Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2024;49(2):407-414
DOI: 10.17826/cumj.1392668

RESEARCH

Evaluation of the tissue doppler-derived myocardial performance index in fetuses of mothers infected with COVID-19 during pregnancy with mild symptoms

Hafif semptomları olan gebelikte COVID-19 bulaşmış annelerin fetüslerinde doku doppler türevli miyokard performans indeksinin değerlendirilmesi

Cenk Soysal[1], Rahmi Özdemir[2]

[1]Kütahya Health Sciences University, Kütahya, Türkiye
[2]Health Scıences Unıversıty İzmir Tepecik Educatıon and Research Hospıtal, İzmir, Türkiye

Abstract

Purpose: To compare cardiac functions evaluated with echocardiography and tissue Doppler (TD) imaging between fetuses of pregnant women who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and were asymptomatic or had mild symptoms and fetuses of pregnant women who were not infected.

Material and Methods: Early diastolic myocardial velocities (Em) and late myocardial velocities (Am) and Em/Am ratios were measured in the lateral annuli of tricuspid and mitral valves of fetuses of pregnant women with COVID-19 at more than 20 weeks of gestational age who had COVID-19 (n=45) and gestational age-matched healthy pregnant women's fetuses (n=43). The TD-derived myocardial performance index (MPI) was also measured.

Results: The gestational ages of the fetuses were found as 26.1 ± 3.3 and 26.6 ± 3.5 weeks, respectively. The mitral valve Em/Am ratio was 0.56±0.08 and 0.61±0.06 in the study group and the control group, respectively. The tricuspid valve Em/Am ratio was 0.58±0.11 and 0.63±0.10 in the study group and the control group, respectively. The TD-derived mitral valve MPI was 0.48±0.07 and 0.40±0.07 in the study group and the control group, respectively.

Conclusion: Maternal COVID-19 affects fetal MPI and diastolic function. Fetal cardiac echocardiography should be performed during antenatal follow-up of low-risk, mildly symptomatic pregnant women infected with SARS-CoV-2 without concomitant maternal comorbidity.

Keywords:. COVID-19, E/A ratio, fetal echocardiyography, myocardial performance index

Öz

Amaç: Şiddetli akut respiratuar sendromu koronavirüs 2 (SARS-CoV-2) ile enfekte olmuş ve asemptomatik veya hafif semptomları olan hamile kadınların fetüsleri ile enfekte olmamış hamile kadınların fetüslerinin, ekokardiyografi ve doku Doppler (TD) görüntüleme ile değerlendirilen fetal kardiyak fonksiyonlarını karşılaştırmaktır.

Gereç ve Yöntem: Gestasyonel yaşları 20 haftadan fazla olan ve COVID-19 enfekte, hafif ya da asemptomatik gebe kadınların fetüslerinin triküspit ve mitral kapakların lateral anülüslerinde erken diyastolik miyokardiyal hızlar (Em) ve geç miyokardiyal hızlar (Am) ve Em/Am oranları ölçülmüştür (n=45). Aynı gestasyonel yaşa sahip sağlıklı hamile kadınların fetüsleriyle Fetal eko sonuçları (n=43) karşılaştırılmıştır. Ayrıca doku doppler türevli miyokard performans indeksi (MPI) de ölçülmüştür.

Bulgular: Fetüslerin gestasyonel yaşları sırasıyla 26.1 ± 3.3 hafta ve 26.6 ± 3.5 hafta olarak tespit edilmiştir). Araştırma grubunda mitral kapak Em/Am oranı 0.56±0.08 iken, kontrol grubunda 0.61±0.06 olarak bulunmuştur. Araştırma grubunda triküspit kapak Em/Am oranı 0.58±0.11 iken, kontrol grubunda 0.63±0.10 olarak ölçülmüştür. Doku doppler türevli mitral kapak MPI'si araştırma grubunda 0.48±0.07, kontrol grubunda ise 0.40±0.07 olarak belirlenmiştir.

Sonuç: Maternal COVID-19 enfeksiyonu fetal MPI ve diyastolik fonksiyonları etkilemektedir. Eşlik eden maternal komorbidite olmaksızın SARS-CoV-2 ile enfekte olmuş, düşük riskli, hafif semptomatik hamile kadınların antenatal takibinde fetal kardiyak ekokardiyografi yapılmalıdır.

Anahtar kelimeler: COVID-19, E/A oranı, fetal ekokardiyografi, miyokard performans indeksi

Address for Correspondence: Cenk Soysal, Department of Obstetrics and Gynecology, Kutahya Health Sciences University Faculty of Medicine, Kütahya, Turkey E-mail: drsoysalcenk@gmail.com
Received: 18.11.2023 Accepted: 16.05.2024

INTRODUCTION

The onset of the COVID-19 pandemic, precipitated by the emergence of the novel coronavirus SARS-CoV-2, has been acknowledged as a pivotal challenge to the integrity of the global public health system. This viral agent, implicated in a range of respiratory conditions, has caused extensive morbidity and mortality, compelling an immediate and collaborative response from the global medical and scientific communities. In the initial stages of the pandemic, the potential for obstetric complications arising from vertical transmission in pregnant women infected with SARS-CoV-2 is a source of significant concern[1].

Several viral infections during pregnancy are noted for their propensity for vertical transmission, which can lead to congenital infections that are detrimental to fetal development[2]. These pathogens possess the ability to infiltrate and disrupt various components of the feto-maternal interface, including the syncytiotrophoblast and cytotrophoblast layers, endothelial and hematopoietic cells, and the amniotic membrane, thereby presenting hazards to the fetus. Maternal infections such as those caused by parvovirus B-19, cytomegalovirus, and rubella virus have been identified as primary infections with a predilection for fetal cardiac complications [3,4].

A plethora of respiratory viral infections have been implicated in elevating the risk of neonatal and obstetric complications attributable to certain immunologic modifications that transpire during pregnancy to avert fetal rejection[5]. Documented instances of vertical transmission of maternal SARS-CoV-2 are confined to a limited number of case series in the scientific literature[6-8]. This viral agent is associated with several adverse obstetric outcomes including spontaneous abortion (2%), intrauterine growth restriction (IUGR) (10%), and premature labor (39%)[9]. Despite the attenuated clinical severity of COVID-19 in adults consequent to vaccine development, the clinical prognosis for the fetus remains ambiguous owing to the paucity of vaccine research conducted in pregnant populations[10].

In the present investigation, we scrutinized the prospective impact of maternal SARS-CoV-2 infection on fetal cardiac function. This study evaluated fetal cardiac functions using tissue Doppler (TD) echocardiography in pregnant women beyond the 20th week of gestation, who manifested only mild COVID-19 symptoms. The myocardial performance index (MPI) obtained from tissue Doppler (TD) metrics in fetuses exposed to maternal COVID-19 has been explored in this study.

This study aims to contribute to the existing literature by providing insights into the MPI derived from tissue Doppler (TD) metrics in fetuses of mothers who contracted COVID-19 during pregnancy with mild symptoms. The hypothesis of the study is that maternal COVID-19 infection, even with mild symptoms, may affect fetal myocardial function, as indicated by changes in the MPI.

MATERIALS AND METHODS

Sample

This study enrolled pregnant women who presented with mild COVID-19 symptoms during gestation and attended the Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital's Gynecology and Obstetrics outpatient clinic for routine check-ups from March 2021 to June 2021. Informed consent was obtained from all participants included in this study. Fetal echocardiographic assessments were conducted in consultation with the Pediatric Cardiology Unit. Informed consent was obtained from all participants in written form. The study was approved by the University Ethics Committee (Dated 10.03.2021 decision number: 2021/04–02). The cohort comprised 88 fetuses, with 43 in the control group and 45 in the study group. Exclusion criteria included intrauterine growth restriction, multiple gestations, fetuses with cardiac or structural anomalies, and maternal systemic diseases, such as diabetes, hypertension, or cases of severe COVID-19. In total, 102 individuals were approached for this study. Of these, 14 patients were excluded due to exclusion criteria. The final sample consisted of 88 participants who met all the inclusion criteria and provided complete data. This study was conducted at Kutahya Health Sciences Universty. This institution follows rigorous practices to ensure the reliability and accuracy of data. All procedures were carried out by experienced professionals, including obstetrician (C.S.) and pediatric cardiologists (R.Ö.), who are well-versed in fetal echocardiography and tissue Doppler imaging. Their competencies are validated by years of clinical experience and relevant certifications in their respective fields.

Examination of fetal systolic and diastolic functions

Cardiac ultrasound evaluations were meticulously performed in strict conformance with the guidelines prescribed by the American Society of Echocardiography and European Society of Cardiology. Tissue Doppler imaging (TDI) coupled with two-dimensional echocardiography was used to delineate the systolic and diastolic functions of the fetal heart. For these assessments, a Philips Affiniti 50 ultrasound system (Philips Healthcare, Andover, Netherlands) was used, which was outfitted with an S4-2 cardiac probe transducer, offering tissue Doppler capabilities.

TDI, an advanced modality for the evaluation of ventricular systolic and diastolic function, was employed to capture waveforms from the four-chamber view of the heart. Our TDI protocol entailed the use of pulsed-wave Doppler with a transducer frequency of 3 MHz. The sample volume was meticulously positioned at the lateral annulus of the mitral valve within the left ventricle and tricuspid valve within the right ventricle. Subsequent analyses of myocardial velocities were conducted across ventricular systole and diastole phases. The systolic myocardial velocity (Sm), early diastolic myocardial velocity (Em), late diastolic myocardial velocity (Am), Em/Am ratio, and MPI were meticulously recorded and calculated using TDI techniques. A reduction in Sm is indicative of impaired fetal ventricular systolic function, whereas diastolic dysfunction is inferred from an increase in Am, decrease in Em, and diminished Em/Am ratios. Additionally, augmented MPI denotes overall deterioration in both systolic and diastolic fetal heart function.

The myocardial performance index (MPI) was calculated using the formula: MPI = (ICT + IRT) / ET. The isovolumetric contraction time (ICT) is defined as the interval from the cessation of atrial filling, identified by the culmination of the 'A wave,' to the onset of ventricular systolic myocardial contraction. The isovolumetric relaxation time (IRT) is the period from the end of ventricular contraction to the commencement of atrial filling, indicated by the start of the 'A wave.' Ejection time (ET) represents the span from the beginning to the conclusion of the systolic phase of myocardial contraction. Ejection time (ET) was determined from the duration between the initiation and cessation of ventricular contraction. Measurements were meticulously performed in the absence of fetal respiratory movements and without any maternal or fetal motility. Recordings were obtained from a minimum of four cardiac cycles and were subsequently averaged to ensure accuracy. To maintain uniformity and minimize variability in the assessment, a single experienced pediatric cardiologist (initials R.Ö.) executed all the Doppler evaluations and associated calculations.

Statistical analysis

Data analysis was conducted using SPSS software (IBM Corp., released in 2012, Version 25.0 for Windows, Armonk, NY, USA). The conformity of the variables to a normal distribution was assessed using the Shapiro-Wilk test. In the statistical analysis section, we performed various tests to analyze our data. For continuous variables such as maternal age, BMI, gestational week, and echocardiographic parameters (S, E, A, E/A, ICT, IRT, ET, MPI), we used Student's t-test to compare the means between the control and study groups. For non-normally distributed variables such as parity, IRT, and ET, we employed the Mann-Whitney U test to compare the medians between the groups.A p-value of less than 0.05 was deemed indicative of statistical significance.

RESULTS

The mean age of the pregnant women participating in the study was 28.7 ± 4.9 years, the body mass index (BMI) was 26.1 ± 3.6 kg/m^2, and their mean gestational age was 26.3 ± 3.3 weeks. The mean maternal age in the study group was 28.4 ± 4.7 years, and it was 29 ± 5.1 years in the control group. The median gestational age was 27 (24-29) weeks in the study group and 26 (23-28) weeks in the control group. No significant differences were observed between the groups in terms of maternal age, BMI, parity, or gestational age ($p = 0.405$, $p = 0.394$, $p = 0.924$, and $p = 0.429$, respectively). The mean time between positive polymerase chain reaction (PCR) results in pregnant women and fetal cardiac evaluation was 62.6 ± 18.3 days (Table 1).

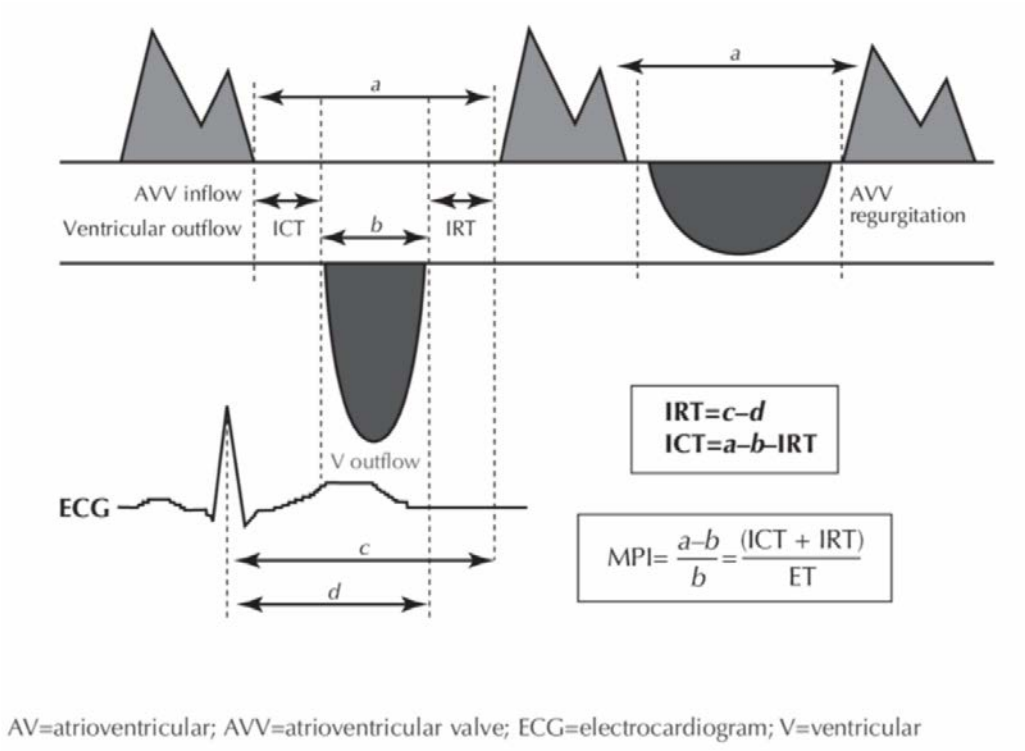

Figure 1. Demonstration of myocardial performance index formula.

Table 1. Characteristics of the groups

Variable	Control Group (n=43)	Study Group (n=45)	p values
Maternal Age	29.2±5.1 30 [26; 34]	28.4±4.7 28 [25; 32]	0.405[a]
BMI	25.8±3.9 27 [22; 29]	26.5±3.3 26 [25; 29]	0.394[a]
Parity	1±1 1 [0; 2]	1±1 1 [1; 2]	0.924[b]
Gestational Week	26.1±3.3 26 [23; 28]	26.6±3.5 27 [24; 29]	0.429[a]
From Onset of COVID-19 to Fetal Assesment (days)		62.6±18.3 62 [53; 74]	

BMI: Body mass index; Values are presented as mean ± SD. median [interquartile range], n; number p-values were calculated with aStudent's t-test or bMann-Whitney U test.

In the left ventricular fetal echocardiographic examination, no significant difference was observed between the groups in terms of Am and Sm values obtained from the mitral lateral annulus (p=0.77 and p=0.642, respectively). There was a significant difference between the groups in terms of Em, Em/Am ratio, ICT, IRT, and left heart MPI values (p=0.015, p=0.003, p=0.003, p=0.012, and p <0.001, respectively) (Table 2). In the right ventricular fetal echocardiographic examination, no significant differences were observed between the groups in terms of Sm, Am, and IRT parameters obtained from the tricuspid lateral annulus (p=0.58, p=0.66, and p=0.18, respectively). There was a significant difference between the groups in terms of right heart Em/Am ratio and MPI measurements, showing diastolic function and global cardiac performance among other parameters (p=0.047 and p=0.001, respectively) (Table 3).

Table 2. Fetal echocardiographic mitral valve measurements

	Control Group (n=43)	Study Group (n=45)	p values
S (cm/s)	3.9±1.0	3.9±0.7	0.642[a]
	3.9 [3.3; 4.6]	3.6 [3.3; 4.5]	
E (cm/s)	3.2±0.5	2.9±0.5	0.015[a]
	3.2 [2.8; 3.5]	2.9 [2.6; 3.2]	
A (cm/s)	5.2±0.6	5.3±0.8	0.771[a]
	5.3 [4.8; 5.8]	5.2 [4.7; 6.1]	
E/A	0.61±0.06	0.56±0.08	0.003[a]
	0.61 [0.57; 0.66]	0.56 [0.50; 0.61]	
ICT (ms)	28.6±6.0	32.4±5.9	0.003[a]
	27.0 [23.0; 34.0]	31.0 [29.0; 36.0]	
IRT (ms)	41.4±6.6	45.3±7.6	0.012[a]
	42.0 [37.0; 46.0]	45.0 [39.0; 51.0]	
ET (ms)	178.3±25.7	164.4±15.8	0.003[a]
	173.0 [156.0; 205.0]	166.0 [150.0; 175.0]	
MPI	0.40±0.07	0.48±0.07	<0.001[a]
	0.40 [0.36; 0.44]	0.47 [0.42; 0.52]	

S: Systole peak flow velocity; E: Early diastole peak flow velocity; A: Atrial contraction peak flow velocity; ICT: Isovolumetric contraction time; IRT: Isovolumetric relaxation time; ET: Ejection time; MPI: myocardial performance index; Values are presented as mean ± SD, median [interquartile range], n; number p-values were calculated with [a]Student's t-test or [b]Mann-Whitney U test.

Table 3. Fetal echocardiographic tricuspit valve measurements

	Control Group (n=43)	Study Group (n=45)	p values
S (cm/s)	6.1±1.6 5.6 [4.6; 7.6]	6.8±1.7 7.0 [5.4; 8.0]	0.58[a]
E (cm/s)	3.6±0.6 3.6 [2.9; 3.8]	3.2±0.6 3.1 [2.9; 3.6]	0.023[a]
A (cm/s)	5.8±1.2 5.9 [4.8; 6.6]	5.7±1.1 5.8 [4.9; 6.6]	0.664[a]
E/A	0.63±0.10 0.65 [0.54; 0.70]	0.58±0.11 0.61 [0.48; 0.66]	0.047[a]
ICT (ms)	29.6±5.9 28.0 [26.0; 31.0]	33.3±7.0 32.0 [28.0; 40.0]	0.008[a]
IRT (ms)	40.8±6.9 41.0 [35.0; 46.0]	43.3±8.7 44.0 [35.0; 51.0]	0.189[b]
ET (ms)	179.8±21.3 175.0 [163.0; 200.0]	168.5±22.5 166.0 [149.0; 186.0]	0.026[b]
MPI	0.40±0.07 0.40 [0.34; 0.44]	0.46±0.10 0.44 [0.38; 0.53]	0.001[a]

S: Systole peak flow velocity; E: Early diastole peak flow velocity; A: Atrial contraction peak flow velocity; ICT: Isovolumetric contraction time; IRT: Isovolumetric relaxation time; ET: Ejection time; MPI: myocardial performance index; Values are presented as mean ± SD, median [interquartile range], n; number ; p-values were calculated with aStudent's t-test or bMann-Whitney U test.

DISCUSSION

In the analysis, we observed a significant elevation in the MPI of both the right and left ventricles in the fetuses of pregnant women diagnosed with COVID-19, in contrast to the control group. Furthermore, a notable decrease was observed in the Em/Am ratio, a cardinal indicator of diastolic heart function, in both the right and left heart. These observations suggest that the fetal myocardium may be adversely impacted, even in cases where pregnant women experience only mild symptoms of COVID-19. Consequently, it is recommended that fetal echocardiography be incorporated into the antenatal monitoring regimen for pregnant women with COVID-19. Congenital viral infections during gestation can precipitate various adverse fetal outcomes, including congenital anomalies, spontaneous abortion, premature labor, and fetal demise through disparate pathogenic pathways. Reflecting on historical precedents, the

1918 influenza pandemic yielded long-term sequelae such as diminished high school graduation rates, heightened cardiovascular disease burden, and reduced lifespan among the offspring of affected mothers[11]. Although the corpus of evidence regarding the vertical transmission of COVID-19 remains limited, existing studies substantiate instances of such transmission[12-14]. The predominant pathology discerned in placentas from fetuses of COVID-19 positive mothers is vascular malperfusion[15]. Additional pathologies include thrombosis, intramural fibrin deposition, villous stromal-vascular caryorrhexis, and villous infarction[16,17]. Villar et al. identified an increase in mortality, morbidity, and neonatal intensive care unit admissions among neonates born to COVID-19-infected mothers in one of the most extensive studies to date involving 706 women[18]. The present study, although not conclusive of vertical transmission, implies that fetuses could be affected by maternal COVID-19 through alternative mechanisms, as evidenced by the cardiac dysfunction observed in fetuses of infected mothers.

In this investigation, echocardiographic analyses conducted via tissue Doppler imaging (TDI) revealed a diminution in the myocardial Em velocity in the fetuses of mothers afflicted with COVID-19. Consequently, the Em/Am ratio was lower than that in the control group. It is postulated that the decrease in myocardial Em velocity may be attributed to impaired relaxation during the early ventricular filling phase, resulting in lower Em/Am ratios than those observed in healthy fetuses. This supposition is supported by similar findings in other studies that have explored the relaxation capabilities of the fetal heart. For instance, Dervisoglu et al. investigated tricuspid valve velocities in 32-week gestation fetuses across gestational diabetes, pre-gestational diabetes, and control groups. Utilizing echocardiographic spectral pulsed-wave Doppler and TDI to measure velocities, they determined that Em/Am ratios were depressed in diabetic cohorts by both methodologies[19]. Davutoglu et al. documented that mitral valve Em/Am ratios were inferior in fetuses of pregnant women with early onset intrauterine growth restriction (IUGR), correlating with diastolic dysfunction[20].

In the literature, conventional modified MPI is frequently utilized as an echocardiographic metric for assessing fetal myocardial performance. Research indicates that TDI MPI, a relatively nascent methodology compared to conventional MPI, exhibits reduced intra- and interobserver variability, enhanced utility, and more accurately encapsulates the overall myocardial performance[21,22]. Bui et al. conducted a comparative analysis between spectral pulsed-wave Doppler, a more traditional approach, and the TDI method implemented in our study, focusing on the right ventricular myocardial performance in fetuses from diabetic mothers. Their findings posited that TDI was superior in sensitivity to fetal myocardial performance, and that MPI values were elevated in fetuses from diabetic pregnancies[23]. Similarly, in a study by Irani et al., which assessed fetal cardiac function amidst intrauterine infection, an increase in MPI corresponded with an increase in N-terminal fragment brain natriuretic protein level (NT-proBNP), a biomarker of fetal myocardial distress[24]. Another pertinent study reported increased MPI values in pregnancies complicated by preterm premature rupture of membranes (PPROM)[25]. Our study's evaluation of right and left myocardial performance, utilizing TD-derived MPI, delineated higher MPI values in fetuses of mothers who had contracted COVID-19 relative to a control group. This outcome suggests that fetal myocardial tissue may be affected by maternal viremia through various mechanisms, notwithstanding the ongoing debate surrounding the vertical transmission of COVID-19, and that the observed elevation in left and right tissue-derived MPIs could be indicative of mild cardiac diastolic dysfunction in the affected fetuses.

The present investigation is subject to certain constraints, the most salient being the scant data on the vertical transmission of maternal COVID-19 infection, which inhibits a definitive explanation of the precise impact of this viremia on fetal cardiac function within the context of the existing literature. Moreover, any prognostications regarding the future cardiac functionality of these fetuses remain speculative, as postnatal echocardiographic evaluations of newborns from COVID-19-affected pregnancies are yet to be performed. However, the study's principal strength lies in its novelty; it is the first in the scholarly literature to employ TDI to assess the MPI of fetuses born to mothers with COVID-19. This methodology represents a substantial advancement over traditional echocardiographic measurements of MPI, offering a more nuanced understanding of fetal cardiac function.

This study had several limitations. First, due to the

COVID-19 isolation measures, echocardiographic evaluations were performed later than planned, limiting accessibility to patients and early assessments. Second, the study required waiting until later gestational weeks, the ideal time frame for fetal cardiac evaluation, for pregnant women with mild symptoms in the first trimester. The waiting period is another factor that influences the timing of the study. Furthermore, the presence of vertical transmission and long-term effects of COVID-19 infection on fetal hearts remain uncertain, with this study focusing only on potential intrauterine impacts. In this context, the relationship between the results obtained and COVID-19 should be interpreted considering the ongoing debates in the literature. These limitations may affect the general applicability of the study findings and highlight the need for more comprehensive and detailed evaluations in future research. In this study, power analysis could not be conducted to determine the sample size. This limitation may affect the generalizability of our results and reduce the statistical power of the study. Future research should aim to include a larger sample size and conduct a power analysis to obtain more robust and reliable findings.

In summary, fetal echocardiographic evaluation of pregnant women with SARS-CoV-2 infection revealed subtle alterations in diastolic function and MPI when assessed using TDI. The long-term significance of intrauterine fetal cardiac involvement remains uncertain, necessitating the consideration of antenatal fetal echocardiography or postnatal cardiac evaluation for infants, irrespective of any suspected fetal anomaly or absence of additional maternal pathologies. For a more comprehensive definition of TDI metrics in fetuses of mothers afflicted with COVID-19, there is a compelling need for larger, randomized, prospective, and multicentric research endeavors.

Author Contributions: Concept/Design : CS, RÖ; Data acquisition: CS; Data analysis and interpretation: RÖ; Drafting manuscript: CS; Critical revision of manuscript: RÖ; Final approval and accountability: CS, RÖ; Technical or material support: RÖ; Supervision: RÖ; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Kütahya Health Sciences University (Dated 10.03.2021 and numbered 2021/04-02).
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support
Acknowledgments: The authors would like to express their gratitude to Dr. Anita L. Akkas (Middle East Technical University, English Division, retired, Ankara, Turkey) for her contribution to the English editing, and to M.D. Selim Mısırlıoğlu (NYC Health + Hospitals, New York) for his assistance in proofreading to enhance the quality of the English.

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