First-Trimester Echocardiographic Features and Perinatal Outcomes in Fetuses With Congenital Absence of the Aortic Valve

Rong Yu, MD, Sheng-li Li, MD, Guo-yang Luo, MD, PhD, Hua-xuan Wen, MS, Shu-yuan Ouyang, MS, Cong-ying Chen, MD, Ying Yuan, MD

Objective—The purpose of this study was to describe the echocardiographic features and perinatal outcomes of congenital absence of the aortic valve diagnosed by first-trimester echocardiography.

Methods—This retrospective study assessed the feasibility of first-trimester echocardiography in detecting absence of the aortic valve. All cases of absence of the aortic valve diagnosed by first-trimester fetal echocardiography from January 2010 to December 2014 were identified at a single referral center using an established perinatal database. Demographic information, echocardiograms, perinatal outcomes, and autopsy reports were reviewed. Echocardiographic features were described.

Results—A total of 50,822 fetuses underwent first-trimester echocardiography during the study period. Ten cases of congenital absence of the aortic valve were diagnosed, for an overall incidence rate of 0.019%. The earliest gestational age at diagnosis was 11 weeks 6 days. The mean crown-lump length was 61.9 mm; mean gestational age was 12 weeks; and mean maternal body mass index ± SD was 21.2 ± 3.9 kg/m². Nine fetuses had increased nuchal translucency ranging from 2.4 to 12.4 mm (mean ± SD, 6.4 ± 3.6 mm). Color Doppler flow imaging revealed biphasic bidirectional flow in the ascending aorta and aortic arch and reversed flow in the ductus venosus during atrial systole in all cases. Reversed diastolic flow was present in the umbilical arteries and thoracic aorta. All cases had complex cardiac malformations as well as extracardiac abnormalities.

Conclusions—Our study confirms that absence of the aortic valve is a rare cardiac defect that can be diagnosed by first-trimester fetal echocardiography. A "to-and-fro" flow pattern or biphasic bidirectional flow in the great arteries is a key echocardiographic feature in fetuses with absence of the aortic valve.

Key Words—absence of the aortic valve; congenital heart disease; fetal echocardiography; fetus; prenatal diagnosis

Congenital absence of the aortic valve is a rare cardiac anomaly that usually results in hydrops, fetal demise, or early neonatal death. In most instances, the only remnants of the aortic valve are nonobstructive fibrous ridges. Absence of the aortic valve was first described in association with a double-outlet right ventricle in a pathologic specimen. The incidence of absence of the aortic valve diagnosed prenatally is gradually increasing because of the advances in diagnostic techniques and growing interest in this particular malformation. In most reported cases, the diagnosis was
made in the second and third trimesters. The earliest gestational age at diagnosis was 14 weeks in a fetus with cystic hygroma.

Absence of the aortic valve is not typically an isolated anomaly. In a review of 15 reported cases, hypoplasia of the left heart was seen in 11 cases (73%), a double-outlet right ventricle in 5 (33%), and aortic arch malformations in 6 (40%). The prognosis of this condition is very poor, with only 2 reported cases having successful surgical palliation.

First-trimester fetal echocardiography is feasible in skilled hands but challenging, especially in visualizing the outflow tracts and valves. Here, we present our experiences in diagnosing absence of the aortic valve using first-trimester fetal echocardiography. The echocardiographic features as well as perinatal outcomes of our cases are described.

Materials and Methods

We retrospectively analyzed the records of all fetal echocardiographic examinations performed at gestational ages of 11 weeks to 13 weeks 6 days at our tertiary referral center between January 2010 and December 2014 to identify all cases of absence of the aortic valve using an established perinatal database. The Prenatal Diagnosis Center at Shenzhen Maternity and Child Healthcare Hospital was designated a national prenatal diagnosis training center in 2004, and it serves as a national referral center for patients throughout China. This study was approved by the Institutional Review Board.

All fetal echocardiographic examinations were performed by qualified physicians with up to 10 years of experience in first-trimester sonography, second-trimester anatomy scanning, and fetal echocardiography using a high-definition ultrasound machine (Acuson Sequoia; Siemens Medical Solutions, Mountain View, CA; Voluson E8, GE Healthcare, Milwaukee, WI; or Accuvix A30; Samsung Medison, Seoul, Korea). All patients underwent a routine nuchal translucency scan at our center. Early fetal echocardiography was performed by using a segmental approach. For the purposes of this study, the diagnosis of absence of the aortic valve was confirmed by review of the images by a single senior physician (S.L.).

Crown-lump length and nuchal translucency thickness were measured at 11 weeks to 13 weeks 6 days. Doppler sonography was performed by using transabdominal phased array transducers (4.0 and 8.0 MHz) with color and pulsed wave Doppler options. We attempted pulsed wave and color Doppler evaluations of all 4 cardiac valves. Cases with a “to-and-fro” flow pattern or biphasic bidirectional flow in the ascending aorta and aortic arch were identified. The maximal velocity of antegrade flow in systole and retrograde flow in diastole, the presence of atrioventricular valve regurgitation, and any additional cardiac defects were all recorded. The maternal weight and height were measured on the day of the scan, and the body mass index was calculated. Dynamic and static images of each of these cases, including follow-up scans, were reviewed from the perinatal database. Fetal extracardiac abnormalities and pregnancy outcomes were also collected. Autopsy was performed on cases that ended with termination of pregnancy.

Results

Incidence of Congenital Absence of the Aortic Valve

From January 2010 to December 2014, a total of 50,822 fetuses underwent first-trimester echocardiography at our center. Ten cases of congenital absence of the aortic valve were diagnosed, for an overall incidence rate of 0.019%. The earliest gestational age at diagnosis was 11 weeks 6 days. Among these, 2 cases were twin gestations. The mean crown-lump length of the 10 fetuses at diagnosis was 61.9 mm; mean gestational age at diagnosis was 12 weeks; and mean maternal body mass index ± SD was 21.2 ± 3.9 kg/m².

Echocardiographic Features of Congenital Absence of the Aortic Valve

Nine of the 10 fetuses had increased nuchal translucency; only 1 fetus had normal nuchal translucency (Table 1). Nuchal translucency thickness ranged from 2.4 to 12.4 mm (mean ± SD, 6.4 ± 3.6 mm). The fetal heart was enlarged in 8 cases. The cardiothoracic ratio ranged from 0.28 to 0.44 (average, 0.36).

Color Doppler flow imaging revealed that all 10 cases had pandiastolic reversed flow in the ascending aorta and aortic arch. Pulsed wave Doppler imaging showed biphasic bidirectional flow in both great arteries in all cases. Biphasic bidirectional flow consisted of antegrade flow in systole and retrograde flow in diastole, which we called the to-and-fro sign. The to-and-fro flow pattern in the aorta is the key color and pulsed Doppler feature of congenital absence of the aortic valve that can be detected in the first trimester. Typical color Doppler images and pulsed wave Doppler tracings are shown in Figure 1. Five fetuses had regurgitation in one or both atrioventricular valves. Ductus venosus Doppler imaging showed a reversed A wave in all cases (Figure 1E). In addition, thoracoabdominal aorta Doppler sampling showed pandiastolic retrograde flow in all cases. Umbilical artery Doppler imaging showed absent or reversed end-diastolic flow in 5 cases.
All 10 cases showed additional cardiac malformations (Table 1). The most common associated cardiac malformation was absence of the pulmonary valve (10 of 10). As summarized in Table 1, there were 2 cases with atrioventricular canal defects, 5 cases with ventricular septal defects, and 1 case with a double-outlet right ventricle and mitral valve atresia. All 10 cases also had extracardiac abnormalities (Table 1), including generalized edema (n = 9), cystic hygroma (n = 4), holoprosencephaly (n = 2), omphalocele (n = 1), exencephaly (n = 1), pleural effusion (n = 1), and spina bifida (n = 1).

### Perinatal Outcomes

Of the 10 cases, 2 (cases 6 and 8) had intrauterine deaths at 13 weeks and 13 weeks 6 days, respectively, and 8 cases underwent elective termination secondary to multiple fetal anomalies. Autopsy was performed on 4 fetuses (cases 1, 2, 8, and 10), and the autopsy results confirmed the in utero findings (Figure 2, A–C). Macroscopically, the following abnormalities were common: fluid accumulation at the nucha, generalized edema, enlarged heart, and dilated aorta and pulmonary trunk. Microdissection revealed that the aortic leaflets were completely absent (Figure 2B). There was only a small ridge of mesenchymal tissue at the pul-

### Table 1 Summary of Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>MA, y</th>
<th>GA at Diagnosis, wk+d</th>
<th>CRL, mm</th>
<th>NT, mm</th>
<th>Additional Cardiac Abnormality</th>
<th>Additional Extracardiac Abnormality</th>
<th>Associated Abnormality Soft Marker</th>
<th>Outcome and GA, wk+d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>12+4</td>
<td>59.3</td>
<td>3.7</td>
<td>APV, AVSD</td>
<td>Generalized edema, holoprosencephaly, polydactyly</td>
<td>Increased NT thickness, inverted DV A wave, tricuspid regurgitation</td>
<td>TOP at 13+5</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>12+6</td>
<td>62.7</td>
<td>12.4</td>
<td>APV, VSD</td>
<td>Cervical cystic hygroma with generalized edema</td>
<td>Increased NT thickness, inverted DV A wave, tricuspid regurgitation</td>
<td>TOP at 13+6</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>13+2</td>
<td>69.2</td>
<td>11.3</td>
<td>APV, AVSD</td>
<td>Generalized edema</td>
<td>TOP at 14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>13+2</td>
<td>69.7</td>
<td>6.9</td>
<td>APV, VSD</td>
<td>Generalized edema, Holoprosencephaly</td>
<td>TOP at 14+2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>13+4</td>
<td>72.1</td>
<td>3.6</td>
<td>APV, DORV</td>
<td>Cervical cystic hygroma with generalized edema, omphalocele</td>
<td>TOP at 14+4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>11+6</td>
<td>57</td>
<td>5.0</td>
<td>APV</td>
<td>Cervical cystic hygroma with generalized edema</td>
<td>IUD at 13</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>11+6</td>
<td>56.5</td>
<td>6.7</td>
<td>APV, mitral atresia, SV</td>
<td>Generalized edema</td>
<td>TOP at 12+6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>12+6</td>
<td>65.4</td>
<td>9.1</td>
<td>APV</td>
<td>Generalized edema</td>
<td>IUD at 13+6</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>13+1/12+2</td>
<td>70.5/60.7</td>
<td>1.6/2.4</td>
<td>APV</td>
<td>Exencephaly</td>
<td>Selective termination at 13+5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>12+0/12+0</td>
<td>573/573</td>
<td>8.0/77</td>
<td>VSD</td>
<td>Generalized edema, conjoined twins, dicephaly, spina bifida</td>
<td>TOP at 12+5</td>
<td></td>
</tr>
</tbody>
</table>

Cases 1 to 9 were diagnosed antenatally, and case 10 was diagnosed by necropsy. Case 9 was one of a pair of dichorionic diamniotic twins. Case 10 was conjoined twins. APV indicates absence of the pulmonary valve; AVSD, atrioventricular septal defect; CRL, crown-lump length; DORV, double-outlet right ventricle; DV, ductus venosus; GA, gestational age; IUD, intrauterine death; MA, maternal age; NT, nuchal translucency; SV, single ventricle; TOP, termination of pregnancy; and VSD, ventricular septal defect.
Figure 1. Echocardiograms of congenital absence of the aortic valve in a fetus. **A** and **B**, Fetal Color Doppler echocardiograms showing a to-and-fro flow pattern in the 3-vessel view. Antegrade flow is shown in both great arteries in systole (**A**), and retrograde flow is shown in both great arteries in pandiastole (**B**). **C** and **D**, Fetal pulsed Doppler echocardiograms showing biphasic bidirectional flow (arrows) in the pulmonary artery (**C**) and aorta (**D**). **E**, Reversed A-wave in the ductus venosus flow. MPA indicates main pulmonary artery; and SP, spine.
Figure 2. A–C. Photomicrographs of the heart in case 2. A, Slightly dilated heart and dilated ascending aorta. B, Dilated aorta with complete absence of the aortic valve. C, Absence of pulmonary valve leaflets with the exception of membranous remnant tissues (arrow) at the pulmonary cusps. D, Microscopic section through the aortic orifice. No valve leaflets are present in both great arteries. Arrow indicates coronary arteries (original magnification ×20). AAO indicates absent ascending aorta; AO, aorta; LAA, left atrial appendage; LCA, left carotid artery; LSA, left subclavian artery; LV, left ventricle; MPA, main pulmonary artery; PA, pulmonary artery; RAA, right atrial appendage; RCA, right carotid artery; and RV, right ventricle.
monary cusps where normal leaflets are usually located (Figure 2C). The aortic sinus of Valsalva was also absent. The heart was then serially sectioned at 10 μm and examined microscopically. The aorta and pulmonary trunk were enlarged; there were no semilunar valve leaflets present. The coronary arteries usually originated from the aorta (Figure 2D).

Discussion

Absence of the aortic valve leaflet is an extremely rare congenital cardiac defect. The incidence in our study population was 0.019%. The semilunar valves are formed at the site of the ventriculoarterial junction (Carnegie embryologic stages 15–17) out of 4 swellings of endocardial cushion tissue: 2 larger ones and 2 small or intercalated cushions at the conotruncus of the embryonic heart, which suggests that the development of the semilunar valves is closely linked to that of conotruncal septation. The relatively frequent association between both the missing aortic and semilunar valve leaflets had led some investigators to conclude that aplasia of the semilunar valve leaflets reflects an underdevelopment of the endocardial cushion swellings at the ventriculoarterial junction, rather than arising from abnormal septation of the outflow tracts. The development of semilunar valves is influenced by several factors, including the location and volume of the endocardial cushion swelling and invasion by mesenchymal cells. Abnormal development of early cardiogenesis and hemodynamic changes are thought to interfere with the formation of the semilunar valve. In one report, all 7 cases were male, which suggests an X-linked process. DiGeorge syndrome has been reported in 1 case. Unfortunately, none of the 10 cases in our study underwent chromosomal evaluation.

Absence of the aortic valve is not typically an isolated anomaly. It is frequently associated with other cardiac malformations. In our study, the pulmonary valve was conspicuously absent in all cases. Ventricular septal defects were often present. Interestingly, the association with other anomalies may be protective. In one report, a fetus with a hypoplastic left ventricle and mitral atresia survived fetal life to term and underwent bilateral pulmonary artery banding after birth, followed by Norwood and bidirectional Glenn procedures at 3 months of age. Along with hypoplasia of the left ventricle, a stiff left ventricle with elevated end-diastolic pressure may limit the volume of regurgitation across the aortic valve, reducing the physiologic effect of a perfusion steal. In patients with absence of the aortic valve, the noncompliant hypoplastic left ventricle and mitral atresia appear to affect the clinical outcome.

Absence of a competent aortic valve results in severe aortic insufficiency, which affects the fetal circulation in various ways. During diastole, blood regurgitates back into the ventricle, which leads to a reduction in the blood supply to organs and tissues. The volume overload results in left ventricle enlargement and ultimately heart failure, fetal hydrops, and fetal death. Most fetuses with this anomaly die early in the first weeks of gestation, which may explain the rare nature of the anomaly.

Absence of the aortic valve is commonly associated with increased nuchal translucency and cystic hygroma, which may offer clues to finding this rare anomaly in the first trimester. However, in the early fetus, it is very difficult to detect the aortic annulus and aortic valve directly because the fetal heart is too small. Prenatal detection of congenital absence of the aortic valve at the first-trimester scan is possible by observing reversed flow in the 3-vessel view or in the aortic arch in an oblique view of the fetal thorax. Bidirectional flow is distinct from monophasic-reversed flow in systole, which is characteristic of duct-dependent cardiac defects: eg, retrograde flow in the aortic arch in hypoplastic left heart syndrome. Retrograde flow is observed in the aortic arch and arterial duct in aortic atresia and severe stenosis and in pulmonary atresia, respectively. In these cases, the retrograde flow is mainly systolic. However, the reversed component of the bidirectional flow in our study was mainly diastolic or pandiastolic, and the width of the insufficient aortic flow was almost as great as that of the aortic annulus. No turbulent antegrade systolic flow at the aortic annulus was noted on color Doppler echocardiography. In addition, severe aortic insufficiency with a wide jet of color flow should be carefully distinguished from inflow across the mitral valve by appropriate angulation of the transducer. Color and pulsed wave Doppler imaging may be helpful in defining the exact site of reversed flow. The results of our study indicate that a to-and-fro flow pattern or biphasic bidirectional flow in the great artery on color and pulsed Doppler imaging is an unusual finding at early fetal echocardiography. We should recognize these conditions when scanning at 11 weeks to 13 weeks 6 days. Major congenital heart defects, which might be among the causes of abnormal ductus venosus waveforms in the first trimester, are thought to be reasons for increased nuchal translucency. In our cases, severe heart failure led to abnormal ductus venosus waveforms with increased nuchal translucency and abnormal umbilical artery waveforms during the first trimester. Diastolic reversal in the descending aorta is to be anticipated with reversal in the umbilical artery, which is an ominous sign and an indication for a poor prognosis during the first trimester.
Most cases of absence of the aortic valve end with termination because of a chromosomal abnormality or progressive deterioration, and the remainder end in spontaneous intrauterine death. In our study, 2 fetuses had intrauterine deaths, and the remaining 8 fetuses had elective terminations for associated fetal anomalies.

In conclusion, absence of the aortic valve is a rare cardiac defect that may affect both of the semilunar valves. We have shown the feasibility of first-trimester fetal echocardiography in detecting this condition. A to-and-fro flow pattern or biphasic bidirectional flow in the great arteries is a key feature of this condition on first-trimester fetal echocardiography. Early diagnosis of absence of the aortic valve and knowledge of its progression in utero are critical in the context of potential intrauterine treatment and counseling patients about their pregnancy outcomes.

References