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# Fetal cardiac function in recipient twins undergoing fetoscopic laser ablation of placental anastomoses for Stage IV twin–twin transfusion syndrome

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**KEYWORDS:** aortic atresia; echocardiography; fetal surgery; fetoscopy; heart; pulmonary atresia; TTTS; twin

## ABSTRACT

***Objective*** *Cardiac dysfunction is common in the recipient fetus of twin–twin transfusion syndrome (TTTS). In this study, we aimed to document the severity of fetal cardiac dysfunction in Stage IV TTTS (fetal hydrops) and assess evolution of cardiac function longitudinally after fetoscopic laser surgery.*

***Methods*** *We reviewed obstetric ultrasound examination data, pre- and postoperative echocardiograms and neonatal outcomes for 22 cases of Stage IV TTTS undergoing fetoscopic laser ablation of placental anastomoses between 1998 and 2011. Myocardial performance index, atrioventricular valve flow patterns, ventricular shortening fraction, ventricular hypertrophy, outflow tract obstruction and venous Doppler waveforms were assessed.*

***Results*** *Nineteen fetuses (86.4%) had ascites, eight (36.4%) had pleural effusions, nine (40.9%) had a pericardial effusion and 12 (54.5%) had subcutaneous edema at presentation. Preoperatively, cardiac function was grossly abnormal in all. Eight fetuses (36.4%) had functional pulmonary atresia and one (4.5%) had functional aortic atresia. Seventy-seven percent of recipient fetuses survived until birth. Postoperative echocardiographic follow-up (mean, 26 days) showed that indices of fetal cardiac function improved considerably, but never completely normalized. Six of the eight fetuses with functional pulmonary atresia (75.0%), as well as the fetus with functional aortic atresia, survived to birth. In all cases, the functional atresia resolved within 48 h of laser ablation therapy and none had structural valve anomalies at birth. All fetal effusions resolved after the laser.*

***Conclusions*** *Fetoscopic laser ablation of placental anastomoses reverses cardiac dysfunction and valvulopathy, even in the most severe cases of TTTS. However, recovery takes longer than in early stage disease.* *Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.*

## INTRODUCTION

Twin–twin transfusion syndrome (TTTS) complicates 9–15% of monochorionic twin pregnancies[1,2]. The etiology is not fully understood[3], but a deregulation of endocrine factors (including those involved in the renin–angiotensin system and endothelin-1[3]) in combination with placental vascular anastomoses connecting the fetal circulations plays a role in the 'recipient' fetus developing polyuric polyhydramnios, hypertension and cardiac dysfunction and the 'donor' twin developing oligouric oligohydramnios[4–6]. Ablation of the communicating intertwin vessels by fetoscopic laser is the optimal therapy for TTTS[7], and normalizes both the oligohydramnios/polyhydramnios sequence and the recipient's cardiac dysfunction within 6–8 weeks[8,9]. Although congenital heart disease is 3–4 times more common after TTTS than in uncomplicated monochorionic twins[10], the long-term cardiac outcome for recipient fetuses with TTTS is generally good[11].

Approximately 10% of cases of TTTS present at referral centers at Stage IV (hydrops in the recipient fetus)[12,13]. Although this subgroup might behave differently from those with less advanced stages of TTTS, owing to the more severe fetal cardiac involvement, large studies assessing recipient cardiac function in Stage IV disease and documenting the cardiac response to fetal therapy in this subpopulation are lacking. Some centers even consider severe cardiac dysfunction in the recipient as an indication for selective fetal reduction, rather than laser therapy[14,15].

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The aim of this study was to report on cardiac and obstetric outcomes of a large cohort of fetuses with Stage IV TTTS treated by laser ablation of the placental vascular anastomoses.

## METHODS

This was a retrospective study of all recipient fetuses with Stage IV TTTS who underwent fetal echocardiography before and after fetoscopic laser ablation of placental anastomoses at Mount Sinai Hospital, Toronto, Canada from February 1998 to October 2011. The study was approved by the research ethics boards of the participating centers.

TTTS was defined as oligouric oligohydramnios in one fetus and polyuric polyhydramnios in the other of a monochorionic–diamniotic twin pair. Chorionicity was determined based on first-trimester ultrasound findings and confirmed on placental pathology after birth. Polyhydramnios was defined as a deepest vertical amniotic fluid pocket of > 10 cm after 20 weeks, > 8 cm between 16 and 20 weeks and > 6 cm before 16 weeks' gestation. Oligohydramnios was defined as a deepest vertical amniotic fluid pocket of < 2 cm. TTTS severity was staged according to Quintero's criteria[13].

Maternal medical records, pre- and postoperative ultrasound scans, fetal echocardiograms and postnatal survival until 6 months of age were reviewed. The majority of fetal echocardiograms were performed in the fetal cardiology unit at the Hospital of Sick Children, Toronto, Canada, but some were obtained from fetal echocardiography units in other tertiary care referral centers.

Fetal echocardiography was performed by experienced cardiac sonographers with linear and curved array transducers with variable frequency (3.5–7 MHz) on high-definition ultrasound machines. All studies included a complete two-dimensional examination of cardiac anatomy using standard fetal echocardiographic views and spectral and color Doppler ultrasound. Frozen images and clips were stored digitally or on tape. All echocardiograms were reviewed retrospectively by two authors (E.J., T.V.M.) and all measurements were repeated offline. The following functional parameters were assessed: ventricular hypertrophy (subjective assessment), left and right ventricular shortening fraction (normal > 31%[16]), presence of moderate/severe atrioventricular valve regurgitation, monophasic ventricular inflow Doppler pattern, ratio of ventricular inflow duration over cardiac cycle length (normal > 38%[17]), left and right ventricular Tei index, absent or reversed a-wave in the ductus venosus and presence of umbilical vein pulsations and flow reversal in the cardiac outflow tracts compatible with (functional) pulmonary or aortic atresia.

Fetoscopic laser ablation of placental anastomoses was performed by an experienced surgeon as previously described, using a sterile technique under local anesthesia and intravenous maternal sedation or regional anesthesia[18]. A 2-mm 0° fetoscope (Karl Storz GmbH, Tüttlingen, Germany) and a 600-μ laser fiber (Surgical Laser Technologies Inc., Montgomeryville, PA, USA) were introduced through a 3.7-mm (11-F) operating sheath and a 12-F plastic port. Maternal positioning, curved sheaths and a 70° fetoscope (Karl Storz GmbH) were used as necessary for anterior placentae. All visualized anastomoses were ablated using neodymium:yttrium aluminum garnet laser energy. At the end of each procedure, amnioreduction was performed. Postoperatively, antibiotics and tocolysis (oral and rectal indomethacin ± oral nifedipine) were continued for 24 h.

Ultrasound examinations to confirm fetal viability and to exclude recurrent TTTS or twin anemia–polycythemia syndrome were performed after 24 h, then on a weekly basis for the first month, and then every 2 weeks for the remainder of the pregnancy. Postoperative echocardiograms were obtained at 24–48 h, 3 weeks and 6–8 weeks postoperatively. Infant outcomes were recorded at birth and at 6 months of age.

### Statistical analysis

Descriptive statistics are provided. Distribution of data was assessed using the D'Agostino and Pearson omnibus normality test. Pre- and postoperative cardiac functions were compared using paired *t*-tests for continuous data and Fisher's exact test for nominal data. Cardiac function in recipient fetuses surviving *in utero* was compared to that of non-survivors using *t*-tests for continuous data and Fisher's exact test for nominal data. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

## RESULTS

Of 316 monochorionic pregnancies undergoing fetoscopic laser therapy for TTTS in the study period, 34 (10.8%) were classified as Stage IV. Of these, 12 were excluded as they did not have complete preoperative cardiac function assessment. Lack of echocardiography was mainly owing to the fact that the laser procedure was performed too soon after the initial ultrasound scan in the fetal medicine unit to allow for a formal fetal echocardiographic study to be performed. Gestational age and obstetric ultrasound findings at presentation in these 12 excluded cases were similar to those of the included cases (Table 1).

Baseline characteristics for the 22 cases in which echocardiography was performed prior to intervention are presented in Table 1. None of the fetuses had a structural heart defect. As expected, fetal cardiac function was severely abnormal on first assessment in all cases (Table 2). Nineteen (86.4%) recipient fetuses had ascites, eight (36.4%) had pleural effusions, nine (40.9%) had a pericardial effusion and 12 (54.5%) had subcutaneous edema. Eight fetuses (36.4%) had echocardiographic images compatible with functional pulmonary atresia and one (4.5%) had functional aortic atresia. Two pregnancies were complicated by 'maternal mirror syndrome' and presented with hypertension, proteinuria and low platelet counts. One patient required admission to the intensive care unit owing to severe pulmonary edema.

**Table 1** Baseline characteristics of study population and excluded cases in pregnancies with Stage IV twin–twin transfusion syndrome that underwent laser ablation

| *Variable* | *Study population (n = 22)* | *Excluded cases* (n = 12)* |
|---|---|---|
| Maternal characteristics | | |
| Age (years) | 29.5 (20–37) | 31 (25–38) |
| Parity | | |
| 0 | 10 (45.5) | 5 (41.7) |
| 1 | 7 (31.8) | 4 (33.3) |
| > 1 | 5 (22.7) | 3 (25.0) |
| Ultrasound characteristics | | |
| GA first assessment (weeks) | 22.2 ± 3.6 | 22.7 ± 3.6 |
| Estimated fetal weight (g) | | |
| Donor | 380 (120–1047) | 350 (280–756) |
| Recipient | 585 (150–1655) | 418 (350–1373) |
| Intertwin weight discordance (%) | 35 (1–59) | 31 (9–52) |
| DVP, recipient (cm) | 11 (6.3–17.0) | 14 (7.5–21) |
| Abnormal UA flow Donor | 4 (18.2) | 4 (33.3) |
| Recipient | 4 (18.2) | 4 (33.3) |
| Absent/reversed DV a-wave, recipient | 20 (90.9) | 12 (100.0) |
| Cervical length at presentation (mm) | 35 ± 9 | 33 ± 10 |

Data are expressed as median (range), mean ± SD or *n* (%).
*Exclusion due to incomplete preoperative cardiac function assessment. DV, ductus venosus; DVP, deepest vertical amniotic fluid pocket; GA, gestational age; UA, umbilical artery.

All 22 pregnancies underwent uncomplicated fetoscopic laser ablation of the placental vascular anastomoses. Mean amnioreduction volume at the procedure was 1691 ± 820 mL. Postoperatively, cervical cerclage was performed in one pregnancy, as the cervix measured < 15 mm.

Pregnancy outcomes for all 22 cases are presented in Table 3. Ten fetuses (22.7%) died *in utero*, immediately after surgery (five donors and five recipients) and two cases did not have postoperative echocardiography, leaving 15 recipient fetuses that had long-term postoperative cardiac function assessment. Mean number of follow-up echocardiograms per pregnancy was 2.2 ± 1 (range, 1–4). At the time of writing, the last follow-up echocardiogram was at a median of 26 (range, 1–82) days after the procedure. As illustrated in Figure 1 and Table 4, all indices of fetal cardiac function improved considerably after the laser procedure, yet did not normalize completely within the observation period. Six of eight fetuses with functional pulmonary atresia, as well as the fetus with functional aortic atresia, survived until birth. The functional atresia resolved in all surviving fetuses, often within the first 48 h after laser therapy. Two fetuses with functional pulmonary atresia died immediately after the procedure, so evolution of cardiac function could not be assessed postoperatively in these cases. All fetal effusions regressed and eventually disappeared after the laser procedure and both cases of maternal mirror syndrome resolved completely. Preoperative fetal cardiac function in recipient fetuses that survived to birth was similar to that in recipients that died *in utero* after the laser procedure (Table 5).

**Table 2** Baseline cardiac function in recipient fetus at first preoperative assessment in cases of Stage IV twin–twin transfusion syndrome ($n = 22$)

| *Variable* | *Outcome* |
|---|---|
| Right heart function | |
| Absent/reversed a-wave in ductus venosus | 20 (90.9) |
| Umbilical vein pulsations | 17 (77.3) |
| Tricuspid regurgitation | 19 (86.4) |
| Monophasic tricuspid inflow | 19 (86.4) |
| Tricuspid inflow duration/cardiac cycle length (%) | 28.7 ± 7.2 |
| Right ventricular hypertrophy | 19 (86.4) |
| Shortening fraction right ventricle (%) | 22.1 ± 9.5 |
| Right ventricular Tei index | 0.81 ± 0.21 |
| Functional pulmonary atresia | 8 (36.4) |
| Left heart function | |
| Mitral regurgitation | 17 (77.3) |
| Monophasic mitral inflow | 13 (59.1) |
| Mitral inflow duration/cardiac cycle length (%) | 35 ± 7 |
| Left ventricular hypertrophy | 15 (68.2) |
| Shortening fraction left ventricle | 29.4 ± 6.9 |
| Left ventricular Tei index | 0.70 ± 0.16 |
| Functional aortic atresia | 1 (4.5) |

Data are expressed as mean ± SD or *n* (%).

**Table 3** Pregnancy and fetal outcomes after laser ablation therapy for Stage IV twin–twin transfusion syndrome

| *Variable* | *Outcome* |
|---|---|
| Pregnancy outcome ($n = 22$) | |
| Gestational age at delivery (weeks) | 32.7 ± 3.0 |
| PPROM < 37 weeks' gestation | 8 (36.4) |
| Gestational age at PPROM (weeks) | 29.5 ± 4.0 |
| Donor demise | 5 (22.7) |
| Recipient demise | 5 (22.7) |
| Double survival at 6 months of age | 11 (50.0) |
| Single survival at 6 months of age | 10 (45.5) |
| Double demise before 6 months of age | 1 (4.5) |
| Fetal outcome ($n = 44$) | |
| Recipient birth weight (g) | 1789 ± 605 |
| Donor birth weight (g) | 1706 ± 498 |
| Intrauterine fetal demise | 10 (22.7) |
| Neonatal demise | 2 (4.5) |
| Overall survival at 6 months of age | 32 (72.7) |

Data are expressed as mean ± SD or *n* (%). PPROM, preterm premature rupture of membranes.

Mean gestational age at delivery was 32.7 ± 3.0 weeks. Seven pregnancies (31.8%) delivered before 32 weeks. Mean interval between laser and delivery was 10.6 ± 4.0 weeks. None of the six surviving infants with functional pulmonary atresia at the time of laser for TTTS had residual pulmonary stenosis at birth. Two recipient fetuses died in the neonatal period. The first had functional pulmonary atresia before laser, which resolved completely after surgery. The child was born at 27.4 weeks' gestation and died as a result of the consequences of prematurity. The other infant was born at 29.1 weeks' gestation and had more severe respiratory insufficiency than expected from gestational age alone. This could potentially have been accounted for by the presence of

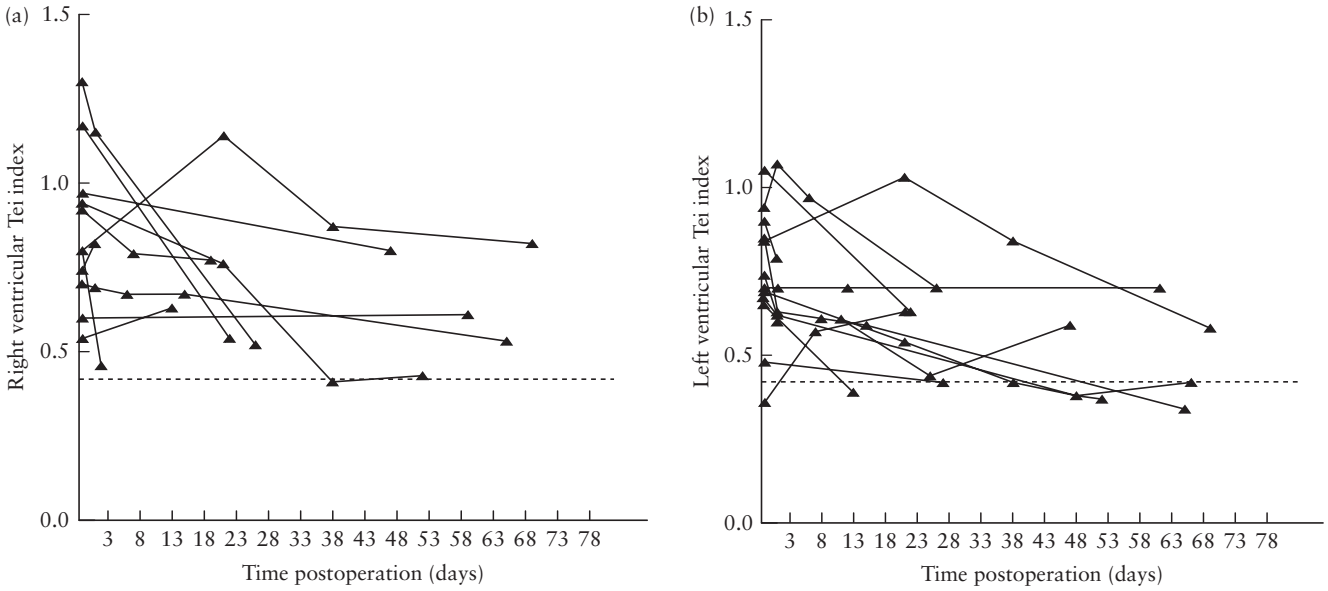


**Figure 1** Longitudinal evolution of echocardiographic parameters in recipient fetus after fetoscopic laser ablation for twin–twin transfusion syndrome. (a) Right ventricular Tei index ($n = 11$ fetuses without pulmonary atresia); (b) left ventricular Tei index ($n = 14$ fetuses without aortic atresia). -----, Normal cut-off.

**Table 4** Cardiac function in 15 surviving recipient fetuses followed longitudinally after laser surgery for Stage IV twin–twin transfusion syndrome

| *Variable* | *Preoperative* | *At last observation* | P |
|---|---|---|---|
| Right heart function | | | |
| Abnormal flow in ductus venosus | 13 (86.7) | 2 (13.3) | 0.0001 |
| Umbilical vein pulsations | 11 (73.3) | 1 (6.7) | 0.0005 |
| Tricuspid regurgitation | 13 (86.7) | 5 (33.3) | 0.008 |
| Fusion of tricuspid inflow | 12 (80.0) | 4 (26.7) | 0.009 |
| Tricuspid inflow duration/cardiac cycle length (%) | 28.2 ± 8.2 | 38.6 ± 7.2 | < 0.0001 |
| Shortening fraction right ventricle (%) | 25.7 ± 6.9 | 30.5 ± 7.4 | 0.1 |
| Right ventricular Tei index | 0.86 ± 0.23 | 0.62 ± 0.15 | 0.02 |
| Functional pulmonary atresia | 6 (40.0) | 0 (0.0) | 0.02 |
| Left heart function | | | |
| Mitral regurgitation | 11 (73.3) | 3 (20.0) | 0.009 |
| Fusion of mitral inflow | 8 (53.3) | 0 (0.0) | 0.002 |
| Mitral inflow duration/cardiac cycle length (%) | 33.7 ± 8.3 | 37.9 ± 8.1 | 0.15 |
| Shortening fraction left ventricle (%) | 29.6 ± 7.7 | 30.8 ± 6.7 | 0.69 |
| Left ventricular Tei index | 0.74 ± 0.19 | 0.55 ± 0.15 | 0.005 |
| Functional aortic atresia | 1 (6.7) | 0 (0.0) | 1.00 |

Data are expressed as mean ± SD or *n* (%).

long-standing pleural effusions in this fetus. Survival until 6 months of age was 72.7% (32/44 fetuses). Double survival was seen in 11 pregnancies (50.0%) and survival of ≥ 1 fetus in 21 pregnancies (95.5%). In our total cohort of 34 TTTS Stage IV pregnancies (including the 12 pregnancies excluded from the current study owing to the lack of a prenatal echocardiogram), survival until 6 months of age was 69.1% (47/68 fetuses). Double survival was seen in 17 pregnancies (50.0%) and survival of ≥ 1 fetus in 28 pregnancies (82.4%).

## DISCUSSION

In the present study, we documented cardiac function in the recipient fetus of Stage IV TTTS before and after laser ablation of placental anastomoses. Fetal cardiac function was severely abnormal at the time of initial presentation. After therapy, cardiac function improved at a similar rate to that seen in earlier stages of TTTS, with dramatic changes within the first 48 h and slightly slower recovery thereafter[9]. Given the highly abnormal preoperative cardiac function, however, resolution takes longer than in earlier stages of TTTS, and some fetuses may not recover entirely before birth. This, in addition to the well known increased incidence of congenital heart disease in TTTS, which often goes undiagnosed antenatally, stresses the importance of thorough neonatal cardiologic follow-up for recipient fetuses of TTTS[19,20].

In our study, the rapid improvement in ventricular function seen in the first 48 h after laser was paralleled by the resolution of functional pulmonary and aortic atresia in all cases. As can be expected from a physiological

 

**Table 5** Preoperative cardiac function parameters in recipients that survived and those that died following fetoscopic laser ablation of placental anastomoses for Stage IV twin–twin transfusion syndrome

| *Variable* | *Survivors* (n = *17*) | *Non-survivors* (n = *5*) | P |
|---|---|---|---|
| Right heart function | | | |
| Absent/reversed a-wave in ductus venosus | 15 (88.2) | 5 (100.0) | 1.00 |
| Umbilical vein pulsations | 13 (76.5) | 4 (80.0) | 1.00 |
| Tricuspid regurgitation | 15 (88.2) | 5 (100.0) | 1.00 |
| Fusion of tricuspid inflow | 13 (76.5) | 5 (100.0) | 0.53 |
| Tricuspid inflow duration/cardiac cycle length (%) | 28.7 ± 7.8 | 28.7 ± 2.9 | 1.00 |
| Right ventricular hypertrophy | 15 (88.2) | 4 (80.0) | 1.00 |
| Shortening fraction right ventricle (%) | 22.6 ± 9.5 | 20.4 ± 10.4 | 0.66 |
| Right ventricular Tei index | 0.82 ± 0.21 | 0.72 ± 0.11 | 0.32 |
| Functional pulmonary atresia | 6 (35.3) | 2 (40.0) | 1.00 |
| Left heart function | | | |
| Mitral regurgitation | 13 (76.5) | 4 (80.0) | 1.00 |
| Fusion of mitral inflow | 10 (58.8) | 4 (80.0) | 0.61 |
| Mitral inflow duration/cardiac cycle length (%) | 34.0 ± 7.9 | 36.8 ± 3.3 | 0.48 |
| Left ventricular hypertrophy | 12 (70.6) | 3 (60.0) | 1.00 |
| Shortening fraction left ventricle (%) | 29.6 ± 7.5 | 28.6 ± 5.2 | 0.78 |
| Left ventricular Tei index | 0.73 ± 0.17 | 0.63 ± 0.09 | 0.25 |
| Functional aortic atresia | 1 (5.9) | 0 (0.0) | 1.00 |

Data are expressed as mean ± SD or *n* (%).

point of view, fetal effusions took longer to resolve, but ultimately all disappeared. This is in line with a previous study looking at the evolution of hydrops after fetoscopic laser surgery in 16 pregnancies complicated by Stage IV TTTS[21].

The presence of functional pulmonary or aortic atresia before fetoscopic laser surgery was unrelated to fetal survival or postnatal outflow tract pathology. Indeed, none of the fetuses with functional pulmonary atresia prior to laser had residual outflow tract obstruction at birth. This corroborates the observations of Gray *et al.*[21], who reported that none of five fetuses with Stage IV TTTS and functional pulmonary atresia had evidence of right ventricular outflow tract obstruction on neonatal echocardiography before laser. Similarly, Moon-Grady *et al.*[22] reported that two of three fetuses with functional pulmonary atresia prior to laser had normal pulmonary valves on follow-up and that there was no association between the severity of fetal pulmonary stenosis or pulmonary insufficiency and postnatal pulmonary valve pathology. The lack of association between severity of prenatal disease and postnatal outcome could lead one to speculate that the duration, rather than the severity, of prenatal cardiac involvement impacts on long-term valve development. The latter speculation, however, contradicts the observation that the incidence of pulmonary obstruction at birth in recipient twins following laser (4–7.8%)[11,19,20] was similar to that in recipient fetuses managed with amnioreduction (7.5%)[23], where the effects of TTTS on the fetuses are more protracted. Further large follow-up studies with systematic antenatal and neonatal echocardiography in recipient fetuses of TTTS are required to identify predictors of pulmonary valve disease at birth.

Similarly, follow-up studies are required to assess the impact of the severe cardiac dysfunction seen in Stage IV TTTS on postnatal neurological outcome. Indeed, severe cardiac impairment can lead to decreased end-organ perfusion, and the neurological outcome for Stage IV TTTS fetuses could be worse than outcomes for fetuses with earlier stage disease. This theory is further substantiated by the 6-year follow-up analysis of the randomized Eurofetus trial, which compared amnioreduction to laser[24], and by a large cohort study showing a trend towards more neurodevelopmental impairment with increasing Quintero stage[25].

Finally, our study confirmed the high survival rates previously reported for Stage IV TTTS[12]. Indeed, overall neonatal survival in our series was 69.1%, with at least one infant surviving until 6 months of age in 82.4% of cases, and both infants surviving in 50.0%. The rate of fetal demise was similar in donors and recipients; recipients with functional outflow tract atresia had a survival rate similar to those without atresia and preoperative cardiac function in recipient fetuses that died was comparable with that in those that survived, which suggests that demise of the recipient fetus is unrelated to the severity of cardiac dysfunction. However, the relatively small number of recipient deaths in the current series limits the strength of conclusions from these findings.

The dissociation between cardiac dysfunction and survival rate, in combination with the high rate of double survival, suggests that selective fetal reduction, with an inherent maximum survival of 50%, should not be considered as the therapy of choice for Stage IV TTTS. In our experience and that of others[12], survival in Stage IV TTTS cases was better than in Stage III TTTS, where cardiac function in the recipient can similarly improve, but the donor often has to face the additional challenge of severe placental discordance.

The most important limitation of our study is the lack of longer-term follow-up in some of the cases. This was due to the retrospective study design, the occurrence of complications inherent to the disease (such as fetal demise

 

and preterm delivery) and the very large geographic referral pattern of our patients, which precluded on-site follow-up. Secondly, we only included 22 of 34 pregnancies with Stage IV TTTS in this analysis. The primary reason for this was the lack of preoperative echocardiography in the remaining 12 cases, which was largely due to logistical scheduling issues at the time of presentation, and should not have induced any significant bias. Moreover, obstetric characteristics in cases that were included and excluded were similar. A strength of this study is that it is the largest to date reporting on the cardiac changes in Stage IV TTTS following fetal therapy.

In conclusion, recipient fetuses in Stage IV TTTS have severely altered cardiac function, leading to functional pulmonary and aortic atresia. Laser ablation of communicating placental vessels enables cardiac function to improve and functional atresia and effusions to reverse. Recipient demise is unrelated to the severity of cardiac impairment. Further studies are necessary to assess the impact of transiently impaired cardiac function on longer-term neurodevelopment. In the absence of these data, we do not consider Stage IV TTTS as an indication for selective fetal reduction.

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