Clinical and echographic features of in utero cardiac dysfunction in the recipient twin in twin-twin transfusion syndrome

Nurit Zosmer, Rekha Bajoria, Ehud Weiner, Michael Rigby, Janet Vaughan, Nicholas M Fisk

Abstract
Objective—Fetal twin-twin transfusion syndrome (TTTS) presenting in the second trimester has been associated with almost no perinatal survival until recently, when serial drainage of amniotic fluid has improved the prognosis to 70%–80%. Most recipient twins now survive but develop cardiac dysfunction. The study was undertaken to evaluate the abnormal echocardiographic features and clinical complications of cardiac disease in the recipient twin of TTTS.

Design—Antenatal and postnatal echocardiographic and clinical observational study.

Setting—Antenatal studies in a tertiary referral centre. Postnatal management and follow up were performed by the same paediatric cardiologist, either at the obstetric hospital or at the regional referral centre.

Patients—Twin pregnancies complicated by TTTS with severe polyhydramnios diagnosed earlier than 25 weeks that proceeded until viability (n = 5).

Intervention—Serial fetal echocardiography with colour Doppler. Postnatal echocardiography in the first week and between two and seven months. Serial amnioreduction was performed in all pregnancies. Digoxin treatment, pericardiocentesis, paracentesis, or laser ablation of placental anastomoses was undertaken when there was hydrops.

Results—Increased cardiothoracic ratio and tricuspid regurgitation were seen in all recipient twins. High pulmonary artery velocities developed in three. One recipient twin died a week after delivery of endocardial fibroelastosis and infundibular pulmonary stenosis. Two others had balloon dilatation for pulmonary stenosis, one shortly after birth and one at four months. A further twin has apical thickening of the right ventricle at six months. The remaining recipient twin had normal echocardiographic findings at follow up.

Conclusion—This report characterises for the first time a cardiac disease acquired in utero in the recipient twin in pregnancies complicated by TTTS. Clinical manifestations in utero range from mild to critical pulmonary stenosis or lethal cardiomyopathy. Although perinatal prognosis seems to be related to the severity of dysfunction when first diagnosed in utero, follow up in infancy is recommended in view of the possibility of progressive pulmonary stenosis.

(Twin-twin transfusion syndrome (TTTS) is a severe complication of monzygotic twinning. It arises in 4%-26% of diamniotic monochorionic gestations, presumably as the result of vascular anastomoses between the circulation of one twin (the donor) and that of its co-twin (the recipient) leading to circulatory disequilibrium.® As a result of the transfusion, the donor twin becomes growth retarded and oliguric and develops oligohydramnios, whereas the recipient twin becomes polyuric with severe hydramnios and may develop hydrops. The traditional explanation that transfusion of blood from one twin to the other along placental vascular anastomoses produces hypovolaemia and anaemia in the donor and circulatory overload with polycythaemia and hyperviscosity in the recipient® may be oversimplified. Recent evidence suggests that haematological discordance is unlikely in second trimester TTTS as investigated by fetal blood sampling.® Also, umbilical venous pressure is not significantly raised in all hydropic recipient twins.® These are features inconsistent with the simple explanation of circulatory overload.

Severe TTTS presenting in the second trimester has until recently been associated with nearly 100% perinatal death.® The main cause of perinatal loss is premature delivery due to severe polyhydramnios. Serial amnioreduction now allows survival in 70%-80% mainly by allowing prolongation of pregnancy, but also possibly by improving fetal condition® with most cases of severe second trimester TTTS now progressing into the third trimester. We have found that most recipient twins develop cardiac dysfunction in utero, predominantly affecting the right ventricle and pulmonary artery, which can result in neonatal morbidity and mortality.

This report describes the clinical and echocardiographic features of cardiac dysfunction in recipient twins in second trimester TTTS.

Patients and methods
We studied five pregnancies complicated with TTTS. Gestational age at referral was 17–25 weeks (median 19). The inclusion criteria were: (a) monochorial twins of the same sex;
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(b) between twin membrane thickness <2-0mm; (c) growth discordancy (>20% of the abdominal circumference on ultrasound); (d) discordant amniotic fluid volume. The larger twin with the polyhydramnios was termed the recipient and the smaller with oligohydramnios the donor. Polyhydramnios in each recipient was severe (amniotic fluid index (AFI) > 30 (range: 32-65, normal: < 25). There was no family history of congenital heart disease.

Management was at the discretion of the consultant in charge (NF or JV). All patients underwent serial amnioreduction (range one to eight procedures) until 24–27 weeks to restore AFI to normal (<25). Additional treatments were used in the presence of moderate or severe hydrops in the recipient (skin oedema, pleural effusion, and ascites). Maternal digoxin treatment was given from 24–27 weeks until delivery in fetuses A and B who showed features of hydrops. In recipient twin A paracentesis of 162 ml and direct intraperitoneal injection of 50 µg per kg digoxin was given before maternal treatment was started. Recipient twin C had a large pericardial effusion (5 ml) successfully drained at 28 weeks which did not recur. One patient (B) with progressive hydrops despite amniotic fluid volume being controlled, underwent ablation of 11 anastomosing placental surface vessels, unfortunately death of the donor twin occurred 24 hours later. Hydrops subsequently resolved in the recipient.

High resolution ultrasound with pulsed, continuous wave, and colour echocardiograms were examined weekly (Acuson XP/10 or Hewlett Packard Sonos 1000). The power output was <100 mW/cm². The measurements attempted were cardiothoracic ratio, maximal velocity in the aortic and common pulmonary arteries, right ventricular shortening fraction, and qualitative analysis of the venous waveform in the umbilical vein. Some examinations were rendered suboptimal by the degree of polyhydramnios, the mobility of the fetus, the distance of the fetus from the transducer, or the inability of the mother to tolerate prolonged scanning. Cardiomegaly was defined as cardiothoracic area ratio >1/3 measured on transverse section of the fetal thorax at the level of the atrioventricular valves. Right ventricular shortening fraction was measured by M mode as was the left ventricle postnatally, and was compared with normal data in monochorial twins without TTTS. Continuous wave Doppler sampling near the inlet of the right or left ventricles was used to measure the maximal velocities of the backward flow and to calculate the pressure gradients with the modified Bernoulli equation. Umbilical vein pulsation was defined as notchting of the umbilical venous flow during ventricular diastole. All examinations were recorded on tape for later analysis.

Gestational age at delivery ranged from 31 to 36 weeks and birthweights were all above the 5th centile (twin A at 36 weeks, 2-25 kg; twin B at 36 weeks, 2-95 kg; twin C at 31 weeks, 1-39 kg; twin D at 34 weeks, 1-87 kg; twin E at 31 weeks, 1-32 kg). Placenta tion was confirmed histologically as monochorionic diamniotic in all cases.

Neonatal echocardiography was done on day 2, 3, or 4 and a follow up examination at two to seven months in all surviving twins. A detailed postmortem cardiac examination was performed on recipient twin B.
Table 1  Most abnormal clinical and echocardiographic findings in recipient twins in the second trimester

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Severity of hydrops</th>
<th>Tricuspid regurgitant velocity (m/s)</th>
<th>Right ventricular shortening fraction (normal 25%-35%)</th>
<th>Pulmonary artery velocity (normal &lt; 0.8 m/s)</th>
<th>搏起 umbilical vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Severe</td>
<td>4</td>
<td>25</td>
<td>4-5</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td>Severe</td>
<td>3-5</td>
<td>10</td>
<td>1-5</td>
<td>+</td>
</tr>
<tr>
<td>C</td>
<td>Moderate</td>
<td>3</td>
<td>20</td>
<td>1-5</td>
<td>–</td>
</tr>
<tr>
<td>D</td>
<td>Mild</td>
<td>3</td>
<td>25</td>
<td>0-7</td>
<td>–</td>
</tr>
<tr>
<td>E</td>
<td>None</td>
<td>2</td>
<td>25</td>
<td>0-8</td>
<td>–</td>
</tr>
</tbody>
</table>

Results

Table 1 shows the most abnormal clinical and echocardiographic features in the recipient fetuses. In each case these were found between 20 and 24 weeks. Twins A and B were severely affected in utero. Each had cardiomegaly with thickening of the right ventricle, tricuspid regurgitation (fig 1), and high velocities in the pulmonary artery. Recipient twin B showed left sided involvement as well: a dilated extremely poorly contractile left ventricle with a large early/atrial filling (E/A) ratio across the mitral valve was consistent with a restrictive cardiomyopathy. The other recipient twins (C, D, and E) were less severely affected, with mild tricuspid regurgitation and an increased pulmonary artery velocity in one case only (C). Twin E showed mild and transient tricuspid regurgitation between 20 and 27 weeks.

All the recipient twins, except twin E, developed varying degrees of hydrops early in pregnancy (24–25 weeks), which resolved between 25–28 weeks. Hydrops was classified as mild, moderate, or severe (mild, ascites; moderate, ascites and pleural or pericardial effusion; and severe, skin oedema, ascites, and pleural or pericardial effusion (table 1).

Umbilical vein pulsation, considered to reflect atrial contraction when there is high pressure in the right ventricle,16 was seen in recipient twins A and B, but disappeared later when the hydrops resolved and polyhydramnios did not recur.

Table 2 shows the postnatal clinical and echocardiographic features. Twin A had critical pulmonary artery stenosis with a postnatal Doppler derived systolic gradient >75 mm Hg, and balloon dilatation was performed. The ventricular systolic pressure before dilatation was 140 mm Hg, decreasing to 75 after the procedure. The peak to peak gradient across the pulmonary valve was 18 mm Hg after the procedure. Follow up four months later showed a thick right ventricular wall, mild tricuspid regurgitation (peak Doppler velocity of 3-5 m/s), and mild stenosis of the pulmonary valve (instantaneous peak systolic pressure drop of 36 mm Hg). Twin B had progressive left ventricular failure over the first 12 hours of life and was initially suspected of having hypoplastic left heart syndrome; he collapsed three days after delivery and died on day 4. A postmortem examination showed a very small left ventricle with the typical appearance of endocardial fibroelastosis. The right ventricle showed severe hypertrophy of the septomarginal trabeculation producing a typical two chamber right ventricle (fig 2) and functional pulmonary stenosis.13 The histology of the right ventricle showed myocardial hypertrophy with endocardial and subendocardial fibrosis (fig 3). Twin C immediately after delivery presented with moderate infundibular pulmonary stenosis and slight hypertrophy of the right ventricle. Seven months later, a scan showed only mild apical thickness of the right ventricle.

Twin A is currently growing normally at 6 months of age with few episodes of peripheral cyanosis. Twin E was assessed echographically as normal at delivery. This twin remained asymptomatic at follow up at the age of 4 months, but echocardiography showed severe supravalvar pulmonary stenosis with severe biventricular hypertrophy. Balloon dilatation failed, and this child is

Table 2  Postnatal findings in recipient twins

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Week 1</th>
<th>Month 2-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Critical pulmonary stenosis, balloon dilatation on day 2.</td>
<td>Thick right ventricular wall, tricuspid regurgitation 3 m/s. High velocities in pulmonary artery 3-5 m/s. Narrow pulmonary valve diameter (5-4 mm).</td>
</tr>
<tr>
<td>B</td>
<td>Small poorly contractile left ventricle, Small A waves at the mitral valve. Normal flow through aortic valve and arch. Moderate tricuspid regurgitation 3 m/s with narrow pulmonary valve.</td>
<td>Pump failure on day 3 leading to neonatal death. Postmortem examination: endocardial fibroelastosis, extremely small left ventricle, mitral stenosis with normal aortic arch, two chamber right ventricle.</td>
</tr>
<tr>
<td>C</td>
<td>Mild to moderate pulmonary stenosis. Slight hypertrophy of right ventricle.</td>
<td>Apical thickness of right ventricle. Normal velocities in the pulmonary artery and normal valve diameter (8-5 mm).</td>
</tr>
<tr>
<td>D</td>
<td>Asymptomatic with normal echocardiography.</td>
<td>Asymptomatic with normal echocardiography.</td>
</tr>
<tr>
<td>E</td>
<td>Asymptomatic with normal echocardiography.</td>
<td>Biventricular hypertrophy at month 4. Severe supravalvar pulmonary stenosis (100 mm Hg). Narrow pulmonary valve annulus (5 mm).</td>
</tr>
</tbody>
</table>

Figure 2  The outlet portion of the right ventricle is separated from the inlet portion by an apical shelf. Apical shelf, curved arrow; continuation between inlet and outlet, *; pulmonary valve, arrow.
Figure 3  Right ventricular wall of recipient twin B showing focal myocardial hypertrophy with endocardial (E) and subendocardial (SE) fibrosis. Haematoxylin and eosin; originally x 150.

currently awaiting surgical repair. Follow up between two and seven months in all other twins showed normally growing babies without any clinical manifestations of heart disease. None of our twins showed high blood pressure in the postnatal period nor was there evidence of cardiac dysfunction in any of the donor twins either in utero or postnatally.

Discussion
This paper describes the clinical and echocardiographic features of cardiac disease that develops in utero in the recipient twin in TTTS. The opportunity of documenting this condition has only recently arisen because until the advent of serial amnioreduction all these babies died in utero or in the early postnatal period.

Our findings are consistent with the earlier histopathological study of Naeye showing myocardial hypertrophy in 10 out of 11 transfused infants in monozygotic twin pregnancies and more recent ultrasonic descriptions of congenital congestive heart failure in utero. Our findings, however, suggest that this disease may have a variable manifestation from mild transient dysfunction to severe cardiac disease resulting in neonatal morbidity or mortality. The main features are: (a) cardiomegaly with increased C/T ratio (>1/3); (b) predominantly right ventricular hypertrophy; (c) reduced right ventricular shortening fraction; (d) tricuspid regurgitation; (e) high flow velocities in the pulmonary artery. Other variable findings include hydrops, a pulsatile umbilical venous waveform, and involvement of the left ventricle.

In normal pregnancies, Doppler recorded blood velocities in the umbilical vein do not show pulsations after 20 weeks. Recipients A and B with tricuspid regurgitation presented with umbilical vein pulsation reflecting abnormal reversal of blood velocities in the central veins extending beyond the ductus venosus into the umbilical vein. This finding suggests increased fetal central venous pressure. The correlation between valvar regurgitation and umbilical vein pulsation is still unclear; in hydrpocic fetuses venous pulsation seems more related to atrial systole than to valvar regurgitation. Techniques have recently been described for evaluating venous waveforms in the fetal ductus venosus and inferior vena cava, which should allow more definitive study of the phenomenon.

Recipients A and B had evidence of severe cardiac dysfunction on presentation before 20 weeks and had a poor outcome with irreversible myocardial fibrosis. Recipients C and E on the other hand presented with mild to moderate dysfunction in utero but with mild or no dysfunction neonatally. As there were no differences between their gestational age at presentation we suggested from these findings that the perinatal prognosis for the recipient twin depends on the severity of the disease when first diagnosed in the second trimester. Echocardiographic follow up is recommended in view of the possibility of progressive pulmonary stenosis as occurred in recipient E.

The postmortem examination of recipient twin B showed a severely diminished left ventricle with secondary endocardial fibroelastosis and mitral stenosis but with a normal aortic outlet and severe hypertrophy of the right ventricle with an obstructed pulmonary outflow. Hypoplastic left heart syndrome is the diagnosis applied to a neonate with critical stenosis or atresia of the aortic valve associated with diminutive left ventricle, mitral valve, and ascending aorta. Only a small percentage of these babies will have notable right heart malformation. We do not consider the cardiac pathology in this case to be an example of classic hypoplastic left heart syndrome because the left ventricular outflow tract and the ascending aorta were normal. The severe malformation of the right ventricle was consistent with the recipient cardiac disease (abnormal right ventricle and pulmonary valve) found in the other cases.

Although serial amnioreduction prevents premature delivery, it is not clear whether it improves cardiac function. Our limited findings indicate that pulsation of the umbilical vein tended to disappear after several amnioreduction procedures and that the combination of amnioreduction, pericardiocentesis, and paracentesis may anecdotally result in resolution of the hydrops. An alternative hypothesis is that recipient cardiac dysfunction resolves with increasing gestational age. Hydrops resolved in the two severe cases (A and B) treated with digoxin, although we are unable to determine if this was related to the amnioreduction, or the digoxin, or was spontaneous. Digoxin has anecdotally been used to improve hydrops in a single case report in which there was no evidence of recipient cardiac disease.

The aetiology of cardiac dysfunction in the recipient twin in TTTS syndrome is not understood. Cardiac dysfunction may be due to: (a) increased preload; (b) primary cardiac pathology - that is, congenital cardiomyopa-

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thy; or (c) increased afterload. Increased preload because of volume overload from placental vascular anastomotic transfusion as the mechanism does not explain the reported lack of difference in the haemoglobin levels between the twins, but could be a stimulus to right ventricular hypertrophy. A primary cardiomyopathy is a further possibility. The only documented hypertrophic cardiomyopathy to develop in utero is in fetuses of insulin dependent diabetic mothers although the pathogenesis is not understood. Similarly the aetiology of other neonatal hypertrophic cardiomyopathies is unknown. Ferrans and Rodriguez have suggested that cardiomyopathies result from hypercontractility during embryonic life. This is supported by the fact that obstructive cardiomyopathy occasionally occurs in patients with disorders involving excess circulatory catecholamines and sympathetic nervous system activation. Although 10% of adults with cardiomyopathy have systemic hypertension, none of the recipient twins in our study developed hypertension in the perinatal period. Furthermore, unlike the cardiomyopathy seen in fetuses of diabetic mothers, the cardiac dysfunction described here in recipient twins is more severe and may result in considerable morbidity and even mortality.

Vascular anastomoses between the two circulations occur in all monochorial twins, not just those with TTTS. It might be argued that cardiac disease was the primary cause of circulatory instability in these monochorial twins, thus leading to manifestation as TTTS. We think this unlikely for three reasons. Firstly, structural congenital heart disease rarely causes hydrops in the absence of atrioventricular valvar anomalies or arrhythmias. These features were not present in our cases, yet four of five developed hydrops. Secondly, these pregnancies represented cases of consecutive recipients with TTTS diagnosed before 25 weeks that were successfully managed until after 31 weeks. This frequency of cardiac dysfunction seems much greater than that of congenital heart disease. Thirdly, increasing evidence supports several types of congenital heart disease being the consequence of abnormal haemodynamics during early development.

All fetuses showed tricuspid regurgitation in utero. This is well known to occur after maternal indomethacin treatment for preterm labour, which causes constriction of the ductus arteriosus. The ductus acts as a right to left shunt in fetal life, and its constriction increases right ventricular afterload. Thus increased pressure in the right ventricular outflow tract could lead to cardiomegaly and tricuspid valve incompetence as well as chronically diminished blood flow through the pulmonary valve and hence narrowing and stenosis. On the basis of these findings we speculate that the mechanism of recipient cardiac dysfunction may be due to increased afterload. High resistance to umbilical arterial flow in the monochorial placenta could lead to increased afterload, increased pressure in the systemic circulation of the recipient twin, high pressure in the ductus arteriosus, and obstructed outflow to the right ventricle resulting in the development of congestive heart failure and a right ventricular hypertrophy. Another possibility is that high pressure in the systemic fetal circulation could be the result of vasoconstrictive substances such as endothelin, troponin, or renin angiotensin released by the monochorial placenta in TTTS. Biochemical investigation of fetal blood is under way to examine this hypothesis.

Unfortunately the features of the cardiac pathology emerged during the period of the study and we are aware that our data are incomplete. To explore our hypothesis of increased afterload a longitudinal prospective study of cardiac output would be required. Unfortunately this is technically difficult due to the small diameters of the valves of the outflow tract early in the second trimester, which are near the limits of ultrasonic resolution. Estimation of the cardiac output is particularly prone to errors due to inaccuracies in the valve area in fetuses with stenotic valves, such as in recipient A and B in the study. Further studies are required to determine the E and A wave ratio at the level of the atrioventricular valves, as an index of cardiac compliance and indirectly of preload in the recipient twin, as well as the effect of amnioreduction on these variables.

Better understanding of the underlying pathophysiology of cardiac dysfunction in TTTS may facilitate therapeutic strategies and thus improve outcome in this disease.

NZ was funded in part by a grant from the Special Trustees of Queen Charlotte's and Chelsea Hospital. We acknowledge the cooperation of Professor L Allan, who saw some of these patients for a second opinion. Professor J Wigglesworth and Dr S Yen Ho provided helpful comments and advice on the postmortem examination.

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Br Heart J 1994 72: 74-79
doi: 10.1136/hrt.72.1.74

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