU required neonates, which was consistent with neonatal RDS pathogenesis. In RDS, high impedance of the lungs leads to low pulmonary artery Doppler values.[10,15,19] Even observation of increased blood flow in COVID-19 group, COVID-19 NICU positive group had lower AT levels. When gestational weeks of the groups evaluated NICU positive group has lower mean gestational week than both NICU negative group and controls. AT value increases throughout gestation due to fetal pulmonary maturation.[13] This situation might be the explanation of this contrast results.

Although 1 year has passed since the COVİD-19 pandemic started, many questions about fetal consequences remain unanswered. Vertical transmission is possible, but it has not yet been confirmed clearly.[36,37] SARS-CoV-2 infection may have a negative effect on placental tissues microscopically[20,21] without clinical significance. This point can only be proven by further studies on the placenta and fetal organs, correlated with clinical findings.

The main strengths of the present study were its novelty and prospective design. The main limitations were the relatively low number of COVID-19 cases, a lack of information related to the long-term outcomes of the cases, and the absence of both severe cases and severe hypoxic levels in participants.

In conclusion, COVID-19 infection slightly increased fetal pulmonary blood flow, which appears to increase AT on Doppler parameters in pregnant women with mild or moderate symptoms. We did not find any other study evaluating these effects. New researches with larger numbers of patients are necessary to confirm the results and, to verify the clinical significance of this increment reported here.

ACKNOWLEDGMENTS

The authors thank Dr Deniz Yüce, Epidemiologist, had PGD on medical statistics for revising the article for statistical analyses. Additionally, they give special thanks to all the healthcare staff at the hospital, who work so hard during the pandemic period.

FUNDING SOURCES

None

DISCLOSURES

None

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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How to cite this article: Sule GA, Aysegul A, Selcan S, et al. Effects of SARS-COV-2 infection on fetal pulmonary artery Doppler parameters. *Echocardiography*. 2021;38:1314–1318. https://doi.org/10.1111/echo.15146