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THE INFLUENCE OF MATERNAL COVID-19 ON CARDIAC FUNCTIONS: FROM FETAL LIFE TO INFANCY

Yasemin ÖZDEMİR ŞAHAN[1], Bedri Sakcak[1], Sule Goncu Ayhan[2], Atakan Tanacan[1], Ayse Kibar[1], Dilek Sahin[1], and İlker Çetin[1]

[1]Ankara Sehir Hastanesi
[2]Memorial Sisli Hastanesi

June 8, 2023

Abstract

Objective: To evaluate both short and mid-term effects of maternal COVID-19 on cardiac functions of fetuses and children. **Methods:** The present case-control study was conducted on 36 pregnant women who had COVID-19 infection in the second trimester of pregnancy and 30 pregnant women as healthy controls. Fetal, neonatal and infant cardiac functions were compared between the groups. Assessment of fetal cardiac functions were performed in the last trimester of the pregnancy at least 6 weeks after the recovery of infection. The first postnatal echo was performed within the first two weeks and the follow-up (second) echo was performed in the 6-8 weeks of life. **Results:** The demografic data were similar between groups. Interventricular septum and left ventricular posterior wall end-diastolic dimensions were significantly higher in the study group in both fetal, neonatal and infant periods. Impaired diastolic functions of right and left ventricles were detected and myocardial performance indexes with tissue doppler imaging of both lateral walls and septum were significantly higher than controls at all periods. **Conclusion:** Maternal COVID-19 seems to have a global impact on cardiac functions of babies in the short and mid-term periods after maternal recovery.

TITLE

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AUTHORS

Yasemin ÖZDEMİR ŞAHAN[1], Bedri SAKCAK[2], Şule GÖNCÜ AYHAN[3], Atakan TANAÇAN[2], Ayşe Esin KİBAR GÜL[1], Dilek ŞAHİN[2], İbrahim İlker ÇETİN[1]

[1] Department of Pediatric Cardiology, Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkiye

[2] Department of Obstetrics and Gynecology, Division of Perinatology, Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkiye

[3] Department of Obstetrics and Gynecology, Division of Perinatology, Bahcelievler Hospital, İstanbul, Turkiye

CORRESPONDENCE

Yasemin ÖZDEMİR ŞAHAN, Department of Pediatric Cardiology, Turkish Ministry of Health, Ankara City Hospital, 1604th Street, No: 9, Cankaya/Ankara, 06800, Turkiye

Tel: +905062915824 e-mail:*dr.yaseminozdemir@gmail.com*,

ORCID: 0000-0003-4219-9532

ABSTRACT

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Methods: The present case-control study was conducted on 36 pregnant women who had COVID-19 infection in the second trimester of pregnancy and 30 pregnant women as healthy controls. Fetal, neonatal and infant cardiac functions were compared between the groups. Assessment of fetal cardiac functions were performed in the last trimester of the pregnancy at least 6 weeks after the recovery of infection. The first postnatal echo was performed within the first two weeks and the follow-up (second) echo was performed in the 6-8 weeks of life.

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KEY WORDS: maternal COVID-19, cardiac function, miyocardial performance index, fetal, infant, echocardiography.

INTRODUCTION :

Pregnant women with COVID-19 are at greater risk for pregnancy complications like preterm delivery and fetal distress. Their newborns are more likely to be admitted to the neonatal ICU [1,4]. SARS-CoV-2 related excessive inflammation, coagulation disorders and hypoxemia may cause placental insufficiency leading to adverse perinatal outcomes and fetal mortality [5].

COVID-19 infection in neonates and children showed mild symptoms and better outcomes compared to adults. But cardiovascular involvement of the SARS-CoV-2 virus and multisystem inflammatory syndrome in neonates and children (MIS-N, MIS-C) seems to be crucial and life-threatening [6,7]. Although, there are some studies in the literature evaluating the effect of COVID-19 on fetal and neonatal cardiac functions, the evidence of long-term cardiovascular outcome of COVID-19 infection and/or MIS-N is scant [8,9]. We aimed to investigate the short and mid-term influence of maternal mild to moderate COVID-19 infection on cardiac functions of fetus, neonate and infant.

MATERIAL AND METHODS:

Study Population:

This prospective case-control study was conducted between March 2022 and November 2022 at the Perinatology Clinic of the Obstetrics and Gynecology Department and Pediatric Cardiology Department of Ministry of Health Ankara City Hospital. The study was designed in accordance with the principles of the Declaration of Helsinki and approved by the Turkish Ministry of Health and Human Ethics Committee of the hospital (date: 02/02/2022, number: E2-22-1277). Written informed consent was obtained from all the participants.

Inclusion Criteria:

Thirty six healty pregnant women who had COVID-19 infection with mild to moderate symptoms according to The National Institutes of Health (NIH) classification in the second trimester of pregnancy were included in the patient group (COVID group)[10,11]. Infection was confirmed with a reverse transcription-polymerase chain reaction (RT-PCR) test with nasopharyngeal swab in all patients and none of them hospitalized. Six

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weeks after recovery, fetal echocardiogram performed. During the same period, thirty gestational and maternal age-matched unvaccinated pregnant women monitored for routine prenatal care who had no history or symptoms of COVID-19 infection included in control group (CONTROL group). Pregnant women with chronic systemic diseases (diabetes mellitus, hypertension, chronic renal failure), gestational diabetes, smokers, and those with fetal anomalies, fetal growth restriction, multifetal pregnancy were excluded the study. On the postnatal period, pregnancies complicated by preterm delivery before 37^{th} week and neonatal intensive care unit admission (NICU) were not included. The patients' descriptive data were recorded. Seven participants were excluded from the study due to preterm birth (One delivered at 33^{th}, four delivered at 35^{th}, 2 delivered at 36^{th} GW), 3 participants were excluded from the study due to the NICU admission for respiratory distress although they were term born. The participants who met the study criteria but did not continue postnatal follow-up excluded from study data (8 patients and 5 controls). The first postnatal echo was performed within the first two weeks, after 4^{th}day of life for ductus closure. The follow-up (second) echo was performed at 6-8 weeks of life for the pulmonary pressure to return to normal.

Fetal Echocardiography:

Measurements were performed using the Voluson S10 (GE Medical Systems) ultrasonography device with a 3.5 MHz convex transducer (6C1-PVT-375BT) transabdominal probe by the same experienced maternal fetal medicine specialist. To avoid variations, the three clearest waveforms with the normal range of fetal heart rate were obtained and averaged. The two-dimensional (2D) and M-mode imaging of apical four-chamber and parasternal long axis view at the end-diastol was used for fetal heart rate (FHR), left ventricle posterior wall thickness (LVPWd), septum thickness (IVSd), right and left ventricular end-diastolic dimensions (RVEDD, LVEDD), mitral and tricuspid annular plane systolic excursion (MAPSE, TAPSE) measurements. Mitral and tricuspid peak early ventricular filling (E) wave velocity, maximum active atrial filling (A) wave velocity (cm/s) E wave deceleration time (msn) of mitral and tricuspid valve (MEDT, TEDT), max peak velocity of aortic (AV) and pulmonary valves (PV) obtained from pulsed wave doppler imaging (PW). Tissue doppler imaging (TDI) measurements were performed on the basal septum and on the lateral walls of right and left ventricle. TDI parameters the maximal systolic myocardial velocity (S_m), early and late diastolic myocardial velocities (E_m, A_m waves), isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET) of the walls are measured. Myocardial performance index (MPI, Tei index) was calculated according to the formula (IVCT+IVRT)/ET).

Conventional Transthoracic Echocardiography:

A ultrasound system (iE33, Philips, The Netherlands, Eindhoven), equipped with a broadband S8-3(8-3 MHz) Sector Array transducer was used to obtain images. Postnatal first and second echo were performed when baby is asleep or at rest. 2D, M-mode, PW doppler and TDI measurements described above were applied in accordance with the guidelines of the American Society of Echocardiography [12,13]. Left ventricular mass (LVM) measurements were normalised to body surface area (BSA) as indexed LVM index (LVMi) as using the equation $(0.8\{1.04[([LVDD+IVSd+LVPWd]^3\text{-}LVDD^3)]\}+0.6)/BSA$.

Statistical analysis

Before the study, power analysis was performed using the G*power program 3.1.9.4 version. Power analysis revealed that 17 patients should be included in both groups at the 0.363 effect size with α:0.05, and 80% power [14]. The data of the study were analyzed by SPSS 25.0 (IBM, USA). The findings of the study are expressed as frequency and percentages. Normality analysis was carried out using the Kolmogorov-Smirnov test. The variables without normal distribution are presented as the median and interquartile range (IQR) with 25-75th percentiles. Categorical variables were compared with the Chi-square test. Numerical variables with and without normal distribution were compared using the independent samples t-test and Mann-Whitney U. Postnatal echocardiography findings of the first and control measurements were compared with the paired samples t-test. Spearman correlation analysis was used to determine possible correlations. $p < 0.05$ was accepted for statistical significance value.

RESULTS:

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The maternal characteristics of the groups were similar (p >0.05, Table 1). The median gestational week at COVID-19 diagnosis is 24 (23-26.75) weeks. The mean duration time between COVID-19 infection and fetal echocardiography is 7.97±1.84 weeks.

Fetal cardiac findings:

End-diastolic diameters of ventricles, FHR, E and A wave velocities of mitral and tricuspid valves, MAPSE-TAPSE values, IVCT of both three segments were similar between groups as presented in the Table 2. IVSd and LVPWd significantly higher in COVID group (p <0.001,p =0.007 respectively).

Myocardial velocities of both three segments by TDI (S_m, E_m, A_m) and IVRT of lateral walls were found significantly higher and E/A, E_m/A_m, E/E_m ratios of both mitral and tricuspid valves were significantly lower, mitral and tricuspid E wave DT measurements were significantly higher in COVID group as an indicator of impaired diastolic function (Table 2). MPI values of both segments calculated significantly higher on COVID group as an important marker of global ventricular dysfunction (p <0.001 for LV and RV lateral walls; p =0.009 for bazal septum). Aortic insufficiency (mild) was observed in 3 fetuses, tricuspid insufficiency (mild) observed in 1 fetus, 3 of which regressed on the follow-up. Anatomy of valves were normal.

Neonatal and infant cardiac findings:

Clinical characteristics of groups at the postnatal period are noted in the Table 3. Neonates were similar for demografic features. IVSd and LVPWd values remained higher on postnatal first and follow-up echoes. Both LV mass and LV mass index calculated significantly higher on COVID group (p <0.001). E/A ratio of mitral and tricuspid and E_m/A_m ratios of both segments of first and follow-up echoes were significantly lower, IVRT of both segments were significantly higher of all periods as an indicator of diastolic dysfunction similar to fetal period (Table 4,5). However, mitral E/E_m values of both postnatal echoes were not differed statistically but tricuspid E/E_m value of follow-up echo remained statistically higher in COVID group (p <0.01).

On the infant period, MAPSE, TAPSE values do not differ significantly but LVEF (p< 0.01), LVSF (p <0.001), ET of septum (p =0.031) and RV lateral wall (p <0.01) were measured significantly lower and IVCT of RV is higher on COVID group as an indicator for systolic dysfunction (Table 4,5). MPI of both segments were significantly higher on postnatal first and second echoes.

Correlation analysis of mitral and tricuspid E and $E_m$values for postnatal second echo in the COVID-19 group showed a strong correlation of mitral E and LV MPI (Rho=,609; p <0.001). There is a moderate positive correlation between tricuspid E and LVEDD (Rho=,398; p =0.016), a strong positive correlation between tricuspid E and LV mass (Rho=,586; p <0.001), moderate positive correlation between tricuspid E and LVMi (Rho=,403;p =0.015).

DISCUSSION:

Main Findings

LV lateral wall and septal thickening, reduced biventricular diastolic functions in both fetal, neonatal and infant periods, and impaired left ventricular systolic functions in infant period were found in the COVID group compared with controls. Most of the cases reported in the literature focused specifically on maternal outcomes and possible vertical transmission, but less attention was paid to the fetus as the patient in such pregnancies [3,4].

The cardiovascular system is usually the main target of COVID-19 infection and post-infection hyperimmune response with myocarditis and systemic vasculitis [15,16]. In keeping with this, MIS-N/MIS-C is considered to be a multifactorial disease with an unknown pathophysiology. The most widely accepted mechanism is the postinfectious immune response to SARS-CoV-2 antibodies that initiate a cascade of inflammation and multi-organ involvement [17]. Pawar et al. were the first to distinguish early MIS-N with a case-series of neonates. Eighteen of twenty neonates (90%) had cardiac involvement with prolonged QTc, 2:1 AV block, cardiogenic shock, or coronary dilatation [7]. Shaiba et al. presented a systematic review of 47 neonates and 77% of which

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had cardiovascular compromise (arrhythmias, dilated coronaries/aneurysm, pericardial effusion, persistent pulmonary hypertension, intracardiac thrombus)[18]. De Rose et al. had investigated clinical features of MIS-N and MIS-C under six months of age and they demonstrated that cardiovascular dysfunction and respiratory distress are the prevalent findings both in neonates with MIS-N and in neonates/infants with MIS-C differently from older children with MIS-C. Moreover, cardiovascular dysfunction was the relevant pathology of disease mortality [19]. However influence of maternal COVID-19 to fetal and infant heart without clinical presentation of MIS-N is still uncertain. In our present study, we focused to evaluate the effects of maternal COVID-19 on cardiac features and functions of these delicate patients. Mainly our study mentioned diastolic dysfunction and persistent wall thickness in the foreground. These findings may be due to pancarditis caused by inflammatory environment of maternal COVID-19 infection.

Structural Findings

Rizzo et al. found no difference in umblical vein blood flow, atrial area, ventricular sphericity indices (VSİ) between pregnancies complicated by SARS-CoV-2 infection during second half of pregnancy compared to those not complicated by infection [20]. Fetal cardiac morphological parameters (VSİ, İVS and lateral wall thicknesses) were found to be similar between group of pregnancies who were after recovery of COVID-19 and non-COVID group by Goncu et al. [21]. In our study, we found significantly higher LVPW and IVS thicknesses in all periods. In keeping with this, LV mass and LVMi were significantly higher in postnatal echoes like fetuses and infants born to gestational diabetic mothers [22, 23]. These structural changes were significantly correlated with tricuspid E wave which demonstrates passive phase of ventricular filling. This may be due to decreased ventricular compliance associated with the increase in septum and posterior wall thickness, like cardiac findings of infants of diabetic mothers. This thickening may be due to myocarditis in the inflammatory process.

Diastolic Parameters

Diastolic dysfunction is characterized by decreased E/A, E_m/A_m, E/E_m ratio, prolonged E DT, and prolonged IVRT [12]. MPI is the ratio of time interval that is proved to be reliable method for the evaluation of both systolic and diastolic functions, not depending volume and pressure conditions of ventricles, and high heart rate [13]. Goncu et al. found mitral E/A ratio significantly lower in pregnant women that recovered moderate COVID-19 infection [21]. Similarly, we found both mitral and tricuspid E/A ratios, in addition E_m, E_m/A_m values of COVID-19 group significantly lower both in prenatal and postnatal period. MEDT, TEDT, IVRT of LV and RV lateral walls were significantly longer in fetal period. IVRT of all segments were significantly prolonged in postnatal echoes. These findings demonstrate that diastolic dysfunction of both ventricles, which started with wall thickening in post-COVID fetal life, continues in the infancy. These findings may be the long-term negative effects of the maternal COVID-19.

Placental SARS-CoV-2 infection can lead to massive local inflammation with the formation of fibrin deposits, thus, fetal and subsequent neonatal distress due to placental dysfunction caused by placental immunological findings and inflammation may transiently have a clinical course resembling the fetal presentation of SARS-CoV-2-associated MIS-N [5]. Although the hyperinflammatory response developing in the neonatal period with perinatal asphyxia is associated with enlargement of the coronary arteries, severe myocardial dysfunction and left ventricular dilatation, it has thought to be related with neonatal myocarditis [24].

Gestational/pregestational diabetes mellitus has been used as a model of fetal diastolic dysfunction due to myocardial hypertrophy and the consequent reduction of ventricular compliance. In this respect, as a result of an increased myocardial mass and left ventricular hypertrophy, fetuses of diabetic mothers may have a higher preload than normal controls. Significantly lower E/E_m ratios were observed in both atrioventricular valves in fetuses of diabetic mothers when compared to control fetuses. This is the result of higher myocardial velocities at the mitral and tricuspid annuluses, rather than because of changes in early atrioventricular diastolic flows. In the fetus, the impaired ventricular diastolic function as a result of decreased relaxation and compliance occurring in maternal diabetes seems to prompt higher myocardial velocities in the atrioventricular annuluses, in order to counter the limited ventricular distensibility in early diastole [22]. Similar to this hypothesis,

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myocardial velocities of three segments were found to be significantly higher, mitral and tricuspid E/E_m ratios were significantly lower in the fetal period in our study. These findings did not persist postnatally except E_m. Because of persisting wall thickening and decreased compliance, E_m remained significantly low on the postnatal long-term.

Systolic Parameters

The systolic dysfunction results in a prolongation of IVCT by TDI with preserved EF/SF [13]. In our study we did not find significant difference in the values of MAPSE, TAPSE, LVEF, LVSF, which are systolic parameters, between groups in fetal and neonatal periods. However, IVCT values of RV TDI of neonatal and infant period were significantly higher. But LVEF, LVSF are significantly lower in infant period at normal range. Impaired ventricular compliance and persisting myocardial dysfunction with hypertrophy may repress the LV systolic functions on the long term.

LIMITATIONS AND STRENGHT

The limitation of our study is the lack of evaluation of cardiac functions of these fetuses by more recent further imaging techniques like strain echocardiography and lack of long-term results of these babies.

CONCLUSION

Maternal COVID-19 seems to have both morphological and functional effects on the fetal, neonatal and infant heart. To date, this is the first case-control, longitudinal study evaluating the comprehensive effect of maternal COVID-19 disease on cardiac functions of the fetuses and infants.

AUTHOR CONTRIBUTIONS YÖŞ prepared and wrote the original draft, analysis, interpretation and contributed to data collection. BS contributed to data collection, ŞGA contributed to data collection and literatüre search. AEKG performed the literature search and was responsible for conceptualization, methodology. AT performed the project development. İİÇ and DS were responsible for visualization, and reviewing and editing.

ACKNOWLEDGMENT Special thanks to all healthcare staff who works very hard to improve the health standards of the pregnant women, newborns and children during pandemic period.

CONFLICT OF INTEREST The authors declare no conflict of interest.

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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TABLES:

Table 1: Maternal characteristics of the study groups

	COVID (n=36)	**CONTROL (n=30)**	p
Age of the mother (year) (mean±SD)	30.00±5.17	28.43±4.65	0.205
BMI (kg/m^2)	29.25±4.34	29.00±4.80	0.822
Gravidity (median (IQR))	2(1-4)	2(1-3)	0.730
Parity	1(0-2)	1(0-2)	0.666
Fetal echocardiography time (week) (mean±SD)	31.86±2.07	31.73±2.46	0.820

Abbreviations: ***BMI:*** *Body mass index,* ***SD****: standard deviation,* ***IQR****: Interquartile range (25-75)*

Table 2: Fetal echocardiography findings of the groups

	COVID group (n=36)	**CONTROL group (n=30)**	p
2D/M-mode			
FHR (beats/s)	134.64±5.77	135.83±6.99	0.450
IVSd (mm)	4.35±0.70	3.42±0.59	**<0.001**
LVPWd (mm)	4.27±0.90	3.69±0.76	**0.007**
LVEDD (mm)	9.03±1.63	9.12±1.72	0.830
RVEDD (mm)	10.16±1.88	9.55±1.24	0.120
MAPSE (mm)	7.54±1.12	7.37±0.98	0.508
TAPSE (mm)	8.27±0.97	8.10±1.06	0.498
PWD			
Mitral E (cm/s)	29.26±7.98	33.29±9.99	0.081
A (cm/s)	39.33±9.03	42.03±11.09	0.280
E DT (ms)	38.02±11.01	30.66±5.98	**0.002**
E/A	0.73±0.10	0.79±0.08	**0.015**
Tricuspid E (cm/s)	34.63±9.19	38.26±9.73	0.125
A (cm/s)	44.19±10.44	46.63±10.36	0.347
E DT (ms)	34.86±9.89	30.20±6.27	**0.029**
E/A	0.78±0.07	0.81±0.07	**0.028**
AV (cm/s)	60.03±15.31	62.47±12.72	0.490
PV (cm/s)	62.41±12.72	64.83±9.41	0.392
TDI			
LV S_m (cm/s)	7.8±3.7	4.4±3.1	**<0.001**
E_m (cm/s)	9.0±5.9	4.7±3.2	**<0.001**
A_m (cm/s)	13.2±9.2	6.2±5.3	**<0.001**
E_m/A_m	0.74±0.15	0.82±0.17	**0.012**
IVCT (ms)	32.20±9.27	29.33±5.83	0.132

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	COVID group (n=36)	**CONTROL group (n=30)**	p
IVRT (ms)	36.72±5.46	31.60±6.54	**0.001**
ET (ms)	167.92±25.47	174.30±19.24	0.263
MPI	0.42±0.09	0.35±0.04	**<0.001**
Mitral E/E_m	5.0±3.5	10.2±6.7	**<0.01**
SEPTAL S_m (cm/s)	9.0±8.0	4.7±4.1	**<0.01**
E_m (cm/s)	9.9±7.0	5.2±4.7	**<0.01**
A_m (cm/s)	13.2±9.2	6.2±5.3	**<0.001**
E_m/A_m	0.76±0.12	0.83±0.10	**0.015**
IVCT (ms)	33.17±8.11	30.06±5.90	0.086
IVRT (ms)	38.36±8.90	36.83±9.44	0.502
ET (ms)	169.83±26.72	179.10±14.63	0.080
MPI	0.43±0.09	0.37±0.07	**0.009**
RV S_m (cm/s)	7.7±3.6	4.6±4.2	**<0.001**
E_m (cm/s)	9.1±4.7	5.1±3.0	**<0.001**
A_m (cm/s)	11.9±5.8	6.7±4.5	**<0.001**
E_m/A_m	0.74±0.1	0.81±0.17	**0.018**
IVCT (ms)	31.11±7.48	29.5±6.76	0.155
IVRT (ms)	39.44±8.45	34.53±6.41	**0.011**
ET (ms)	172.28±26.76	181.20±17.48	0.109
MPI	0.42±0.08	0.36±0.05	**<0.001**
Tricuspid E/E_m	4.80±2.51	9.57±5.21	**<0.001**

Note: *Data given as mean ± SD.*

Abbreviations: ***FHR:*** *fetal heart rate;* ***IVSd:*** *Interventricular septum diastolic thickness;* ***LVEDD:*** *left ventricular end-diastolic dimension;****RVEDD:*** *right ventricular end-diastolic dimension;****MAPSE:*** *mitral annular plane systolic excursion;* ***TAPSE:****tricuspid annular plane systolic excursion;* ***PWD:*** *pulsed wave doppler;* ***E:*** *peak early ventricular filling wave velocity,****A:*** *maximum active atrial filling wave velocity;* ***E DT:****E wave deceleration time(msn);* ***AV, PV:*** *max peak velocity of aortic and pulmonary valves* ***TDI:*** *Tissue doppler imaging;****LV****: left ventricle ;* ***RV****: right ventricle****S_m:*** *maximal systolic myocardial velocity,****E_m , A_m :*** *early and late diastolic myocardial velocities;* ***IVRT:*** *isovolumic relaxation time;* ***IVCT:*** *isovolumic contraction time;* ***ET:*** *ejection time* ***MPI:*** *myocardial performance index;*

The bold value in the table was only statistically significant value (p<0.05).

Table 3: Demografic features of the groups at the time of postnatal period

		COVID group (n=36)	**CONTROL group (n=30)**	p
At the time of postnatal first echo	**At the time of postnatal first echo**	**At the time of postnatal first echo**	**At the time of postnatal first echo**	**At the time of postnatal first echo**
Age (day)	Age (day)	7.50 (5.00-11.75)	8.0(5.0-12.25)	0.912[a]
Gender (n%)	Female Male	19 (52.8%) 17 (47.2%)	16 (53.3%) 14 (46.7%)	0.924 [b]
Birth weight (g)	Birth weight (g)	3105.69±477.40	3166.83±100.11	0.630 [b]
Body weight (g)	Body weight (g)	3171.50±674.973	3152.00±974.440	0.898[b]
BSA (m^2)	BSA (m^2)	0.21±0.03	0.22±0.02	0.907 [b]
Gestational weeks at delivery	Gestational weeks at delivery	39.0(37.25-39.00)	39.0(37.0-39.0)	0.915 [c]

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		COVID group (n=36)	**CONTROL group (n=30)**	p
At the time of postnatal second echo	**At the time of postnatal second echo**	**At the time of postnatal second echo**	**At the time of postnatal second echo**	**At the time of postnatal second echo**
Age (day)	Age (day)	47.50(45.25-56.75)	49.00(44.75-60.00)	0.703 [c]
Body weight (g)	Body weight (g)	4600.00±989.95	4793.30±1156.37	0.467 [b]
BSA (m^2)	BSA (m^2)	0.27±0.04	0.28±0.05	0.473 [c]

Abbreviations: ***BSA:*** *body surface area*[a]*: Mann-Whitney U test,* [b]*: Chi-square test,* [c] *: Independent samples t-test*

Table 4: Comparison of postnatal conventional and PW doppler echocardiographic findings within and between groups

Postnatal Echocardiography (1^{st} and 2^{nd} echo)	**Postnatal Echocardiography (1^{st} and 2^{nd} echo)**	**COVID group (n=36)**	***p* (for 1^{st} and 2^{nd} echo)**	**Control group (n=30)**	***p* (for 1^{st} and 2^{nd} echo)**	***p* (for COVID-CONTROL group)**
2D-M mode	**2D-M mode**					
IVSd	1	4.9±0.9	**<0.01**	3.6±0.5	**<0.001**	**<0.001**
	2	5.5±0.7		4.4±0.5		**<0.001**
LVPWd	1	4.7±0.8	**0.025**	3.6±0.4	**<0.001**	**<0.001**
	2	5.0±0.6		4.5±0.5		**<0.001**
LVEDD	1	15.2±1.7	**<0.001**	15.5±1.6	**<0.001**	0.543
	2	17.7±1.4		17.8±1.7		0.467
RVEDD	1	16.1±1.4	**<0.001**	16.7±1.2	**<0.01**	0.128
	2	16.6±1.3		16.9±2.0		0.520
LV mass	1	10.7±3.2	**<0.001**	6.7±1.6	**<0.001**	**<0.001**
	2	14.6±2.8		11.7±2.1		**<0.001**
LVMi	1	50.4±11.8	0.053	31.9±6.2	**<0.001**	**<0.001**
	2	54.8±8.3		43.4±9.5		**<0.001**
MAPSE	1	6.3±1.1	**<0.001**	6.6±1.2	**<0.001**	0.299
	2	7.5±1.2		8.3±1.2		**0.011**
TAPSE	1	9.5±1.8	**<0.001**	9.9±1.4	**<0.001**	0.288
	2	12.4±2.1		12.6±2.1		0.635
Mitral	**Mitral**					
E	1	48.4±9.2	**<0.001**	52.6±10.2	**<0.001**	0.084
	2	70.3±16.0		75.4±14.4		0.184
A	1	61.41±12.5	**<0.001**	52.9±11.0	**<0.001**	**<0.01**
	2	76.3±14.3		69.4±11.8		**0.038**
DT	1	73.6±22.4	0.204	69.4±10.5	0.450	0.316
	2	80.2±23.0		71.2±14.6		0.059
E/A	1	0.80±0.14	**<0.01**	1.01±0.16	**0.042**	**<0.001**
	2	0.92±0.16		1.10±0.18		**<0.001**
Tricuspid	**Tricuspid**					
E	1	48.00±8.40	**<0.001**	51.9±7.8	**<0.001**	0.055
	2	57.7±10.8		60.4±8.5		0.263

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Postnatal Echocardiography (1st and 2nd echo)	**Postnatal Echocardiography (1st and 2nd echo)**	**COVID group (n=36)**	***p* (for 1st and 2nd echo)**	**Control group (n=30)**	***p* (for 1st and 2nd echo)**	***p* (for COVID-CONTROL group)**
A	1	59.8±12.9	**<0.01**	56.1±7.6	**<0.001**	0.145
	2	70.1±12.9		63.5±7.1		**0.011**
DT	1	73.6±23.5	**<0.01**	66.9±12.7	**<0.001**	0.151
	2	87.4±17.1		83.3±11.0		0.252
E/A	1	0.81±0.12	0.620	0.93±0.11	0.311	**<0.001**
	2	0.82±0.09		0.96±0.13		**<0.001**
Aorta-pulmonary	**Aorta-pulmonary**					
AV	1	83.8±10.5	**<0.001**	83.0±8.3	**<0.001**	0.754
	2	99.9±14.8		99.5±9.0		0.889
PV	1	85.3±10.7	**<0.001**	85.9±7.5	**<0.001**	0.789
	2	99.2±13.0		103.93±9.5		0.094
LVEF	1	73.3±3.2	0.021	73.0±2.6	0.337	0.765
	2	71.7±2.4		73.9±3.2		**<0.01**
LVSF	1	39.0±2.7	0.117	39.6±2.6	0.165	0.340
	2	38.1±2.8		40.8±2.4		**<0.001**

Note: *Data given as mean ± SD.*

Abbreviations as in Table 2, also LVMi: *left ventricular mass index;* ***EF:****ejection fraction;* ***SF:*** *shortening fraction.*

Table 5: Comparison of postnatal tissue doppler echocardiographic findings within and between groups

Postnatal Echocardiography (1st and 2nd echo)	**Postnatal Echocardiography (1st and 2nd echo)**	**COVID group (n=36)**	***p* (for 1st and 2nd echo)**	**CONTROL group (n=30)**	***p* (for 1st and 2nd echo)**	***p* (for COVID-CONTROL)**
LV TDI	**LV TDI**	**LV TDI**				
S_m	1	5.6±1.2	**0.033**	5.2±0.9	**<0.01**	0.203
	2	6.1±1.1		6.0±0.9		0.623
E_m	1	6.5±1.5	**<0.001**	7.7±1.3	**<0.001**	**<0.01**
	2	8.5±1.8		9.9±1.9		**<0.01**
A_m	1	8.0±2.5	**0.013**	7.7±1.5	0.437	0.512
	2	9.4±2.1		8.0±1.6		**<0.01**
E_m/A_m	1	0.86±0.20	0.133	1.0±0.1	**<0.001**	**<0.001**
	2	0.93±0.24		1.2±0.2		**<0.001**
IVCT	1	48.1±9.7	0.436	42.7±8.1	0.755	**0.018**
	2	46.4±9.2		43.2±5.8		0.099
IVRT	1	50.7±9.4	**0.043**	46.3±7.4	0.286	**0.042**
	2	46.4±9.4		44.3±6.6		**0.031**
ET	1	178.64±14.2	0.574	188.00±17.0	0.781	**0.017**
	2	181.03±19.5		187.07±10.6		0.116
MPI	1	0.55±0.09	0.124	0.47±0.05	0.840	**<0.001**

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Postnatal Echocardiography (1st and 2nd echo)	**Postnatal Echocardiography (1st and 2nd echo)**	**COVID group (n=36)**	***p* (for 1st and 2nd echo)**	**CONTROL group (n=30)**	***p* (for 1st and 2nd echo)**	***p* (for COVID-CONTROL)**
	2	0.51±0.11		0.47±0.06		**0.031**
Mitral E/E_m	1	7.7±1.9	0.069	7.0±1.7	0.248	0.125
	2	8.5±2.1		7.6±2.0		0.083
SEPTAL TDI	**SEPTAL TDI**					
S_m	1	4.5±0.8	**<0.001**	4.8±0.9	**<0.001**	0.141
	2	5.3±0.7		6.8±1.2		0.543
E_m	1	5.7±1.6	**<0.001**	6.1±1.4	**<0.001**	0.332
	2	7.3±2.1		8.1±1.7		0.119
A_m	1	6.7±2.1	**0.036**	6.1±1.3	**<0.01**	0.181
	2	7.5±1.8		7.3±1.6		0.542
E_m/A_m	1	0.88±0.23	**0.033**	1.0±0.15	**<0.01**	**0.023**
	2	0.98±0.18		1.1±0.15		**<0.01**
IVCT	1	46.2±11.6	0.125	42.5±6.7	0.678	0.109
	2	42.8±6.4		41.8±6.9		0.543
IVRT	1	49.1±9.6	0.247	42.0±7.1	0.600	**<0.01**
	2	46.5±8.4		41.1±6.6		**<0.01**
ET	1	184.03±17.5	0.299	183.83±12.5	0.177	0.960
	2	179.39±18.6		188.37±13.4		**0.031**
MPI	1	0.53±0.14	0.672	0.46±0.06	0.373	**0.012**
	2	0.51±0.11		0.44±0.08		**<0.01**
RV TDI	**RV TDI**	**RV TDI**				
S_m	1	6.3±1.4	**<0.01**	6.5±1.2	0.349	0.522
	2	7.2±1.4		6.8±1.2		0.176
E_m	1	7.6±1.9	0.078	8.6±1.4	**<0.01**	**0.017**
	2	8.3±1.6		9.8±1.6		**<0.001**
A_m	1	10.0±2.1	0.200	8.9±1.5	**<0.01**	**0.024**
	2	10.6±2.4		10.0±1.6		0.216
E_m/A_m	1	0.77±0.14	0.526	0.99±0.14	0.820	**<0.001**
	2	0.79±0.10		0.99±0.13		**<0.001**
IVCT	1	48.5±7.7	0.063	41.0±7.2	0.354	**<0.001**
	2	45.2±6.1		42.5±5.2		**0.042**
IVRT	1	47.5±8.5	0.366	43.2±6.9	0.171	**0.030**
	2	49.2±5.9		41.2±5.3		**<0.001**
ET	1	185.14±18.1	0.085	185.70±16.3	0.148	0.896
	2	178.97±15.4		190.57±14.4		**<0.01**
MPI	1	0.52±0.08	0.688	0.46±0.65	0.220	**<0.01**
	2	0.53±0.07		0.44±0.05		**<0.001**
Tricuspid E/E_m	1	6.5±1.4	0.099	6.1±0.8	0.362	0.140
	2	7.1±1.5		6.3±1.0		**<0.01**
Valvular insufficiency	1	Aortic insufficiency(mild): 2	Aortic insufficiency(mild): 2	None	None	

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Postnatal Echocardiography (1st and 2nd echo)	**Postnatal Echocardiography (1st and 2nd echo)**	**COVID group (n=36)**	p **(for 1st and 2nd echo)**	**CONTROL group (n=30)**	p **(for 1st and 2nd echo)**	p **(for COVID-CONTROL)**
	2	Aortic insufficiency (mild): 1	Aortic insufficiency (mild): 1	None		