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Aortic Stenosis and Severe Mitral Regurgitation in the Fetus Resulting in Giant Left Atrium and Hydrops

Pathophysiology, Outcomes, and Preliminary Experience With Pre-Natal Cardiac Intervention

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Objectives The objective of this article is to review anatomic, physiologic, and clinical features of fetuses and neonates with severe mitral regurgitation (MR) in conjunction with aortic stenosis (AS) and left ventricular (LV) and left atrial (LA) dilation and to present preliminary results of pre-natal intervention for this condition.

Background Severe fetal valvar AS with an abnormal mitral valve (MV) and MR can lead to left heart dilation, with consequent compression of the right ventricle (RV); hydrops and low cardiac output are often associated.

Methods This is a retrospective review of fetuses diagnosed with AS, severe MR, and LA dilation (2002 to 2009) and neonates with the same combination of abnormalities (1988 to 2009).

Results Fourteen fetuses and 7 neonates were investigated. Eleven fetuses had severe hydrops; all had polyhydramnios and a structurally abnormal MV, abnormal MV inflow pattern, restrictive/intact atrial septum, retrograde flow in the transverse aortic arch, and compression of the right heart. The mean indexed RV output was 326 ± 160 ml/kg/min, lower than the normal average fetal combined ventricular output of 550 ± 150 ml/kg/min. Ten fetuses underwent pre-natal cardiac intervention: aortic valvuloplasty (n = 8) and/or atrial septal dilation/stenting (n = 5). Seven of these, and 11 overall, were live born. Nine patients died (median age 6 days), and 2 patients are currently alive. All 7 patients diagnosed in the neonatal period died (median age 1 day).

Conclusions Aortic stenosis associated with significant MR in the fetus can cause severe LA and LV enlargement, leading to low cardiac output and hydrops. Despite the potential advantages of early pre-natal diagnosis and both fetal and neonatal interventions, this rare complex of anomalies carries a poor prognosis. (J Am Coll Cardiol 2011;57:348–55) © 2011 by the American College of Cardiology Foundation

Clinically significant mitral regurgitation (MR) in fetal life is rare. It may occur in isolation or in conjunction with other structural and functional abnormalities, such as aortic stenosis (AS) with global left ventricular (LV) dysfunction and dilation (1–4). Mitral regurgitation can also occur in conditions with high fetal cardiac output, such as anemia or extracardiac arteriovenous malformations, or with arrhythmias (5–8). Mild to moderate MR is most commonly observed in evolving or established hypoplastic left heart syndrome (HLHS) (1–4). In rare instances, AS with an abnormal mitral valve (MV) and MR can lead to left atrial (LA) dilation with consequent MV annular dilation, with further exacerbation of MR. The aim of this study was to review the anatomic, physiologic, and clinical features of fetuses and neonates with the rare but distinct combination of severe MR, AS, and severe LA enlargement who were managed at Children's Hospital Boston and to report our preliminary experience with pre-natal intervention for this condition.

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Methods

Patients. We included all fetuses with valvar AS, severe MR, and severe LA dilation evaluated by echocardiography at Children's Hospital Boston from 2002 to 2009. This is a different cohort than the fetuses with AS and evolving

HLHS or with established HLHS and an intact or restrictive atrial septum, which have been the subject of prior reports from our group (1–4). We also evaluated patients that did not undergo fetal echocardiography but were diagnosed in the first week of life with the same combination of abnormalities from 1988 to 2009. The study was performed in conjunction with a protocol that was approved by the Children's Hospital Committee for Clinical Investigations.

Cardiovascular and noncardiovascular ultrasound. All fetal patients underwent at least 1 detailed obstetric sonogram and echocardiogram, during which a full anatomic and Doppler survey was performed. Evaluations included fetal biometry, anatomic measurement of left and right heart structures, and cardiac and extracardiac Doppler measurements.

Fetal biometry consisted of measurement of the biparietal diameter, head circumference, femur length, and abdominal circumference. In fetuses with ascites, the abdominal circumference measurement was taken in the standard fashion, recognizing that this would likely lead to an overestimate of fetal weight. Fetal weight was estimated using the method of Hadlock et al. (9). Gestational age–based *z*-scores were calculated for fetal weight from equations reported by Doubilet et al. (10) and for head circumference, biparietal diameter, femur length, and abdominal circumference from equations reported by Hadlock et al. (11). Because measurement of abdominal circumference was confounded by the presence of ascites and weight calculated by the Hadlock method was above the 50th percentile for gestational age in almost all cases, the mean (50th percentile) weight for gestational age was used to index right ventricular (RV) output to avoid underestimation of output. Other factors recorded on noncardiovascular ultrasound included the presence of polyhydramnios, fetal hydrops, skin edema, ascites, pericardial or pleural effusion, and fetal sex (10).

Anatomic assessment included measurement of the following left and right heart structures: LA dimensions, MV annulus in diastole, LV length (diastole and systole), LV volume (using the 5/6 area × length method), aortic valve and ascending aorta diameters, tricuspid valve (TV) and pulmonary valve annulus diameter, and RV end-diastolic length. The MV was described as anatomically normal or abnormal, and the presence of accessory chordal attachments and echogenic papillary muscles was recorded. The LV was further characterized as normal or dilated, and the presence or absence of endocardial fibroelastosis was noted. The pulmonary veins were categorized as normal, dilated, or compressed, and the patency and size of the foramen ovale was recorded. All reported *z*-scores are based on gestational age and were calculated from unpublished normative data collected at Children's Hospital Boston between 2005 and 2007 on 232 normal fetuses.

Cardiac Doppler evaluation included measurement of MV and TV inflow patterns and durations, MV and TV regurgitant jet color Doppler vena contracta width, LV pressure (maximum instantaneous MR jet velocity), and maximum instantaneous AS gradient and color Doppler jet width. The direction of patent foramen ovale flow was described. The RV output was calculated as: the product of pulmonary valve velocity-time integral (*m*) × heart rate (beats/min) × valve area (cm^2).

Extracardiac Doppler measurements included velocities and flow patterns in the middle cerebral artery, umbilical artery, umbilical vein, and ductus venosus.

Abbreviations and Acronyms

AS = aortic stenosis
HLHS = hypoplastic left heart syndrome
LA = left atrial/atrium
LV = left ventricular/ventricle
MR = mitral regurgitation
MV = mitral valve
RA = right atrial/atrium
RV = right ventricular/ventricle
TV = tricuspid valve

Data analysis. Because of the small number of fetuses and neonates, data are presented primarily in descriptive fashion. Anatomic and physiologic variables for which internally derived *z*-scores were available were compared with normal ($z = 0$) using 1-sample *t* test. The RV output indexed to calculated weight and to the 50th percentile weight for gestational age (assuming that hydrops would confound estimation of weight) was compared with published normal values of fetal combined ventricular output (429 ± 100 ml/kg/min to 550 ± 150 ml/kg/min) (12–15) and with previously published cardiac output data for fetuses with HLHS (16) using 1-sample *t* test. Indexed RV output was also compared with unpublished pre-intervention data in 75 fetuses that underwent pre-natal aortic valvuloplasty for AS with evolving HLHS at our center, using the Wilcoxon rank sum test. In all cases, LV output was negligible; therefore, the RV was assumed to provide essentially all cardiac output. No other statistical analysis was performed. Data are presented as frequency (%), median (range), or mean ± SD. For 1-sample *t* test analysis, only $p \leq 0.01$ was considered significant.

Results

Patients. Fourteen fetuses with severe MR, AS, and severe LA and LV dilation underwent echocardiography at a median gestational age of 28.6 weeks (range 21.6 to 33.3 weeks) (Table 1). Four of these 14 patients were from the usual referral base of Children's Hospital, and 10 were referred from elsewhere. Eight of these fetuses were included in a prior report dealing with fetal cardiac instability during pre-natal intervention, but none of the data included in this report were presented in the prior report (17). One patient was known to have an abnormal karyotype (mosaic Turners [XY, XO]). Two patients had a significant family history: 1 had a sibling with trisomy 18 and another had a sibling that underwent heart transplant for dilated cardiomyopathy. Thirteen fetuses were male and 1 was female.

In addition to the above fetuses, 7 neonates with a median age of 1.0 day (1.0 to 8.0 days) presented to Children's Hospital between 1988 and 2000 with an en-