Long-term cardiac follow-up of severe twin-to-twin transfusion syndrome after intrauterine laser coagulation

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ABSTRACT

Objective: To assess long-term changes on cardiac morphology and function in survivors of severe twin-to-twin transfusion syndrome (TTTS) following intrauterine laser coagulation of placental anastomoses.

Design: Prospective follow-up of fetuses with severe TTTS, treated by laser coagulation of intrauterine placental anastomoses. Fetal echocardiography and Doppler studies of feto-placental haemodynamics were performed at the time of laser coagulation (median gestational age of 21.7 weeks). Postnatal cardiac follow-up included a detailed echocardiographic study of systolic and diastolic cardiac function at a median age of 21.1 months.

Setting: Paediatric cardiology unit.

Patients: 89 survivors from 73 consecutive pregnancies with severe TTTS.

Results: Prior to laser therapy, 54.9% of the recipient twins revealed typical signs of cardiac dysfunction due to volume overload and 23.7% of the donors had absent or reversed enddiastolic flow in the umbilical artery. 87.6% of the survivors (34/38 donors, 44/51 recipients) showed normal echocardiography. The prevalence of congenital heart disease (CHD) and particularly that of pulmonary stenosis (PS), which was only recorded in recipients, was increased in comparison to the general population (CHD: 11.2% v. 0.3%; PS: 7.8% v. 0.03%). There was no correlation between findings before laser therapy and the development of structural heart disease.

Conclusions: In spite of the high rate and severity of prenatal cardiac overload in recipients, normalisation occurs in the majority of cases after laser therapy. However, given the increased prevalence of congenital heart disease, and in particular pulmonary stenosis, intrauterine and postnatal follow-up is warranted.

Key words: twin-twin transfusion syndrome – long-term follow-up – congenital heart disease – prenatal diagnosis – pulmonary stenosis

List of abbreviations:
TTTS - twin-to-twin transfusion syndrome
PS – pulmonary stenosis
INTRODUCTION

Twin-to-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancies. It carries a high risk of fetal death if left untreated (80-100%) and a high perinatal morbidity and mortality.[1][2] In TTTS, genetically identical twins are exposed to different haemodynamic conditions and environmental factors. Placental vascular anastomoses provide the anatomical basis for the unbalanced intertwin transfusion from donor to recipient.[2][3][4] In the hypervolemic recipient, cardiomegaly, biventricular hypertrophy, and tricuspid and mitral regurgitation precede the development of more severe cardiac dysfunction and may result in hydrops fetalis as the end stage of intrauterine heart failure.[5][6] Cardiac dysfunction progresses with increasing gestational age.[7][8] In addition, various types of cardiac defects predominantly affecting the right ventricle and pulmonary artery have been reported.[5][7][8][9] These include muscular right ventricular outflow obstruction, valvular pulmonary stenosis and atresia, and left ventricular hypertrophic non-obstructive and obstructive cardiomyopathy. In contrast, the hypovolemic donor twin shows little cardiac pathology on fetal echocardiography, but does manifest signs of increased afterload due to raised placental resistance, as well as evidence of poor renal perfusion.

The two alternative treatments are serial amnioreduction and laser coagulation of placental vascular anastomoses.[10] Amniocentesis reduces the volume and pressure of the amniotic fluid without altering the anatomical substrate. Consequently, volume overload and cardiac dysfunction continue. Interruption of intertwin vascular anastomoses by laser coagulation offers a causal treatment. The volume load is normalised in the recipient, and, after a short period of acute volume overload, the donor fetus shows normal Doppler indices.[11][12][13] However, postnatal discordance of arterial distensibility, seen in successfully treated survivors[14], provides evidence of the altered vascular programming in the developing heart. The effect of long-standing, differing haemodynamic loading conditions on the developing heart has been examined prenatally. Postnatal follow-up studies of survivors following serial amniocentesis have been restricted to the neonatal period.

To exclude progression and ensure a long-term resolution of haemodynamic abnormalities, we studied the outcome of all survivors from a large well-defined cohort of consecutive pregnancies with severe TTTS, treated by laser coagulation.
MATERIALS AND METHODS

Study population
This is a prospective study of 89 survivors from 73 consecutive twin pregnancies (146 fetuses) following prenatal endoscopic laser treatment of severe TTTS. The survival rate and fetal outcome of this cohort were reported by Hecher.[10] In all cases, severe TTTS was diagnosed prenatally, fulfilling the following criteria: gestational age <25.0 weeks, single monochorionic placenta with massive polyhydramnios of the recipient and severe oligohydramnions or anhydramnios in the donor twin.
In all pregnancies, endoscopic laser coagulation of the vascular placental anastomoses was performed at a median gestational age of 21.7 weeks (range 17.7-25.0) at the Department of Prenatal Diagnosis and Therapy, Barmbek Hospital, Hamburg, Germany. Of the 51 fetuses that died intrauterine or through miscarriage, only one recipient showed a pulmonary stenosis on prenatal echocardiography. Further sonographic follow-up and delivery was performed at the local referring hospital. The median gestational age at delivery was 33.7 (24.9-40.3) weeks. There were 6 neonatal deaths, but none were related to cardiac disease.
All 89 surviving infants were included in a neurodevelopmental [15] and echocardiographic follow-up study. The median age of the 51 recipients and 38 donors at examination was 21.5 months (range 15.5-45 months). 82 of the 89 surviving infants underwent detailed echocardiography. Of the remaining 7 survivors, 4 had normal echocardiographic findings in the neonatal period, and all 7 patients were found to have no murmur on clinical examination. An informed consent was obtained from all parents.

Investigations
Prenatally, detailed fetal echocardiography and Doppler sonography were performed shortly before and after laser coagulation in all fetuses. Holosystolic tricuspid regurgitation and mitral regurgitation of more than half of the systole, hydrops (skin oedema and ascites, pericardial or pleural effusion), or structural cardiac disease were assessed in both twins. Umbilical artery velocimetry was recorded and classified as positive, absent or reversed end-diastolic flow; and ductus venosus waveforms according to positive, absent or reversed-flow during atrial contraction. Absent or reversed end-diastolic flow in the umbilical artery is a sign of increased afterload due to increased placental resistance; a pathologic ductus venosus waveform is an indicator for increased right ventricular end-diastolic pressure. The results of the Doppler studies have previously been reported as part of a larger study.[12]
At the postnatal examination, parents were interviewed with regard to postnatal cardiac abnormalities and the postnatal course of both twins. The patient files were reviewed for all patients who were found to have abnormal cardiac findings, or a pathological ECG or echocardiography on postnatal examination.
A 12-lead ECG was recorded (CS 100, Schiller). Blood pressure, recorded on the right arm, was obtained in a supine position.[16] After the physical examination, a complete echocardiography, including M-Mode, two-dimensional echocardiography, CW- and PW-Doppler and colour-Doppler-echocardiography (Vingmed 800, 5 MHz and 3.5 MHz transducer), was performed by 2 experienced pediatric cardiologists (W.G., U. H.). Quantitative M-Mode data were recorded over three cardiac cycles and the mean values for the right and left ventricular enddiastolic and endsystolic diameter (RVEDD, LVEDD, RVESD, LVESD), thickness of the interventricular septum and left ventricular posterior wall (IVSD, IVSS, LVPWD, LVDS), and the left atrial (LA)
and aortic dimension (AO) and fractional shortening of the left ventricle (FS) were obtained. The results were compared with normal values for Central-European children.[17] To assess the diastolic ventricular function of both the right and left ventricles, PW-Doppler measurements at the mitral valve, pulmonary vein, tricuspid valve and hepatic vein were determined [18] and compared to age-related normal values from the literature.[19][20][21][22][23][24][25] Variables measured at the mitral and tricuspid valve inlets included the early (E) and late (A) flow velocities and their ratios (E/A- ratio), the deceleration time of the E-wave, the velocity time integral (VTI) of the E and A waves, the ratio of VTI E/VTI A, and the duration of the A-wave. At the pulmonary vein, the variables measured included the peak flow velocities during systole (S) and diastole (D), and the peak flow velocity of reversed flow during atrial contraction (A), as well as the duration of the A velocity. Sites of Doppler investigation included the orifice of the right upper pulmonary vein in the four chamber view, and the mitral and tricuspid valve inflow at the leaflet tip. Standard echocardiography assessments of the cardiac anatomy and Doppler velocimetry were also obtained. The presence of valve regurgitation was determined by colour Doppler. Right- and left-ventricular outflow tract velocities, as well as the flow across the pulmonary and aortic valves were recorded. Pulmonary valve stenosis was classified as mild (maximal pressure gradient Pmax 25-49 mm Hg), moderate (Pmax 50-79 mm Hg) and severe (Pmax > 80 mm Hg or equal to systemic blood pressure).

An existing atrial septal defect was classified as medium-sized if the defect had a maximum diameter of ≥6 mm, the ratio RVDd/LVDd was increased, and the ECG revealed signs of right ventricular hypertrophy; and small, if there was no sign of right ventricular hypertrophy on echocardiography, and the size of the defect was between 3 and 6 mm. Interatrial left-to-right shunts with a diameter of less than 3 mm were defined as patent foramen ovale.[26] Patent foramen ovale are said to be present in more than 10% of people depending on the age of the cohort and study design [27], and were considered to be a non-pathologic cardiac finding.

Statistical analysis
The binominal distribution and Fisher’s exact test for the two-way contingency tables were used for statistical analysis. For Fisher’s exact test, p<0.05 was considered to indicate a statistical significance. For statistical analysis, cardiac dimensions were transformed into z-scores for a given body surface area.
RESULTS

Seventy-eight survivors (87.6%) showed no signs of congenital heart disease on physical examination, ECG and conventional echocardiography. One child showed signs of pulmonary hypertension secondary to bronchopulmonary dysplasia. The remaining 10 infants had structural heart disease.

Structural heart disease in TTTS

In surviving twins, the prevalence of congenital heart disease (Table 1) was increased (10/89=11.2%, 95% confidence interval (CI) 5.5 to 19.7) in comparison to that of the normal population (0.29-0.56%).[28][29]

Pulmonary stenosis was only recorded in recipients (4/51=7.84%; CI 2.2 to 18.9%) and was more common than in the general population (prevalence 0.033-0.038%).

Two recipients suffered from a severe pulmonary valve stenosis, which required balloon-dilatation immediately postnatally and at the age of 4 months, respectively. One recipient had a moderate valvular, and another one a minimal supravalvular pulmonary stenosis.

Medium-sized and small atrial septal defects were found in the same frequency in both the acceoptor and donor cohorts. In comparison to the normal population, the number of medium-sized atrial septal defects was increased (2.3%, CI 0.3 to 7.9; prevalence 0.023-0.032).

Correlation between prenatal and postnatal cardiac findings

Overall, 28 of the 51 (55%) recipient twins had pathologic findings prenatally. The most common abnormalities were cardiac chamber enlargement and hypertrophy, holosystolic tricuspid and mitral valve regurgitation, and pathological Doppler velocities of the ductus venosus as an indicator for increased right ventricular end-diastolic pressure. Nine of the 38 donors exhibited absent or reversed end-diastolic blood flow in the umbilical arteries. There was no statistically significant difference in the incidence of postnatal congenital heart disease between fetuses with and without abnormal cardiac findings before laser coagulation (Table 2).

Prenatal findings in pulmonary stenosis

Pulmonary stenosis occurred only in recipients; therefore prenatal findings were reviewed separately. There was no statistically significant difference in the occurrence of pulmonary stenosis between fetuses with normal and abnormal cardiac findings before laser coagulation. Table 3 shows the pre- and postnatal findings of all children with pulmonary stenosis.

Postnatal myocardial function

In children without structural heart disease, cardiac dimensions and systolic function were within the normal range at follow-up (Figure 1). The right ventricular diameters were normal or less than normal in both the recipient and donor without intertwin discordance.

The complete evaluation of all diastolic parameters necessitated a prolonged and standardised investigation. This was not always tolerated by the young children. Left and right ventricular inflow parameters were recorded in all except 6 survivors, but reliable Doppler velocities of the pulmonary vein could be acquired in 29/51 (56.8%) recipients and 18/38 (47.3%) donors. All donors and recipients without any heart disease had normal diastolic myocardial function (data not shown). Even in recipients
with severe prenatal cardiac insufficiency, systolic and diastolic variables were within the normal range.
Table 1: Prevalence of congenital heart disease in survivors after twin-to-twin-transfusion syndrome.
Rate of heart disease in the study cohort compared to the prevalence at birth reported by the Baltimore-Washington Infant study [28] and Wren [29].

<table>
<thead>
<tr>
<th>Postnatal examination</th>
<th>All No. (%) [95 CI]</th>
<th>Recipients No. (%) [95 CI]</th>
<th>Donors No. (%) [95 CI]</th>
<th>Prevalence per 100 live births WIS [28]</th>
<th>Wren [29]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>89 (86.64)</td>
<td>51 (86.28)</td>
<td>38 (89.47)</td>
<td>0.49</td>
<td>0.559</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired pulmonary hypertension</td>
<td>1 (100.00)</td>
<td>0 (0.00)</td>
<td>1 (100.00)</td>
<td>0.038</td>
<td>0.033</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>10 (11.24)</td>
<td>7 (13.72)</td>
<td>3 (7.89)</td>
<td>0.49</td>
<td>0.559</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>4 (4.49)</td>
<td>4 (7.84)</td>
<td>0 (0.00)</td>
<td>0.038</td>
<td>0.033</td>
</tr>
<tr>
<td>Atrial septal defect all</td>
<td>5 (5.62)</td>
<td>2 (3.92)</td>
<td>3 (7.89)</td>
<td>0.038</td>
<td>0.033</td>
</tr>
<tr>
<td>Medium-sized atrial septal defect</td>
<td>2 (2.25)</td>
<td>1 (1.96)</td>
<td>1 (2.63)</td>
<td>0.032</td>
<td>0.023</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>1 (1.12)</td>
<td>1 (1.96)</td>
<td>0 (0.00)</td>
<td>0.146</td>
<td>0.188</td>
</tr>
</tbody>
</table>
Table 2: Incidence of postnatal congenital heart disease and prenatal haemodynamic findings

<table>
<thead>
<tr>
<th>Prenatal abnormal finding</th>
<th>Present</th>
<th>Absent</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient DVnegA</td>
<td>3/16 (18.8%)</td>
<td>4/35 (11.4%)</td>
<td>0.66</td>
</tr>
<tr>
<td>TR</td>
<td>5/26 (19.2%)</td>
<td>2/25 (8.0%)</td>
<td>0.42</td>
</tr>
<tr>
<td>MR</td>
<td>2/7 (28.6%)</td>
<td>5/44 (11.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hydrops</td>
<td>0/3</td>
<td>7/48 (14.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Donor UAEDFneg</td>
<td>1/9 (11.2%)</td>
<td>2/29 (6.9%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Fisher’s exact test showed no significant differences in the incidence of congenital heart disease in fetuses with and without abnormal prenatal haemodynamic findings. Statistical significance was considered for values of p<0.05.

DVnegA, ductus venosus negative a-wave (absent or reversed flow during atrial contraction); MR, mitral regurgitation; TR, tricuspid regurgitation; UAEDFneg, umbilical artery end-diastolic flow absent or reversed.
Table 3: Prenatal and postnatal course of recipients with pulmonary stenosis

<table>
<thead>
<tr>
<th>Postnatal cardiac diagnosis</th>
<th>GA at LC (wk)</th>
<th>Recipient fetal echocardiography</th>
<th>Rec. TR</th>
<th>Rec. MR</th>
<th>Rec. DV nega</th>
<th>Rec. IU PS</th>
<th>Rec. UA veloc. and echocardiography</th>
<th>Course during pregnancy</th>
<th>GA at delivery (wk)</th>
<th>Postnatal course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient 1</td>
<td>18+5</td>
<td>normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>UAEDF: normal</td>
<td>Recipient echocardiography: week 20 + 25: normal week 29: valvular PS, small valvular annulus</td>
<td>33+5</td>
<td>Postnatal severe pulmonary stenosis requiring balloon valvuloplasty at the age of 1 and 9 months. Normal valvular morphology. Residual mild PS (32 mmHg*)</td>
</tr>
<tr>
<td>Severe pulmonary stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fetal death 5 days after LC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient 2</td>
<td>20+3</td>
<td>congestive heart failure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>UAEDF: normal</td>
<td>UAEDF: negative</td>
<td>39+0</td>
<td>Progression from moderate (Pmax 68 mmHg*) to severe pulmonary stenosis (Pmax 90mmHg*) within 4 months, no TR, small pulmonary annulus of 7 mm at 4 months, thickening of pulmonary valve leaflets. Balloon valvuloplasty at 4 months of age. Residual mild pulmonary stenosis of 30 mmHg*</td>
</tr>
<tr>
<td>Severe pulmonary stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fetal death 1 day after LC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient 3</td>
<td>19+0</td>
<td>mild signs of congestive heart failure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>UAEDF: normal</td>
<td>UAEDF: normal</td>
<td>35 + 1</td>
<td>Post-partum systolic heart murmur. Moderate pulmonary stenosis (Pmax 40 mmHg*), thickening of pulmonary valve leaflets</td>
</tr>
<tr>
<td>Moderate pulmonary stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PI normal</td>
<td>echo: normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient 4</td>
<td>19+4</td>
<td>congestive heart failure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>UAEDF: normal</td>
<td>UAEDF: normal</td>
<td>35+4</td>
<td>Mild increase in the velocity within the pulmonary trunk (1.8 m/sec)</td>
</tr>
<tr>
<td>Mild supravalvular stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PI normal</td>
<td>echo: normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DV neg a, ductus venosus negative a-wave (absent or reverse flow with atrial contraction); GA, gestational age; LC, Laser coagulation; MR, mitral valve regurgitation; PI, pulsatility index of the umbilical artery; PS, pulmonary stenosis, Rec, recipient; TR, tricuspid valve regurgitation.; UA, umbilical artery, UAEDF, umbilical artery end-diastolic flow; * instantaneous pressure measured using the Bernoulli equation of echocardiography
DISCUSSION

This long-term follow-up study of surviving twins following prenatal laser coagulation of severe TTTS shows two important results. Firstly, 87% of the survivors had a normal cardiac examination. Inspite of the high rate and severity of prenatal cardiac impairment in recipients, complete normalisation of systolic or diastolic ventricular function occurs over the long-term. This illustrates the remarkable capacity of the fetal heart for ventricular remodelling.

Secondly, the rate of pulmonary stenosis and atrial septal defects in surviving twins is increased. Pulmonary stenosis is only recorded in recipients. Possible mechanisms for this are discussed below.

In previous studies, the frequency and spectrum of heart disease in TTTS has been reported with varying incidence.[2] [7] [8] [9] [30] [31] Postnatal studies have focused on complications in the neonatal period. Follow-up beyond the neonatal period has been done in small study cohorts [7] and restricted to survivors with structural heart disease. However, more than half of the recipient twins in severe TTTS exhibit various stages of volume overload and congestive heart failure antenatally, and haemodynamic changes of the donor twins include signs of hypovolemia and increased afterload.

Diastolic dysfunction preceeds systolic dysfunction and the study of the diastolic inflow is a more sensible parameter to determine ventricular performance. The typical pattern of diastolic dysfunction has been described in children with cardiomyopathy resulting from increased volume or pressure load of either the right or left ventricle.[18] [32] [33] After relief of the pressure load, or extra- or intracardial shunting, the systolic and diastolic indices in successfully treated patients improve and, over the long-term, approach values found in normal subjects.[33] It is important to note that these parameters are sensitive to loading conditions, heart rate, and age, and can vary significantly with inspiration and expiration.[18] [19] [21] [32] Standardised investigation parameters are difficult to obtain in children below three years of age, resulting in highly variable results. This may be the reason, why normal values for this age group have – if at all - only been recorded on small study cohorts. We were able to show that, at least beyond 15 months of age, regression of even severe prenatal cardiac disease without any signs of systolic or diastolic dysfunction occurs. However, we were not able to investigate the exact time point of the normalisation of the ventricular function because prenatal and neonatal follow-up after laser coagulation was done at the referring hospitals. Longitudinal observations in a small cohort of twins treated with intrauterine amniocentesis showed that ventricular hypertrophy, contractility and atrioventricular valve regurgitation gradually regressed and returned to normal within 40 days to 6 months after birth.[7]

Congenital heart disease

Previous studies have reported an increased frequency of structural heart disease in TTTS. Twins are known to have an increased incidence of congenital malformations. However, even in monochorionic twins, in more than 90% of cases only one individual is affected.[34] In a prospective study, Karatza [9] compared monochorionic diamniotic pregnancies with and without TTTS (uncomplicated monochorionic diamniotic pregnancies without circulatory imbalance and haemodynamic impairment). They were able to show that the overall prevalence of congenital heart disease in monochorionic diamniotic twins was increased above that in singletons (6.9% in TTTS and 2.3% in uncomplicated monochorionic diamniotic
twins compared to 0.56% in singletons). The increased frequency of congenital heart disease in fetuses with TTTS was related to the significantly increased number of recipients with congenital heart disease (11.9%). This is in accordance with the incidence of 13.7% found in our study.

The mechanism for the increased rate of congenital heart disease in monochorionic twins remains unknown. The monozygotic twinning process itself may increase the incidence of congenital heart disease, with unequal postzygotic division of the inner cell mass being responsible for the discordant cardiovascular anatomy. Another explanation might be the phenotypic variability of the same genome. Even genetic discordances may occur as a consequence of variations in gene expression secondary to postzygotic mutation, parental imprinting effects, asymmetric X-inactivation and DNA methylation, or possibly even genetic inter-twin differences caused by new mutations.

Additionally, circulatory imbalance in chronic twin-to-twin syndrome may contribute to the development of pulmonary stenosis. Blood flow appears to play a crucial role in the development and growth of the cardiac chambers, valves and arteries. Abnormal blood flow may lead to abnormal growth of cardiac and vascular structures. In recipients, a possible mechanism for this may be severe and long-standing heart failure due to chronic right ventricular volume overload, or muscular hypertrophy with severe outflow tract obstruction resulting in diminished antegrade flow with diminished growth of the right ventricular outflow tract and pulmonary artery. Additional environmental factors, such as the release of vasoactive peptides or growth factors may contribute to the development of haemodynamic imbalance and cardiac disease.

Effect of laser coagulation

In this study, cardiological follow-up was performed for the first time after laser coagulation of placental anastomoses. Endoscopic laser coagulation offers a causal treatment option by interruption of the intertwin-blood flow resulting in normalisation of the right ventricular volume load in the recipient. In contrast, amnioreduction reduces amniotic fluid volume and pressure, but not the underlying cause of TTTS. After serial amniocenteses, cardiac dysfunction progresses with advancing gestational age, increasing the risk of more severe postnatal cardiac disease. Therefore, one may expect that fetuses treated with laser coagulation would develop structural heart disease less frequently. Inspite of successful laser coagulation, we found congenital heart disease and pulmonary stenosis to be present in the same frequency as after serial amniocentesis. This suggests that, as previously discussed, factors in very early pregnancy may lead to congenital heart disease and the development of right ventricular outflow tract obstruction in the recipient.

Gardiner et al showed that abnormal fetal haemodynamic loading is associated with increased arterial wall stiffness in childhood in the donor following serial amniocenteses. Mid trimester laser therapy could not prevent discordant intertwin arterial wall stiffness, but did alter the pattern with increased pulse wave velocity in the heavier twin. Further follow-up studies – including the possible effect on long-term cardiovascular performance - are needed.

Study limitations:

After prenatal laser coagulation, additional follow-up data on serial echocardiographic assessments were not available for all fetuses, because follow-up was performed in
the local referring units. Serial measurements of pulmonary valve diameter and Doppler velocities of the outflow tract are crucial for detecting emerging pulmonary stenosis in the fetus.
Since the start of this prospective study, additional parameters obtained from tissue Doppler imaging have been developed to describe systolic and diastolic function in more detail. Therefore, further studies involving this new technology may be necessary.

**Conclusion**
This study provides evidence of normalisation of cardiac function in fetuses with severe TTTS even after severe prenatal haemodynamic overload following intrauterine laser coagulation. This illustrates the remarkable adaptability of the developing heart and shows that cardiac hypertrophy and failure regress once the underlying cause has been removed. However, the increased prevalence of pulmonary stenosis in recipients justifies the need for prenatal and postnatal echocardiographic surveillance.

**ACKNOWLEDGEMENTS**
We should like to thank Dr. M. Knapp, PHD, Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany, for his support in statistical analysis of the study results.

**COMPETING INTERESTS STATEMENT**
The authors have not competing interests to declare.

**LEGENDS**
Figure 1: Enddiastolic dimensions of the left ventricle (LVDD), the interventricular septum (IVSD) and the right ventricle (RVDD) beyond the age of 15 months in survivors of severe TTTS. Cardiac dimensions are transformed into z-scores for a given body surface. There are no intertwin differences.
REFERENCES


