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Initial Fetal Cardiovascular Profile Score Predicts Recipient Twin Outcome in Twin-Twin Transfusion Syndrome

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Abstract

Objective—To assess the relationship between cardiomyopathy and recipient twin (RT) outcome in twin-twin transfusion syndrome (TTTS).

Methods—Fetal echocardiography and outcomes data in 62 consecutive pregnancies with TTTS was reviewed. The primary outcome was neonatal RT survival. Severity of RT cardiomyopathy at presentation was assessed by the Cardiovascular Profile Score (CVPS). RT outcome and odds of survival were compared between groups, stratified by CVPS.

Results—Overall neonatal survival for all fetuses was 61% (76/124). RT survival was 58% (36/62). Grouped by CVPS, RT survival was greater (50%) for those with a CVPS ≥ 9 and even higher (74%) for a CVPS =10. Amongst components of the CVPS, atrioventricular valve regurgitation (AVVR) was associated with negative RT outcome. Other factors at presentation were not predictive of RT outcome.

Conclusions—Normal CVPS in the RT in TTTS is predictive of improved survival compared to RT with abnormal CVPS, even RT with minor deductions. Standard clinical staging did not predict outcome. Cardiac assessment by CVPS may improve clinical decision making and timing of fetal interventions.

Keywords

twin-twin transfusion syndrome; fetal echocardiography; fetal cardiovascular profile score

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) affects approximately 10–15% of monochorionic, diamniotic twin pregnancies(1,2). Although the pathophysiology of TTTS is not yet fully understood, abnormal exchange of blood and/or humoral factors occurs from the donor twin (DT) to the recipient twin (RT) via placental vascular connections. Both circulating

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endothelin-1(3) and activation of the renin-angiotensin-system (RAS)(4,5) have been implicated in the pathophysiology of TTTS, which—as potent vasoconstrictors—may account for some of the cardiac manifestations noted in RT(4,6). Regardless of the mechanism, TTTS manifests clinically with the development of oligohydramnios and growth restriction in the DT, while the RT has polyhydramnios. In addition, although not generally occurring in the DT (7), the RT can develop signs of a characteristic cardiomyopathy specific to TTTS. These changes include atrioventricular valve regurgitation (AVVR), ventricular hypertrophy, and systolic and diastolic ventricular dysfunction(8–12).

Severity of TTTS has typically been described by a staging system proposed by Quintero(13, 14). Despite its widespread use, the prognostic value of Quintero staging remains unclear(15, 16). In addition, the Quintero staging relies on findings obtained primarily by obstetrical ultrasound, and does not incorporate fetal echocardiographic findings. It is known, however, that subtle changes in cardiac function can be identified by careful fetal echocardiography even in early Quintero stages, which may worsen without treatment(8,10). The relationship between presence of cardiovascular findings in the RT and outcome has yet to be firmly established.

The fetal cardiovascular profile score (CVPS)(17,18) has been proposed as an echocardiographic method of assessing cardiovascular well-being in at risk fetuses. The CVPS is a 10 point scale, which incorporates the presence or absence of hydrops, abnormal venous and arterial Doppler findings, cardiomegaly, atrioventricular valve regurgitation and cardiac dysfunction; there are 1–2 point deductions from the total score depending on the extent of cardiovascular abnormalities noted (Table 1).

It was the purpose of this study to assess the severity of RT cardiomyopathy at presentation, characterized by CVPS, and to evaluate the relationship of CVPS with RT outcomes. It was our hypothesis that worse cardiovascular status at presentation, as indicated by lower CVPS, would be associated with poorer RT outcome.

METHODS

Study design

Study consisted of a single center, retrospective review of all cases of suspected TTTS referred to the Fetal Care Center of Cincinnati from January 2004 and April 2006.

Study subjects

All data collection and storage was done with the approval of the Institutional Review Board and in congruency with HIPAA. The immediate pre-procedure fetal echocardiogram and clinical records were reviewed. Exclusion criteria included twin pregnancies where either twin had significant congenital heart disease, severe non-cardiac fetal anomalies, and cases where one twin underwent selective fetocide in the attempt to preserve survival of the co-twin.

Echocardiographic study

Each twin underwent a detailed fetal echocardiogram performed in accordance with published standards(19). All studies were performed on a Siemens Sequoia C512 using commercially available curvilinear transducers. The presence or absence of hydrops was noted.

Doppler interrogation of the ductus venosus, umbilical vein, and umbilical artery was performed. Doppler flow patterns were described as either normal or abnormal; abnormal Doppler flow patterns were defined as atrial systolic flow reversal in the ductus venosus, umbilical venous pulsation in a free loop of cord, or absent or reverse of diastolic flow in the

umbilical artery. This is in accordance with both Quintero staging(14) and with assignment of the CVPS(17,20).

The presence or absence of atrioventricular valve regurgitation was assessed by color flow and pulsed Doppler interrogation. Severity of AVVR was graded semi-quantitatively as mild (narrow jet ≤ ½ atrial length), moderate (narrow jet > ½ atrial length), or severe (wide jet > ½ atrial length).

Ventricular systolic function was assessed by shortening fraction, and classified as either normal (≥ 28%) or depressed (<28%)(17). Overall cardiac size was assessed as the ratio of the cardiac area in the 4 chamber view to the thoracic cross-sectional area at the same level. Cardiomegaly was defined as a cardiac/thoracic area ratio > 0.35(17).

The myocardial performance index (MPI) was measured in both the right and left ventricles in the majority of patients. The MPI is a Doppler index, measuring both systolic and diastolic myocardial function(21). It is defined as the sum of isovolumic relaxation and isovolumic contraction time, divided by the ejection time, measured using Doppler inflow and outflow spectral profiles. An increase in the MPI has been linked to fetuses in an un-well state(20,22, 23). An abnormal MPI was defined as a value more than two standard deviations above the normal mean, which at our institution equals an RV MPI > 0.48 and an LV MPI > 0.43.

Assignment of the CVPS and Quintero Stages

CVPS was assigned to each RT by a single investigator (A.S.) blinded to outcome status. The CVPS was assigned as previously described (Table 1)(17,18). Quintero stage was assigned as previously described(14) by a single investigator (T.M.C.), blinded to CVPS assignment.

Statistical Analysis

Thirty-day neonatal survival data was tabulated for all RT. RT were stratified by CVPS and comparisons in survival between groups were made using Chi-square analysis. Odds of thirty-day survival were examined using univariate logistic regression, with CVPS as an independent variable. The individual components of the CVPS were also examined. Finally, Quintero stage and CVPS at presentation were related to outcome using multivariate logistic regression, adjusting for gestational age at presentation and intervention performed (selective fetoscopic laser procedure (SFLP) or amnioreduction (AR).

RESULTS

Study population

Sixty-two consecutive pregnancies of suspected TTTS were included. The mean gestational age was 21 ± 2.8 weeks. The Quintero staging assignment distribution was 17 in stage I, 12 in stage II, 30 in stage III, 3 in stage IV and 0 in stage V. Initial treatment groups were similar, with 51% (32/62) receiving AR and 48% (30/62) receiving SFLP. Twenty five percent (8/32) of those patients who initially received AR received further treatment with SFLP. The distribution of Quintero staging within each treatment group is as follows: 12 in stage I, 8 in stage II and 12 in stage III for those in the AR group and 5 in stage I, 4 in stage II, 18 in stage III and 3 in stage IV in the SFLP group. Overall birth survival was 76% (94/124), with a decrease in survival at 30 days to 61% (76/124). The RT 30 day survival was similar at 58% (36/62).

Relationship of Cardiac Findings to Survival

RT survival by CVPS grouping was 74% (25/34) for a CVPS =10, 50% (6/12) for a CVPS = 9 and 31% (5/16) for a CVPS < 9(χ^2 = 8.4, p < 0.02). For CVPS ≥ 9, there was a significantly

higher 30 day RT survival (odds ratio 3.7, 95% confidence interval 1.1–11.8, p<0.03) than those with a CVPS < 9. For CVPS equal to 10, there was a significantly higher RT survival at 30 days (odds ratio 4.3, 95% confidence interval 1.5–12.6, p<0.008) than those with a CVPS less than 10 (Table 2).

Individual components of the CVPS and MPI were assessed in relation to RT 30 day survival. With the exception of AVVR, neither the other individual components of the CVPS nor the right or left ventricular MPI significantly predicted RT 30 day mortality (Table 3). The presence of AVVR in the RT was associated with a considerably decreased RT survival (odds ratio 0.3, 95% confidence interval 0.1–0.8, p<0.02). Though not statistically significant, a trend was noted between the presence of cardiomegaly and worsening survival (odds ratio 0.3, 95% confidence interval 0.1–1.1, p=0.06).

Relationship of Non-Cardiac Variables and Quintero Staging to Survival

Gestational age at presentation was divided into those who presented at < 20 weeks and those > 20 weeks. Though presentation at < 20 weeks trends towards increasing RT mortality at 30 days, the trend did not achieve significance (odds ratio 2.7, 95% confidence interval 1.0–7.7, p=0.06). The type of treatment, either AR or SFLP, the twins ultimately received, also did not correlate to RT survival at 30 days (odds ratio 1.9, confidence interval 0.7–5.3, p=0.22). Quintero stage at presentation was not predictive of RT survival at 30 days.

DISCUSSION

The development of TTTS in monochorionic, diamniotic gestations has significant morbidity and mortality(24,25). Currently, most centers describe severity using the Quintero staging system. However, although recent reports have suggested that worsening Quintero stage is associated with poorer outcomes following SFLP(26), the relationship between Quintero stage and outcome remains controversial(15,16). The proposed Quintero staging assesses the severity of TTTS, but in the early stages, focuses on changes predominantly seen in the DT. Findings describing RT cardiomyopathy—although well described(8–12)—are not incorporated into early Quintero staging, and thus, not incorporated into the formal assessment of disease severity. The more advanced findings of elevated central venous pressure found in higher Quintero stages—specifically, absence or reversal of venous flow during atrial contraction in the ductus venosus or pulsatility in the umbilical vein—has been associated with poorer RT outcome(25), suggesting a link between cardiovascular compromise and RT outcome. It was the goal of the current study to examine the relationship between a more comprehensive assessment of fetal cardiovascular well-being, the CVPS, and RT outcomes.

The current study, in a relatively large cohort, establishes the association between recipient twin cardiovascular status and postnatal survival. Although a relatively nonspecific predictor of recipient twin outcome, the CVPS nonetheless serves as a tool characterize degree of cardiovascular derangement. As such, use of the CVPS demonstrated that any cardiac findings, e.g., atrioventricular valve regurgitation, cardiomegaly, or ventricular systolic dysfunction are associated with poorer RT outcome. Moreover, as cardiac abnormalities “accumulate,” outcomes are even worse. In our series, many of the cardiac findings resulting in deductions in CVPS were not venous Doppler changes, and thereby would not be incorporated into assessment of disease severity if applying the widely utilized Quintero staging, nor would they be assessed by standard obstetric ultrasonography. Importantly, our data also demonstrated that Quintero staging did not predict RT outcome in our study population.

A comprehensive fetal cardiac assessment by echocardiography may therefore be an important component of clinical evaluation in pregnancies complicated by TTTS. For example, inclusion of cardiac findings, such as those incorporated into the CVPS, may result in a clinically useful

modification of Quintero staging that could improve patient risk stratification. Such modifications have been proposed by Harkness, et al.(27), and would result in "upstaging" of Quintero Stage I and II when RT cardiac findings are present. By using this modification, determination for the type and timing of treatment has been adjusted at our institution. For example, in cases of early stage I or II TTTS *in which there is evidence of recipient twin cardiovascular changes*, "upstaging" results in proceeding with a fetoscopic laser procedure rather than a trial of therapeutic amnioreduction.

Limitations to our study include its retrospective design, and the lack of stratification to the type of therapeutic intervention performed. This was not analyzed in the current study for two reasons. First, it was the primary aim of this study to assess the relationship between RT cardiovascular status at presentation and RT outcomes, irrespective of treatment method. Secondly, we pooled data on RT outcome for all treatment modalities with the understanding that neither AR nor SFLP has clearly been established as a superior, with reported overall survival being similar for either treatment in some studies(28), and SFLP shown to be superior in others(15). We nonetheless acknowledge that the relationship between specific therapy and outcomes is important, and should be further analyzed in larger studies. The current study is also likely limited by both a selection and referral bias at our center. Our center is a large regional referral center for TTTS, and thus, the patient population likely includes a disproportionate number of advanced cases of TTTS. Furthermore, it is likely that these cases are referred specifically for SFLP by the referring physician.

In summary, the current study establishes an association between cardiovascular abnormalities and outcome in recipient twins affected by TTTS. The findings suggest that echocardiography may have an important role in the evaluation of twin pregnancies affected by TTTS, particularly in the assessment of recipient twin cardiomyopathy.

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Table 1

Cardiovascular Profile Score (CVPS)(17,18)

	Normal (2 points)	**−1 point**	**−2 points**
Hydrops Fetalis	None	Ascites, pleural effusion, or pericardial effusion	Skin edema
Abnormal Venous Doppler	Normal venous Doppler	Ductus venosus atrial systolic reversal	Umbilical venous pulsations
Cardiomegaly (CT ratio= cardiac area/thoracic area)	CT ratio ≤ 0.35	CT ratio >0.35 & <0.50	CT ratio >0.50
Abnormal myocardial function	Ventricular SF >0.28 & no valve regurgitation	SF <0.28 or TR or semilunar valve regurgitation	TR + dysfunction or any MR
Abnormal Arterial Doppler	Normal umbilical artery diastolic flow	Absent end-diastolic flow in the umbilical artery	Reverse end-diastolic flow in the umbilical artery

CT, cardiothoracic; MR, mitral regurgitation; SF, shortening fraction; TR, tricuspid regurgitation

Table 2

Recipient twin 30 day survival in relation to CVPS

	Total	Survival
CVPS =10	34	25 (74%)
CVPS = 9	12	6 (50%)
CVPS < 9	16	5 (31%)

CVPS, cardiovascular profile score

Table 3

RT % survival by specific cardiac findings

	Present	Absent	X^2 / p value
Hydrops	2/3 (67%)	34/59 (58%)	0.1/ NS
Ductus venous atrial reversal	7/14 (50%)	29/48 (60%)	0.48/ NS
Umbilical venous atrial pulsations	3/8 (38%)	33/54 (61%)	1.6/ NS
Cardiomegaly	5/14 (36%)	31/48 (65%)	3.7/ 0.06
Ventricular dysfunction	5/10 (50%)	31/52 (60%)	0.3/ NS
AVVR	9/23 (39%)	27/39 (69%)	5.4/ 0.02
Umbilical artery arterial changes	1/4 (25%)	35/58 (60%)	1.9/ NS
Abnormal RV MPI	19/34 (56%)	10/16 (63%)	0.19/ NS
Abnormal LV MPI	20/34 (59%)	12/17 (71%)	0.67/ NS

AVVR, atrioventricular valve regurgitation; LV, left ventricular; MPI, Doppler myocardial performance index; RT, recipient twin; RV, right ventricular; SD, standard deviation