Fetal Aortic Valve Stenosis and the Evolution of Hypoplastic Left Heart Syndrome

Patient Selection for Fetal Intervention

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Background—Fetal aortic valvuloplasty may prevent progression of aortic stenosis (AS) to hypoplastic left heart syndrome (HLHS). Predicting which fetuses with AS will develop HLHS is essential to optimize patient selection for fetal intervention. The aim of this study was to define echocardiographic features associated with progression of midgestation fetal AS to HLHS.

Methods and Results—Fetal echocardiograms were reviewed from 43 fetuses diagnosed with AS and normal left ventricular (LV) length at ≤30 weeks' gestation. Of 23 live-born patients with available follow-up data, 17 had HLHS and 6 had a biventricular circulation. At the time of diagnosis, LV length, mitral valve, aortic valve, and ascending aortic diameter Z-scores did not differ between fetuses that ultimately developed HLHS and those that maintained a biventricular circulation postnatally. However, all of the fetuses that progressed to HLHS had retrograde flow in the transverse aortic arch (TAA), 88% had left-to-right flow across the foramen ovale, 91% had monophasic mitral inflow, and 94% had significant LV dysfunction. In contrast, all 6 fetuses with a biventricular circulation postnatally had antegrade flow in the TAA, biphasic mitral inflow, and normal LV function. With advancing gestation, growth arrest of left heart structures became evident in fetuses developing HLHS.

Conclusions—In midgestation fetuses with AS and normal LV length, reversed flow in the TAA and foramen ovale, monophasic mitral inflow, and LV dysfunction are predictive of progression to HLHS. These physiological features may help refine patient selection for fetal intervention to prevent the progression of AS to HLHS. (Circulation. 2006;113:1401-1405.)

Key Words: aortic valve stenosis | echocardiography, Doppler | fetal monitoring | hypoplastic left heart syndrome | valvuloplasty

Hypoplastic left heart syndrome (HLHS) is a complex congenital cardiovascular anomaly that is increasingly diagnosed in utero. At the time of prenatal diagnosis in midgestation, a subset of fetuses that will eventually be born with HLHS do not yet have significant left ventricular (LV) hypoplasia but rather, valvar aortic stenosis (AS) with a dilated or normally sized left ventricle (LV). In this subset of patients, the initial LV outflow tract obstruction may lead to secondary failure of left heart growth, with ultimate progression to HLHS at birth, presumably due to LV dysfunction, myocardial damage, and decreased flow through the left heart.1-4 However, not all midgestation fetuses diagnosed with valvar AS will progress to HLHS at birth.

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Traditional therapeutic options for a fetus diagnosed with HLHS include staged surgical palliation to a functionally univentricular circulation, neonatal heart transplantation after birth, or termination of pregnancy. Recently, however, several centers have offered in utero aortic valvuloplasty as an alternative form of treatment for midgestation fetal AS that has a high probability of progression to HLHS.5-9 The objective of fetal aortic valvuloplasty is to relieve the obstruction to LV ejection, thereby reducing LV work and damage, increasing flow through the left heart, and slowing or even preventing the progression to HLHS. Recent studies from our center demonstrate that fetal aortic valvuloplasty may increase blood flow through the left heart and improve left heart growth.8,9

To prevent the progression of AS to HLHS, fetal aortic valvuloplasty must be performed before the development of significant left heart hypoplasia. However, based on our current understanding of the risk-benefit ratio of fetal inter-
vention, fetal aortic valvuloplasty should not be performed in fetuses with AS that will not progress to HLHS. Thus, a crucial step in selecting patients for fetal intervention is defining the anatomic and physiological variables in the midgestation fetus with AS and normal LV size that are predictive of progression to HLHS. To date, however, criteria for predicting outcome in midgestation fetuses with AS have not been established. The aim of this study was to define anatomic and physiological echocardiographic features in midpregnancy that predict progression of fetal AS to HLHS at birth.

Methods

Patient Identification
Fetuses diagnosed with valvar AS between 1992 and 2004 were identified through a computerized search of the Children’s Hospital cardiology database. The diagnosis of AS was based on echocardiographic visualization of a thickened, immobile aortic valve with turbulent or decreased color Doppler flow. The Doppler-derived AS gradient was not used to select patients because the gradient in the fetus may be an unreliable index of severity, owing to coexistent LV dysfunction. For this study, we included only fetuses in which all of the following criteria were met: (1) AS was assessed to be the dominant lesion, (2) the LV diastolic length was above the lower limit of normal (Z-score ≥2) at the time of diagnosis, (3) the diagnosis was made at ≤30 weeks’ gestational age, (4) the fetus had not undergone a fetal intervention, and (5) there were no additional major cardiac or noncardiac malformations. The study was approved by the Children’s Hospital Institutional Review Board.

Echocardiographic Analysis
Videotapes from the diagnostic echocardiograms in midpregnancy (between 16 and 30 weeks of gestation) and at the last examination in late gestation (between 31 weeks and term) were digitized by using EchoTrace software (Ed Marcus Laboratories, Boston, Mass). Measurements were made off-line by a single investigator who was blinded to the clinical outcome. Gestational age was determined from the last menstrual period and confirmed by fetal biometry.10

Anatomic Measurements
LV and right ventricular lengths were measured at end-diastole from the level of the atroventricular valve annulus centered between the hinge points of the valves to the apical endocardium. Diameters of the aortic and pulmonary valves and of the ascending aorta were measured in systole. The annular diameters of the tricuspid and mitral (MV) valves were measured in diastole. Z-scores for anatomic measurements were calculated on the basis of unpublished institutional data derived from normal fetuses.

Physiological Measurements
Color and pulsed-wave Doppler echocardiography techniques were used to assess the MV inflow profile, direction of blood flow in the transverse aortic arch (TAA), and direction of blood flow across the foramen ovale, when available. The transverse arch was defined as the aortic segment between the first 2 brachiophecal vessels (typically, the innominate and left common carotid arteries). Retrograde or competing flow in the transverse arch at any time during the cardiac cycle was defined as retrograde flow. Flow across the foramen ovale was considered left to right when flow was completely or predominantly left to right. LV function was assessed qualitatively and classified as a binary variable: normal to mildly depressed or moderately to severely depressed. Although the majority of the fetuses had at least some degree of endomyocardial echogenicity suggestive of endocardial fibroelastosis, we did not include this in the analysis because there are no verified criteria for assessing severity.

Statistical Analysis
The primary outcome measure was development of HLHS, defined as left heart hypoplasia of severity sufficient to warrant a neonatal Norwood procedure. During the study period, patients with hypoplastic left heart disease were typically managed according to a univentricular or biventricular approach at our institution, based on a combination of anatomic and physiological factors, including but not limited to the criteria defined by Rhodes et al.11 The demographic, anatomic, and physiological variables summarized earlier were analyzed for association with the development of HLHS. For between-patient comparison of continuous variables at the time of diagnosis and at the last fetal echocardiogram, an independent-sample t test was used. For within-patient comparison of continuous variables between the first and last fetal echocardiograms, a paired-sample t test was used. Categorical data were compared at the time of diagnosis and at the last fetal echocardiogram between patients that did and did not develop HLHS, according to the Fisher exact test. Data are presented as either mean±SD or median and (range). The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the article as written.

Results
Forty-three fetuses with AS were identified and included in this study. The median maternal age was 31 years (17 to 43 years), and the median gestational age at the time of diagnosis was 21 weeks (16 to 30 weeks). At the time of diagnosis, LV length was above the lower limit of normal (Z-score ≥2) in all fetuses. Z-scores were below normal (≤2) for the diameter of the aortic valve annulus in 24 fetuses (56%), the diameter of the ascending aorta in 4 (9%), and the diameter of the MV in 6 (14%). Among fetuses with available data, flow in the TAA was reversed in 34 of 43 (79%), flow across the foramen ovale was left to right in 33 of 41 (80%), MV inflow was monophasic in 22 of 29 (76%), and LV function was moderately to severely depressed in 33 of 43 (77%).

Fetal and neonatal outcomes are shown in Figure 1. Among 23 live-born fetuses with available follow-up data, 17 were born with HLHS and 6 had a biventricular circulation. Three neonates with HLHS at birth died before a planned stage 1 Norwood operation, and the rest underwent stage 1 palliation. Five of the 6 neonates with AS and a biventricular circulation at birth underwent neonatal balloon aortic valvuloplasty (n=5) and/or coartation repair/dilatation (n=4), whereas the other did not undergo any intervention. All 6 of the patients managed according to a biventricular strategy are alive with a biventricular circulation, without transplant, at a median age of 4 years.
Demographic, anatomic, and physiological data at diagnosis and late gestation in fetuses with AS that evolved to HLHS and those maintaining a biventricular circulation at birth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diagnosis</th>
<th>Late Gestation</th>
<th>Diagnosis</th>
<th>Late Gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk</td>
<td>22.4±4.1</td>
<td>32.4±2.8</td>
<td>23.2±3.8</td>
<td>34.7±2.2</td>
</tr>
<tr>
<td>LV length Z-score</td>
<td>1.1±1.9</td>
<td>−3.4±2.1†</td>
<td>0.7±1.0</td>
<td>−0.2±0.9§</td>
</tr>
<tr>
<td>MV diameter Z-score</td>
<td>−1.0±0.9</td>
<td>−4.3±1.3‡</td>
<td>−0.8±1.2</td>
<td>−1.9±1.2§§</td>
</tr>
<tr>
<td>AoV diameter Z-score</td>
<td>−2.4±1.0</td>
<td>−4.6±0.9‡</td>
<td>−2.0±2.5</td>
<td>−3.2±0.8§§</td>
</tr>
<tr>
<td>AAo diameter Z-score</td>
<td>−0.4±1.9</td>
<td>−2.1±2.9‡</td>
<td>−0.4±2.1</td>
<td>1.7±3.9§</td>
</tr>
<tr>
<td>RV length Z-score</td>
<td>0.9±1.0</td>
<td>0.7±1.3</td>
<td>0.1±1.3</td>
<td>−0.3±0.9</td>
</tr>
<tr>
<td>TV diameter Z-score</td>
<td>1.5±1.5</td>
<td>1.9±0.8</td>
<td>0.5±1.8</td>
<td>1.6±1.6</td>
</tr>
<tr>
<td>PV diameter Z-score</td>
<td>1.0±1.1</td>
<td>2.0±1.6</td>
<td>0.3±1.3</td>
<td>1.7±2.0</td>
</tr>
<tr>
<td>Retrograde TAA flow</td>
<td>17/17 (100)*</td>
<td>14/14 (100)*</td>
<td>0/6 (0)† †</td>
<td>0/6 (0)† §</td>
</tr>
<tr>
<td>Left-to-right FO flow</td>
<td>15/17 (88)*</td>
<td>14/14 (100)*</td>
<td>1/6 (17)† †</td>
<td>1/5 (20)† §</td>
</tr>
<tr>
<td>Monophasic MV inflow</td>
<td>10/11 (91)*</td>
<td>8/8 (100)*</td>
<td>0/4 (0)† †</td>
<td>0/2 (0)† §</td>
</tr>
<tr>
<td>Moderate to severe LV dysfunction</td>
<td>16/17 (94)*</td>
<td>14/14 (100)*</td>
<td>0/6 (0)† †</td>
<td>1/6 (17)† §</td>
</tr>
</tbody>
</table>

AoV indicates aortic valve; AAo, ascending aorta; RV, right ventricle; TV, tricuspid valve; PV, pulmonary valve; and FO, foramen ovale. Data are presented as mean±SD or n (%).

*Percentage represents the variable for identifying patients who will progress to HLHS
†Percentage represents 100%-specificity of the variable for identifying patients who will progress to HLHS
‡P<0.01 vs HLHS at diagnosis.
§P<0.01 vs HLHS at late gestation.
||P<0.05 vs biventricular circulation at diagnosis.

Aortic valve and MV length Z-scores decreased slightly with advancing gestation (Table 2 and Table). The presence of retrograde flow in the TAA alone at the time of diagnosis was 100% sensitive and specific for progression to neonatal HLHS.

Among fetuses ultimately born with HLHS, Z-scores of all measured left heart structures decreased between the first and last prenatal echocardiograms (Figure 2). In fetuses with available data, all of the physiological parameters that were abnormal at the time of diagnosis remained abnormal later in gestation. In contrast, fetuses that ultimately achieved a biventricular circulation maintained normal LV length, although aortic valve and MV Z-scores decreased slightly with advancing gestation (Figure 2 and Table). In addition, fetuses with AS and a biventricular circulation maintained a normal prograde flow in the TAA, right-to-left flow across the foramen ovale, and biventricular MV inflow with advancing gestation (Table). One of the 6 fetuses in this group developed moderate LV dysfunction in late gestation and was delivered at 35 weeks, surviving with a biventricular circulation after neonatal balloon aortic valvuloplasty.

Pregnancy was terminated in 17 of 43 fetuses, and there was 1 case of spontaneous fetal demise. Comparison of live-born and terminated fetuses revealed no significant differences in any of the demographic, anatomic, or physiological variables assessed. Sixteen of the 17 terminated fetuses (94%) had retrograde flow in the TAA and significantly depressed LV function. Left-to-right flow across the foramen ovale was present in 14 of 16 cases with available data (88%), and all 10 of the terminated fetuses in which Doppler MV inflow analysis was performed had monophasic MV inflow.

Discussion

Natural History of Fetal AS

Severe AS in the midgestation fetus with a normal-sized or dilated LV can progress to HLHS at birth. The aim of this study was to identify anatomic and/or physiological features in fetuses with AS that are predictive of ultimate progression to HLHS. At the time of diagnosis (between 16 and 30 weeks gestation), there were no differences in Z-scores of left heart anatomic structures between fetuses with evolving HLHS and those that maintained a biventricular circulation postnatally. The majority of fetuses in both groups had normal MV annulus and ascending aortic diameters, whereas the aortic valve annulus was frequently hypoplastic. Smaller series including fetuses diagnosed later in gestation have reported similar findings. It therefore appears that in midgestation fetuses with AS and normal LV size, it is not possible to distinguish evolving HLHS from fetal AS that will not progress to HLHS on the basis of anatomic measures alone. The growth arrest of left heart structures in fetuses with AS and evolving HLHS only becomes evident later in gestation.

In contrast, physiological features at the time of diagnosis in midgestation were significantly different between fetuses that ultimately progressed to HLHS and those born with a biventricular circulation. At the time of diagnosis, all of the
fetuses with AS and evolving HLHS had reversal of flow in the TAA, all but 1 had monophasic MV inflow and moderate-to-severe LV dysfunction, and all but 2 had left-to-right flow across the foramen ovale. However, all of the fetuses with AS that maintained a biventricular circulation had normal prograde flow in the TAA, biphasic MV inflow, and normal LV function, and only 1 had reversed flow across the foramen ovale at the time of diagnosis.

**Implications**
These findings are potentially important because they (1) may allow for more objective prenatal counseling for parents of midgestation fetuses diagnosed with AS, (2) support the hypothesis that in utero flow disturbances contribute to the development of chamber hypoplasia, and (3) facilitate optimal selection of fetuses for in utero aortic valvuloplasty.

In appropriately selected midgestation fetuses with AS and normal LV length, relief of aortic valve obstruction during fetal life may reduce secondary damage to the developing heart and allow functional recovery of the LV before delivery. Early efforts at 6 international centers to relieve severe AS in utero between 27 and 33 weeks’ gestation resulted in poor outcomes. However, recent results have demonstrated higher technical success when the intervention was performed at an earlier gestational age. Among 20 fetuses with AS, a normal-size or dilated LV, and retrograde flow in the TAA that underwent technically successful aortic valve dilation (of 26 attempted procedures), all had improved antegrade aortic flow and ongoing LV and aortic growth, and a subset have survived with a biventricular circulation postnatally. Given these promising early results, it is even more important to optimize patient selection for fetal aortic valvuloplasty, including identification of features that predict evolving HLHS in the midgestation fetus with AS. The findings of this study demonstrate that fetuses with AS that do not manifest LV hypoplasia but are nonetheless likely to progress to HLHS can be clearly identified at the time of initial diagnosis on the basis of a constellation of physiological findings.

**Limitations**
This study of the natural history of fetal AS is unable to address a critically important issue for the selection of patients for fetal aortic valvuloplasty, namely, the capacity of the dysfunctional LV to recover after fetal aortic valvuloplasty in any given patient. This question is as important for the optimal selection of patients for in utero therapy and will need to be addressed as more data on fetal intervention become available. As a result of the retrospective nature of this study, complete Doppler data, particularly MV inflow pattern, were not available for all patients. However, data at the time of diagnosis were complete for most patients, and the differences between fetuses progressing to HLHS and those above and below the mean, which correspond to Z-scores of 2 and -2, respectively. Fetuses that ultimately developed HLHS (n=17) are denoted by the solid triangles connected by solid lines, and fetuses that maintained a biventricular circulation (n=6) are denoted by the open squares connected by dashed lines.

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**Figure 2.** A, Aortic valve diameter; B, ascending aorta diameter; C, MV diameter; and D, LV length in fetuses with AS at the time of diagnosis and at the last fetal echocardiogram. The gestational age at the time of measurement is indicated on the x axis, and the absolute value of the measurement is indicated on the y axis. The 3 solid lines represent the mean value of the measure in fetuses without heart disease and 2 standard deviations above and below the mean, which correspond to Z-scores of 2 and -2, respectively. Fetuses that ultimately developed HLHS (n=17) are denoted by the solid triangles connected by solid lines, and fetuses that maintained a biventricular circulation (n=6) are denoted by the open squares connected by dashed lines.
Conclusions

Among fetuses diagnosed with valvar AS and normal LV size in midgestation, anatomic dimensions of left heart structures at the time of diagnosis do not predict ultimate progression to HLHS. However, fetuses with AS and evolving HLHS almost invariably demonstrate reversed blood flow in the TAA, left-to-right flow across the foramen ovale, monophasic MV inflow, and moderate-to-severe LV dysfunction in midgestation. These findings may aid in parental counseling about postnatal outcome and may be useful for identification of appropriate candidates for fetal aortic valvuloplasty in an effort to prevent the progression of AS to HLHS.

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Disclosures

None.

References


At the time of prenatal diagnosis in midgestation, a subset of fetuses that will eventually be born with hypoplastic left heart syndrome (HLHS) do not yet have significant left ventricular (LV) hypoplasia but rather, valvar aortic stenosis (AS) with a dilated or normally sized LV. In this subset of patients, the initial LV outflow tract obstruction may lead to secondary failure of left heart growth, with ultimate progression to HLHS at birth, presumably due to LV dysfunction, myocardial damage, and decreased flow through the left heart. Among 23 fetuses diagnosed with AS and normal LV length at ≤30 weeks’ gestation, 17 were born with HLHS and 6 had a biventricular circulation. Anatomic dimensions of left heart structures at the time of diagnosis did not predict ultimate progression to HLHS. However, fetuses with AS and evolving HLHS almost invariably demonstrated reversed blood flow in the transverse aortic arch (TAA), left-to-right flow across the foramen ovale, monophasic mitral valve (MV) inflow, and moderate-to-severe LV dysfunction in midgestation. These findings allow for accurate prediction of ultimate progression to HLHS among midgestation fetuses diagnosed with AS and normal LV size and may aid in parental counseling about postnatal outcome, as well as the possible identification of appropriate candidates for fetal aortic valvuloplasty in an effort to prevent the progression of AS to HLHS.

CLINICAL PERSPECTIVE

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Maintaining a biventricular circulation were so pronounced that the limited availability of Doppler MV inflow data does not limit the significance of our findings.

Although our findings were striking, the number of patients in this series was relatively small, and they were managed over a wide time period. A larger prospective, multicenter study may allow for more incisive differentiation of factors associated with evolution of fetal AS to HLHS and optimization of patient selection for prenatal intervention.

References

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