Post-COVID-19 fetal cardiac evaluation in moderate infection group of pregnant women

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Abstract

**Purpose:** To determine the long-term fetal cardiac effects of the SARS-CoV-2 infection in pregnant women recovered from moderate COVID-19 with fetal echocardiography (ECHO).

**Methods:** Forty-five pregnant women that recovered from moderate COVID-19 (CRG) 4 weeks after the infection confirmation, were compared with 45 gestational and maternal age-matched control groups (CG) in terms of demographic features fetal cardiac morphological (sphericity index, cardiothoracic ratio), and functional (myocardial performance index, mitral E/A, tricuspid E/A, mitral and tricuspid annular plane systolic excursion) parameters.

**Results:** There was no difference in demographic features between the groups. Fetal cardiac morphologic parameters were found to be similar between the two groups. When the fetal cardiac functional assessment of the two groups was compared, only mitral E/A ratio results were found to be statistically significantly lower in the CRG than in the control group (p = 0.030).

**Conclusion:** The fetal heart does not seem to be negatively affected by COVID-19 after recovery from moderate infection. These results about the fetal effect of SARS-CoV-2 may improve our limited knowledge of the utility of fetal ECHO in pregnant women who recovered from COVID-19.

**KEYWORDS**

COVID-19, fetal cardiac function, fetal echocardiography, post-COVID, pregnant women

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is causing the current 2019 novel coronavirus disease (COVID-19) pandemic and remains challenging for clinicians for both acute and post-infection effects. Pregnant women are designated as a high-risk group for severe infection and increased risk of obstetric complications like preterm labor, intrauterine growth restriction (IUGR), and stillbirth. Hyperimmune response, hyper coagulopathy and hypoxia are well-known effects of SARS-CoV-2 and might be the reasons for the negative consequences of pregnancy. Post-COVID manifestations of COVID-19 survivors have attracted attention recently in different populations, such as children. For example, multisystem inflammatory syndrome in children (MIS-C) is a new phenomenon and is defined as post-infectious inflammatory vasculopathy and myocarditis in children following COVID-19. This condition is related to a hyper-immune response rather than an unremitting infection. In addition, Centers for Disease Control and Prevention (CDC) released a case definition report for MIS-C and, concluded COVID-19 exposure within 4 weeks prior to the onset of the symptoms for diagnosis.
Since the start of the pandemic, COVID-19 still is a mystery regarding its fetal effects. To date, there is no evidence to prove vertical transmission, but we know that the fetus is affected by the disease during both the acute and post-infection periods. We hypothesized that fetal cardiac morphology and functions might be influenced negatively in pregnant women after recovering from COVID-19.

In this study, we aimed to evaluate the long-term effects of the SARS-CoV-2 infection on the fetal heart with fetal echocardiography (ECHO).

2 | MATERIALS AND METHODS

This prospective study was conducted in..., between January 15, 2021 and June 15, 2021 with pregnant women hospitalized for moderate COVID-19 infection according to World Health Organization COVID-19 Clinical Management: living guidance (2021 and June 15, 2021 with pregnant women hospitalized for COVID-19 infection confirmation. The ECHO examinations were performed between 30 and 36 gestational weeks by the same experienced maternal-fetal medicine specialists using software of GE Voluson E8 Ultrasound machine C 2-9 convex probe (3–9 MHz). To avoid orthostatic hypotension, examinations were performed in the semi-Fowler position.

For fetal cardiac morphology, sonographic two-dimensional imaging was performed at the end-diastolic period of the cardiac cycle, and the ventricular chambers and valve dimensions were measured. Both the left and right ventricular sphericity index (SI) were calculated by dividing the longitudinal diameter (from the base-to-apex diameter) by the transverse diameter (from the septal to the lateral atrioventricular valve annulus). The four-chamber view was used for cardiothoracic ratio (CTR) (cardiac area/thoracic area), right and left ventricle free wall thickness, septum thickness, and right and left ventricular end-diastolic dimensions (EDD) measurements. The myocardial performance index (MPI) was used for systolic and diastolic function evaluation. The MPI was obtained in an apical four chamber view by including both aortic and mitral flows. The Doppler sample gate was set 3–4 cm, and the intonation angle was less than 15°. The wall motion filter was calibrated to 300 Hz and the Doppler sweep velocity was 5 cm/s. The MPI was calculated as follows: isovolumetric contraction time (IVCT) + isovolumetric relaxation time (IVRT)/ejection time (ET) (Figure 1).

Diastolic function was evaluated with both mitral and tricuspid maximum early ventricular filling (E) wave velocity (m/s), maximum active atrial filling (A) wave velocity (m/s), E/A ratio (Figure 2). E and A wave measurements were obtained in an apical four-chamber view under the atrioventricular valve. The systolic function was evaluated by measuring MPI, mitral and tricuspid annular plane systolic excursion (MAPSE and TAPSE), and the pulmonary and aortic artery peak velocities (Figure 3). MAPSE and TAPSE measurements were performed with M-mode imaging on the free walls. The cursor was replaced vertical to the atrioventricular junction in the four-chamber view (Figure 4).

Statistical analysis was performed using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY). Descriptive statistics were given as mean ± standard deviation (SD) for numerical data with normal distribution or median and minimum and 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. The groups were compared with the Student’s t-test.
FIGURE 2  Tricuspid maximum early ventricular filling (E) wave velocity (m/s), maximum active atrial filling (A) wave velocity (m/s). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve

FIGURE 3  Aortic peak velocity. LVOT, left ventricular outflow

FIGURE 4  Mitral annular plane systolic excursion (MAPSE). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle
In our study, only mitral E/A were found to be reported cardiac systolic and diastolic dysfunction in ECHO. Fetal cardiac functional parameters provide a comparison of fetal cardiac functional and morphological parameters of the CR-G and the controls 4 weeks after the infection confirmation. The bold value in the table was only statistically significant value (p < 0.05). (p = 0.030). Table 4 provides a comparison of fetal cardiac functional parameters.

### 4 | DISCUSSION

The heart is an exact target for SARS-CoV-2 in different groups and in both acute and post-recovery periods.7,13 SARS-CoV-2 has a potential effect for post-infection myocarditis due to a hyperimmune response to the viral genomic materials, even after full recovery from an acute infection.7 However, to date, there are no available data about the fetal cardiac effects of the COVID-19. In the present study, we did not find a major difference about the fetal cardiac functional and morphological parameters of the CRG and the controls 4 weeks after the infection confirmation.

Increased fetal MPI has been demonstrate to be a reliable parameter for impaired fetal cardiac function in high-risk pregnancies like IUGR, maternal diabetes mellitus, and polyhydramnios.16-18 Inter-calarly, aortic and pulmonary peak systolic flow velocities, TAPSE, and MAPSE were used to evaluate cardiac systolic function before.19 In this study, there was no difference between the groups in terms of systolic function and MPI.

MIS-C is characterized by a hyperinflammatory syndrome with multi-organ dysfunction, including heart, due to COVID-19 in children.20 This situation is a late reaction rather than an acute response to the virus, and symptoms generally occur within a 4-week period8 and, clinically severe illness was not necessary to develop MIS-C, some children were asymptomatic for SARS-CoV-2.21 Matsubara et al.25 reported cardiac systolic and diastolic dysfunction in ECHO examinations of patients diagnosed MIS-C. Their results also showed a greater degree of left ventricular dysfunction in the MIS-C group. Another study was pointed particularly depressed LV function in patients with MIS-C.23 In our study, only mitral E/A were found to be statistically significantly lower in the CRG than in the control group, and Mann–Whitney U test. A type-1 error below 0.05 was considered statistically significant.

### 3 | RESULTS

The COVID-19 recovered group (CRG) (n = 45) and control group (CR) (n = 45) were homogenous, and there were no significant differences in the demographic data (Table 1). Clinical features of CRG were given in Table 2. Fetal cardiac morphologic parameters were found to be similar between the two groups (Table 3). When the fetal cardiac functional assessment of the two groups were compared, only mitral E/A ratio results were found to be statistically significantly lower in the CRG than in the control group.
significantly lower in CRG than CR, which is consistent with left ventricular diastolic dysfunction. However, we did not find any difference in the MPI that also evaluated diastolic function or in systolic functional parameters. Mitral E/A might be inclined to be affected earlier than other parameters and these conflicting results could reflect different stages of diastolic dysfunction.

Fetal heart is one of the main organs in adaptation to hypoxia and placental insufficiency. Oxygen deprivation displays circulatory changes to preserve vital organs (heart, brain, and kidney) and as a result of cardiac remodeling, globular heart morphology has been detected in IUGR fetus’s due chronic hypoxia using CTR and SI. Cohen et al. reported lower left ventricular wall thickness in infants born with IUGR. Similarly, lower SI values were found in fetuses with an estimated fetal weight <10th centile, regardless of their umbilical artery Doppler and cerebroplacental ratio measurements. We did not find any cardiac morphological changes in the CRG when compared the CG. This result may be related to the fact that cardiac functional parameters were not affected by SARS-CoV-2 and severe hypoxia was not observed in the study group. In addition, Faure-Bardon et al. reported that fetal heart tissue does not express ACE2 receptors, which is a gate for SARS-CoV-2 to the cell entrance and will not be a target for the SARS-CoV-2, that might be an explanation for the findings of this study.

After all this time, the pathophysiology of fetal complications from COVID-19 remains enigmatic, and vertical transmission has not yet been clearly confirmed. However maternal viral infection does not demand to bypass the placenta to affect fetal development and, might be connected with poor perinatal outcome. Recent data showed that during the acute phase of the COVID-19, fetal circulation is preserved, while some negative alterations were detected after recovery. Similarly, post-COVID manifestations become more challenging in different population age groups. Myocardial dysfunction is one of the leading causes of deaths from COVID-19 and can emerge even after full recovery from the infection. Although, there is a report in the literature with autopsy findings and there was evidence of myocarditis, endocarditis and, pericarditis typifies by inflammatory cell infiltration in fatal MIS-C cases. The importance of fetal heart evaluation in SARS-CoV-2 infected patients was highlighted in recent review. At this point, we believed that fetal cardiac function and morphology might be impaired in pregnant women who survived COVID-19. However, despite our expectations, we could not find any difference between the CRG and the control group. These results should be clarified by further studies that will evaluate fetal heart longitudinally from the COVID-19 infection to the delivery additionally new-born ECHO examination.

The main strengths of the present study were its novelty, prospective design, and high number of study parameters. The main limitations were the relatively low number of subjects, a lack of information related to the long-term outcomes of the fetuses, and the absence of severe infection category patients in participants.

In conclusion, the fetal heart does not seem to be negatively affected by moderate COVID-19 after recovery. To date, this is the first study evaluating this fetal effect of SARS-CoV-2 in the literature and these specific findings may improve our limited knowledge of the utility of fetal ECHO in pregnant women who recovered from COVID-19. Further studies with larger numbers of patients with long-term follow-up are necessary to confirm the results reported here.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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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