Early postnatal cardiac follow-up of survivors of twin-twin transfusion syndrome treated with fetoscopic laser coagulation

Gijtenbeek, M.; Haak, M.C.; Eschbach, S.J.; Buijnsters, Z.A.; Middeldorp, J.M.; Klumper, F.J.C.M.; ... ; Harkel, A.D.J. ten

Note: To cite this publication please use the final published version (if applicable).

ARTICLE

Early postnatal cardiac follow-up of survivors of twin–twin transfusion syndrome treated with fetoscopic laser coagulation

Manon Gijtenbeek [1] · Monique C. Haak[1] · Sanne J. Eschbach[1] · Zoë A. Buijnsters[1] · Johanna M. Middeldorp[1] · Frans J.C.M. Klumper[1] · Dick Oepkes[1] · Arend D.J. ten Harkel[2]

Abstract

Objective To assess the cardiac function and prevalence of congenital heart defects (CHD) in twin–twin transfusion syndrome (TTTS) survivors.

Study design Prospective follow-up of TTTS pregnancies treated with laser surgery (2015–2018). Echocardiography was performed 1 day and 1 month after birth (corrected for prematurity). Results were compared with a control group of age-matched uncomplicated monochorionic twin-pairs at 1 month.

Result Eighty-nine TTTS (168 neonates) and nine control pregnancies (18 neonates) were enrolled. CHD birth prevalence was 9.2% (8/87) in recipients and 13.6% (11/81) in donors ($p = 0.37$). Four of 19 (21%) were detected prenatally, all pulmonary stenosis. Donors had lower aortic peak velocities compared with recipients at day 1 (0.66 ± 0.15 m/s vs 0.71 ± 0.19 m/s, $p = 0.04$) and 1 month (1.04 ± 0.21 m/s vs 1.11 ± 0.18 m/s, $p = 0.02$), but not compared with controls.

Conclusion CHD prevalence in TTTS survivors is high, with a low prenatal detection of minor abnormalities. Follow-up fetal echocardiograms and a postnatal echocardiogram should be offered.

Introduction

Monochorionic (MC) twins are at increased risk of congenital heart defects (CHDs) [1]. The development of CHD can partly be attributed to twin–twin transfusion syndrome (TTTS) [2, 3], which affects 10–15% of MC pregnancies and carries a 12-fold increased risk of CHD as compared with singletons [4]. Fetoscopic laser coagulation (FLC), as the curative treatment for TTTS, results in major cardiovascular improvement in affected twins [3, 5–7], but does not prevent the development of subsequent cardiac defects in all cases [8]. There are only a few reports on the effect of

TTTS on postnatal cardiac function, and the majority are focused on cardiac function later in childhood [5, 9–12]. Childhood cardiac function seems normal, but large short-term cardiac function studies after FLC are still lacking [13]. To what rate normalization of cardiac function occurs and whether cardiac function is completely normal at birth remains unknown.

As MC twins complicated by TTTS are at high risk for CHD, a detailed postnatal echocardiogram may be an advantage for early detection of CHD and might improve neonatal management. With this study we aimed to assess cardiac function and postnatal CHD prevalence in TTTS survivors to determine if a postnatal echocardiogram in all TTTS survivors is necessary.

Materials and methods

This was a prospective follow-up study of TTTS survivors after FLC, recruited from a cohort of MC twin pregnancies with TTTS consecutively operated between January 2015 and August 2018 at the Leiden University Medical Center (LUMC). The LUMC is the national referral center for fetal therapy in The Netherlands. A group of age-matched

---

✉ Manon Gijtenbeek
   m.gijtenbeek@lumc.nl

1   Division of Fetal Medicine, Department of Obstetrics, Leiden University Medical Center, Leiden, The Netherlands

2   Division of Pediatric Cardiology, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

healthy MC twin pairs without TTTS born at the LUMC during the study period was used as a control group. MC triplets ($n = 8$) were excluded.

In all cases a comprehensive preoperative ultrasound examination was performed to confirm the TTTS diagnosis and to assess fetal cardiac anatomy. TTTS severity was classified according to the Quintero staging system [14]. Details on the laser technique (either with or without the Solomon technique [15]) at our center and short-term outcome results have previously been reported [16]. All patients in this study were treated with the Solomon technique. Standard echocardiographic assessments of the cardiac anatomy were obtained using a Canon Aplio 500 (Canon Medical Systems Corporation, Otawara, Tochigi, Japan). Cardiac abnormalities detected at follow-up scans were recorded. Prenatal right ventricular (RV) outflow tract obstruction (RVOTO) was classified as functional pulmonary atresia (absence of forward flow across the pulmonary valve (PV) with an exclusive reverse direction of flow in the ductus arteriosus), pulmonary stenosis (PS) (turbulent flow with a peak systolic velocity of >1 m/s), or isolated pulmonary insufficiency (PI) (reversed flow from main pulmonary artery entering the right ventricle) [17].

The following antenatal and neonatal data were recorded: gestational age (GA) at laser surgery, Quintero stage, GA at birth, birth weight and diagnosis of persistent pulmonary hypertension of the newborn (PPHN). PPHN was defined as severe hypoxemia ($PaO_2 < 37.5$–45 mm Hg in a FiO_2 of 1.0) requiring mechanical ventilation and inhaled nitric oxide treatment. Diagnosis of PPHN was only reached if right-to-left shunting in the ductus arteriosus was observed by echocardiography, in the absence of a structural heart defect or severe lung hypoplasia [18].

Postnatal echocardiography using a Vivid E9 or S6 (GE Healthcare, Wauwatosa, WI, USA) was performed according to the guideline of the American Society of Echocardiography [19] in the first days of life (if born in the LUMC) and at the age of 1 month (corrected for prematurity). Standard echocardiographic assessments of the cardiac anatomy and Doppler velocimetry were obtained. PS was diagnosed by pulsed-wave Doppler and was defined as mild (peak velocity < 3 m/s), moderate (peak velocity 3–4 m/s), or severe (peak velocity > 4 m/s). An existing atrial septal defect (ASD) was considered small (>3 to <6 mm), moderate (≥6 and < 8 mm) or large (≥8 mm) [20]. An ASD <3 mm was defined as a persistent foramen ovale and considered as a nonpathological cardiac finding [21]. The images and cine loops were stored as raw data for offline analysis.

Offline analysis

Analyzes were performed using EchoPAC software (GE Healthcare, Wauwatosa, WI, USA) by using the apical 4-chamber view. Left ventricular (LV) and RV diastolic performance were assessed by measurements of peak early-wave velocity (E) (in m/s) and peak atrial contraction wave velocity (A) (in m/s) from spectral Doppler tracings at the tip of the mitral and tricuspid valve. The E/A ratio was calculated. The peak velocity, mean systolic flow velocity, and the velocity time integral (VTI) across the aortic and pulmonic valve were measured using pulsed-wave Doppler. In addition, Tissue Doppler Imaging (TDI) was performed at the LV lateral wall, the interventricular septum (IVS) and the RV-free wall. Longitudinal myocardial velocity curves were obtained by placing the cursor at the basal part of each region. Subsequently, peak systolic velocities (s') and peak early (e') and late diastolic velocities (a') were assessed in each myocardial velocity curve. The mean of three good-quality waveforms was used for all analyses. LV and RV global longitudinal strain were obtained from the apical four-chamber view using speckle-tracking strain analysis, as previously described and according to the international guidelines [22, 23]. The IVS was included in the LV strain analysis.

In TTTS survivors, aortic dimensions were measured. Echocardiographic measurements included the aortic annular diameter, aortic root, sinotubular junction, ascending aorta, proximal transverse arch, distal transverse arch, aortic isthmus, and the distance between the left common carotid and left subclavian arteries. To eliminate the effect of weight and body size, the distal transverse arch/ascending aorta ratio, carotid-subclavian artery index and isthmus/ascending aorta ratio were calculated [24].

Statistical analysis

Data are reported as n (%), mean (standard deviation) or median (interquartile range), as appropriate. For comparisons between donors and recipients we used univariate regression models with a generalized estimated equation module to account for the effect that observations of twin pairs are not independent. Linear regression analysis was used to compare TTTS twins with uncomplicated MC twins. No adjustment was made for multiple comparisons, and results should be interpreted accordingly. Data were analyzed using SPSS v23 (IBM, USA) and the level of significance was set at $p < 0.05$. The population risk of CHDs was based on the study by van der Linde et al. [25].

Results

During the study period, 173 consecutive TTTS pregnancies were treated by FLC. Fetal echocardiography revealed no cardiac anomalies in donor twins. The only CHD detected in recipient twins was RVOTO. Prenatal RVOTO

was detected in 23 out of 173 recipient twins (13.3%); pulmonary atresia $n = 7$, PS $n = 6$, PI $n = 10$. One recipient showed PV calcification. In eight cases, abnormal flow velocity wave form across the pulmonary artery (FWV-PA) became apparent after FLC. In 17 cases, the FVW-PA normalized before birth (in one case the pregnancy was terminated because of intracranial abnormalities in the co-twin). Three recipients with PI demised after FLC.

Of the 173 TTTS pregnancies, 148 had at least one survivor. The 25 other pregnancies resulted in double demise ($n = 3$), inviable delivery ($n = 20$) or termination of pregnancy ($n = 2$). Of the 148 pregnancies, 89 (168 neonates) agreed to participate in this follow-up study. Echocardiography at day 1 was performed in 121 neonates and at the age of 1 month in 143 neonates. The baseline characteristics are depicted in Table 1. Median birthweight was similar between recipients and donors (2001 g vs 1814 g, $p = 0.10$). The second echocardiogram was performed 11 weeks after delivery (range 9–14 weeks) in TTTS twins and and 9 weeks after delivery (range 7–11 weeks) in uncomplicated MC twins. At 44 weeks the weight of TTTS twins was 4271 g, as compared with 4486 g in uncomplicated MC twins ($p = 0.23$). PPHN occurred in three infants (1.8%), all three were recipient twins (3 of 87, 3.4%). Nine uncomplicated MC pregnancies (18 neonates) were enrolled for the second echocardiogram.

Postnatal structural heart disease

The prevalence of CHD (Table 2) in TTTS twins was 11.3% (19/168, 95% CI 7.4–37.7), which was considerably higher than the population prevalence of 0.9% (RR 12.4,

95% CI 7.8–19.9). A heart defect was detected in 9.2% (8/87) of recipients and in 13.6% (11/81) of donors ($p = 0.37$) PS was the most frequently diagnosed defect, detected in 4.2% of TTTS survivors (7/168), of whom five were recipients (five of 87, 5.7%) and two were donors (two of 81, 2.5%). In donors, also three ventricular septal defects (VSDs), three ASDs and three bicuspid aortic valves (BAVs) were detected. There was no family history of BAVs. Two BAV cases were really bi-leaflet. One case appeared functionally bi-leaflet at birth with minimal aortic insufficiency, with a normal follow-up scan (which was not performed as part of this study). Three recipients had a VSD. Two recipients had severe PS, one of whom required balloon valvuloplasty at day 20 and at the age of 7 months. The other recipient with severe PS suffered from a severe infection and died at day 4 before surgery could be performed. Three recipients and two donors had mild valvular stenosis, which did not require intervention so far. These infants with mild PS had normal velocities across the PV valve at birth, but mildly increased velocities at 1 month.

The prenatal detection rate of CHD was 21% (4/19). The donor twin group had a prenatal detection rate of 0%, compared with a detection rate of 50.0% (4/8) in the recipient twin group, which were all PS cases. All ASDs ($n = 6$), BAVs ($n = 3$) and VSDs ($n = 3$) and three mild PS (two donors and one recipient) were undiagnosed before birth. The two other recipients with mild PS had transient increased FVW-PA and PV calcifications post FLC.

Postnatal myocardial function

The only within-twin-pair differences in Doppler echocardiography at day 1 (Table 3) were a lower peak velocity across the aortic valve (AoV) (0.66 ± 0.15 m/s vs 0.71 ± 0.19 m/s, $p = 0.04$) and lower mean velocity across the AoV (0.43 ± 0.10 m/s vs 0.47 ± 0.13 m/s, $p = 0.04$) in donors as compared with recipients. Neonates with BAV had a nonsignificantly lower velocity across the AoV compared with TTTS twins without BAV (0.63 m/s vs

Table 1 Baseline characteristics of the patient population.

Number of TTTS pregnancies	89
Maternal age, years	30 (4.5)
Maternal BMI, kg/m^2	24 (19–30)
Nulliparous	41 (46)
Quintero stage	
1	16 (18)
2	35 (39)
3	34 (38)
4	4 (5)
GA at laser, weeks	19.3 (16.7–21.9)
Number of neonates	168 (87 recipients)
Single survivor	8 (9)
GA at birth, weeks	33.7 (31.3–36.1)
Birthweight, g	1924 (606)

Values are presented as the median (IQR), mean (SD) or n (%).

TTTS twin–twin transfusion syndrome, *BMI* body mass index, *GA* gestational age.

Table 2 Prevalence of CHD in TTTS twins and prenatal findings.

	Recipient	Donor	Prenatally diagnosed
Number of infants	87	81	–
CHD	8 (9.2)	11 (13.6)	4/19 (21.1)
Pulmonary stenosis	5 (5.7)	2 (2.5)	4/7 (57.1)
VSD	0	3 (3.7)	0
ASD	3 (3.4)	3 (3.7)	0
Bicuspid AoV	0	3 (3.7)	0

Values are presented as n (%).

CHD congenital heart defect, *VSD* ventricular septum defect, *ASD* atrial septum defect, *AoV* aortic valve.

Table 3 Cardiac variables in TTTS twins day 1 postpartum.

		Recipient Mean (SD)	Donor Mean (SD)	R–D p value
Doppler echocardiography				
Pulmonary valve	Vmax (m/s)	0.72 (0.188)	0.73 (0.132)	0.92
	Vmean (m/s)	0.51 (0.136)	0.51 (0.096)	0.67
	VTI (m)	0.10 (0.031)	0.10 (0.023)	0.99
Aortic valve	Vmax (m/s)	0.71 (0.193)	0.66 (0.147)	**0.04**
	Vmean (m/s)	0.47 (0.130)	0.43 (0.099)	**0.04**
	VTI (m)	0.09 (0.026)	0.08 (0.021)	0.23
Mitral valve	E (m/s)	0.45 (0.128)	0.45 (0.112)	0.76
	A (m/s)	0.45 (0.121)	0.41 (0.093)	0.08
	E/A ratio	1.01 (0.236)	1.08 (0.351)	0.16
Tricuspid valve	E (m/s)	0.43 (0.116)	0.41 (0.134)	0.24
	A (m/s)	0.49 (0.097)	0.46 (0.105)	0.15
	E/A ratio	0.88 (0.376)	0.89 (0.531)	0.93
Tissue Doppler velocities				
Right ventricle	s' (m/s)	0.049 (0.0011)	0.049 (0.0111)	0.78
	e' (m/s)	0.066 (0.0239)	0.064 (0.0224)	0.65
	a' (m/s)	0.072 (0.0163)	0.067 (0.0136)	**0.04**
Left ventricle	s' (m/s)	0.032 (0.0109)	0.030 (0.0104)	0.17
	e' (m/s)	0.043 (0.0163)	0.041 (0.0177)	0.45
	a' (m/s)	0.040 (0.0174)	0.040 (0.0164)	0.87
Septal	s' (m/s)	0.033 (0.0083)	0.033 (0.0019)	0.82
	e' (m/s)	0.047 (0.0151)	0.042 (0.0107)	**0.03**
	a' (m/s)	0.047 (0.0125)	0.044 (0.0096)	0.12
Deformation measurements				
LV global longitudinal strain (%)		−13.4 (2.56)	−12.8 (3.21)	0.39
RV global longitudinal strain (%)		−15.5 (4.78)	−15.2 (3.93)	0.80

R recipient, *D* donor, *Vmax* maximum velocity, *Vmean* mean velocity, *VTI* velocity time integral, *E* early filling velocity, *A* late filling velocity, *E/A* early/late filling velocity measured with blood flow Doppler, s' ventricle contraction, e' ventricle relaxation, a' atrial contraction measured with TDI, *LV* left ventricle, *RV* right ventricle.

Bold values indicate statistical significance.

0.67 m/s, $p = 0.55$). At birth none of the four PS cases had increased velocities across the PV. Two neonates with pulmonary atresia with minimal or no antegrade flow across the PV. One neonate had turbulent flow across the valve without increased velocities. Another showed only PV calcifications. Diastolic function was similar between donors and recipients and all measures were within the upper level of published normal ranges [26]. Overall donors showed a trend toward lower myocardial motion velocities as compared with recipients, but the only significant differences were lower velocities of late myocardial relaxation (a' wave) at the RV wall and early myocardial relaxation (e' wave) at the basal IVS as measured with TDI. After exclusion of twins with CHD, only the a' wave at the RV wall remained significantly different between donors and recipients (0.073 ± 0.017 cm/s vs 0.067 ± 0.013 cm/s, $p = 0.02$).

At the age of 1 month (Table 4), donors had persisting lower velocities across the AoV compared with recipients (1.04 ± 0.21 m/s vs 1.11 ± 0.18 m/s, $p = 0.02$), but not compared with MC controls (1.10 ± 0.14 m/s, $p = 0.19$). The maximum velocity across the AoV in infants with BAV was 0.92 m/s compared with 1.08 m/s in TTTS infants without BAV ($p = 0.18$). Neonates with PS had higher velocities across the PV compared with TTTS twins without (1.81 m/s vs. 0.98 m/s, $p < 0.001$). Tissue Doppler-derived velocities differed between donors and MC controls in velocities of late myocardial relaxation (a') at the RV wall and early myocardial relaxation (e') at the LV wall.

Aortic dimensions

The results of echocardiographic measurements of the aorta can be found in Supplementary Tables S1 and S2. Donors

Table 4 Cardiac variables in TTTS twins and uncomplicated MC twins one month postpartum.

		Recipient Mean (SD)	Donor Mean (SD)	Control Mean (SD)	R–D *p* value	R–C *p* value	D–C *p* value
Doppler echocardiography							
Pulmonary valve	Vmax (m/s)	1.00 (0.240)	1.02 (0.292)	1.05 (0.226)	0.52	0.44	0.66
	Vmean (m/s)	0.71 (0.152)	0.71 (0.198)	0.73 (0.133)	0.90	0.48	0.54
	VTI (m)	0.14 (0.036)	0.14 (0.038)	0.14 (0.028)	0.67	0.86	0.56
Aortic valve	Vmax (m/s)	1.11 (0.177)	1.04 (0.208)	1.10 (0.135)	**0.02**	0.97	0.19
	Vmean (m/s)	0.73 (0.111)	0.70 (0.136)	0.76 (0.094)	0.10	0.38	0.11
	VTI (m)	0.14 (0.026)	0.13 (0.030)	0.15 (0.027)	0.06	0.51	0.15
Mitral valve	*E* (m/s)	0.95 (0.187)	0.95 (0.185)	0.89 (0.136)	1.00	0.30	0.25
	A (m/s)	0.79 (0.140)	0.78 (0.230)	0.82 (0.148)	0.74	0.41	0.65
	E/A ratio	1.08 (0.418)	1.33 (0.672)	1.08 (0.151)	0.34	0.85	0.49
Tricuspid valve	*E* (m/s)	0.70 (0.178)	0.71 (0.194)	0.79 (0.244)	0.37	0.10	0.20
	A (m/s)	0.63 (0.238)	0.61 (0.149)	0.70 (0.159)	0.89	0.38	0.17
	E/A ratio	1.06 (0.581)	1.00 (0.391)	0.98 (0.160)	0.71	0.72	0.92
Tissue Doppler Imaging							
Right ventricle	*s′* (m/s)	0.096 (0.0173)	0.092 (0.0215)	0.093 (0.0117)	0.25	0.48	0.85
	e′ (m/s)	0.152 (0.0467)	0.149 (0.0496)	0.163 (0.0447)	0.69	0.28	0.18
	a′ (m/s)	0.112 (0.0271)	0.096 (0.0306)	0.127 (0.0233)	0.16	0.16	**0.04**
Left ventricle	*s′* (m/s)	0.056 (0.0128)	0.054 (0.0152)	0.056 (0.0109)	0.42	0.78	0.73
	e′ (m/s)	0.096 (0.0300)	0.090 (0.0290)	0.108 (0.0286)	0.23	0.10	**0.02**
	a′ (m/s)	0.070 (0.0220)	0.072 (0.0273)	0.073 (0.0197)	0.63	0.54	0.76
Septal	*s′* (m/s)	0.056 (0.0104)	0.055 (0.0100)	0.058 (0.0078)	0.48	0.31	0.17
	e′ (m/s)	0.095 (0.0233)	0.092 (0.0263)	0.103 (0.0259)	0.51	0.13	0.10
	a′ (m/s)	0.077 (0.0215)	0.071 (0.0163)	0.080 (0.0243)	0.23	0.68	0.42
Deformation measurements							
LV global longitudinal strain (%)		−13.6 (3.23)	−13.4 (3.33)	−13.2 (3.14)	0.61	0.44	0.85
RV global longitudinal strain (%)		−18.6 (5.39)	−19.2 (4.28)	−20.2 (6.00)	0.45	0.40	0.70

R recipient, *D* donor; *C* control, *Vmax* maximum velocity, *Vmean* mean velocity, *VTI* velocity time integral, *E* early filling velocity, *A* late filling velocity, *E/A* early/late filling velocity measured with blood flow Doppler, *s′* ventricle contraction, *e′* ventricle relaxation, *a′* atrial contraction measured with TDI, *LV* left ventricle, *RV* right ventricle.

Bold values indicate statistical significance.

had significantly smaller dimensions of the aortic annulus, aortic root, sinotubular junction and ascending aorta compared with recipients. After adjustment for weight (since cardiac dimensions are weight dependent), there were no statistically significant differences. Measurements of the aortic arch were similar between donors and recipients. The distal transverse arch/ascending aorta ratio, carotid-subclavian artery index, and isthmus/ascending aorta ratio were smaller in donors compared with recipients, but these results did not reach statistical significance.

Discussion

The main findings of the present study were a high birth prevalence of structural CHD (11.3%) after FLC and a low prenatal detection rate. Both recipient and donor twins were

at risk of a CHD, with a prevalence of 9.2% and 13.6%, respectively. We found an increased prevalence of PS, ASD, VSD, and BAV. The only significant functional echocardiographic parameter was a lower peak aortic velocity in donor twins compared with recipient twins, but not compared with controls. To rule out any CHD in both recipient and donor twins, we therefore advise follow-up fetal echocardiograms and a postnatal echocardiogram.

Fetal cardiovascular development is influenced by genetic as well as environmental and hemodynamic factors such as blood flow, shear stress, preload and afterload [8]. In the event of TTTS, recipient and donor twins experience extremely different cardiac loading conditions in utero. Ventricular hypertrophy in recipients is suggested to be a consequence of hemodynamic changes, increased cardiac afterload, and the exposure to abnormal concentrations of vasoactive mediators such as endothelin-1, renin, and

angiotensin II [27]. Myocardial hypertrophy and increased systemic afterload can result in insufficient closure of the PV, resulting in pulmonary insufficiency and eventually bidirectional flow in the ductus arteriosus [17]. Further deterioration of cardiac function with progression of the TTTS may cause functional pulmonary atresia with no RV outflow. FLC improves cardiac function, and the FVW-PV normalizes in over two-thirds of cases, in the absence of irreversible anatomical changes to the PV. Isolated pulmonary insufficiency, previously suggested to be a mild anomaly [17], resulted in fetal demise in three cases in this study. In donor twins the occurrence of PS can be attributed to the postinterventional deterioration of cardiac function secondary to an acute increase in afterload after FLC [28, 29]. It is furthermore suggested that the increased rate of postnatal ASDs in recipient twins may result from increased right-to-left shunting at the atrial septum secondary to RV dysfunction and tricuspid regurgitation [30]. The increased prevalence of BAV in donors is a new finding with clinical importance, since it may result in aortic valvular stenosis and/or regurgitation and endocarditis later in life [31, 32]. It may be explained by hypovolemia and decreased cardiac output [8]. This explanation is supported by the lower aortic Doppler peak velocity in donor twins as compared with recipient twins, which suggest persistent reduced cardiac output in these twins. Karatza et al. [33] furthermore showed that recipient twins had higher aortic peak velocities than donors at time of TTTS. Whether decreased velocities in donors as compared with recipients have any clinical relevance should be the topic of further research. As suggested by Van den Boom et al. [34], donors are also at increased risk of other left-sided defects such as aortic coarctation due to decreased circulatory volume [35]. We hypothesized that due to decreased cardiac output and decreased aortic peak velocity during pregnancy until the early neonatal period, donor twins have smaller aortic arches even in the absence of true aortic coarctation. This study did not have the power to detect true differences in aortic dimensions however.

Our results are in accordance with earlier prospective studies that showed a prevalence of 9–16% [30, 36] and equal CHD rates in recipients and donors [30]. The low prenatal detection rate of 21% in our study is explained by, first, the difficult scanning conditions in TTTS due to the combination of polyhydramnios of the recipient twin and the 'stuck' anhydramniotic donor. Second, minor defects (ASDs and small VSDs) and BAVs are considered to be undetectable before birth. And last, three infants who subsequently developed neonatal PS, which became apparent 1 month after birth, had a normal fetal PV morphology and velocity during pregnancy and at birth. In the study by Pruetz et al. the fetal CHD detection rates in case of TTTS was 42.9% in recipient twins and 16.7% in donor twins [30]. Postnatal echocardiograms in this study were, however, only performed in a select group of patients. Minor defects could therefore be left undetected in this study and the true prenatal detection rate may be lower. The low prenatal detection rate, and the fact that RVOTO may evolve even after delivery and can become apparent after postnatal decrease in pulmonary vascular resistance, highlights the importance of caution in counseling in early pregnancy and the need for serial fetal and neonatal echocardiograms.

This study has strengths and limitations. First, this is the largest short-term prospective follow-up study to date, with a control group of age-matched unaffected MC twins at the age of 1 month. Since there is a limited number of studies into cardiac function in (premature) newborns [37], the use of MC twins as a control group is superior to a control group of singletons or comparison to reference values from the literature. Second, we studied infants at the age of 1 month, corrected for prematurity, to eliminate the response to hemodynamic, hormonal, and biochemical stressors at birth. And last, this is the first study in which the Solomon technique was used in all cases. This technique is known for lower TTTS recurrence rates and improved survival and neonatal outcome [15]. In studies in which the selective approach was used, results may also have been influenced by an unstable hemodynamic environment after laser surgery if residual anastomoses were present. There are also limitations to this study. Because routine neonatal echocardiography was not performed in referring hospitals, we choose to exclude patients who did not undergo an echocardiogram as part of this study. This could have introduced a selection bias, which may have upwardly biased the prevalence of PS. Inclusion of sparse echocardiography data from other centers, with different scanning protocols, could however have introduced large variation in the data. Our control group of MC twins is small, our results must therefore be interpreted with caution. And last, multiple comparisons performed in this study may have increased the likelihood of statistical significant differences resulting from random rather than systematic variation. Correction for multiple testing is however a subject of debate, and is not always advised if study aims have an exploratory nature [38, 39].

Conclusion

Data from this study support the recommendations of the American Institute of Ultrasound in Medicine that MC twin pregnancy should be considered an indication for fetal echocardiography [40]. To rule out any CHD in both recipient and donor twins, follow-up fetal echocardiograms should be performed and a postnatal echocardiogram should be offered to all TTTS survivors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the medical ethical committee of the Leiden University Medical Center (NL 45251.058.13).

Informed consent Written informed consent was obtained from the parents.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Best KE, Rankin J. Increased risk of congenital heart disease in twins in the North of England between 1998 and 2010. Heart. 2015;101:1807–12.
2. Habli M, Lim FY, Crombleholme T. Twin-to-twin transfusion syndrome: a comprehensive update. Clin Perinatol. 2009;36: 391–416.
3. Moon-Grady AJ, Rand L, Lemley B, Gosnell K, Hornberger LK, Lee H. Effect of selective fetoscopic laser photocoagulation therapy for twin-twin transfusion syndrome on pulmonary valve pathology in recipient twins. Ultrasound Obstet Gynecol. 2011;37:27–33.
4. Gijtenbeek M, Shirzada MR, Ten Harkel ADJ, Oepkes D, Haak MC. Congenital heart defects in monochorionic twins: a systematic review and meta-analysis. J Clin Med. 2019;8:902.
5. Herberg U, Gross W, Bartmann P, Banek CS, Hecher K, Breuer J. Long term cardiac follow up of severe twin to twin transfusion syndrome after intrauterine laser coagulation. Heart. 2006;92: 95–100.
6. Sueters M, Middeldorp JM, Vandenbussche FP, Teunissen KA, Lopriore E, Kanhai HH, et al. The effect of fetoscopic laser therapy on fetal cardiac size in twin-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2008;31:158–63.
7. Barrea C, Hornberger LK, Alkazaleh F, McCrindle BW, Roberts A, Berezovska O, et al. Impact of selective laser ablation of placental anastomoses on the cardiovascular pathology of the recipient twin in severe twin-twin transfusion syndrome. Am J Obstet Gynecol. 2006;195:1388–95.
8. Gardiner HM, Taylor MJ, Karatza A, Vanderheyden T, Huber A, Greenwald SE, et al. Twin-twin transfusion syndrome: the influence of intrauterine laser photocoagulation on arterial distensibility in childhood. Circulation. 2003;107:1906–11.
9. Gardiner HM, Matsui H, Roughton M, Greenwald SE, Diemert A, Taylor MJ, et al. Cardiac function in 10-year-old twins following different fetal therapies for twin-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2014;43:652–7.
10. Halvorsen CP, Bilock SL, Pilo C, Sonesson SE, Norman M. Childhood cardiac function after twin-to-twin transfusion syndrome–a 10-year follow up. Acta Paediatr. 2009;98:1468–74.
11. Halvorsen CP, Mohlkert LA, Norman M, Sonesson SE. Childhood cardiac outcome after intrauterine laser treatment of twin-twin transfusion syndrome is favourable. Acta Paediatr. 2015;104: 252–8.
12. Herberg U, Bolay J, Graeve P, Hecher K, Bartmann P, Breuer J. Intertwin cardiac status at 10-year follow-up after intrauterine laser coagulation therapy of severe twin-twin transfusion syndrome: comparison of donor, recipient and normal values. Arch Dis Child Fetal Neonatal Ed. 2014;99:F380–385.
13. Breatnach CR, Bussmann N, Levy PT, Vincent DF, Malone FD, McCallion N, et al. Postnatal myocardial function in monochorionic diamniotic twins with twin-to-twin transfusion syndrome following selective laser photocoagulation of the communicating placental vessels. J Am Soc Echocardiogr. 2019; 32:774–84.
14. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol. 1999;19:550–5.
15. Slaghekke F, Oepkes D. Solomon technique versus selective coagulation for twin-twin transfusion syndrome. Twin Res Hum Genet. 2016;19:217–21.
16. Middeldorp JM, Sueters M, Lopriore E, Klumper FJ, Oepkes D, Devlieger R, et al. Fetoscopic laser surgery in 100 pregnancies with severe twin-to-twin transfusion syndrome in the Netherlands. Fetal Diagnosis Ther. 2007;22:190–4.
17. Michelfelder E, Tan X, Cnota J, Divanovic A, Statile C, Lim FY, et al. Prevalence, spectrum, and outcome of right ventricular outflow tract abnormalities in twin-twin transfusion syndrome: a large, single-center experience. Congenit Heart Dis. 2015;10: 209–18.
18. Greenough A, Milder AD. Pulmonary disease of the newborn. In: Rennie JM, editor. Textbook of neonatology. 4th ed. London, UK: Elsevier; 2005.
19. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23:465–95.
20. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr. 2009;22:1–23.
21. McMahon CJ, Feltes TF, Fraley JK, Bricker JT, Grifka RG, Tortoriello TA, et al. Natural history of growth of secundum atrial septal defects and implications for transcatheter closure. Heart. 2002;87:256–9.
22. Dragulescu A, Mertens LL. Developments in echocardiographic techniques for the evaluation of ventricular function in children. Arch Cardiovasc Dis. 2010;103:603–14.
23. Sutherland GR, Di Salvo G, Claus P, D'Hooge J, Bijnens B. Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. J Am Soc Echocardiogr. 2004;17:788–802.
24. Al Akhfash AA, Almesned AA, Al Harbi BF, Al Ghamdi A, Hasson M, Al Habshan FM. Two-dimensional echocardiographic predictors of coarctation of the aorta. Cardiol Young. 2015;25: 87–94.

25. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58:2241–7.

26. Ciccone MM, Scicchitano P, Zito A, Gesualdo M, Sassara M, Calderoni G, et al. Different functional cardiac characteristics observed in term/preterm neonates by echocardiography and tissue doppler imaging. Early Hum Dev. 2011;87:555–8.

27. Van Mieghem T, Done E, Gucciardo L, Klaritsch P, Allegaert K, Van Bree R, et al. Amniotic fluid markers of fetal cardiac dysfunction in twin-to-twin transfusion syndrome. Am J Obstet Gynecol. 2010;202:e41–47.

28. Van Mieghem T, Lewi L, Gucciardo L, Dekoninck P, Van Schoubroeck D, Devlieger R, et al. The fetal heart in twin-to-twin transfusion syndrome. Int J Pediatr. 2010;2010.

29. Zikulnig L, Hecher K, Bregenzer T, Baz E, Hackeloer BJ. Prognostic factors in severe twin-twin transfusion syndrome treated by endoscopic laser surgery. Ultrasound Obstet Gynecol. 1999;14:380–7.

30. Pruetz JD, Sklansky M, Detterich J, Korst LM, Llanes A, Chmait RH. Twin-twin transfusion syndrome treated with laser surgery: postnatal prevalence of congenital heart disease in surviving recipients and donors. Prenat Diagn. 2011;31:973–7.

31. Tutar E, Ekici F, Atalay S, Nacar N. The prevalence of bicuspid aortic valve in newborns by echocardiographic screening. Am Heart J. 2005;150:513–5.

32. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol. 2010;55:2789–2800.

33. Karatza AA, Wolfenden JL, Taylor MJ, Wee L, Fisk NM, Gardiner HM. Influence of twin-twin transfusion syndrome on fetal cardiovascular structure and function: prospective case-control study of 136 monochorionic twin pregnancies. Heart. 2002;88:271–7.

34. van den Boom J, Battin M, Hornung T. Twin-twin transfusion syndrome, coarctation of the aorta and hypoplastic aortic arch: a case series report. J Paediatr Child Health. 2010;46:76–79.

35. Buyens A, Gyselaers W, Coumans A, Al Nasiry S, Willekes C, Boshoff D, et al. Difficult prenatal diagnosis: fetal coarctation. Facts Views Vis Obgyn. 2012;4:230–6.

36. Springer S, Mlczoch E, Krampl-Bettelheim E, Mailath-Pokorny M, Ulm B, Worda C, et al. Congenital heart disease in monochorionic twins with and without twin-to-twin transfusion syndrome. Prenat Diagn. 2014;34:994–9.

37. Cantinotti M, Lopez L. Nomograms for blood flow and tissue Doppler velocities to evaluate diastolic function in children: a critical review. J Am Soc Echocardiogr. 2013;26:126–41.

38. Feise RJ. Do multiple outcome measures require p-value adjustment? BMC Med Res Methodol. 2002;2:8.

39. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990;1:43–46.

40. Fetal Echocardiography Task F, American Institute of Ultrasound in Medicine Clinical Standards C, American College of O, Gynecologists, Society for Maternal-Fetal M. AIUM practice guideline for the performance of fetal echocardiography. J Ultrasound Med. 2011;30:127–36.