OBSTETRICS

Assessment of fetal cardiac function before and after therapy for twin-to-twin transfusion syndrome

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OBJECTIVE: We sought to assess fetal cardiac function in monochorionic twins before and after therapy for twin-to-twin transfusion syndrome (TTTS) and compare it with control subjects.

STUDY DESIGN: We conducted prospective longitudinal assessment of fetal cardiac function in cases undergoing curative fetal therapy for TTTS (n = 39) until 4 weeks postoperatively and in uncomplicated monochorionic twins (n = 23). Fetal cardiac function was assessed by the left and right ventricular myocardial performance index, atrioventricular valve flow pattern, ductus venosus a-wave, and umbilical vein pulsations.

RESULTS: Nomograms for the myocardial performance index were constructed. Fetal cardiac function was grossly abnormal in recipient twins of TTTS when compared with control subjects ($P < .001$ for all indices) but normalized by 4 weeks postoperatively. The donor developed abnormal ductus venosus flow and tricuspid regurgitation postoperatively that regressed within 4 weeks.

CONCLUSION: The cardiac dysfunction in the recipient twin of TTTS normalizes within 1 month after laser. The donor develops a transient impairment of cardiac function postoperatively.

Keywords: echocardiography, fetoscopy, laser coagulation, monochorionic twins, twin-to-twin transfusion syndrome

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Monochorionic diamniotic (MCDA) twin pregnancies are at a 9%-15% risk of developing a twin-to-twin transfusion syndrome (TTTS).[1,2] In TTTS, the cardiac function in the recipient fetus is typically compromised because of chronic volume overload as a consequence of the net transfer of blood from the donor twin to the recipient through placental vascular anastomoses[3] and a subsequent deregulation of the fetal, placental, and maternal renin-angiotensin-aldosterone system.[4-6] Severe cardiac dysfunction is diagnosed in current clinical practice by abnormal fetal venous Doppler waveforms or, at a later stage, when hydrops appears. This is integrated in the staging system described by Quintero et al,[7] which is quite universally used but has recently been questioned.[8] Fetal survival after therapy depends on stage before laser treatment,[9] but individual outcome is also closely tied to cardiac function.[10] Hence, a direct and more refined measurement of cardiac function may improve evaluation of disease severity and prediction of outcome.[8]

Doppler-based methods to assess the fetal cardiac function, such as the myocardial performance index (MPI) and the atrioventricular early (E) to late (A) Doppler peak flow velocity index have been introduced and validated in fetal medicine by us and others.[11-14] Several groups have demonstrated that alterations in these indices occur in the recipient's heart at the time of TTTS and that this is not strictly related to Quintero stage at the time of presentation.[15-18] In a retrospective study, Habli et al[19] showed that fetoscopic laser coagulation of anastomoses did not improve average fetal cardiac function, as assessed by the MPI, immediately after the operation. This contrasts with what was initially described by others.[20] The lagging time required for recovery of the recipient's cardiac function, however, would be in concordance with what was observed postnatally in neonates born with untreated TTTS.[21]

Given the possible role of fetal cardiac function as a prognostic factor for fetal outcome and the apparent contradiction in the current literature regarding the normalization of fetal cardiac function after therapy for TTTS, we aimed to determine the evolution of fetal cardiac function in monochorionic twins treated for severe midgestational TTTS.

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As fetal cardiac function changes during gestation and reference curves for the MPI in MCDA twin pregnancies were lacking, we first constructed nomograms based on a prospective cohort of uncomplicated MCDA twin pregnancies to allow adjustment of data from TTTS pregnancies.

MATERIALS AND METHODS

All uncomplicated MCDA twin pregnancies referred in the first trimester of pregnancy to our university hospital were prospectively enrolled for the construction of reference curves (controls). These pregnancies are followed in the framework of a study that was designed to define the natural history of monochorionic twins and to detect parameters predictive of outcome, as already reported elsewhere.[1,22] For the current study, we used observations made between Dec. 1, 2007, and July 31, 2008. The left ventricular (LV) and right ventricular (RV) MPI was measured at 16, 20, 26, and 30 weeks of gestation. Observations in pregnancies that developed a TTTS, severe intertwin growth discordance (defined as a discordance in estimated fetal weight > 20%), or single or double intrauterine fetal death; had cardiac malformations detected either in utero or after birth; or delivered before 30 weeks of gestation were excluded.

The second group (cases) consisted of all consecutive pregnancies complicated by TTTS and treated by fetoscopic laser ablation of the placental vascular anastomoses or selective feticide by cord coagulation between Nov. 1, 2007, and Sept. 30, 2008. TTTS was defined as the presence of oligohydramnios in the donor twin with a deepest vertical amniotic fluid pocket ≤ 2 cm and a polyhydramnios in the recipient with a deepest amniotic fluid pocket ≥ 8 cm before 20 weeks and ≥ 10 cm after 20 weeks.[23] Cases were staged at presentation according to the Quintero classification system.[7] Fetal cardiac function was assessed preoperatively, 24-48 hours postoperatively, and in cases from our national population also at 2 and 4 weeks thereafter. All ultrasound examinations were performed using Voluson 730 Expert or E8 (GE Medical Systems, Zipf, Austria). Doppler measurements were obtained in the absence of fetal movements. The Doppler sweep speed was set to maximum (10 cm/s) and the angle between the sample volume and the blood flow was kept below 15 degrees. All measurements were obtained in triplicate and averaged.

To obtain the LV-MPI, the Doppler sample volume was positioned on the mitral and aortic valve in an apical 5-chamber view.[12] The isovolumetric contraction, isovolumetric relaxation, and ejection times were determined using the valve click method. The MPI was calculated as: (+ isovolumetric relaxation time)/ejection time. This index is a reflection of both ventricular systolic and diastolic function and a higher MPI corresponds to a worse ventricular function.[13] The RV-MPI cannot be obtained on a single Doppler trace as a result of the implantation of the tricuspid and pulmonary valve. Therefore, the RV-MPI was calculated based on separate Doppler images of the duration between 2 tricuspid inflows (DBTI) and the pulmonary outflow (PF); RV-MPI is calculated as: (DBTI − PF)/PF and only recorded when the heart rate difference between tricuspid and pulmonary Doppler tracings is ≤ 5 beats/min.[18]

The mitral and tricuspid flow waveforms were obtained by positioning the Doppler sample volume at the tip of the atrioventricular valve leaflets in an apical 4-chamber view.[13] The waveforms were classified as normal (ie, clearly distinct E and A wave) or abnormal (fusion of both waves). The presence of atrioventricular regurgitation was assessed using color and pulsed Doppler and classified as present (holosystolic regurgitation) or absent.

The ductus venosus was assessed on a transverse or sagittal section through the fetal abdomen. The junction between the umbilical vein and the ductus was identified using color Doppler and sampled at the area of maximal aliasing. Ductus venosus waveforms were classified as normal (positive a-wave) or abnormal (absent or reversed a-wave).

The umbilical vein was sampled at the level of its intraabdominal course and its Doppler pattern was classified as normal (no pulsations) or abnormal (venous pulsations).

This study was approved by the ethics committee on clinical studies of our university hospitals and all patients gave written informed consent.

Statistical analysis was done using software (JMP, Version 7.0; SAS Institute, Cary, NC) and MLwiN program (Centre for Multilevel Modeling, Bristol, United Kingdom). Normality of the data was assessed using the D'Agostino Omnibus test. Normal distribution in the first group was obtained after log transformation of LV- and RV-MPI. Regression curves were fitted to the data, and mean and SD were calculated. The 2.5th, 5th, and 10th percentiles were then calculated by subtracting 1.96 SD, 1.645 SD, or 1.282 SD from the mean; the 90th, 95th, and 97.5th percentiles were obtained by adding the respective multiples of the SD to the mean. Based on the regression curves obtained in the control population, the LV-MPI and RV-MPI were transformed to *z* scores. Preoperative fetal cardiac function in TTTS fetuses was compared with control subjects using Mann-Whitney test for continuous data and Fisher exact test for categorical data.

Paired comparisons within the TTTS group were made between the preoperative cardiac function and the cardiac function of fetuses surviving the first 48 hours postoperatively. Continuous variables were compared using Wilcoxon signed rank test. Nominal data were compared using McNemar test. Bonferroni correction for multiple testing was applied. A P value $< .006$ was considered as significant. In fetuses with follow-up until 2 and 4 weeks postoperatively, cardiac function was compared at the different time points using 1-way analysis of variance with Tukey post hoc test when $P < .05$. For nominal data, contingency tables were constructed and Pearson χ^2 test was applied. All values are reported as mean ± SD.

RESULTS

Nomograms

In all, 28 women with uncomplicated MCDA pregnancies were included in the