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## **Twin-to-twin transfusion syndrome : from placental anastomoses to long term outcome**

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## *Chapter 10*

# Congenital heart disease in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery

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*Submitted*

## Abstract

*Objectives:* To determine the incidence of congenital heart disease (CHD) and right ventricular outflow tract obstruction (RVOTO) in twin-to-twin transfusion syndrome (TTTS) treated with fetoscopic laser surgery and evaluate the role of increased afterload by determining the difference in blood pressure and endothelin-1 at birth between donor and recipient twins.

*Methods:* All consecutive cases of monochorionic twins with TTTS treated with laser ( $n = 46$  twin pairs) and monochorionic twins without TTTS ( $n = 55$  twin pairs) delivered at our center between June 2002 and June 2005 were included in the study. Echocardiography was performed within one week after delivery. At birth, blood pressure was measured in all survivors and endothelin-1 was determined in umbilical cord blood. Data on RVOTO in TTTS treated with laser surgery at our center but delivered elsewhere were reviewed retrospectively from medical records.

*Results:* The incidence of CHD in the TTTS group and no-TTTS group was 5.4% (4/74) and 2.3% (2/87), respectively ( $p = 0.42$ ). RVOTO was diagnosed in one recipient twin delivered at our center and two recipient twins delivered elsewhere. The incidence of RVOTO in recipients was 4% (3/75). Mean systolic blood pressure at birth was similar in donor and recipient twins, 53 mmHg versus 56 mmHg, respectively ( $p = 0.42$ ). Mean endothelin-1 level at birth was also similar between donors and recipients, 14.3 ng/L and 13.2 ng/L, respectively ( $p = 0.64$ ).

*Conclusions:* The incidence of CHD in TTTS treated with fetoscopic laser surgery is higher than in the general population (5.4% versus 0.5%). We found no difference in afterload parameters between donors and recipients after laser treatment.

## Introduction

Congenital heart disease (CHD) occurs 12 times more frequently in monochorionic twins with twin-to-twin transfusion syndrome (TTTS) than in the general population<sup>19</sup>. TTTS is a severe complication of monochorionic twinning and affects 15% of monochorionic twin gestations<sup>11</sup>. TTTS results from unbalanced inter-twin blood transfusion via placental vascular anastomoses leading to hypovolemia, oliguria and oligohydramnios in the donor twin and hypervolemia, polyuria and polyhydramnios in the recipient twin<sup>11</sup>. Recipient twins are especially at risk for cardiovascular disorders. The etiology of cardiovascular disorders in recipients is still unclear and may result either from increased preload due to chronic hypervolemia<sup>162</sup> or increased afterload due to high levels of vasoconstrictive substances such as endothelin-1<sup>84</sup>. Reported cardiovascular abnormalities in recipient twins include hypertension<sup>12;83;154</sup>, (bi-)ventricular hypertrophic cardiomyopathy<sup>18;19;155</sup>, tricuspid regurgitation<sup>156</sup> and most importantly right ventricular outflow tract obstruction (RVOTO)<sup>19;159</sup>. RVOTO may occur at subvalvular, valvular or supra-valvular level and the severity of the obstruction determines the necessity of treatment<sup>244</sup>.

The first objective of this study was to determine the incidence of CHD, and particularly of RVOTO, in monochorionic twins with TTTS treated with laser compared to a control group of monochorionic twins without TTTS. The second objective was to study the potential role of increased afterload in CHD in TTTS after laser treatment by measuring endothelin-1 and blood pressure at birth.

## Patients and methods

All consecutive cases of monochorionic twins with TTTS treated with laser (TTTS group) and monochorionic twins without TTTS (no-TTTS group) delivered at our center between June 2002 and June 2005 were prospectively included in our study. Pregnancies complicated by intrauterine fetal demise of both twins, major congenital non-cardiac anomalies, triplets and TTTS-pregnancies not treated with fetoscopic

laser surgery were excluded from the study. The Leiden University Medical Center is a tertiary medical center and is the national referral center for fetal therapy including laser treatment for TTTS in the Netherlands. The institutional review board of the Leiden University Medical Center approved the study and all parents gave written informed consent for their children. TTTS was diagnosed using standard prenatal ultrasound criteria<sup>105</sup> and staged according to the criteria of Quintero<sup>9</sup>. Monochorionicity was confirmed after delivery by histopathological examination of the placenta. Postnatal trans-thoracic echocardiography was performed in all surviving infants by experienced pediatric cardiologists within one week of delivery. Standard echocardiography included two-dimensional echocardiography, M-Mode and color Doppler studies. All examinations were performed with an Aloka 5000 scanner (Biomedic Nederland B.V., Almere, The Netherlands) with 8 MHz transducers.

We recorded the presence of the following findings: atrial septal defect (ASD), ventricular septal defect (VSD), RVOTO, right or left ventricle hypertrophy, atrio-ventricular regurgitation and decreased shortening fraction. Patent ductus arteriosus and patent foramen ovale were not recorded as pathological cardiac findings. RVOTO was diagnosed in the presence of subvalvular, valvular or supra-valvular obstruction<sup>245</sup>. Gradients were calculated using the modified Bernoulli formula<sup>245</sup>. Right or left ventricular hypertrophy was diagnosed if the anterior wall thickness of the right or left ventricle was more than the 95% confidence limits for estimated gestational age<sup>245</sup>. The presence of atrioventricular regurgitation was determined by color Doppler and classified as absent, mild-to-moderate and severe<sup>245</sup>. Left ventricular shortening fraction was calculated as the end-diastolic diameter minus the end-systolic diameter divided by the end-diastolic diameter<sup>245</sup>. Left ventricular shortening fraction was reported as decreased if less than 25%.

After birth, endothelin-1 was measured from umbilical cord blood. Endothelin was measured with a radioimmunoassay after C18 extraction and concentration. The interassay coefficient of variation ranged from 6.8 to 9.7 % at different levels (Nichols Institute, San Juan Capistrano, CA 92675, USA). Blood pressure was measured in each neonate on the right arm by Dinamap (Model XL, Critikon, Inc) with an appropriately sized cuff between 4 and 24 hours after birth, while the baby was supine and

quiet or asleep. A minimum of two blood pressure readings were taken and averaged. High systolic blood pressure at birth was defined as a systolic blood pressure above the 97<sup>th</sup> percentile for gestational age<sup>246</sup>.

To assure that exclusion of out born cases does not create a bias on the incidence of RVOTO, we also reviewed the medical records of all twins with TTTS treated at our center between August 2000 (start of laser treatment program at the Leiden University Medical Center) and June 2005, including those delivered at other centers. The choice for in-institution or out-of-institution delivery depended on the clinical picture and the wish of the parents.

The primary outcome measures were CHD and RVOTO. The secondary outcome measures were blood pressure and endothelin-1 levels at birth. Results were compared between the TTTS and the no-TTTS group and between donors and recipients in the TTTS group.

### *Statistics*

Results of categorical variables were compared using Fisher's exact test or Chi-square test, as appropriate. Unpaired Student's t test was used to compare normally distributed values between two groups. For comparisons between donors and recipients, the paired Student t test was used for normally distributed continuous variables and the Mc Nemar test for analysis of paired nominal variables. A p-value < 0.05 was considered to indicate statistical significance. Analysis was performed using SPSS version 11 (SPSS, Inc., Chicago, Illinois, USA).

## **Results**

Over the 3-year study period, 46 monochorionic pregnancies with TTTS treated with laser and 55 monochorionic pregnancies without TTTS were delivered at our center. All parents agreed to have their children participate in our study. Patient's characteristics are presented in Table 1. The median Quintero stage in the TTTS group was II. Seventeen percent (8/46) of pregnancies were stage I, 37% (17/46) stage II, 41% (19/46) stage III and 4% (2/46) stage IV. The overall neonatal outcome of monochorionic twins

TABLE 1 *Baseline characteristics.*

	TTTS group (n = 64 pregnancies; 92 fetuses)	No-TTTS group (n = 55 pregnancies; 110 fetuses)
Gestational age at birth – weeks <sup>a</sup>	32.0 ± 3.7	33.6 ± 3.1
Female – no. (%)	44 (48%)	60 (55%)
Birth weight – grams <sup>a</sup>	1706 ± 679	2075 ± 670
Intrauterine fetal demise – no. (%)	6 (7%)	2 (2%)
Neonatal death – no. (%)	7 (8%)	3 (3%)
Hydrops – no. (%)	2 (2%)	0 (0%)

<sup>a</sup>Value given as mean ± SD

delivered at our center has been published before<sup>207</sup>.

A total of 194 live-born infants were eligible for the study.

Echocardiography was performed in 86% (74/86) of infants in the TTTS group and 81% (87/108) of infants in the no-TTTS group. Two neonates in the TTTS group died shortly after birth before echocardiography could be performed. One neonate, a recipient twin, died due to severe perinatal asphyxia. The other neonate, a donor twin, developed severe fetal hydrops after laser treatment in association with massive tricuspid regurgitation and died at delivery due to intractable cardiac failure. The parents refused to authorize autopsy. Echocardiography was also not performed in one premature neonate in the no-TTTS group who died on day 1 due to early onset sepsis. We were not able to perform echocardiograms in 5 pairs of twins in the TTTS group and 10 twin pairs in the no-TTTS group due to early discharge from the hospital after delivery or transfer to

TABLE 2 *Findings on postnatal echocardiography.*

	TTTS group (n = 74 infants)	No-TTTS group (n = 87 infants)
Right ventricular hypertrophy – no. (%)	5 (7%)	2 (2%)
Left ventricular hypertrophy – no. (%)	1 (1%)	0 (0%)
Tricuspid regurgitation mild-moderate – no. (%)	4 (5%)	4 (5%)
ASD – no. (%)	1 (1%)	0 (0%)
VSD – no. (%)	2 (3%)	2 (2%)
RVOTO – no. (%)	1 (1%)	0 (0%)
Overall CHD – no. (%)	4 (5%)	2 (2%)

another hospital. These 15 pairs of twins were all alive and well at birth. Abnormalities detected on echocardiography are presented in Table 2. The overall incidence of CHD in monochorionic twins was 3.7% (6/161). The incidence of CHD in the TTTS group was 5.4% (4/74) (RVOTO,  $n = 1$ ; VSD,  $n = 2$ ; ASD,  $n = 1$ ). The incidence of CHD in the no-TTTS group was 2.3% (2/87) (VSD,  $n = 2$ ). The incidence of CHD in the subgroup of recipient twins in the TTTS group was 7.9% (3/38). No significant difference was found in incidence of CHD between the TTTS group and no-TTTS group ( $p = 0.42$ ) or between recipient twins and infants in the no-TTTS group ( $p = 0.14$ ).

RVOTO was diagnosed in one recipient twin born at 29 weeks of gestation. This patient has been reported earlier<sup>207</sup>. Routine echocardiography performed on day 1 showed pulmonary valve stenosis. The degree of pulmonary valve stenosis increased during neonatal life from moderate to severe. At one month of age the Doppler-gradient at the valvular level increased up to 125 mm Hg requiring balloon valvuloplasty. Serial echocardiographic examinations until one year of age showed no residual pulmonary valve stenosis and a mild pulmonary valve regurgitation. Since the start of the laser treatment program in August 2000, a total of 112 TTTS twin pairs treated with fetoscopic laser surgery at our center were born. Overall perinatal survival was 70% (156/224) (intrauterine fetal demise:  $n = 58$ ; neonatal death:  $n = 10$ ). Eighty-one (52%) survivors were donor twins and 75 (48%) were recipient twins. RVOTO (valvular pulmonary stenosis,  $n = 2$ , supravulvular pulmonary stenosis,  $n = 1$ ) was diagnosed in three TTTS survivors, including the previously reported patient and 2 other patients born elsewhere after fetoscopic laser treatment at our center. All patients with RVOTO were recipient twins. The overall rate of RVOTO in recipient twins with TTTS treated with laser was therefore 4% (3/75). Detailed information on the three recipients with RVOTO is presented in Table 3.

Results of blood pressure measurements and endothelin-1 concentrations in the TTTS group and no-TTTS group are shown in Table 4. We found no significant differences in blood pressure and endothelin-1 levels at birth between both groups or between donor and recipient twins. None of the neonates had persistent hypertension or required treatment for hypertension at the time of study.



TABLE 3 Prenatal and postnatal findings in the 3 recipients (1 born at our center and 2 born elsewhere) with RVOTO after laser therapy.

GA at laser (wk)	Quintero stage	Recipient fetal echocardiography	GA at birth (wk)	Postnatal cardiac diagnosis and course
15	2	Evidence of RVOTO AP max 4.5 m/s	29	Progression from moderate to severe valvular PS Balloon valvuloplasty at 1 month of age No residual PS. Mild PI
22	2	No evidence of RVOTO	37	Systolic heart murmur detected at 2 months of age Severe supravulvular PS detected at 2 months of age Surgical repair at 2 months of age No residual PS. Mild PI
18	2	No evidence of RVOTO	33	Severe respiratory failure at birth requiring ECMO Severe valvular PS detected at 1 week of age Balloon valvuloplasty at the age of 1 week Repeat balloon valvuloplasty at the age of 4 months No residual PS. Mild PI

GA, gestational age; RVOTO, right ventricular outflow tract obstruction; AP, pulmonary artery flow velocity; PS, pulmonary stenosis; PI, pulmonary valve insufficiency; ECMO, extra corporeal membrane oxygenation

TABLE 4 Systolic blood pressure and endothelin-1 levels at birth in donor and recipient twins.

	TTTS group (n = 86 infants)	No-TTTS group (n = 108 infants)	p-value
<b>All monochorionic twins</b>			
Systolic blood pressure <sup>a</sup> – mm Hg	55 ± 13	55 ± 10	0.91
Systolic blood pressure > 97th centile – no. (%)	8 (9%)	5 (4%)	0.08
Endothelin-1 <sup>a</sup> – ng/L	15.3 ± 7.7	15.3 ± 8.8	0.97
	Donors (n = 41 infants)	Recipients (n = 45 infants)	p-value
<b>TTTS group</b>			
Systolic blood pressure <sup>a</sup> – mm Hg	53 ± 14	56 ± 11	0.21
Systolic blood pressure > 97th centile – no. (%)	5 (12%)	5 (11%)	1.0
Endothelin-1 <sup>a</sup> – ng/L	15.6 ± 7.7	15.1 ± 8.2	0.64

<sup>a</sup>Value given as mean ± SD

## Discussion

In this study, we report a high incidence of CHD in TTTS survivors (5.4%) after fetoscopic laser surgery and particularly in recipient twins (7.9%). The actual incidence of CHD in TTTS in this study is probably underestimated as prenatal findings of fetuses who died in utero or were aborted were not included, and postnatal cardiac evaluation was not assessed in one hydropic infant who died at birth due to intractable cardiac failure. Overall, the reported rates of CHD in TTTS are higher than in the general population (0.5%)<sup>247</sup>. These results are in accordance with two previous studies on CHD in TTTS survivors<sup>19;248</sup>. Karatza *et al* reported an overall prevalence of CHD of 6.9% (6/87) in TTTS and 11.9% (5/42) in recipients<sup>19</sup>, whereas Herberg *et al* reported a prevalence of CHD of 11.2% (10/89) in TTTS and 13.7% (7/51) in recipients<sup>248</sup>. The overall incidence of RVOTO in all TTTS survivors treated with laser at our center was 4%. The RVOTO was hemodynamically significant in all patients requiring surgical or catheter-interventional treatment. As echocardiographic examination is not routinely performed in TTTS survivors born in other hospitals, however, mild RVOTO may not have been recognized. Herberg *et al* reported a 7.8% postnatal rate of RVOTO (4/51) in recipient twins with TTTS treated with fetoscopic laser surgery, but also included 2 cases with moderate and mild RVOTO treated expectantly<sup>248</sup>. The prenatal and postnatal rate of RVOTO in recipient twins with TTTS not treated with laser ranges from 4.8% to 11.3%<sup>19;159;162</sup>. Whether cardiovascular morbidity in recipient twins, and in particular RVOTO, is associated with the type of antenatal treatment is not known. The two current treatment options in TTTS are serial amnioreduction and fetoscopic laser treatment. A recently published randomized controlled trial comparing both treatments showed that perinatal mortality and neurological morbidity were significantly lower after laser surgery<sup>10</sup>. However, cardiovascular morbidity was not reported in this trial<sup>10</sup>.

This study is the first controlled single center study reporting cardiovascular morbidity in TTTS after fetoscopic laser surgery. Comparison with a control group of monochorionic twins without TTTS is of crucial importance because monochorionicity is associated with increased incidence of CHD even in the absence of TTTS<sup>19</sup>. We found no difference

in incidence of CHD in recipient twins treated with laser compared to monochorionic twins without TTTS. A possible reason for the lack of difference between the two groups may have been that our study was underpowered. To detect a 10% difference in CHD rate (12% versus 2%) between recipient twins and monochorionic infants without TTTS we would have needed a sample size of at least 100 children in each group (with 0.05 significance and a power of 80% by two-tailed analysis). Such large cohorts in TTTS studies can only be achieved with multi-center studies or longer study-periods.

The etiology of CHD in recipients with TTTS has been linked with increased preload due to volume overload following fetofetal transfusion, as well as increased afterload due to high levels of vasoconstrictive hormones, such as endothelin-1<sup>249</sup>. Endothelin-1 levels have been reported to be 2 ½ -fold higher in recipients than in donors<sup>84</sup>. Increased afterload and systemic hypertension during fetal life may then lead to the development of hypertrophic cardiomyopathy and eventually RVOTO. Reports of high blood pressure in recipient twins in fetal and neonatal life are consistent with this hypothesis<sup>12;83;154</sup>. We, as well as others, have previously shown that systemic hypertension, a clinical parameter for increased afterload, occurs more often in recipient twins than in donor twins<sup>12;83;154</sup>. In this study, however, we found no difference between donors and recipients in blood pressure and endothelin-1 concentrations at birth. Absence of difference in blood pressure and endothelin-1 levels may be related to the type of antenatal treatment. Other reports showing increased afterload in recipients, have been performed in TTTS not treated with laser<sup>12;83;84;154</sup>, whereas in our study all TTTS cases were treated with laser antenatally. Fetoscopic laser surgery occludes the placental vascular anastomoses and is therefore considered to be a causal treatment. Hypothetically, initial differences in blood pressure and endothelin-1 levels that were present before laser treatment may have gradually diminished and disappeared after laser treatment.

In conclusion, the incidence of CHD in TTTS survivors treated with fetoscopic laser occlusion of vascular anastomoses is low, but still higher than in the general population. In particular, the increased risk for RVOTO in recipient twins warrants close cardiac monitoring during fetal and neonatal life.