Diastolic Dysfunction and Cerebrovascular Redistribution Precede Overt Recipient Twin Cardiomyopathy in Early-Stage Twin-Twin Transfusion Syndrome

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Background: Indications for intervention in early-stage (Quintero I and II) twin-twin transfusion syndrome (TTTS) are not standardized. Fetal echocardiography can be used to guide the management of early-stage patients. The aim of this study was to identify early cardiovascular findings that may precede progression to overt recipient twin (RT) cardiomyopathy in early-stage TTTS.

Methods: This was a retrospective review of pregnancies evaluated from 2004 to 2010. Subjects were included when initial evaluation identified Quintero I or II TTTS without evidence of "overt" RT cardiomyopathy, defined on the basis of atrioventricular valve regurgitation, ventricular hypertrophy, and abnormal Doppler myocardial performance indices. Patients elected management with observation or amnioreduction. Pregnancies were grouped by whether the RT developed overt cardiomyopathy. Initial values, including myocardial performance index, diastolic filling time corrected for heart rate (Doppler inflow duration/cardiac cycle length), pulsatility indices of the ductus venosus, umbilical artery, and middle cerebral artery, and cerebroplacental ratio (middle cerebral artery PI/umbilical artery PI), were compared.

Results: Of 174 pregnancies evaluated with early-stage TTTS, 45 (26%) did not show evidence of RT cardiomyopathy. Follow-up echocardiography identified cardiomyopathy in 20 of 45 RTs (44%). Those RTs with subsequent cardiomyopathy had shorter diastolic filling times corrected for heart rate, higher ductus venosus PIs, lower middle cerebral artery PIs, and lower cerebroplacental ratios on initial echocardiography.

Conclusion: Diastolic dysfunction and cerebroplacental redistribution precede findings of overt cardiomyopathy in RTs with early-stage TTTS. Assessment of these parameters may allow earlier identification of RTs with cardiac disease and help guide management. Prospective studies are needed to assess the role of echocardiography in patient selection for the treatment of early-stage TTTS. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Fetal echocardiography, Twin-twin transfusion syndrome, Cardiomyopathy, Diastolic function, Cerebroplacental redistribution

Twin-twin transfusion syndrome (TTTS) is a serious complication affecting 10% to 15% of monochorionic twin gestations, resulting from an imbalance of blood flow between twins through vascular anastomoses within the placenta. This imbalance of placental flow results in hypervolemia in one twin, termed the recipient twin (RT), who develops polyhydramnios, and hypovolemia in the other, termed the donor twin (DT), who develops oligohydramnios and growth restriction. The volume-loaded recipient is additionally at risk for developing cardiac pathology, including ventricular hypertrophy, cardiomegaly, ventricular dysfunction, atrioventricular valve regurgitation, and even right ventricular outflow tract obstruction.[1-3]

Staging of TTTS at most centers relies on the classification system described by Quintero *et al.*[4] Stage I involves discrepant amniotic fluid volumes, stage II involves progression of hypovolemia in the donor such that the fetal bladder is not visible, stage III involves critically abnormal Doppler patterns in the umbilical vessels or ductus venosus (DV) of either twin, stage IV involves hydrops in either twin, and stage V is the death of either twin. Although treatment with selective fetoscopic laser photocoagulation (SFLP), a maternal surgical procedure using fetoscopic guidance to map and laser-ablate the placental vascular connections, is the standard of care for advanced cases (stage III and above),[5] the management of early-stage TTTS (stages I and II) remains varied. Options for treatment include observation only, reducing the amniotic fluid volume if polyhydramnios is present, and SFLP. Because the Quintero staging system does not incorporate cardiac findings, except by surrogate with critical Doppler

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Abbreviations

CPR = Cerebroplacental resistance ratio

DFTc = Diastolic filling time corrected for heart rate

DT = Donor twin

DV = Ductus venosus

MCA = Middle cerebral artery

MPI = Myocardial performance index

PI = Pulsatility index

RT = Recipient twin

SFLP = Selective fetoscopic laser photocoagulation

TAMX = Time-averaged maximum velocity

TTTS = Twin-twin transfusion syndrome

UA = Umbilical artery

abnormalities or hydrops (stages III and VI), and RT cardiac pathology has been demonstrated with high prevalence even in the early stages of TTTS,[6,7] some centers use fetal echocardiography in conjunction with Quintero score for disease staging and to help guide the management of early-stage TTTS.

Our center has previously shown that among cases of early-stage TTTS with no evidence of cardiac pathology on initial echocardiography, 33% of Quintero stage I and 53% of Quintero stage II RTs go on to develop findings of overt cardiomyopathy, including cardiac hypertrophy, atrioventricular valve regurgitation, and abnormal ventricular function on subsequent echocardiography.[8] We aimed to further analyze the very first echocardiogram from this group of early-stage TTTS with initially no overt cardiac pathology, to evaluate for differences among RTs who did versus did not subsequently develop cardiomyopathy. Parameters of diastolic function were selected for evaluation because previous work has demonstrated that diastolic dysfunction is a commonly observed abnormality in RTs and has been associated with the severity of RT cardiomyopathy.[9-11] Additionally, we investigated cerebrovascular flow in these twins, using Doppler assessment of the middle cerebral artery (MCA), which is not a part of Quintero or cardiomyopathy staging. Abnormalities such as cerebral vasodilation and redistribution of blood flow toward the brain can be seen in times of fetal stress, and have been found to predict adverse perinatal outcome in singleton and twin pregnancies,[12-14] but have not been specifically described in fetuses with early-stage TTTS or cardiomyopathy. The purpose of this study was to identify early cardiovascular parameters that may precede the development of overt RT cardiomyopathy to determine whether patients who may benefit from earlier treatment may be identified sooner in the disease process. We hypothesized that abnormalities of diastolic function and cerebrovascular flow may identify early hemodynamic changes in TTTS.

METHODS

A retrospective review of pregnancies with TTTS evaluated at the Fetal Care Center of Cincinnati between 2004 and 2010 was conducted. The study was approved by the institutional review board of Cincinnati Children's Hospital Medical Center. Fetal echocardiographic reports and maternal clinical records were reviewed for all subjects. Patients were included when initial evaluation identified Quintero stage I or II TTTS without evidence of RT cardiomyopathy on fetal echocardiography. The diagnosis of TTTS was based on a monochorionic-diamniotic twin pregnancy with a single placenta, a thin dividing membrane, and same-gender twins, with polyhydramnios in the recipient (>8 cm depth of amniotic fluid) and oligohydramnios in the donor (<2 cm depth of amniotic fluid). Quintero score was assigned at the initial evaluation on the basis of established criteria.[4] Outcomes analyses for a portion of this cohort have previously been reported.[8] Pregnancies with Doppler abnormalities or hydrops that would meet classification for Quintero stage III or IV were excluded. Cardiomyopathy was defined as presence of ventricular wall hypertrophy (on qualitative assessment), atrioventricular valve regurgitation, and ventricular dysfunction with elevated myocardial performance index (MPI) values above 2 standard deviations of the mean.[6] Patients with Quintero stage I and II TTTS without cardiomyopathy are offered observation, amnioreduction, or SFLP at our center. Patients electing observation or amnioreduction are followed with serial ultrasound and fetal echocardiography. Progression to cardiomyopathy was defined as the development of abnormal recipient echocardiographic parameters, including ventricular wall hypertrophy, atrioventricular valve regurgitation, and/or ventricular dysfunction with elevated MPI. Additional exclusion criteria included patients who underwent initial treatment with SFLP, patients who subsequently underwent SFLP without cardiomyopathy, patients who elected pregnancy termination, in utero demise before echocardiogram, and pregnancies with fetal chromosomal or structural anomalies.

The initial fetal echocardiographic examination performed at the Fetal Heart Program at Cincinnati Children's Hospital at the time of TTTS staging for each RT and DT was reviewed. Fetal echocardiography is performed on all patients undergoing evaluation for TTTS at our center. Complete fetal echocardiograms were obtained according to published standards[15] using either Acuson Sequoia C512 or S2000 (Siemens Medical Solutions, Inc, Malvern, PA) or Vivid 7 (GE Medical Systems, Milwaukee, WI) ultrasound systems. For all pulsed-wave Doppler interrogation, the angle of insonation was kept parallel to or <20° from the direction of flow. Information on ventricular hypertrophy, atrioventricular valve regurgitation, and right and left ventricular MPI and are reported for all TTTS echocardiograms at our center, and data for these values were taken from the echocardiographic reports. MPIs for the right and left ventricles were calculated as described previously[16,17] (Figure 1) and were averaged from three beats. Right ventricular MPI was calculated from tricuspid and pulmonic Doppler tracings with a heart rate difference of ≤5 beats/min. Additionally, a single blinded observer (J.K.V.-S.) reviewed the studies retrospectively to obtain the following measurements: Doppler inflow durations, cardiac cycle length, and digitized analysis of DV, MCA, and umbilical artery (UA) flow patterns, as described below, all of which were measured from a single cardiac cycle taken during fetal apnea. Doppler inflow duration for the mitral and tricuspid valves was measured as E-wave duration + A-wave duration, and corresponding cycle length duration for each filling time was measured as time from beginning of the E wave of one beat to the beginning of the E wave of the subsequent beat. Diastolic filling time corrected for heart rate (DFTc) was calculated as Doppler inflow duration divided by cycle length for each ventricle (Figure 1). MCA and UA measurements included peak systolic velocity, end-diastolic velocity, and time-averaged maximum velocity (TAMX). PI of the MCA and UA were calculated as (peak systolic velocity − end-diastolic velocity)/TAMX (Figure 2). DV measurements included peak systolic velocity (S), velocity during atrial contraction (A), and TAMX. DV pulsatility index (PI) for veins was calculated as (S − A)/TAMX (Figure 2). Because normal values are known to vary over the course of gestation, gestational age–based *Z* scores of PI of the DV, MCA, and UA were calculated using published normal values,[18-20] and MCA peak systolic velocity was assessed by calculating multiple of the median for gestational age.[21] Cerebroplacental resistance ratio (CPR) was calculated as MCA PI/