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Role of fetal cardiac assessment in predicting adverse perinatal outcomes in preterm dichorionic twins

Preterm dikoryonik ikizlerde olumsuz perinatal sonuçları öngörmede fetal kardiyak değerlendirmenin rolü

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ABSTRACT

Aim: To investigate the role of the fetal modified myocardial performance index (Mod-MPI) and fetal cardiac output index measurement in predicting adverse perinatal outcomes amongpreterm dichorionic twins.

Materials and Method: This prospective cohort study was conducted at the X Clinic andincluded 34 dichorionic twinfetuses bornearly preterm and 40 dichorionic twinfetusesborn late preterm.The early preterm group was divided into two according to whether they were admitted to theneonatal intensive care unit (NICU). The groups' cardiac function and Mod-MPI measurements were compared regardingtheir predictive ability for adverse perinatal outcomes.

Results: The Mod-MPI values were similar between theearly and late pretermgroups (p=0.144). The leftventricular cardiac output Z-score was lower in the preterm group (p=0.014). The Mod-MPI and left ventricular outflow tract-isovolumetric contraction and isovolumetric relaxation times were significantly higher among the newborns admitted to the NICU in the early preterm group (p=0.002, p=0.003, and p=0.001, respectively).

Conclusion: Our study suggests that the Mod-MPI measurement can be used to predict adverse perinatal outcomes in dichorionic twin fetusesbornin the early preterm period.

Keywords: Adverse perinatal outcomes, cardiac function, dichorionic twin, myocardial performance index, preterm birth

ÖZ

Amaç: Preterm dikoryonik ikizlerde fetal modifiye miyokardiyal performans indeksi (Mod-MPI) ve fetal kardiyak output indeksi ölçümünün olumsuz perinatal sonuçları öngörmedeki rolünü araştırmak.

Gereç ve Yöntemler: Bu prospektif kohort çalışması X Kliniğinde yürütüldü ve erken preterm doğan 34 dikoryonik ikiz fetüs ile geç preterm doğan 40 dikoryonik ikiz fetüs dahil edildi. Erken preterm grubu yenidoğan yoğun bakım ünitesine (YYBÜ) kabul edilip edilmemelerine göre ikiye ayrılmıştır. Grupların kötü perinatal sonuçları öngörmede kardiak fonksiyonları ve Mod-MPI ölçümleri karşılaştırıldı.

Bulgular: Mod-MPI değerleri erken ve geç preterm grupları arasında benzerdi (p=0.144). Sol ventrikül kalp debisi Z-skoru preterm grupta daha düşüktü (p=0,014). Mod-MPI ve sol ventrikül çıkış yolu-izovolümetrik kasılma ve izovolümetrik gevşeme süreleri erken preterm grubunda YYBÜ'ye kabul edilen yenidoğanlar arasında anlamlı olarak daha yüksekti (sırasıyla p=0.002, p=0.003 ve p=0.001).

Sonuç: Çalışmamız Mod-MPI ölçümünün erken preterm dönemde doğan dikoryonik ikiz fetüslerde olumsuz perinatal sonuçları öngörmek için kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Olumsuz perinatal sonuçlar, kardiyak fonksiyon, dikoryonik ikiz, miyokardiyal performans indeksi, erken doğum

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INTRODUCTION

In the last three decades, the global incidence of twin pregnancies has increased by 70% due to the use of assisted reproductive technologies (1). Among the obstetric conditions known to increase the risk of perinatal mortality, twin pregnancies constitute an important and well-known factor (2). The rate of perinatal mortality may be higher in twin pregnancies compared to singleton pregnancies, which is mostly associated with the higher rates of preterm births observed in the former. Preterm birth and birth weight are also important determinants of morbidity and mortality in infancy (3). Approximately half of all twins are born before 37 weeks of gestation or with a birth weight of <2,500 g (4). In addition, twin pregnancies have been observed to increase neonatal morbidity and mortality, including a six-fold increase in preterm births before 34 weeks of gestation (5).

Parameters evaluated during a fetal cardiac ultrasound examination are closely associated with perinatal mortality (6). The modified myocardial performance index (Mod-MPI) measured by Doppler ultrasonography can assess overall heart function since it includes the systolic and diastolic components of the cardiac cycle (7). Another parameter used to evaluate cardiac function is cardiac output (CO), which can directly represent ventricular systolic function. A normal fetus has a high reserve potential to sustain CO. When compensatory mechanisms are exhausted, CO decreases with decreased myocardial performance, resulting in poor tissue perfusion, progressive acidosis, and ultimately fetal mortality (8).

In this study, we aimed to examine the relationship of the Mod-MPI and CO values with perinatal morbidity and mortality in twin fetusesborn preterm. We specifically focused on dichorionic twins, considering that this type of pregnancy accounts for the majority of twin pregnancies and requires a different antenatal management plan than monochorionic twins (9).

MATERIALS AND METHODS

This prospective cohort study was conducted between January 2022 and January 2023 at the X Clinic. The study was designed following the principles of the Declaration of Helsinki. After the participants were given detailed information about the study, their written consent was obtained. The study was approved by the Number 2 Ethics Committee of the hospital (Number: E2-21-680).

The primary endpoint of the study was cardiac function in dichorionic diamniotic twin fetusesborn preterm. The secondary endpoint was the ability of fetal cardiac function to predictthe requirement for neonatal intensive care unit (NICU) admission in premature dichorionic diamniotic twin fetusesborn preterm.

Study population

The sample consisted of 34 dichorionic twinfetusesbornearly preterm and 40 dichorionic diamniotic twinfetusesborn late preterm. The early preterm group was accepted as those born before 34 weeks of gestation, and the late preterm group as those born between 34 0/7 and 36 6/7 weeks of gestation.The cases constituting the sample were selected from pregnant women at 24-34 weeks of gestation.According to the examination, the cases included in the study did not havea short cervix (<25 mm), vaginal dilatation, uterine contraction, or premature rupture of membranes (PPROM). Dichorionic diamniotic pregnancies where labor occurredafter37 weeks of gestation were also not included in the sample. At least one dose of antenatal corticosteroid was administered to all cases in which delivery occurredbefore 34 weeks of gestation, while tocolytics were administered for 48 hours to thosein which labor started spontaneously. Excluded from the studywere pregnant women withsystemic diseases, such as chronic kidney, liver, lung, and heart diseases, diabetes mellitus, history of malignancy, Rh incompatibility, and comorbidities such as placenta previa.Other exclusion criteria weremonochorionic pregnancies, the use of an invasive diagnostic test during pregnancy, the intrauterine death of one of the twins, and structural or chromosomal fetal anomalies.

The demographic characteristics, fetal biometry, fetal birth weight, gestational week at which ultrasonography was performed, delivery week, first- and fifth-minute Apgar scores, fetal cardiac ultrasonographic parameters, and NICU requirement were noted and compared between the groups.

According to the indication of delivery, the cases were classified as spontaneous preterm, PPROM, or induced delivery. Spontaneous delivery was defined as regular uterine contractions accompanied by cervical dilatation and progressive changes in effacement. Induced delivery was defined as the induction of labor or cesarean delivery due to an unstable fetal condition. Assisted reproductive technology pregnancies referred tothe use of anytreatment method (in vitro fertilization or intracytoplasmic sperm injection) that involved the removal of eggs from the ovaries and combining them with sperm by applying a surgical procedure to achieve pregnancy.

Ultrasonography

The sonographic examinations of all participants were performed by a single obstetrician (X) with more than five years of experience, under the supervision of a professor of maternal-fetal medicine (X). To prevent intra-observer and inter-observer errors, at least three measurements were taken by the same sonographer (X), and the mean values of these measurements were used in statistics. Sonographic evaluations were performed using the Voluson E8 ultrasound device (GE Healthcare, Milwaukee, WI) with a 2.3-8.4 MHz convex transducer (C2-9-D) transabdominal probe. Fetal ultrasonography included biometry, fetoplacental Doppler, and fetal cardiac parameters. The fetal cardiac morphology of all fetuses included in the study was normal. The percentile values for estimated fetal weight were calculated as described by Hadlock et al. (10).

Dichorionic diamniotic twin pregnancies were defined based on the different sexes of the fetuses, two separate placental locations, or the thickness of the membrane where the amniotic membrane entered the placenta creating a "lambda sign" (11). Cases in which chorionicity could not be clearly distinguished were excluded from the study. The measurements of the aortic valve diameter and the pulmonary valve diameter were obtained from the images of the right ventricular outflow tract (RVOT) and the left ventricular outflow tract (LVOT). Using the same images, the flow rates of the left ventricular CO (LVCO) and the right ventricular CO (RVCO) were measured immediately distal to the valves by keeping the insonation angle close to 0 °and adjusting the Doppler cursor to 2-3 mm. The combined CO was obtained as the sum of LVCO and RVCO (12). The Z-scores of the cardiac outflow tracts were calculated according to the study by Mao et al.(13). The Mod-MPI measurement was performed in the left ventricle from the lateral wall of the aorta, including both the aortic and mitral valves, using the Doppler cursor in the apical four-chamber view.The Mod-MPI value was calculated by dividing isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) by ejection time (14). The aortic and pulmonary artery valve Z-scores were determined according to the week of gestation. All cardiac measurements were obtained during fetal silence conditionat a fetal heart rate of 120-160 beats/min.

Statistical analysis

SPSS version 22 (IBM, Chicago, IL, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was conducted to determine whether the data fit the normal distribution. Upon determining that the data did not havea normal distribution, the Mann-Whitney U test was used for the comparison of the two groups. The chi-square test was used when examining categorical variables. Data were presented as median (interquartile range) or number (percentage). $P<0.05$ was considered statistically significant.

RESULTS

A total of 74 dichorionic diamniotic twin fetusesborn preterm were included in the study. The sample was divided into two groups: early preterm (n = 34) and late preterm (n = 40). The demographic characteristics and perinatal outcomes of all participants are presented in Table 1. Age, body mass index (BMI), gestational week at ultrasonography, estimated fetal weight, fifth-minute Apgar score, placental localization, gravidity, parity, and number ofspontaneous abortions were similar between the early and late preterm groups. However, the groups significantly differed in terms of delivery week, delivery indications, birth weight, first-minute Apgar scores, and requirement of NICU admission ($p<0.001$, $p=0.007$, $p<0.001$, $p=0.014$, and $p= 0.003$, respectively).

The comparison of the cardiac functions of the early and late preterm groups is shown in Table 2. Accordingly, the aortic velocity time integral (VTI) and aortic peak systolic velocity (PSV) values were found to be statistically significantly lower among the early pretermdichorionic twins ($p<0.001$ and $p=0.002$, respectively). The LVCO and LVCO Z-scores were also statistically significantly lower in the early preterm group ($p=0.0029$ and $p=0.014$, respectively). The remaining CO parameters and Mod-MPI were similar between the early and late preterm groups.

Table 3 presents the data related to the cardiac function of the dichorionic diamniotic twins in the preterm group according to their status of admission to the NICU. Of the early preterm group, 20 were admitted to the NICU and had significantly higher Mod-MPI, LVOT-ICT, and LVOT-IRT values ($p = 0.002$, $p = 0.003$, and $p = 0.001$, respectively) compared to those who did not require NICU admission (n = 14). In addition, the neonates admitted to the NICU had a statistically significantly lower aortic annulusvalue and Z-score ($p = 0.001$ and $p = 0.039$, respectively). When the pulmonary artery parameters were examined, the pulmonary artery annulus and Z-score were statistically significantly lower in the NICU-admitted group ($p=0.006$ and $p=0.041$, respectively). Lastly, the fetal heart rate was significantly higher in the group requiring NICU admission ($p=0.013$).

Table 1. Comparison of demographic data and perinatal outcomes of dichorionic twin fetuses between the early and late preterm groups.

	Early preterm (n = 34)	Late preterm (n = 40)	P value
Maternal age (years)	30 (8.3)	29.5 (12.5)	0.931
Maternal BMI (kg/m^2)	29.8 (3.8)	28.8 (6.3)	0.543
Gravidity	2 (2)	2 (2)	0.820
Parity	1 (1)	0.5(1.8)	0.523
Abortion	0 (1)	0 (1)	0.871
Conception method, n (%) ART Spontaneous	 14 (41.2%) 20 (58.8%)	 22 (55%) 18 (45%)	0.236
Gestational week[a]	30 (5.3)	30.5 (4.5)	0.469
Delivery week	33 (3)	36 (1.8)	<0.001
Delivery mode, n (%) Cesarean section Vaginal delivery	 32 (94.1%) 2 (5.9%)	 40 (100%) 0	0.120
Complications, n (%) GH GD	 2 (5.9%) 4 (11.8%)	 6 (15%) 4 (10)	0.451
Estimated fetal weight (grams)	1,471 (657.5)	1,625 (781.3)	0.224
Birth weight (grams)	1,805 (757.5)	2,445 (441.3)	<0.001
First-minute Apgar score<7, n (%)	10 (29.4%)	3 (7.5%)	0.014
Fifth-minute Apgar score<7, n (%)	3 (8.8%)	0	0.055
NICU admission, n (%)	20 (58.8%)	10 (25%)	0.003
Placental localization, n (%) Anterior Posterior	 21 (61.8%) 13 (38.2%)	 17 (42.5%) 23 (57.5%)	0.098

(BMI: body mass index, ART: assisted reproductive technology, PPROM: preterm prelabor rupture of membranes, GH: gestational hypertension, GD: gestational diabetes, NICU: neonatal intensive care unit)
Data are expressed as median (interquartile range) or number (percentage). Statistically significant at $p < 0.05$.
[a]Gestational age at which ultrasonogprahy was performed.

Table 2. Comparison of the cardiac functions of the dichorionic twin fetusesbetween the early and late preterm groups.

	Early preterm (n = 34)	Late preterm (n = 40)	P value
Fetal heart rate	150 (13.3)	143 (13.5)	0.078
Aortic VTI (cm)	0.068 (0.027)	0.084 (0.021)	<0.001
Aortic annulus (mm)	4.7 (1.2)	4.9 (0.9)	0.724
Aortic annulus (Z-score)	0.1 (1.2)	0 (1.3)	0.914
Aortic PSV	55.5 (14.3)	63 (9.8)	0.002
PA-VTI (cm)	0.083 (0.027)	0.082 (0.024)	0.944
PA annulus (mm)	5.8 (1.3)	6.1 (1.2)	0.210
PA annulus (Z-score)	0 (1.9)	-0.1 (0.7)	0.308
PAPSV	55 (13.5)	55.5 (18)	0.832
LVCO (ml/ms)	193.2 (83.1)	216.8 (114.3)	0.029
LVCO(Z-score)	-1.3 (1.0)	-0.4 (1.4)	0.014
RVCO (ml/ms)	315.1 (225.1)	351.7 (281.4)	0.179
RVCO(Z-score)	-0.9 (1.7)	-0.8 (1.8)	0.248
CCO (ml/ms)	497.7 (220.5)	582.5 (381.9)	0.099
CCO(Z-score)	-0.9 (1.0)	-0.6 (0.7)	0.063
LVOT-ICT	36.5 (10.3)	37 (10)	0.974
LVOT-IRT	48 (13.3)	47 (10)	0.527
LVOT-ET	152 (30.5)	160 (20)	0.093
Mod-MPI	0.58 (0.15)	0.53 (0.11)	0.144
Mod-MPI (Z-score)	0.8 (1.2)	0.4 (0.9)	0.144
MCA-PSV	31 (11.8)	31.5 (12.5)	0.348
MCA-PI	1.6 (0.4)	1.6 (0.4)	0.618
UA-PI	0.9 (0.3)	1 (0.2)	0.637

(VTI: velocity time integral, LVCO: left ventricular cardiac output, RVCO: right ventricular cardiac output, CCO: combined cardiac output, LVOT: left ventricular outflow tract, ICT: isovolumetric contraction time, IRT: isovolumetric relaxation time, ET: ejection time, Mod-MPI: modified myocardial performance index, MCA: middle cerebral artery, PSV: peak systolic velocity, PI: pulsatility index
Data are expressed as median (interquartile range). Statistically significant at $p < 0.05$.

Table 3. Comparison of the cardiac functions of the early preterm dichorionic twin fetusesaccording to their NICU admission status.

	Admitted to NICU (n = 20)	Not admitted to NICU (n = 14)	P value
Fetal heart rate	153 (7.5)	142 (14.5)	**0.013**
Aortic VTI (cm)	0.072 (0.03)	0.068 (0.02)	0.806
Aortic annulus (mm)	4.5 (1.0)	5.3 (0.6)	**0.001**
Aortic annulus (Z-score)	-0.3 (1.4)	0.4 (1.1)	**0.039**
Aortic PSV	56 (14.5)	53 (14.3)	0.713
PA-VTI (cm)	0.081 (0.03)	0.086 (0.02)	0.327
PA annulus (mm)	5.5 (1.7)	6.5 (1.1)	**0.006**
PA annulus (Z-score)	-0.3 (1.8)	0.5 (1.9)	**0.041**
PAPSV	55 (19)	54.5 (14)	0.563
LVCO (ml/ms)	154.2 (112)	197.9 (60.4)	0.124
LVCO (Z-score)	-1.4 (1.9)	-1.2 (0.8)	0.687
RVCO (ml/ms)	260.2 (185.6)	351.6 (134.4)	**0.025**
RVCO (Z-score)	-1.1 (1.6)	-0.6 (1.4)	0.156
CCO (ml/ms)	447.8 (265.5)	574.7 (179.9)	**0.025**
CCO (Z-score)	-1.1 (1.4)	-0.7 (0.6)	0.335
LVOT-ICT	45 (12.5)	36 (9.8)	**0.003**
LVOT-IRT	55 (11.5)	45.5 (7)	**0.001**
LVOT-ET	149 (30.8)	154.5 (28.8)	0.726
Mod-MPI	0.64 (0.2)	0.51 (0.1)	**0.002**
Mod-MPI (Z-score)	1.2 (1.3)	0.2 (1.1)	**0.002**

(NICU: neonatal intensive care unit, VTI: velocity time integral, PSV: peak systolic velocity, LVCO: left ventricular cardiac output, RVCO: right ventricular cardiac output, CCO: combined cardiac output, LVOT: left ventricular outflow tract, ICT: isovolumetric contraction time, IRT: isovolumetric relaxation time, ET: ejection time, Mod-MPI: modified myocardial performance index
Data are expressed as median (interquartile range). Statistically significant at $p < 0.05$.

DISCUSSION

This prospective study showed that the aortic VTI, aortic PSV, and LVCO values were lower in the dichorionic twins born early preterm compared to those born late preterm.In addition, higher Mod-MPI, pulmonary artery, and aortic annulus values were observed amongthe dichorionic diamniotic twin fetuseswho requiredadmission to the NICUin the early preterm group. Our study provides evidence showing the importance of cardiac functions in dichorionic twin fetusesborn preterm. To the best of our knowledge, this is the first study to examine CO and Mod-MPI in preterm dichorionic twin fetuses.

Twin pregnancies have higher rates of obstetric complications, preterm delivery, and perinatal morbidity and mortality compared to singleton pregnancies(15). Prematurity is one of the most important causes of high perinatal mortality in twin pregnancies (16).Studies have shown that the rates of preterm birth in twin pregnancies range from 31% to 63% (17, 18).In addition to spontaneous prematurity among the causes of preterm birth, nearly half of preterm twin births have been reported to be medically induced (19). However, there are not yet clear markers to predict the occurrence of preterm birth and perinatal morbidity and mortality in twin pregnancies. In a previous study, it was determined that amniotic membrane thickness could be used to determine adverse perinatal outcomes in dichorionic twins (20). In the current study, the Mod-MPI value was found to be higheramongthe dichorionic twins who were admitted to the NICU in the early preterm group. This finding suggests that the Mod-MPI value may be significant in predicting NICU after an early preterm delivery.

The fetal Mod-MPI is a non-invasive measure of myocardial function derived from pulsed-wave Doppler ultrasonography (21). It has become a reliable marker of fetal cardiac dysfunction. Among the components of Mod-MPI, ICT is affected by systolic changes, while IRT is affected by diastolic changes (22). Some studies have shown that fetal MPI is affected by conditions such as diabetic and post-term pregnancies, PPROM, intrauterine fetal growth retardation, and twin-twin transfusion syndrome (23-26). Zhang et al. determined that Mod-MPI could be used to predict adverse perinatal outcomes in fetuses with intrauterine growth retardation (27). In a study consisting of pregnant women with placenta previa

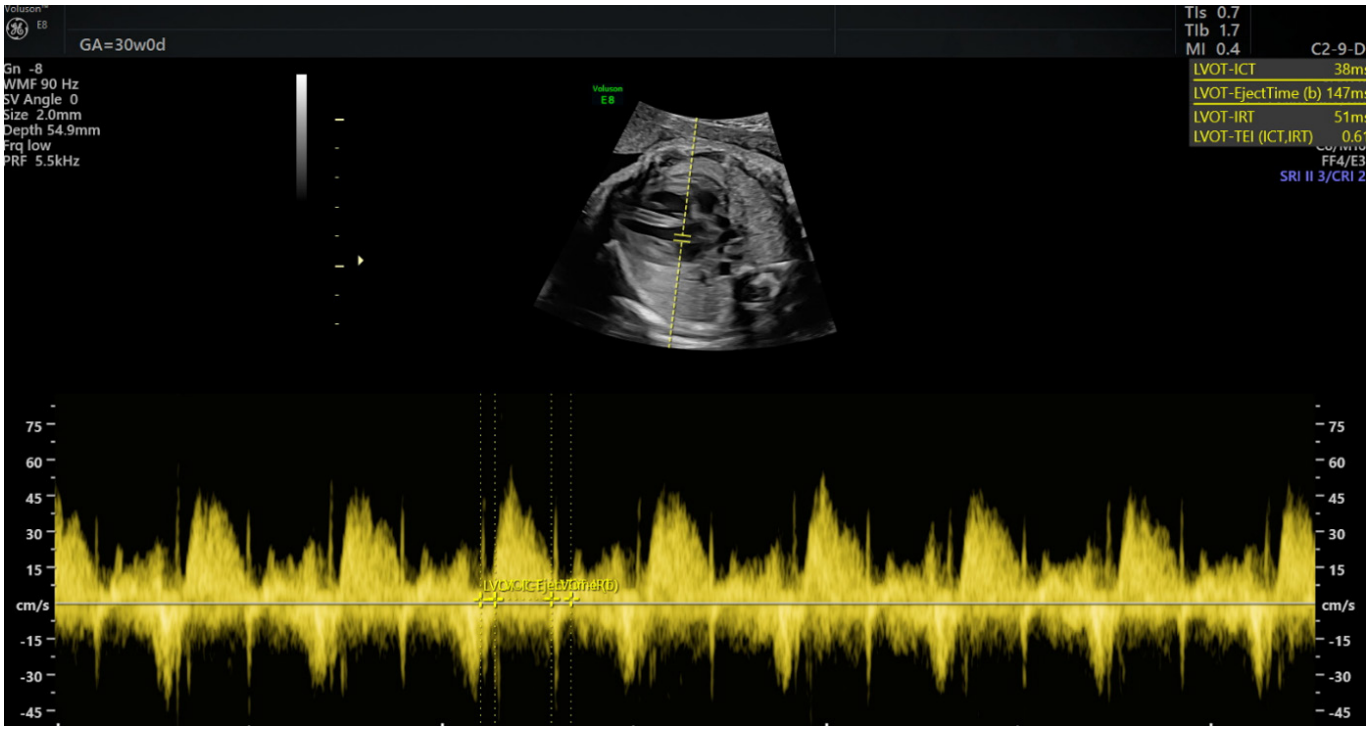

Figure 1. Measurement modified myocardial performance index (Mod-MPI).

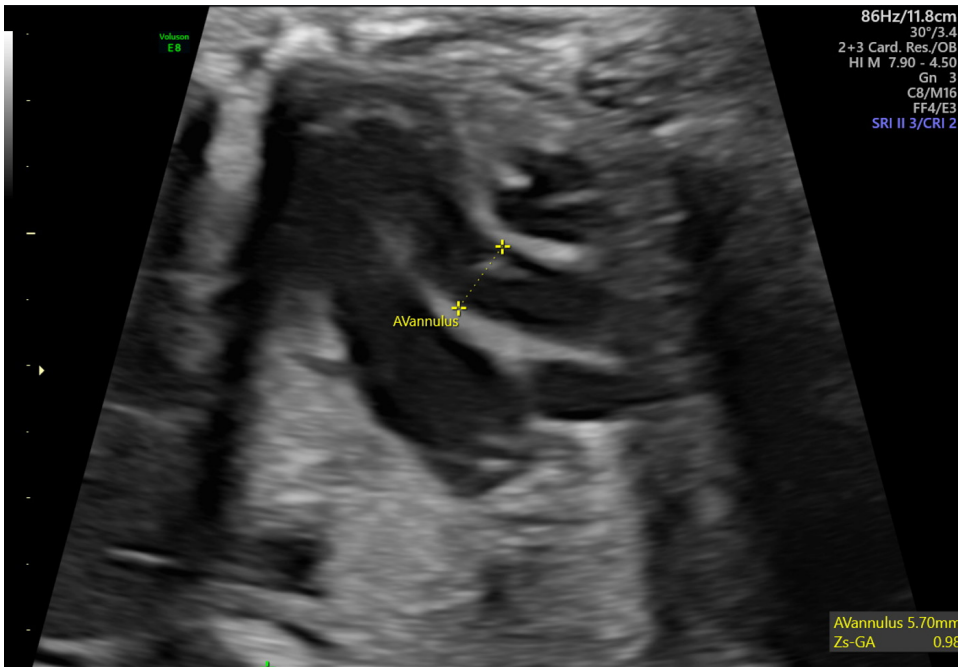

Figure 2. Aortic valve annulus diameter.

and healthy controls without fetal anomalies, the fetal Mod-MPI value was found to be an independent risk factor in demonstrating adverse fetal outcomes in patients with placenta previa (28). In the current study, we observed similar Mod-MPI values between the early and late preterm groups of dichorionic twins. However, we also determined that the Mod-MPI, LVOT-ICT, and LVOT-IRT values were higher among those requiring NICU admission in the early preterm group. The concomitant increase in IRT and ICT may also be an early sign of loss of both systolic and diastolic functions in these patients. Therefore, our study shows the importance of a close follow-up in fetuses with high Mod-MPI values.

CO is obtained by multiplying the stroke volume by the heart rate and depends on three main factors: preload, afterload, and myocardial contractility (29). A functioning heart consistently maintains an appropriate CO and adapts to changing circulatory demands.In fetal

life, both ventricles usually work in parallel, and CO measurements are usually obtained by performing the calculationofeach ventricle separately (30). The distribution of CO in the fetus is likely to be affected by fetoplacental growth and development (31).In some cases, studies have shown that fetal CO is increased. Increased CO has been observed in certain types of fetal arteriovenous shunts, such as fetal anemia, hypoxia, intrauterine fetal growth retardation, fetal teratoma, or placental chorioangioma (32-34). A decrease in CO, defined as a Z-score of less than 2, indicates decreased ventricular filling or contractility, which is responsible for most cases of fetal heart failure, including structural cardiac defects (35). In our study, in which we examined dichorionic twins born preterm, combined CO was found to be similar between the early and preterm groups, while LVCO was lower in the early preterm group. We did not observe any difference in CO according to the NICU admission status in the early preterm group.

Fetal aortic stenosis can lead to increased left ventricular afterload, resulting in the loss of systolic and diastolic functions (8). Fetuses with aortic stenosis are associated with worse diastolic dysfunction, larger left ventricle, more extensive endocardial fibroelastosis, and lower left ventricular pressure (36). Pulmonary stenosis can occur as part of complex congenital heart disease or as an isolated finding, causing unfavorable remodeling of the right ventricle and increased filling pressure (37).The fetal pulmonary artery annulus measurement has been observed to be similar in terms of perinatal outcomes in patients with PPROM (38). In the current study, the aortic annulus and pulmonary artery annulus measurements were lower among the infants admitted to the NICUin the early preterm group.The results of our studyare intriguing in terms of the relationship between the arterial measurementsof fetuses without cardiac anomalies and morbidity in twins.

Fetal cardiac ultrasonography is a non-invasive evaluation that provides valuable information on fetal hemodynamics and cardiovascular adaptation according to intrauterine environment conditions. In recent years, with the increase in the quality of ultrasonography devices and the experience of specialists, the widespread use of fetal cardiac ultrasonography has allowed clinicians to obtainusefulinformation in terms of fetal well-being. Our preliminary data suggest that fetal CO and Mod-MPI may play a role in predicting perinatal outcomes in dichorionic twin pregnancies.

Limitations

This study has certain limitations. First, it was conducted in a singlecenter with a relatively lownumber of patients, which may have resulted inan insufficient analysis. Further comprehensive and multicenter studies are needed to overcome thislimitation. Second, we did not include long-term neonatal outcomes. Despite these limitations, thestrength of our study was that it was undertaken in a tertiary centerwith high-quality equipment and experience infetal ultrasonography.

CONCLUSION

To the best of our knowledge, this is the first study to perform a fetal cardiac ultrasonographic evaluation in dichorionic twin fetusesborn preterm. Our study provides evidence showing the value of Mod-MPI measurement in predicting adverse perinatal outcomes in early preterm dichorionic twin fetuses. The accurate prediction and early detection of complications should be prioritized in the management of twin pregnancies since they offer the opportunity for timely intervention and improved outcomes. However, the mechanisms underlying these changes have not yet been clarified; therefore, there is a need for well-designed, large-population studies to provide a better understanding ofthe role of cardiac function in demonstrating fetal well-being.

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