Original Article

Evaluation of the efficacy of intrauterine treatments of twin-to-twin transfusion syndrome using myocardial performance index

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Background: Prognosis of twin-to-twin transfusion syndrome (TTTS) varies depending on the Quintero stage and fetal cardiac function. The purpose of our study was to evaluate fetal cardiac function before and after different intrauterine treatments of TTTS through myocardial performance index (MPI).

Methods: In this retrospective study, data were collected from August 2016 to December 2022. Totals of 68 cases of TTTS and 68 monochorionic diamniotic (MCDA) twins without TTTS were included. MPI was collected and compared between TTTS and MCDA twins without TTTS before intrauterine treatments. TTTS cases were divided into 3 groups according to different intrauterine treatments: (I) amnioreduction (34 cases), (II) fetoscopic laser photocoagulation (FLPC; 20 cases), and (III) selective reduction (14 cases). The MPI of the left ventricle (LV) and right ventricle (RV) in each surviving fetus were measured 48 hours before and after treatments by pulse Doppler ultrasound. One-way analysis of variance (ANOVA) was employed to assess whether there were statistical differences in LV-MPI and RV-MPI among the donors, recipients, and the control group. Paired *t*-test analysis was used to compare whether there were differences in MPI before and after intrauterine treatments.

Results: The MPIs of the LV and RV in the recipients were significantly higher than those in the MCDA twins without TTTS ($P<0.05$). After the amnioreduction treatment of TTTS, no significant differences were observed in the MPI of either the LV or the RV before and after treatment. At 48 hours after FLPC treatment, the value of the LV-MPI in donors was 0.25±0.08, and the value of the RV-MPI in recipients was 0.58±0.17. Both of them were significantly lower than those before the treatment ($P<0.05$). In the selective reduction group, the value of the RV-MPI in surviving recipients significantly decreased compared to that before treatment ($P<0.05$).

Conclusions: MPI is an effective indicator to evaluate fetal cardiac function of TTTS and assess the efficacy of intrauterine treatments of TTTS.

Keywords: Myocardial performance index (MPI); fetal cardiac function; prenatal ultrasonography; twin-to-twin transfusion syndrome (TTTS)

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Introduction

Twin-to-twin transfusion syndrome (TTTS) primarily affects monochorionic diamniotic (MCDA) twin pregnancies, presenting as a complex condition associated with significant fetal and maternal complications (1). The pathophysiology is unbalanced unidirectional vascular anastomosis on the placenta, causing a net transfer of fluid from one twin to the other, resulting in a donor twin with hypovolemia and a recipient twin with hypervolemia (2). If not treated in time, the fetal mortality rate is very high, and some of the cases of survival have serious sequelae.

In TTTS, a wide spectrum of cardiac findings can occur, ranging from subtle differences in the recipient's cardiac structure to severe abnormalities that can lead to fetal demise (3). In its mild stage, TTTS may present with subtle cardiac changes in the recipient twin, such as ventricular dilation and wall thickening (4). However, as the disease progresses in severity, the recipient twin can exhibit significant cardiac enlargement, hypertrophy, and dysfunction of both valves and ventricles, often resulting in fetal death. Even among fetal survivors, postnatal sequelae can persist, including the persistence of right ventricular outflow tract obstruction in recipients and abnormalities in arterial distensibility in donors (5,6). These cardiovascular abnormalities play a significant role in the overall morbidity and mortality observed in TTTS cases.

Some researchers suggest that prognosis of TTTS varies depending on the Quintero stage and fetal cardiac function (7). The evaluation indexes of fetal cardiac function mainly include: E/A ratio of cardiac inflow flow, venous catheter flow spectrum, ventricular ejection fraction, cardiovascular scoring system, and myocardial performance index (MPI) (8). The E/A ratio of cardiac inflow has been used to evaluate ventricular diastolic function by reflecting cardiac compliance and preload (9). The spectrum of venous catheter flow has a certain value in the evaluation of fetal heart failure. Ventricular ejection fraction is one of the indexes reflecting the systolic function of the heart. A cardiovascular scoring system is mainly used to evaluate the cardiac function of the edematous fetus.

MPI, also known as the Tei index, is the ratio of the sum of the duration of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) to the duration of the ejection time (ET). It has been reported a potentially useful predictor of global cardiac function, which is not influenced by heart size, shape, orientation, geometry, or rate. Its application in the fetus has advantages over that in adults since it is possible to measure the atrioventricular and semilunar valve flows simultaneously, avoiding the inaccuracy predisposed in measuring different heartbeats (10). Therefore, we aimed to evaluate fetal cardiac function of TTTS and preliminarily predict the efficacy of intrauterine treatments of TTTS by MPI. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1669/rc).

Methods

Study population and selection criteria

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Second University Hospital (No. 2016065). The requirement for individual consent for this retrospective analysis was waived.

The study was performed in West China Second University Hospital. Data were collected from August 2016 to December 2022. All pregnant patients included in the study delivered their babies in our hospital. The inclusion criteria were as follows: (I) MCDA; (II) TTTS; (III) complete clinical information; (IV) regular prenatal examination and delivery in our hospital. The exclusion criteria were as follows: (I) one of the twins died; (II) incomplete clinical information; (III) maternal complications such as pregnancy-induced hypertension and gestational diabetes mellitus; (IV) fetal structural abnormality; (V) chromosomal abnormality; (VI) placental abnormalities.

Of 1,620 MCDA, 141 twins were diagnosed with TTTS. According to the exclusion criteria, 68 cases of TTTS were included in this study. In addition, 68 cases of MCDA twins without TTTS with the same gestational age were selected as the control group during the same period in the hospital, gestational age at birth-matched, and without fetal structural malformations, markers of aneuploidy, chromosomal abnormality, and placental abnormalities. For the MCDA twins without TTTS, we measured the MPI of the left ventricle (LV) and right ventricle (RV) of the 2 fetuses respectively, and calculated the average value of LV and RV as the control group.

Definitions of TTTS

Patients were referred to our hospital conducting in the

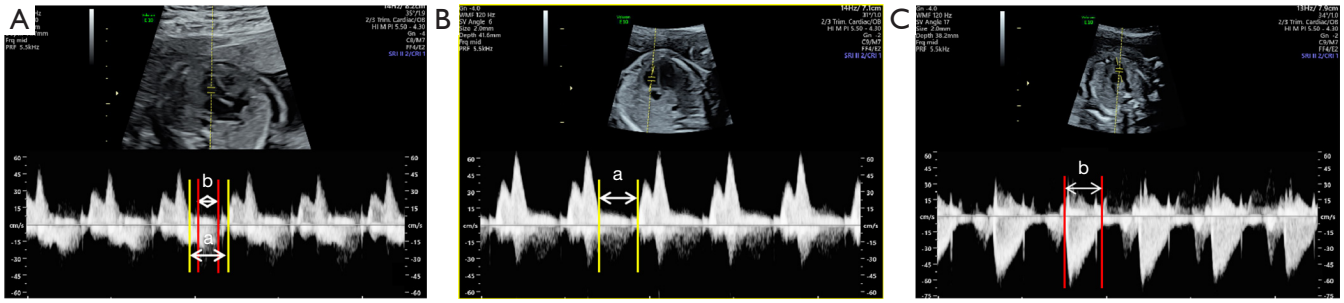

Figure 1 Ultrasound images of LV-MPI and RV-MPI measurements. (A) Ultrasound images of LV-MPI measurement. (B,C) Ultrasound images of RV-MPI measurement. The yellow lines represent the start and end of a's measurement and the red lines represent the start and end of b's measurement. The arrow means the measurement distance. a represents the time of mitral valve from closing to opening, and b represents ejection time. LV, left ventricle; MPI, myocardial performance index; RV, right ventricle.

study for the evaluation of TTTS. The diagnosis of TTTS was confirmed and classified based on the Quintero staging system (7). Demographic data, including maternal age, pregnancies, and parity were collected. Gestation ages at scan and at delivery were also recorded. Gestational age was determined by crown-rump length (CRL) measurement during the first-trimester scan, and the estimated date of delivery was corrected when a discrepancy of ±3 days between the date of delivery estimated by CRL and the estimated date of the last menstrual period was identified.

Ultrasound examination

All ultrasound examinations were performed using GE Voluson E10 and GE Voluson E8 (GE Healthcare, Milwaukee, WI, USA) with a 3.0–6.0 MHz trans-abdominal curved probe. Fetal biological indicators such as biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) were measured. Estimated fetal weight (EFW) was converted into percentiles for gestational age using the ultrasound based adjusted for gestational age nomograms (11). Fetal anatomy scans were performed using color Doppler ultrasound between 18 and 22 weeks of gestational age. The blood flow spectrum of the umbilical artery (UA), ductus venosus (DV), mitral valves (MV), and tricuspid valves (TV) were measured by pulsed Doppler ultrasound.

MPI is defined as the sum of isovolumic contraction and relaxation time (isovolumic time) divided by ventricular ET MPI = (ICT + IRT)/ET = (a-b)/b (10). ICT: isovolumetric contraction time; IRT: isovolumetric relaxation time; ET: ejection time; a represents the time of MV from closing to opening; b represents ET.

LV-MPI measurement (12): the 5-chamber incisal plane of the heart was scanned, the sampling volume was placed between the inflow tract and outflow tract of the LV, and the blood flow spectrum of the inflow tract and outflow tract was obtained (*Figure 1A*). The time of MV from closing to opening was denoted as "a". ET was denoted as "b".

RV-MPI measurement (12): the incisal plane of the 4 chambers of the heart was scanned, the sampling volume was placed in the anterior lobe of the TV respectively, the flow spectrum of the right ventricular inflow tract was obtained, and the measured time from closing to opening of the TV was recorded as "a" (*Figure 1B*). The section of the right ventricular outflow tract was scanned, and the sampling volume was placed under the pulmonary valve to obtain the flow spectrum of the right ventricular outflow tract, and the time from opening to closing of the pulmonary valve was measured as "b" (*Figure 1C*).

MPI of LV and RV in TTTS with intrauterine treatments were measured 48 hours before and after treatments. Fetal heart rate was also recorded during each measurement. Differences in fetal heart rate should remain <10 bpm during measurement. A total of 3 consecutive cardiac cycles were measured and averaged. The sampling angle was <30°, the sampling volume was 1–2 mm, and the recording speed was <200 mm/s.

Imaging evaluation

All ultrasound images and findings were verified by 2 other sonographers with 12 and 10 years of experience, respectively.

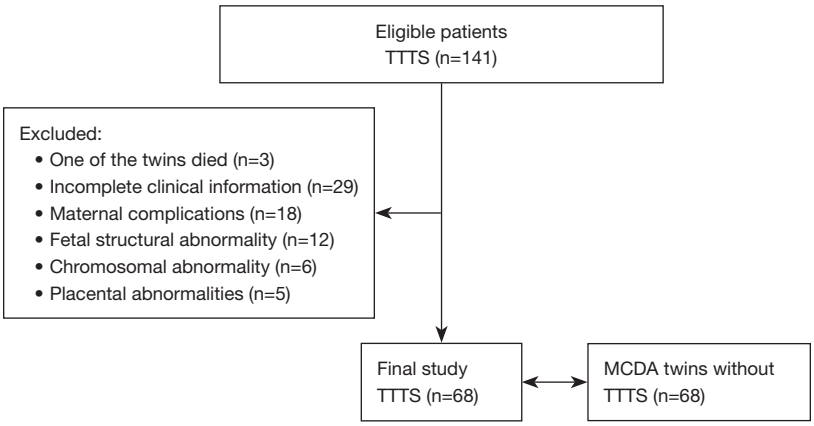

Figure 2 The flowchart of participants throughout the study. TTTS, twin-to-twin transfusion syndrome; MCDA, monochorionic diamniotic.

Statistical analysis

The software SPSS 22.0 (IBM Corp., Armonk, NY, USA) was utilized for statistical analysis. Data are presented as mean ± standard deviation and the number of each group is expressed as n.

Comparison of MPI

The chi-square test was used to determine if there is a significant association between 2 categorical variables, and Student's *t*-test was used to compare in the non-categorical data.

One-way analysis of variance (ANOVA) was employed to assess whether there were statistical differences in LV-MPI and RV-MPI among the donors, recipients, and the control group. If the result was significant, Dunnett's test was used for within-group comparison, including donor versus recipient, donor versus control, and recipient versus control.

Comparison before and after intrauterine treatments

Paired *t*-test was applied to compare the MPI of LV and RV before and after intrauterine treatments. A P value <0.05 was considered statistically significant.

Results

A total of 68 cases of TTTS were collected (*Figure 2*), including 17 cases at stage I, 19 cases at stage II, 22 cases at stage III, and 10 cases at stage IV, based on the Quintero staging system. As shown in *Table 1*, maternal demographic factors and fetal characteristics were compared between the TTTS group and the control group. The estimated weight difference of twins in the TTTS group was 21.64%±6.81%, greater than that of the control group (P<0.05).

In the study, there were 22 cases in stage III and 10 cases in stage IV. *Table 2* presents the abnormal blood flow spectrum in TTTS at stages III and IV.

Through ANOVA, we observed a statistical difference among the recipients, donors, and control groups before treatment (P<0.001) (*Table 3*). Further pairwise analysis revealed that both the LVs and RVs of blood recipients exhibited higher values in LV-MPI (0.57±0.21) and RV-MPI (0.67±0.32) compared to those of donors and the control group (P<0.001). However, there was no significant difference in LV-MPI and RV-MPI between the donors and control group (*Figure 3*).

One-way ANOVA of the LV-MPI and RV-MPI among the control, donors, and recipients groups.

A total of 68 cases of TTTS were included in the study. Among these cases, 34 underwent amnioreduction, 20 underwent fetoscopic laser photocoagulation (FLPC), and 14 underwent selective fetal reduction. Within the amnioreduction group, 28 twins survived, 5 twins died, and in 1 case, 1 twin survived while the other died. In the FLPC group, 14 twins survived and 6 twins died. In the selective reduction group, 6 twins died, 8 recipients survived, and 8 donors died.

After amnioreduction treatment of TTTS, there were no significant differences observed in LV-MPI and RV-MPI between before and after treatment (P>0.05, *Table 4*). However, at 48 hours after FLPC treatment, the LV-MPI in donors was 0.25±0.08, and the RV-MPI in recipients was

Table 1 Demographic and clinical characteristics of the TTTS and control group

Characteristic	TTTS (n=68)	Control (n=68)	P value
Maternal age (years)	28.34±4.43	27.61±3.98	0.321 (*t*-test)
Previous pregnancies, n (%)			0.116 (Chi-square test)
0	20 (29.41)	18 (26.47)	
1	30 (44.12)	34 (50.0)	
2	16 (25.93)	12 (17.64)	
≥3	2 (2.94)	4 (5.88)	
Parity, n (%)			0.210 (Chi-square test)
0	36 (52.94)	42 (61.76)	
1	22 (32.35)	18 (26.47)	
2	8 (11.76)	6 (8.82)	
≥3	2 (2.94)	2 (2.94)	
Gestational age at scan (weeks)	19.36±3.22	20.67±4.28	0.108 (*t*-test)
Differential estimated weight of twins (%)	21.64±6.81	9.85±5.94	0.020 (*t*-test)

Data are presented as mean ± standard deviation. TTTS, twin-to-twin transfusion syndrome.

Table 2 Abnormal blood flow spectrum of fetus of TTTS in stage III and IV

Quintero stage	TTTS	ARUA, n (%)	ARDV, n (%)	MR, n (%)	TR, n (%)
Stage III (n=22)	Recipients	7 (31.8)	6 (27.3)	3 (13.6)	11 (50)
	Donors	10 (45.5)	8 (36.4)	1 (4.5)	2 (9.1)
Stage IV (n=10)	Recipients	5 (50)	4 (40)	4 (40)	4 (40)
	Donors	6 (60)	5 (50)	2 (20)	2 (20)

TTTS, twin-to-twin transfusion syndrome; ARUA, absence or inversion of diastolic blood flow in the umbilical artery; ARDV, absence or inversion of a wave in ductus venosus; MR, mitral regurgitation; TR, tricuspid regurgitation.

Table 3 Comparison of LV-MPI and RV-MPI in donors, recipients in TTTS before treatments and the control group

Groups	LV-MPI (n=68)	RV-MPI (n=68)
Control	0.33±0.03	0.30±0.08
Donors	0.37±0.22	0.31±0.21
Recipients	0.57±0.21	0.67±0.32
F-value	475.125	227.500
P value	<0.001	<0.001

Data are presented as mean ± standard deviation. LV, left ventricle; MPI, myocardial performance index; RV, right ventricle; TTTS, twin-to-twin transfusion syndrome.

0.58±0.17, significantly lower than that before the treatment (P<0.05, *Table 4*). In the selective reduction group, RV-MPI in surviving recipients significantly decreased compared to before the treatment (P<0.05, *Table 4*).

Discussion

Currently, the assessment of fetal cardiac function relies on several key parameters, including the E/A ratio of cardiac inflow flow, venous catheter flow spectrum, ventricular ejection fraction, cardiovascular scoring system, and MPI (8). Among these, MPI stands out as it

offers a comprehensive evaluation of ventricular function. Importantly, its accuracy remains unaffected by factors such as ventricular geometry, 2-dimensional image quality, blood pressure, and heart rate (10).

Nevertheless, Oliveira has raised difficulties in the clinical application of MPI, such as inconsistent measurement results (10). To address these challenges and enhance the reproducibility of MPI measurements, several strategies can be implemented. First, establishing standardized protocols for MPI measurement can improve consistency, including detailed guidelines for image acquisition, Doppler angle correction, and calculation of MPI parameters. Second, calibration and quality control of imaging equipment and adherence to quality control procedures can minimize variability in MPI measurements. Third, providing comprehensive training programs for healthcare professionals involved in MPI measurements can improve the accuracy and reliability of the technique. In addition to the methods mentioned above, some scholars have proposed an Auto Mod-MPI system which employs a methodology where the operator manually selects a region of interest in the Doppler waveform before automated image analysis takes place (13).

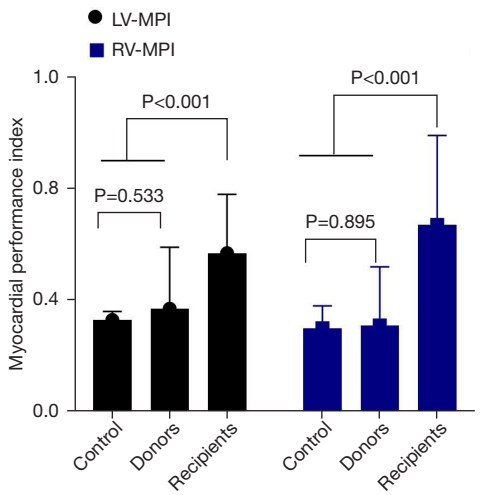

Figure 3 Comparison of LV-MPI and RV-MPI among recipients, donors in TTTS, and control groups before intrauterine treatments by using Dunnett's analysis. LV, left ventricle; MPI, myocardial performance index; RV, right ventricle; TTTS, twin-to-twin transfusion syndrome.

Previous studies (14) have demonstrated that the prognosis of TTTS fetuses is not only correlated with Quintero grade but also closely associated with alterations in cardiac function. Studies have confirmed that an increase in MPI value is associated with an increase in the degree of overall ventricular dysfunction (15). This study showed that before treatment, the RV-MPI value of the recipients was 0.67±0.32, which was significantly higher than that of the normal control group, indicating that the right cardiac function was impaired, resulting in reduced cardiac output and impaired systemic perfusion, such as renal hypoperfusion, oligohydramnios, renal insufficiency, and fetal growth restriction. In addition, reduced cerebral perfusion secondary to cardiac dysfunction may increase the risk of hypoxic-ischemic injury and affect neurodevelopmental outcomes. On the contrary, the RV-MPI value of the donors were 0.31±0.21, which had normal cardiac function before treatments and supported adequate systemic circulation and organ perfusion, including renal

Table 4 The LV-MPI and RV-MPI of TTTS between before and 48 h after intrauterine treatments

Treatment method	Variables	Donors			Recipients		
		Before treatment	After treatment	P value	Before treatment	After treatment	P value
Amnioreduction (n=28)	LV-MPI	0.37±0.22	0.35±0.24	0.24	0.57±0.18	0.55±0.22	0.21
	RV-MPI	0.31±0.21	0.30±0.20	0.39	0.67±0.32	0.64±0.17	0.14
FLPC (n=14)	LV-MPI	0.37±0.15	0.25±0.08	0.01	0.57±0.22	0.54±0.18	0.20
	RV-MPI	0.31±0.11	0.30±0.07	0.41	0.67±0.23	0.58±0.17	0.03
Selective reduction (n=8)	LV-MPI	0.36±0.13	0.33±0.09	0.21	0.56±0.14	0.53±0.12	0.19
	RV-MPI	0.30±0.15	0.28±0.11	0.34	0.69±0.08	0.59±0.17	0.02

Data are presented as mean ± standard deviation. Paired *t*-test was applied to compare the MPI of LV and RV before and after intrauterine treatments. LV, left ventricle; MPI, myocardial performance index; RV, right ventricle; TTTS, twin-to-twin transfusion syndrome; FLPC, fetoscopic laser photocoagulation.

and cerebral blood flow, which is consistent with the findings of Raboisson *et al.* (16).

In this study, RV-MPI in recipients with TTTS was notably higher compared to that in MCDA twins without TTTS before treatments. This result was consistent with previous reports, which showed that the MPI value of recipients was 40% higher than that of singletons (17). This disparity can be attributed to the recipients receiving increased blood perfusion from the donors, leading to an augmented circulating blood volume. Consequently, there is an elevation in RV preload, resulting in decreased RV diastolic function and an extension of the isovolumic diastole period. This suggests that recipients may exhibit severe heart enlargement, hypertrophy, valve and ventricular dysfunction, and the RV is damaged earlier and more significantly than the LV.

The LV-MPI value of recipients was significantly higher than that in MCDA twins without TTTS. This finding is in line with results reported by the Children's Hospital of Philadelphia's (USA) dual-fetal cardiovascular score (CHOP scale) system (18). The possible explanation could be as follows: the increased blood flow in the right atrium of the recipients can enter the left atrium through the foramen ovale, leading to augmented LV preload and constrained LV diastolic function. Consequently, there is an extension of the LV isovolumic diastolic period, contributing to an increase in the MPI. It to some extent reflects the process of cardiac function change in recipients and is also consistent with the pathophysiological process observed in recipients (19).

With the development of maternal-fetal medicine, intrauterine treatments of fetuses becomes more common. Amnioreduction, FLPC, and selective reduction have usually been used in clinical practice (20). Mari *et al.* (21) believed that the prognosis of TTTS was closely related to the gestational week when TTTS occurred, changes in UA, and the appearance of fetal edema. Amnioreduction treatment is performed to release the excess amniotic fluid of the recipient fetus under ultrasound guidance. Becker *et al.* (22) confirmed that it is the preferred treatment for mild TTTS patients at stage I and II. Amnioreduction treatment is a symptomatic treatment. Therefore, it does not improve fetal cardiac function. This is consistent with the results of our study.

A treatment that directly addresses the etiology of anastomotic blood vessels by blocking those between the placenta so that twin fetuses obtain 2 functionally independent circulatory systems greatly improves the prognosis (2). This technique is offered as the first-line treatment option for TTTS at 16–26 weeks of gestation (23). A total of 14 cases of TTTS who underwent FLPC both survived. LV-MPI in donors and RV-MPI in recipients were decreased significantly after FLPC treatment. These findings indicated that FLPC could improve right cardiac function of the recipients and left cardiac function of the donors. In this study, 6 twins died, which may have been due to the rapid increase of peripheral vascular resistance caused by surgery, the sharp increase of RV afterload, or the acute decline of RV systolic function (24), resulting in acute myocardial injury and acute death of the donor fetus (25). The recipients circulate increased blood volume in a short period of time, leading to congestive heart failure (26).

A total of 14 cases of TTTS underwent selective reduction, and 8 fetuses survived. RV-MPI and LV-MPI decreased in surviving fetuses compared to that before treatments. The results showed that selective reduction could improve the surviving fetal cardiac function. MPI is an effective indicator to evaluate fetal cardiac function of TTTS and assess the efficacy of intrauterine treatments of TTTS.

The study has some limitations. First, our study was single-centered and retrospective in design. Second, this study did not determine whether the Tei index was associated with other hemodynamic ultrasound indicators, such as UA, umbilical vein, middle cerebral artery, and DV. Henceforth, we will aim to construct a prognostic model for TTTS utilizing parameters such as MPI, UA, MCA, and DV.

Conclusions

It was found that the cardiac function of the recipients was more likely to change than that of the donors, and the diastolic function was more likely to be affected than the systolic function. MPI applied to TTTS measured by pulsed Doppler ultrasound can evaluate the changes of fetal heart function before and after treatments, and reflect the effect of intrauterine treatments to a certain extent.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1669/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1669/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted according to the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of West China Second University Hospital (No. 2016065) The requirement for individual consent for this retrospective analysis was waived.

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