







Decreased fetal cardiac output in pregnant women with severe SARS-CoV-2 infection

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Abstract

Aim: We aimed to examine fetal cardiac output (CO) in patients who recovered from severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection.

Materials: This prospective study included 48 pregnant women recovered from SARS-CoV-2 infection and 50 control cases. SARS-CoV-2 infection was diagnosed by polymerase chain reaction (PCR) test in patients. Fetal echocardiographic evaluations were performed at 24–37 weeks of gestation in pregnant women who recovered from the infection and control group.

Results: The median value of ultrasound evaluation was 34 (2.6) weeks of gestation in the recovery from the SARS-CoV-2 infection (RSI) group, and 32 (7.6) weeks in the control group ($p = .565$). Left cardiac output (LCO) z score was significantly lower in the RSI group than the control group ($p = .041$). LCO and combine cardiac output (CCO) z score were significantly lower in the severe disease group than mild, moderate disease groups, and controls ($p = .019$ and $p = .013$). CCO (ml/min/kg) was decreased in the severe disease group when compared with control and mild disease groups ($p = .044$).

Conclusion: In the present study, fetal cardiac output in pregnant women who recovered from SARS-CoV-2 infection was found to be significantly reduced in those with severe disease, while there was no significant difference in mild and moderate cases. Placental dysfunction and inflammatory cytokines might cause fetal cardiac changes. Further studies could be clarified on the impact of SARS-CoV-2 infection on fetal cardiac function.

KEYWORDS

fetal cardiac output, fetal echocardiography, severe acute respiratory syndrome coronavirus

1 | INTRODUCTION

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection is a major public health problem, with hospitalizations, admissions to the intensive care unit (ICU), and even deaths.¹ Compared with non-pregnant women of childbearing age with SARS-CoV-2 infection, pregnant women are more likely to be needed for respiratory support and admitted to an ICU.² Pregnant women with SARS-CoV-2 infection are

at high risk for adverse perinatal outcomes such as early pregnancy loss, fetal growth retardation, and preterm delivery.^{3,4}

Impaired placental function, hypoperfusion, and inflammation might lead to fetal decompensation that increased risk of perinatal mortality and morbidity.^{5,6}

Cardiac output depends on heart rate, preload, afterload, and myocardial contractility.⁷ An increase in afterload or a decrease in preload causes a decrease in cardiac output.⁸ Changes in cardiac

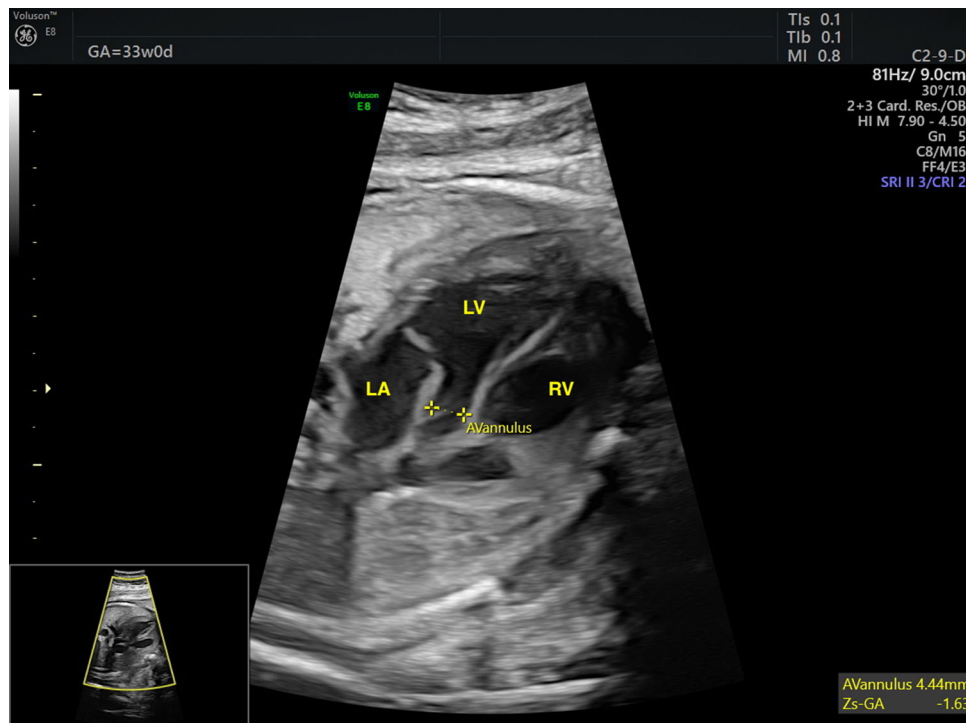


FIGURE 1 Aortic valve annulus diameter. L, left; R, right; AV annulus, aortic valve annulus; LA, left atrium; LV, left ventricle; RV, right ventricle; Zs-GA, Z score for gestational age.

output have been demonstrated in hydrops fetalis, fetal growth retardation (FGR), anemia, and various pathological conditions.^{9–13} In this present study, we aimed to evaluate changes of fetal cardiac output in pregnant women who recovered from SARS-Cov-2 infection.

2 | MATERIALS AND METHODS

This prospective study included 48 pregnant women with recovered from SARS-CoV-2 infection and 50 control cases. The study was conducted in Ankara City Hospital between June 30, 2021 and January 1, 2022. Approval for the study was obtained from Ankara City Hospital Ethics Committee with the decision number E2-21-639. Written consent was obtained from patients. SARS-CoV-2 infection was diagnosed by polymerase chain reaction (PCR) test in patients. Twin pregnancy, maternal systemic disease, fetal anomaly, aneuploidy, and obstetric complications such as oligohydramnios, fetal growth restriction were excluded from the study. Fetal echocardiographic evaluations were performed between 24 and 37 weeks of gestation by the same maternal-fetal medicine specialist using C1-5-RS convex probe (1.75–4.95 Mhz) GE Voluson S10 and E8 Ultrasound. The study group and control group were matched for maternal and gestational age. Control group were consecutive cases matched with study group. The control group consists of pregnant women who were followed up in the same time interval as the patients in the study group in our department. A two-dimensional assessment of the great vessels and Doppler flow interrogation was obtained according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology.¹⁴ Aor-

tic (AV) (Figure 1) and pulmonary artery valve (PV) (Figure 2) diameters were measured in systole.¹⁴ Power Doppler cursor was located in parallel to the long axis of the aorta or pulmonary artery immediately distal to the valves. The angle between the ultrasound cursor and the direction of blood flow was $<10^\circ$. The pulmonary and aortic valves flow velocity waveforms were obtained from the left and right ventricular outflow tract views (Figure 3).¹⁵ Velocity time integral (VTI) and heart rate (HR) were measured and averaged over the three best cardiac cycles. Cardiac outputs for the left and right ventricle (LCO and RCO) were calculated separately as $VTI \times \pi$ (AV or PV diameter/2)² \times HR.¹⁵ Gestational age was determined using first-trimester head-rump length. LCO and RCO z scores were calculated according to the gestational week. Estimated fetal weight (EFW) was calculated with the method of Hadlock et al. Combined cardiac output (CCO = RCO + LCO) was calculated, z score was obtained according to the gestational week.^{16,17} Also, CCO was normalized by estimated fetal weight.¹⁸ Demographic and echocardiographic data were compared between recovery from the SARS-CoV-2 infection (RSI) and control groups. Patients in the study group were divided into subgroups according to the World Health Organization (WHO)'s disease severity classification.¹⁹ Presence of any sign and symptom (e.g., fever, cough, sore throat, muscle pain) for COVID-19 without lower respiratory system involvement was defined as mild disease. Evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) $\geq 94\%$ on room air at sea level was defined as moderate disease. Respiratory frequency > 30 breaths per minute, $SpO_2 < 94\%$ on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 , or lung infiltrates

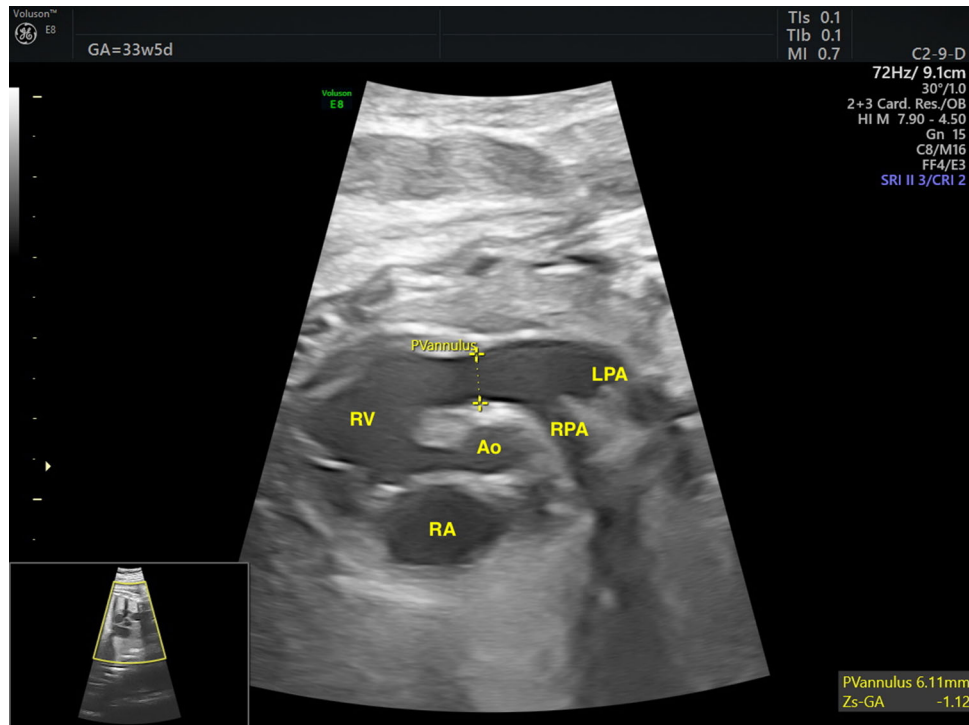


FIGURE 2 Pulmonary valve annulus diameter. Ao, aorta; LPA, left pulmonary artery; PV annulus, pulmonary valve annulus; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; Zs-GA, Z score for gestational age.

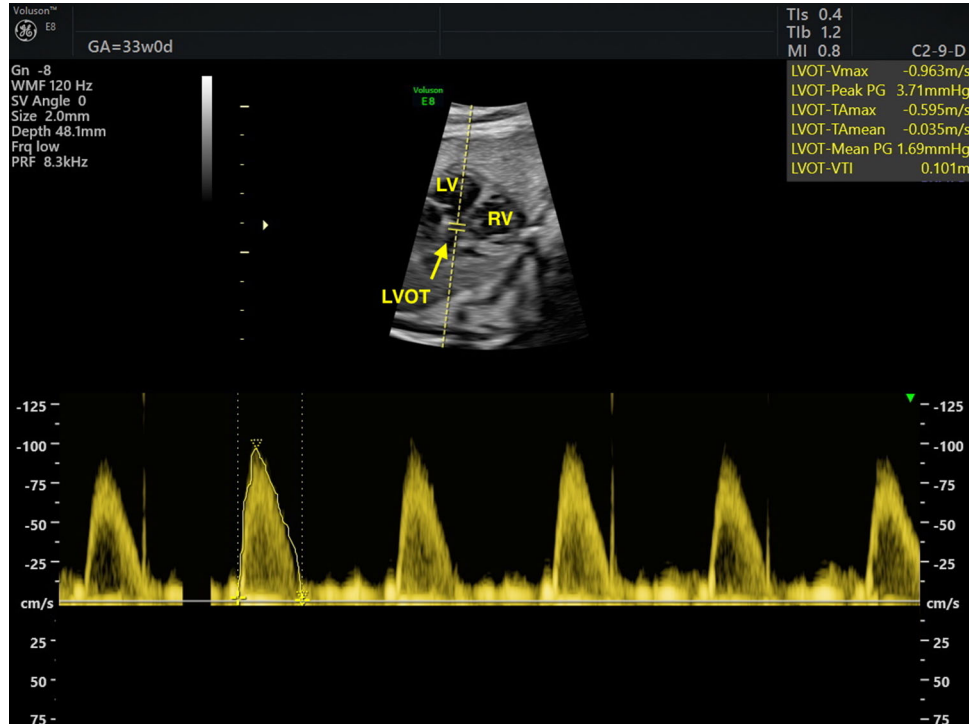


FIGURE 3 The aortic valves flow velocity waveforms and velocity time integral (VTI) were obtained from the left ventricular outflow tract (LVOT) views. Cardiac outputs was calculated as $VTI \times \pi (Aortic\ valve\ diameter/2)^2 \times heart\ rate$. LV, left ventricle; RV, right ventricle.

TABLE 1 Baseline data and characteristics of the groups

	Control (n = 50)	RSI (n = 48)	p-values
Maternal age	27 ± 5	28 ± 4	0.200
BMI	27.2 ± 4.7	29.0 ± 4.7	0.062
Nulliparity	18 (51.4%)	17 (48.6%)	0.952
Gestational age at ultrasound assessment (week)	34 (2.6)	32 (7.6)	.565

Note: Data given as median (interquartile range); number, percentile (n, %). Abbreviations: RSI: Recovery SARS-CoV-2 Infection.

>50% was defined as severe disease. Presence of respiratory failure, septic shock, and/or multiple organ dysfunction was defined as critical disease.¹⁹ Echocardiographic and perinatal outcomes were compared between these subgroups.

Descriptive statistics including the mean, standard deviation or median, and minimum-maximum values for numerical measures were calculated for all patients. The normality of the variables was tested with both Shapiro – Wilk and Kolmogorov – Smirnov tests. Two groups were compared with The Student's *t*-test and Mann–Whitney U test. One Way ANOVA analysis (and post hoc test to compare groups in case of significant difference) and Kruskal Wallis test, Mann–Whitney U-test with Bonferroni correction were used to compare the groups. For categorical variables, a comparison of variables was performed by Pearson Chi-square test and Fisher's exact test. The alpha significance level of .05 was used to assess statistical significance. Statistical analysis was done with IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA).

3 | RESULTS

The demographic data of the study population was shown in Table 1 and the maternal baseline characteristics were similar in both groups ($p > .05$). In Table 2, the clinical points of SARS-CoV-2 infection were shown and the gestational age of the SARS-CoV-2 infection diagnosis was 20 (8–34). In the RSI group, 18 (37.5%) patient had mild disease, 20 (41.6%) patient had moderate disease, and 10 (20.8%) patient had severe disease. There was no critical patient in this group. Thirty (62.5%) of the study patients were hospitalized and 10 (20.8%) of them needed respiratory support. The echocardiographic findings were given in Table 3. All fetuses had normal cardiac morphology. The median value of ultrasound evaluation was 34 (2.6) weeks of gestation in the RSI group, and 32 (7.6) weeks in the control group ($p = .565$). LCO z score was found significantly lower in the RSI group than the control group ($p = .041$). Table 4 shows the relation between SARS-CoV-2 infection severity and fetal echocardiographic findings. LCO and CCO z scores were significantly lower in the severe disease group than mild disease, moderate disease, and control groups ($p = .019$ and $p = .013$). CCO (ml/min/kg) was found to be decreased in the severe disease group than mild disease and control groups ($p = .044$). Perina-

TABLE 2 Clinical characteristics of SARS-CoV-2 infection

Variables	Values
Gestational age at diagnosis (week)	20 (8–34)
Severity of disease	
Mild disease	18 (37.5%)
Moderate disease	20 (41.6%)
Severe disease	10 (20.8%)
Critically severe disease	-
Admission to hospital (n, %)	30 (62.5%)
ICU admission	-
COVID-19 therapy (n, %)	30 (62.5%)
Low molecular weight heparin (n, %)	28 (58.3%)
Lopinavir-ritonavir (n, %)	18 (37%)
Glucocorticoids (n, %)	21 (43.7%)
Respiratory support (n, %)	10 (20.8%)
Nasal oxygen therapy (n, %)	8 (16.6%)
Oxygen mask with reservoir bag (n, %)	2 (4.1%)

Note: Data given as median (interquartile range), max-min value, number, percentile (n, %).

Abbreviations: ICU, intensive care unit; RSI, Recovery SARS-CoV-2 Infection.

TABLE 3 Fetal echocardiographic findings in RSI and control groups

	Control (n = 50)	RSI (n = 48)	p-values
Heart rate	140 ± 12	136 ± 9	.248
Aortic annulus (cm)	5.5 ± .9	5.2 ± .9	.115
PA annulus (cm)	6.4 ± 1.2	6.1 ± 1.2	.087
Aortic VTI (cm)	.083 ± .015	.079 ± .015	.326
PA VTI (cm)	.082 ± .020	.097 ± .116	.849
LCO (ml/min)	285.1 ± 114.7	246.7 ± 109.0	.058
LCO z score	-.4 ± 1	-.8 ± .9	.041
RCO (ml/min)	395.0 ± 193.6	340.5 ± 137.5	.243
RCO z score	-.8 ± 1.3	-.13 ± 1	.121
CCO (mL/min)	681.0 ± 289.6	585.9 ± 225.5	.168
CCO z score	-.6 ± .8	-1.0 ± .6	.058
CCO (ml/min/kg)	352.6 ± 119.9	328.9 ± 108.3	.365
RCO/LCO ratio	1.37 ± .4	1.46 ± .5	.726

Note: Data given as mean ± SD.

Abbreviations: CCO, combined cardiac output; LCO, left cardiac output; PA, pulmonary artery; RCO: right cardiac output; VTI, velocity time integral.

tal outcomes were given in Table 5. Gestational age at birth and birth weight were significantly lower in the severe disease group compared to mild disease, moderate disease, and control groups ($p < .001$ and $p = .020$). Fetal distress, preterm delivery rate, and neonatal intensive care unit (NICU) admission were higher in the severe disease group than controls ($p = .010$, $p = .009$, and $p < .001$, respectively).

TABLE 4 SARS-CoV-2 infection severity and fetal echocardiographic findings

	Control (n = 50)	Mild infection (n = 18)	Moderate infection (n = 20)	Severe infection (n = 10)	p-value
LCO (ml/min)	282.2 ± 114.4	268.6 ± 102.4	248.1 ± 111.5	204.9 ± 114.5	.122
LCO z score	-.4 ± 1	-.6 ± .6	-.7 ± .8	-1.5 ± 1.3***	.019
RCO (ml/min)	385.6 ± 185.2	368.0 ± 147.7	320.9 ± 123.5	330.2 ± 151.2	.324
RCO z score	-.9 ± 1.2	-1.1 ± .7	-1.2 ± 1.3	-1.8 ± .9	.157
CCO (ml/min)	668.7 ± 280.8	637.0 ± 240.9	568.6 ± 208.5	528.7 ± 233.4	.230
CCO z score	-.7 ± .7	-.8 ± .4	-.9 ± .6	-1.5 ± .7***	.013
CCO (ml/min/kg)	361.3 ± 115.3	366.1 ± 105	331.3 ± 96.1	257.3 ± 111.9**	.044

Note: Data given as mean ± SD.

Abbreviations: CCO, combined cardiac output; LCO, left cardiac output; RCO, right cardiac output.

**Severe disease was significantly different with control and mild disease.

***Severe disease was significantly different with control, mild and moderate disease.

TABLE 5 Perinatal outcomes in mild, moderate, severe disease, and control groups

	Control (n = 50)	Mild infection (n = 18)	Moderate infection (n = 20)	Severe infection (n = 10)	p-value
Gestational age at birth (week)	37.3 ± 2.2	36.1 ± 4.5	37.2 ± 2.6	33.6 ± 4.3***	<.001
Birth weight (g)	3049 ± 474	3067 ± 651	3032 ± 405	2391 ± 719***	.020
Preterm delivery rate (n, %)	2 (4%)	3 (16.7%)	2 (10%)	4 (40%)*	0.009
Fetal growth retardation (n, %)	-	1 (5.6%)	1 (5%)	1 (10%)	.133
Fetal distress (n, %)	1 (2%)	1 (5.6%)	1 (5%)	3 (30%)*	.010
1st minApgar <7	2 (4%)	2 (11.1%)	3 (15%)	3 (30%)	.075
5st min Apgar <7	-	-	1 (5%)	1 (10%)	.125
Hospitalization in NICU (n, %)	2 (4%)	2 (11.1%)	4 (20%)	6 (60%)*	<.001

Note: Data given as median (interquartile range); number, percentile (n, %).

Abbreviations: C/S, cesarian section; NICU, Neonatal intensive care unit.

*Severe disease was significantly different with control.

***Severe disease was significantly different with control, mild, and moderate disease.

4 | DISCUSSION

In this study, we found low LCO z scores in the RSI group than the controls. Also, LCO and CCO z scores were found to be lower in the severe disease group when we divided the RSI group according to the disease severity. Additionally, adverse pregnancy outcomes including fetal distress, preterm delivery rate, and NICU admission were increased in the severe disease group.

The SARS-CoV-2 infection causes an excessive inflammatory response with the release of a large number of proinflammatory cytokines.^{20,21} Placental injury and deterioration of fetomaternal perfusion is triggered by inflammation and this have been shown in literature before.^{20,22} Furthermore, this proinflammatory event might affect fetal renin-angiotensin system (RAS) that regulates the uteroplacental blood flow by balancing vasodilator and vasoconstrictive pathways.²³ Down-regulation of RAS also leads to impaired uteroplacental blood flow and might be associated with fetal decompensation and adverse

pregnancy outcomes. The presence of SARS-CoV-2 mRNA or virions on amniotic fluid, placenta, and cord blood could be confirm direct effect of SARS-CoV-2 with vertical transmission.²⁴ However, systematic review and meta-analysis of the available data provide no conclusive evidence of vertical transmission of SARS-CoV-2 to date.^{25,26} In addition, in a study that investigate fetal tissues and their ACE-2 receptors, reported that fetal heart tissue does not express ACE-2 receptors which is a gate for SARS-CoV-2 to the cell entrance.²⁷ Therefore, fetal heart seems not to be an exact target for SARS-CoV-2. These results support that possible cardiac functional changes are more likely to be a result of maternal effects of SARS-CoV-2 rather than a direct fetal effect of virus.

In the literature, there are few Doppler and echocardiographic studies evaluating the effects of SARS-CoV-2 infection on fetal circulation.²⁸⁻³⁰ Rizzo et al. assessed the fetal growth velocity and fetal hemodynamics with pulsatility index of uterine, umbilical, and middle cerebral arteries Doppler in pregnancies complicated and in those not

complicated by SARS-CoV-2 infection.²⁸ They found that pregnancies complicated by SARS-CoV-2 infection are not at higher risk of developing fetal growth restriction through impaired placental function.²⁸ Ayhan et al. evaluated the effect of SARS-CoV-2 on fetal Doppler parameters in patients who tested positive were hospitalized for mild or moderate disease.²⁹ They found that SARS-CoV-2 infection seems to have no effect on Doppler parameters.²⁹ However, there were no severe or critical cases both of these studies. Rizzo et al. also evaluated 54 pregnancies complicated and 108 not complicated by SARS-CoV-2 infection to explore whether SARS-CoV-2 can affect umbilical vein blood flow (UVBF) and fetal cardiac function.³⁰ The areas of atria and the sphericity index of both ventricles were selected among functional indices for assessing cardiac function in their study.³⁰ They found that there was no difference in fetal cardiac function, suggesting that SARS-CoV-2 infection in pregnancy is unlikely to affect fetal venous and cardiac hemodynamic.³⁰ However, they included only mild disease of SARS-CoV-2 infection, none of them required hospitalization and they point out that further studies are needed to elucidate the influence of SARS-CoV-2 infection on fetal cardiac function by the severe spectrum of the disease.³⁰ In present study, we evaluated fetal cardiac output in pregnant women who recovered from SARS-Cov-2 infection and unlike other studies, we were able to evaluate hemodynamic changes in fetal circulation by measuring cardiac output. Also, we detected negative changes only in the severe disease group. The lack of severe disease group in previous studies may be the main reason why they did not find a significant difference in their evaluations.

The potential effects of SARS-CoV infection to the prenatal CO have not been previously studied. In fact, fetal cardiac output has been evaluated in several studies in obstetric conditions associated with cardiac dysfunction, such as hydrops fetalis, FGR, twin to twin transfusion syndrome (TTTS), and diabetes mellitus (DM).⁹⁻¹³ It has been observed that direct calculation of cardiac output could give valuable information for heart failure and is potentially useful in the assessment of fetal well-being.³¹

Cardiac output is dependent on preload (circulatory volume), afterload (circulatory resistance), and myocardial contractility.³² Fetal teratoma, placental chorioangioma, and fetal anemia are known to be associated with high fetal CO as a result of increased preload.^{11,33,34} Rizzo et al. found that left CO increases in FGR fetuses probably due to cerebral vasodilatation and consequently decreased cardiac afterload.³⁵ In our study, a decrease in the left CO z score in the RSI group was observed. In addition, we found a significantly lower left CO z score in the severe disease group than in the other groups. Our findings were explained by either decreased preload or increased afterload, or a combination of both. This result seems to be associated with effect of SARS-CoV-2 infection-related inflammation on fetal circulation.¹⁰ When RSI patients were grouped according to disease severity, CCO and z scores decreased significantly in the severe disease group. It has been shown in previous studies that inflammatory cytokine release is associated with disease severity.^{36,37} The fact that the decrease in CCO could not be detected in the general RSI group while it was only observed in the severe disease group might be related to this excessive inflammatory response in severe group. Also, when

we observed adverse pregnancy outcomes including preterm delivery, fetal distress, NICU admission were significantly higher in severe disease group than the control group. Decreasing fetal cardiac output may have contributed to these adverse pregnancy outcomes.

CO was found to be significantly associated with advancing gestational age and estimated fetal weight (EFW).¹⁶ Pilania et al. found that CO is higher in fetuses of diabetic mothers, but they did not adjust the CO for EFW.¹³ On the contrary, Winter et al. observed a decrease fetal CO in diabetic mother's fetuses when they include fetal EFW to the calculation and they suggest EFW-corrected CO's are valuable for accurate assessment of fetal cardiac function than CO (ml/min) alone.⁹ In our study, CCO (ml/min) measurement without including fetal weight was found similar between all mild, moderate, severe, and control groups. On the other hand, fetal weight-normalized CCO (ml/min/kg) and CCO z score were found to be significantly lower in the severe disease group compared to the control and mild disease groups. This result highlights the importance of standardization according to fetal weight and z scores. Non-normalized cardiac morphological measurements and flow measurements in the growing fetus do not appear to be as significant as Z scores.

The main strength of the study is its novelty, prospective design and evaluation of subgroups according to disease severity. On the other hand, relatively few cases especially in the severe disease group are the main limitation. The other limitation of study was that researchers who performed echo and assessed cardiac function were not blinded to the condition of the women studied.

5 | CONCLUSION

In conclusion, SARS-CoV-2 infections have been conducted on fetal adverse effects.^{3,4,6} The negative impact on placental tissues and fetal organs has been observed.^{38,39} In the present study, we showed a decrease in fetal cardiac output, especially in severe diseases, and this is the first study in the literature to evaluate fetal CO in pregnant women recovering from SARS-CoV-2 infection on this view of point. Further studies are needed to clarify the impact of SARS-CoV-2 infection on fetal cardiac function.

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