Acquired Right Ventricular Outflow Tract Obstruction in the Recipient Twin in Twin-Twin Transfusion Syndrome

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BACKGROUND

Twin-twin transfusion syndrome complicates 4% to 26% of diamniotic monochorionic twin gestations and is associated with high fetal morbidity and mortality. Cardiac dysfunction and biventricular hypertrophy may develop in the recipient twin with the potential for RVOTO.

METHODS

This was a retrospective review of a two-center experience of TTTS to describe the prevalence and evolution of acquired RVOTO in the recipient twin. Right ventricular outflow tract obstruction was diagnosed or excluded by fetal or postnatal echocardiography or clinical assessment.

RESULTS

Of 73 twin pregnancies with TTTS identified between 1994 to 1998, a total of seven (9.6%) were complicated by RVOTO in the recipient twin: two subvalvar/muscular, four valvar and one combined. Of 44 pregnancies with fetal echo, six had in utero RVOTO with antegrade flow diagnosed at gestational ages ranging from 19 to 27 weeks. In utero progression occurred in four cases over a period of four to eight weeks, with the development of RVOT atresia by delivery. Postnatal progression of RVOTO occurred in two cases, one of which required pulmonary balloon valvuloplasty at age two years. Postnatal regression of subvalvar RVOTO occurred in two cases in early infancy. Death related directly or indirectly to the RVOTO occurred in all four patients who developed complete RVOT obliteration.

CONCLUSIONS

Right ventricular outflow tract obstruction may occur in the recipient twin of at least 9% of pregnancies complicated by TTTS. Right ventricular outflow tract obstruction progression is common in utero and may worsen neonatal outcome.

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recipient twins. These perinatal units represent the referral centers for the majority of complicated pregnancies in their respective regions. Right ventricular outflow tract obstruction was diagnosed or excluded by review of perinatal records, obstetrical ultrasounds, fetal echocardiograms, postnatal echocardiograms and postnatal clinical assessments, where available. In the cases with RVOTO, the clinical course and postnatal outcome were documented by a review of prenatal and postnatal medical records. Post-mortem reports were also reviewed.

RESULTS

Seventy-three twin pregnancies complicated by TTTS were identified. Of these, 48 patients (66%) had one or more fetal echocardiograms performed. The remaining 25 patients, most of whom presented in the earlier years of the review, did not have fetal echocardiograms performed, but all had multiple obstetrical ultrasounds (level 2 to 3) performed. Gestational ages at diagnosis of TTTS ranged from 19 to 27 weeks.

Seven of the 73 recipient twins (9.6%) had a prenatal or postnatal diagnosis of RVOTO (95% confidence intervals 3.6% to 15.6%) (Table 1). None of the donor twins had structural or functional heart disease, and no major additional structural heart defect was identified in the recipient twins. Six fetuses had evidence of RVOTO either in utero (n = 4) or in the immediate postnatal period (n = 2), whereas one presented at age two years with more severe obstruction (Fig. 2 and 3). The mechanism of RVOTO varied among cases. Four had primarily pulmonary valve (PV) stenosis, including two with progression to PV atresia with intact ventricular septum. Muscular subvalvular obstruction was predominant in two cases. One case had combined muscular and valvular obstruction, as well as evidence of calcification of the main pulmonary artery and aorta. One fetus (case 3) was diagnosed with critical PV stenosis in utero, with retrograde ductus arteriosus flow, which was confirmed by postnatal echocardiography. This fetus also had significant TR and biventricular dysfunction in utero. Autopsy performed after death at 13 days of age revealed only mild thickening of the PV, with three normal-sized cusps and no significant dysplasia. However, there was severe subvalvar RVOTO from marked right ventricular hypertrophy (Fig. 3).

In utero progression occurred in at least three of the cases. All three (cases 1 to 3) had initial antegrade flow documented across the right ventricular outflow tract (RVOT),

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BVH</td>
<td>biventricular hypertrophy</td>
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<tr>
<td>PS</td>
<td>pulmonary stenosis</td>
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<tr>
<td>PV</td>
<td>pulmonary valve</td>
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<tr>
<td>RVOT</td>
<td>right ventricular outflow tract</td>
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<tr>
<td>RVOTO</td>
<td>right ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>TR</td>
<td>tricuspid regurgitation</td>
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<tr>
<td>TTTS</td>
<td>twin-twin transfusion syndrome</td>
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Figure 1. (A) A two-dimensional image that demonstrates significant biventricular hypertrophy with reduced chamber size in the recipient of a twin-twin transfusion syndrome at 22 weeks of gestation. There is also a pericardial effusion and skin edema, as evidence of fetal hydrops and polyhydramnios. (B) Severe tricuspid insufficiency is also often seen as shown in this image. (C) In this same hydropic recipient twin, there was evidence of diastolic dysfunction including a prolonged isovolumic relaxation time, umbilical venous pulsations and, as shown here, significant A wave reversal in the inferior vena cava (IVC). LV = left ventricle; RA = right atrium; RV = right ventricle.
with development of complete or near-complete RVOTO at the time of delivery. One of the infants with critical pulmonary stenosis (PS) (case 2) demonstrated an initial gradient at 23 weeks of 10 mm Hg with forward ductus arterialis flow. At 34-week follow-up, the gradient had increased to 60 mm Hg, and there was retrograde ductus arterialis flow. In another (case 1), there was a dysplastic PV noted at the initial study without abnormal flow, but the right ventricle was mildly hypoplastic. At 24 weeks, there was only a mildly increased velocity across the PV, and the right ventricle was mildly hypoplastic. When the infant delivered at 26 weeks, there was valvar pulmonary atresia and moderate right ventricular hypoplasia. In the last case (case 3), the initial study at 19 weeks revealed BVH with no evidence of RVOTO. By 25 weeks, there was severe tricuspid insufficiency, mild right ventricular hypoplasia and anatomic evidence of subvalvar and valvar obstruction with only increased flow velocities. After birth, critical PV stenosis was diagnosed with severe tricuspid insufficiency present.

Postnatal progression occurred in two cases. Case 6 demonstrated a threefold increase in the gradient at the subvalvar (muscular) level over the first two weeks of life. The gradient decreased slightly with acute treatment with disopyramide (a negative inotrope), then gradually resolved over the subsequent four months with no further treatment required. Case 5 had no evidence on antenatal echocardiogram or neonatal clinical examination of significant RVOTO but presented by two years of age with severe PS requiring balloon dilation.

In addition to the case with resolution after disopyramide therapy, postnatal regression occurred in one other case. Case 7 had mild subvalvar stenosis, which resolved without therapy over a one-month period.

The outcomes of these fetuses were overall poor. This was, in part, due to their cardiovascular disease and also related to their prematurity and low birth-weight status. Death occurred in five of the seven affected recipient twins (71%), all within the first 4.5 months of life. The causes of death were directly related to the cardiac pathology in two cases, with surgical shunt complications in one very low birth-weight baby (case 4) and severe biventricular dysfunction in the other (case 3). Of the remaining cases, two infants remained on intravenous prostaglandin E1 for ductus arteriosus patency at the time of death and died of

Table 1. Outcomes of Recipient Twin Fetuses With RVOTO

<table>
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<tr>
<th>Case</th>
<th>Gestation at Diagnosis of TTTS</th>
<th>Gestation at Delivery/Weight</th>
<th>Fetal Echocardiogram/ Ultrasound Findings</th>
<th>Postnatal Findings</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>21 weeks</td>
<td>26 weeks/800 g</td>
<td>21 wk—dysplastic PV w/o obstruction. RV mildly small. Forward DA flow. 24 wk—flow acceleration through RVOT, moderately small RV, mild TR, forward DA flow.</td>
<td>Pulmonary atresia/intact ventricular septum. Confluent PAs. Hypoplastic RV cavity with RVH.</td>
<td>Death age 8 weeks—sepsis, renal failure, on PGE.</td>
</tr>
<tr>
<td>2</td>
<td>23 weeks</td>
<td>35 weeks/1,089 g</td>
<td>23 wk—10 mm Hg RVOT gradient. 34 wk—60 mm Hg RVOT gradient, retrograde DA flow, severe RVH, moderate TR.</td>
<td>Critical PS, DA dependent, hypoplastic TV, moderate TR.</td>
<td>Death age 2 days—necrotizing enterocolitis, on PGE.</td>
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<td>3</td>
<td>19 weeks</td>
<td>26 weeks/780 g</td>
<td>22 wk—BVH, no RVOT obstruction, antegrade DA flow. 25 wk—flow acceleration in RVOT (subvalvar and valvar), severe TR, RVH &gt; LVH, mildly small RV, biventricular dysfunction, small pericardial effusion, antegrade DA flow.</td>
<td>Critical PVS, DA dependent, moderate RV hypoplasia, severe TR, poor LV function.</td>
<td>Death age 13 days—autopsy, marked RVH causing severe subvalvular stenosis. Mild PVS. Marked LVH.</td>
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<tr>
<td>4</td>
<td>22 weeks</td>
<td>29 weeks/900 g</td>
<td>22 wk—BVH (OB ultrasound). 28 wk—absent forward flow across PV, retrograde DA flow.</td>
<td>Pulmonary atresia/intact ventricular septum, BVH, mild TR.</td>
<td>Death age 4 wks related to BT shunt complications.</td>
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<tr>
<td>5</td>
<td>27 weeks</td>
<td>35 weeks/1,030 g</td>
<td>31 wk—small pericardial effusion, no RVOTO, antegrade DA flow.</td>
<td>Age 2 years—severe progressive PS, gradient 80 mm Hg.</td>
<td>Successful pulmonary balloon valvuloplasty.</td>
</tr>
<tr>
<td>6</td>
<td>24 weeks</td>
<td>28 weeks/623 g</td>
<td>24 wk—BVH (OB ultrasound).</td>
<td>Subvalvar RVOTO, gradient 33 mm Hg, increased to 93 mm Hg by 2 wks. Severe RVH/LVH. Calcified main PA and aorta.</td>
<td>Improvement in gradient on disopyramide. Death age 4.5 months from chronic lung disease.</td>
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<tr>
<td>7</td>
<td>21 weeks</td>
<td>27 weeks/940 g</td>
<td>21 wk—BVH (OB ultrasound).</td>
<td>Mild subvalvar RVOTO, gradient 20 mm Hg.</td>
<td>Resolution of gradient, RVH by age 1 month.</td>
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BVH = biventricular hypertrophy; DA = ductus arteriosus; LV = left ventricle; LVH = left ventricular hypertrophy; OB = obstetrical; PA = pulmonary artery; PGE = prostaglandin E1; PV = pulmonary valve; PVS = pulmonary valve stenosis; RV = right ventricle; RVH = right ventricular hypertrophy; RVOT = right ventricular outflow tract; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation; TTTS = twin-twin transfusion syndrome; TV = tricuspid valve.
complications of necrotizing enterocolitis and intracranial hemorrhage (case 2) and Candida sepsis with renal failure (case 1). One infant (case 7) died at 4.5 months of age from complications of bronchopulmonary dysplasia.

DISCUSSION

Incidence of RVOTO in recipient twins of TTTS. This study is the first to document the high incidence (9.6%) of
RVOTO in the recipient twins of TTTS. This directly or indirectly was associated with a disproportionate increase in mortality of these twins (71%). The increasing identification of TTTS antenatally and routine fetal cardiac assessment of affected fetuses may further increase the diagnosis of RVOTO. It is likely that this study underestimates the actual incidence of RVOTO in TTTS, as some fetuses who died or were aborted did not undergo prior cardiac assessment, and some cases of mild PS may not have been recognized clinically. Assessing only those pregnancies with a fetal echocardiogram, 5/44 recipient twins or 11.3% developed RVOTO, which may be closer to the true incidence; however, those with milder RVOTO may have gone unrecognized. This incidence of congenital heart disease, particularly pulmonary outflow obstruction, is significantly higher than that observed in the general population and even in many genetic syndromes. Twin pregnancies, particularly monoyzygotic twin pregnancies, are known to be complicated by a higher incidence of congenital heart disease, and this may, in part, be attributable to both recognized and milder unrecognized cases of TTTS (10).

Pathogenesis of RVOTO in the recipient twin of TTTS.
The etiology of RVOTO in TTTS remains speculation. As it occurs only in the recipient twin, it is likely to occur, at least in part, secondary to an altered fetal circulation. One of the most striking cardiac findings in the recipient twin is cardiac hypertrophy. This hypertrophy, particularly of the right ventricle, occurs to varying degrees in the majority of cases of severe TTTS (6,7). Significant hypertrophy of the muscle in the RVOT may cause a direct obstructive effect to pulmonary blood flow. As a consequence of anatomic obstruction, flow may be redistributed away from the right ventricle. Such a decrease in forward flow across the RVOT may result in diminished growth, causing progression to more severe PS or even pulmonary atresia and right ventricular hypoplasia in utero.

Systolic right ventricular dysfunction also occurs in recipient twins (11), contributing further to the decreased flow across the RVOT. This reduction in forward flow as a consequence of systolic dysfunction is similar to observations made in the context of tricuspid valve disease with severe tricuspid insufficiency in which there can be pseudopulmonary atresia and progressive anatomic RVOTO (12).

We have recently described that abnormalities in ventricular diastolic function occur in cases of fetal hypertrophic cardiomyopathy, including the recipient twins in TTTS (Fig. 1) (11). These diastolic abnormalities are more pronounced in the right ventricle as compared with the left, with abnormal ventricular filling patterns, prolonged isovolumic relaxation time (left ventricular assessment) and abnormal flow patterns in the inferior vena cava, hepatic veins and ductus venosus. Such dysfunction may result in a decrease in cardiac filling and, thus, a reduction in flow through right-sided structures such as the PV. As demonstrated in many fetal studies, blood flow appears to play a crucial role in the development and subsequent growth of heart valves, chambers and great arteries. Given the lack of significant RVOT gradients in two of our prenatally assessed cases with progression, we suspect the pathogenesis of RVOTO may have been secondary to right ventricular systolic or diastolic dysfunction; however, we were unable to further delineate the etiology from our retrospective assessment.

Pathophysiology of TTTS. Twin–twin transfusion syndrome is thought to be, at least partly, due to unbalanced placental vascular anastomoses, which result in abnormal shunting of blood from the donor to the recipient. However, such abnormalities of placental vasculature have also been noted in monochorionic pregnancies not complicated by TTTS, suggesting that additional factors must contribute to the development of the syndrome. The placental resistance faced by the recipient twin may be increased to such a degree that a discrepancy occurs between right- and left-sided cardiac outputs and, thus, intracardiac flows. Alterations in placental resistance, as reflected by abnormal pulsatility index in the umbilical artery flows, are not consistently found in all cases of TTTS, making this hypothesis less likely as a sole explanation for the cardiac effects (13). This hypothesis is supported, however, by a case report of “functional” tricuspid valve atresia in a donor fetus after laser coagulation of the placental vascular anastomoses (14). This resulted in a major increase in placental resistance faced by the donor, as evidenced by alterations in umbilical arterial Doppler tracings. This fetus then developed right ventricular enlargement, absent tricuspid valve flow and retrograde filling of the right ventricle via the ductus arteriosus through an incompetent PV. Upon resolution of the abnormal placental resistance (return of normal umbilical artery and descending aorta flows), the cardiac abnormalities resolved. Of interest, the recipient twin in this pair had mild PS detected postnatally.

Mitogenic stimuli for myocardial growth. Right ventricular hypertrophy that occurs initially out of proportion to the degree of pulmonary outflow tract obstruction may point towards a primary myocardial growth abnormality playing a role in the development of hypertrophy. Endothelin–1 concentrations have been found to be significantly higher in in utero and perinatal cord blood samples from recipient twins as compared with donor twins and controls (15). The levels have also been found to be significantly higher in the recipient fetuses with severe hydrops than they were in those with mild or no hydrops. Endothelin is a growth factor and is a potent vasoconstrictor. It causes proliferation of smooth muscle cells in the systemic and pulmonary vasculature. It also can induce fetal ventricular myocyte proliferation in vitro (Hornberger LK, unpublished data, 2000). If endothelin is, indeed, a factor in cellular growth and differentiation, then this may explain the marked ventricular hypertrophy and valvular abnormalities seen in TTTS. As well, endothelin’s vasoconstrictor activity and mitogenic effect on vascular smooth muscle cells
may contribute indirectly to the significant ventricular hypertrophy and explain the frequent finding of hypertension in the recipient twin in the neonatal period.

**Conclusions.** In summary, RVOTO in the recipient twin is a significant complication of TTTS with a high mortality. Its incidence is likely underestimated, as mild PS may only present in the late postnatal period or later in childhood. This antenatally acquired condition, which may be progressive, is likely a consequence directly or indirectly of the hemodynamic changes in the fetus and the presence of circulating growth factors and vasoactive peptides produced by the donor or placenta that affect only the recipient twin. Prospective serial hemodynamic assessment of these fetuses and cellular investigations are warranted to further define the etiologic factors involved. We speculate that delineation of factors involved in the development of RVOTO in TTTS may aid in the elucidation of mechanisms of development of PS or atresia in some singleton pregnancies lacking a genetic syndrome.

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**REFERENCES**