Totally Anomalous Pulmonary Venous Connection and Complex Congenital Heart Disease

Prenatal Echocardiographic Diagnosis and Prognosis

Chandrakant R. Patel, MBBS, John R. Lane, MD, Michael L. Spector, MD, Philip C. Smith, MD, Stephen S. Crane, MD

Objective. The purpose of this study was to determine the accuracy of prenatal cardiac diagnosis, prognosis, and outcome of totally anomalous pulmonary venous connection (TAPVC) and to determine echocardiographic clues in the prenatal diagnosis of isolated TAPVC or TAPVC in association with other complex congenital heart disease (CHD). Methods. We reviewed our 13-year experience of prenatal diagnosis of TAPVC. Thirteen fetuses were identified with the diagnoses of TAPVC. We systematically analyzed the individual pulmonary veins by color and pulsed Doppler imaging, the presence of a pulmonary venous confluence, the pulsed and color Doppler evaluation of the vertical vein, and sites of connections. Prenatal diagnosis was confirmed by postnatal echocardiography, cardiac catheterization, surgery, or autopsy. Results. The mean gestational age at diagnosis of TAPVC was 26.3 weeks (range, 20–33 weeks). There were 8 fetuses with TAPVC and right isomerism, 3 fetuses with other associated CHD, and 2 with isolated TAPVC. There were 7 fetuses with supracardiac TAPVC, 4 with infracardiac TAPVC, and 2 with mixed TAPVC. Pulmonary vein color and pulsed Doppler data were available in 10 of 13 fetuses. The pulmonary venous confluence was visualized in all fetuses except 1. The vertical vein was visualized in all fetuses. Five fetuses had suspected signs of obstruction. The diagnosis was confirmed postnatally or at autopsy in 12 cases. Eight patients underwent surgery; 6 died, and 2 were alive. Two patients had compassionate care and died; 3 pregnancies were terminated. Conclusions. It is possible to diagnose accurately complex CHD, including the pulmonary venous connections. When diagnosed prenatally, TAPVC carries a poor prognosis. Key words: congenital heart diseases; prenatal diagnosis; right isomerism; totally anomalous pulmonary venous connections.

Prenatal echocardiography has been used widely in the diagnosis of complex congenital heart disease (CHD). The segmental approach to making the diagnosis of complex CHD has been widely used postnatally. The segmental approach is now also used prenatally in patients with visceral heterotaxy and complex CHD. Evaluation of pulmonary veins is a routine part of fetal echocardiography. There are published studies of the evaluation of normal pulmonary veins by pulsed flow Doppler mapping at various gestations. Color flow Doppler imaging is an extremely useful tool in locating pulmonary veins and helps determine the precise location for pulsed Doppler interrogation. Refinement in sonographic equipment and accumulation of clinical experience have allowed accurate prenatal diagnosis of
anomalies of pulmonary venous connections. There are studies reporting accurate prenatal diagnosis of complex CHD including visceral heterotaxy with anomalies of pulmonary venous connections. We actively look for anomalies of pulmonary venous connections especially in fetuses with right isomerism. The purposes of this study were (1) to determine echocardiographic clues in making the diagnosis of totally anomalous pulmonary venous connection (TAPVC), (2) to determine the accuracy of prenatal diagnosis of TAPVC and assessing for obstructed TAPVC, and (3) to assess the outcome of cases with and without complex CHD with TAPVC diagnosed parentally.

Materials and Methods

We reviewed all fetal echocardiograms obtained from June 1991 through March 2004 at our institutions. A total of 3292 fetal echocardiographic examinations were performed during this period. There were 264 fetuses with structural cardiac abnormalities diagnosed during this period. There were 13 fetuses with a diagnosis of TAPVC that formed the study group. We reviewed indications for fetal echocardiography, gestational age at diagnosis, types of TAPVC, presence of obstruction, and outcome. Examinations were performed with an ATL Mark 9 system (Philips Medical Systems, Bothell, WA) with a 3.5-MHz linear transducer or a 5-MHz phased array transducer or an Acuson 128XP or Sequoia system (Siemens Medical Solutions, Mountain View, CA) with an 8.0- or 6.0-MHz linear array transducer. Images were recorded on 1/2-in VHS tape for subsequent review.

A perinatologist and a pediatric cardiologist performed all examinations. The fetal ultrasound examination included morphometric analysis for gestational age (biparietal diameter, head circumference, abdominal circumference, and femur length), detailed anatomic survey, and cardiac evaluation. Fetal echocardiography consisted of imaging the 4 chambers, pulmonary veins, right ventricular outflow tract and ductal arch, left ventricular outflow tract and aortic arch, inferior vena cava, and superior vena cava. Doppler imaging (pulsed wave and color flow mapping) was performed in all fetal echocardiograms including pulsed Doppler sonography of the pulmonary veins. The Nyquist limit for color flow Doppler mapping was decreased to less than 25 cm/s to interrogate pulmonary veins. In the 4-chamber view, the area posterior to the left atrium was examined to look for the common pulmonary venous confluence in anomalous pulmonary venous connections. The ascending or descending vertical vein from the pulmonary venous confluence was examined to determine the exact site of the pulmonary venous connection. The cardiac situs and axis and abdominal situs, including the direction of the umbilical vein from left to right, finally terminating into the portal sinus, was shown. The specific diagnosis of asplenia syndrome was made when the spleen was not seen posterior to the stomach, with absence of the splenic artery and vein.

Amniocentesis was offered to all mothers with fetal structural cardiac abnormalities. Diagnoses were confirmed on postnatal echocardiography, cardiac catheterization, surgery, or autopsy.

Results

Thirteen fetuses had the diagnosis of TAPVC. The mean gestational age at the time of diagnosis was 26.3 weeks (range, 20–33 weeks). The indications for fetal echocardiographic examination consisted of an abnormal 4-chamber view in 10 fetuses, non-cardiac abnormalities in 2, and maternal diabetes in 1. Amniocentesis was performed on 8 fetuses; all of them had normal karyotypes. There were 8 fetuses with right isomerism (asplenia) and complex CHD with TAPVC. Three fetuses had complex CHD and TAPVC. Two had isolated TAPVC. The diagnosis was not made initially in 2 fetuses, 1 with supracardiac TAPVC and the other with mixed TAPVC. The infracardiac variety of TAPVC is often obstructive once the ductus venosus closes because blood then must pass through the hepatic sinusoids. The diagnosis was not made initially in 2 fetuses, 1 with supracardiac TAPVC and the other with mixed TAPVC. The characteristic findings in fetuses with right isomerism were a visceralcardiac situs abnormality, aortocaval juxtaposition, an atrioventricular septal defect, a common atrium, a double-outlet right ventricle, dextro-malposed great arteries, pulmonary stenosis or atresia, and anomalous pulmonary venous connections. The major cardiac diagnosis was correct in all fetuses with right isomerism and in the other 3 with complex CHD. The diagnosis was confirmed in all fetuses except 1 whose pregnancy was terminated; the parents refused autopsy.
**Echocardiographic Findings**

The normal pulsed Doppler pattern in the pulmonary vein consists of a first peak during ventricular systole (S wave), a second peak during early diastolic filling (D wave), and atrial contraction (A wave) (Figure 1).

The pulmonary venous confluence was visualized in 12 of 13 fetuses. It was seen as an oval or oblong structure situated posterior to the left atrium and anterior to the descending aorta. Color flow Doppler sonography was very helpful in determining whether the pulmonary veins

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**Table 1. Fetal Diagnoses, Clinical Profiles, and Outcomes**

<table>
<thead>
<tr>
<th>Case</th>
<th>GA at Diagnosis, wk</th>
<th>Pulmonary Venous Connection Site</th>
<th>Obstruction</th>
<th>Associated CHD</th>
<th>Extracardiac Malformations</th>
<th>Diagnosis at Postnatal Echocardiography* or Autopsy†</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>TAPVC supracardiac, right innominate</td>
<td>Absent</td>
<td>RAI, DX, SS, AVSD, D-MGA, PA, LSVC, CA</td>
<td>None</td>
<td>Confirmed*</td>
<td>Died at 1 mo</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>TAPVC infracardiac, portal vein</td>
<td>Absent</td>
<td>RAI, DX, SI, AVSD, corrected MGA, PA, CA</td>
<td>Gut malrotation, midline stomach and liver, left-sided gallbladder, bilateral trilobe lungs</td>
<td>Confirmed†</td>
<td>Died after 2 d</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>TAPVC infracardiac, portal vein</td>
<td>Absent</td>
<td>RAI, DORV, SI, D-MGA, AVSD, PS, CA</td>
<td>Gut malrotation, midline stomach, left-sided gallbladder, absent right umbilical artery</td>
<td>Confirmed†</td>
<td>TOP</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>TAPVC supracardiac, LSVC-RA junction</td>
<td>Absent</td>
<td>RAI, DX, SI, SV, D-MGA, PA, CA</td>
<td>Midline liver</td>
<td>Confirmed*</td>
<td>Alive, s/p BDG, 4 y</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>Mixed TAPVC, right SVC/RA junction, portal vein</td>
<td>Present</td>
<td>RAI, levocardia, SI, DORV, D-MGA, AVSD, PS</td>
<td>Midline liver</td>
<td>Confirmed*</td>
<td>Alive, s/p TAPVC, s/p BDG 5 y</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>TAPVC infracardiac, ductus venosus</td>
<td>Present</td>
<td>RAI, DX, SS, DORV, D-MGA, PS, AVSD, CA</td>
<td>Midline liver</td>
<td>Confirmed*</td>
<td>Died after surgery</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>TAPVC infracardiac, portal vein</td>
<td>Absent</td>
<td>RAI, levocardia, SS, SV, DORV, AVSD, D-MGA, L SVC</td>
<td>Midline liver, gut malrotation</td>
<td>Confirmed†</td>
<td>TOP</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>TAPVC supracardiac, right SVC</td>
<td>Absent</td>
<td>RAI, levocardia, SI, DORV, D-MGA, PS AVSD</td>
<td>None</td>
<td>Not confirmed</td>
<td>TOP</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>TAPVC supracardiac, left innominate vein</td>
<td>Present</td>
<td>DORV, VSD, COA, IUGR</td>
<td>Cerebral encephalocele, single nostril</td>
<td>Confirmed*</td>
<td>Died at 2 mo after surgery</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>TAPVC mixed</td>
<td>Absent</td>
<td>Unbalanced AVSD, HRV</td>
<td>None</td>
<td>Confirmed*</td>
<td>Died after surgery</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>TAPVC supracardiac, left innominate vein</td>
<td>Absent</td>
<td>Mitral atresia, VSD, COA</td>
<td>None</td>
<td>Confirmed*</td>
<td>Died after surgery</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>TAPVC supracardiac, left innominate vein</td>
<td>Present</td>
<td>None</td>
<td>None</td>
<td>Confirmed*</td>
<td>Died after surgery</td>
</tr>
<tr>
<td>13</td>
<td>24</td>
<td>TAPVC supracardiac, left innominate vein</td>
<td>Present</td>
<td>None</td>
<td>None</td>
<td>Confirmed†</td>
<td>Died after surgery</td>
</tr>
</tbody>
</table>

AVSD indicates atrioventricular septal defect; BDG, bidirectional Glenn shunt surgery; CA, common atrium; COA, coarctation of the aorta; D-MGA, dextro-malposition of the great arteries; DORV, double-outlet right ventricle; DX, dextrocardia; GA, gestational age; HRV, hypoplastic right ventricle; IUGR, intrauterine growth restriction; LSVC, left-sided superior vena cava; PA, pulmonary atresia; PS, pulmonary stenosis; RA, right atrium; RAI, right atrial isomerism; SI, situs inversus; s/p, status post; SS, situs solitus; SV, single ventricle; SVC, superior vena cava; TOP, termination of pregnancy; and VSD, ventricular septal defect.
were connected to the left atrium or to the pulmonary venous confluence behind the left atrium. The fetus in which the confluence was not visualized had 2 right pulmonary veins connected to an infracardiac site and 2 left pulmonary veins connected to a supracardiac location emptying to the left innominate vein (case 10). The ascending or descending vertical vein was visualized in all fetuses. Depending on the site of connection of the vertical vein to the systemic veins, abnormalities were seen in certain views. For example, there were 4 fetuses with supracardiac TAPVC to the left innominate vein and 1 to the right innominate vein. In the 3-vessel view in the upper mediastinum, there was a fourth vessel seen, that being the ascending vertical vein connecting to the innominate vein. There was also increased flow seen in the innominate vein on pulsed and color flow Doppler examination. In normal cross-sectional views of the upper abdomen at the level of the stomach, the descending aorta is situated anterior and to the left of the spine, and the inferior vena cava is anterior and to the right. In 4 fetuses with features suggestive of right isomerism and infracardiac TAPVC, there was an extra vessel seen between the inferior vena cava and the descending aorta, which was the descending vertical vein with venous flow directed caudally in the abdomen on pulsed and color flow Doppler examination (Figure 2). All the fetuses with right isomerism had associated juxtaposition of the inferior vena cava and descending aorta.

We were able to diagnose obstruction in the vertical vein prospectively in 5 fetuses. The obstruction was first diagnosed on the basis of a characteristic damped pulsed Doppler pattern of the individual pulmonary vein. On the basis of this Doppler pattern, we actively searched for the site of obstruction in the ascending or descending vertical vein or at the insertion site. On color Doppler imaging, turbulence was noted at the site of obstruction in the vertical vein with increased velocity on pulsed Doppler examination. One fetus had connection to the supracardiac and infracardiac sites with obstruction of the vertical vein at the junction with the right superior vena cava. One fetus with supracardiac TAPVC to the left innominate vein had obstruction noted at the junction with the left innominate vein. One fetus with infracardiac TAPVC to the ductus venosus had obstruction suspected at the level of the ductus venosus. In both fetuses with isolated supracardiac TAPVC, there was obstruction in the ascending vertical vein when it coursed cranially between the left bronchus and left pulmonary artery to join the left innominate vein (Figure 3).

**Postnatal Findings and Outcome**

Nine fetuses were born at term, and 1 fetus was born prematurely at 28 weeks’ gestation. The fetus who was born prematurely had right isomerism, complex CHD, and infracardiac TAPVC and died 2 days after birth. Among 8 fetuses with right isomerism, postnatal cardiac surgery was performed on 3 patients with 2 surviving. Two neonates were given compassionate care and died. Three families chose termination of pregnancy. In 2 of 3 terminated cases, autopsy confirmed the prenatal diagnosis. Three fetuses with complex CHD and TAPVC underwent surgery; all 3 died postoperatively. Of the 2 fetuses with a diagnosis of isolated TAPVC, both died, 1 in the immediate postoperative period due to major pulmonary hypertension related to obstructed supracardiac TAPVC and the other 2 months after surgery due to pulmonary hypertension.
Figure 2. A, Fetus with right isomerism: 4-chamber view shows dextrocardia with a common atrium and single ventricle. The primitive strand of atrial tissue is in the center of the common atrium. B, Cross-sectional view at the level of the abdomen shows the stomach on the left, a midline liver, and right juxtaposition of the inferior vena cava and descending aorta. The extra vessel in front of the descending aorta is the descending vertical vein. C, Color flow Doppler image in right and left pulmonary veins shows absence of connection to the atrium. D, Pulsed Doppler flow pattern in the left pulmonary vein shows phasic flow with absence of clear waveforms, (peak velocity, 18 cm/s). E, Fetal sagittal view shows infracardiac TAPVC to the ductus venosus in the same fetus. The lower 2 pulmonary veins join together to the descending vertical vein, which courses between the inferior vena cava in front and the descending aorta behind through the diaphragm to the liver to join the ductus venosus. On the color flow Doppler image, the blood flow in the descending vertical vein is directed caudally. A indicates atrium; ANT, anterior; DAO, descending aorta; INF, inferior; IVC, inferior vena cava; LPV, left pulmonary vein; LT, left; POST, posterior; PV, pulmonary veins; RA, right atrium; RPV, right pulmonary vein; RT, right; SP, spine; ST, stomach; SUP, superior; UV, umbilical vein; V, ventricle; and VV vertical vein.
Discussion

Totally anomalous pulmonary venous connection is categorized on the basis of the anatomic location of the anomalous connection. These categories are as follows: type 1, anomalous connection at the supracardiac level; type 2, anomalous connection at the cardiac level; type 3, anomalous connection at the infracardiac level; and type 4, anomalous connection at 2 or more levels.

Figure 3. A, Four-chamber view of the fetal heart with color flow Doppler image in the pulmonary veins in a fetus with isolated supracardial TAPVC to the left innominate vein. Note that the pulmonary veins are not communicating with the left atrium. B, The 4-chamber view of the fetal heart slightly cranial to the view in A shows the pulmonary venous confluence behind the left atrium, which is not communicating with the left atrium. C, The 3-vessel view at the level of great arteries shows the ascending vertical vein to the left of the pulmonary artery. D, The pulsed Doppler flow in the right pulmonary vein shows absence of the typical peaks during systole and diastole. Instead, there is continuous low-velocity flow of 19 cm/s suggestive of obstruction. ANT indicates anterior; AO, ascending aorta; CPC, pulmonary venous confluence; DAO, descending aorta; LA, left atrium; LPV, left pulmonary vein; LT, left; LV, left ventricle; POST, posterior; PT, pulmonary trunk; RA, right atrium; RT, right; RPV, right pulmonary vein; RV, right ventricle; SP, spine; and SVC, superior vena cava.
levels (mixed). The clinical appearance depends on whether the pulmonary veins are obstructed or nonobstructed. The obstruction can be intrinsic or extrinsic. Obstruction denotes impedance to the pulmonary flow occurring between the common pulmonary venous confluence and the right atrium. This distinction is important because in patients with obstructed TAPVC, the condition will appear early in life, and these patients are more likely to be symptomatic in the neonatal period.

During the early embryonic phase, the developing lung buds along with foregut drain to the common vascular plexus (splanchnic plexus), which drains through the paired common cardinal veins and umbilicovitelline veins. At 28 to 30 days’ gestation, a small endothelial outgrowth arises to the left of the primum septum and grows into the splanchnic plexus. This common pulmonary vein allows blood to drain directly to the heart, although at this stage it may still have continuity with the primitive venous connections. Once the direct left atrial connection is established, the primitive pulmonary venous connections disappear. The anomalous pulmonary venous connections constitute the persistence of those embryonic connections when the common pulmonary venous chamber does not communicate with the left atrium.

It is our routine practice during fetal echocardiographic examination to evaluate pulmonary veins by 2-dimensional echocardiography as well as by color Doppler and pulsed Doppler interrogation. The color Doppler examination aids in locating the site for the pulsed Doppler examination. There is a progressive increase in the velocity of the above waveforms with increasing gestational age.8 In the human fetus, more than 20% of the combined ventricular output passes to the pulmonary vascular bed and thus returns to the left atrium via the pulmonary veins, and this increases to 25% in the last 10 weeks of pregnancy.9,10

Doppler examination of the individual veins in TAPVC shows a characteristic damped waveform. If the pulmonary veins are not found connected to the left atrium, an ascending or descending vertical vein should be actively looked for. If on color Doppler imaging there is turbulence found in the ascending or the descending vertical vein, the possibility of obstructed TAPVC should be kept in mind. In fetuses with an obstructed pulmonary venous connection, the vertical vein may be small because of diminished pulmonary blood flow. The pulmonary vascular resistance may be elevated, thus diverting the blood away from the branch pulmonary artery to the arterial duct.

The diagnosis of anomalous pulmonary venous connections in the setting of heterotaxy should be actively considered, especially in fetuses with right isomerism. The likelihood of complex CHD with a viscerocardiac situs abnormality and an anomalous pulmonary venous connection is high in fetuses with right isomerism. The prognosis is poor for prenatally diagnosed cases of right isomerism with anomalous pulmonary venous connections. Atkinson and Drant4 reported 13 fetuses with heterotaxy syndrome diagnosed prenatally, 8 with right isomerism and 5 with left isomerism. Seven of them had abnormalities in the pulmonary venous connection. They did not describe the details of the pulmonary venous connections in their report.

In their study of prenatal diagnosis of pulmonary and systemic venous anomalies, Yeager et al11 reported 10 fetuses with suspected abnormalities in the pulmonary venous connections. Subdiaphragmatic connection was suspected in 4 cases; all 4 cases were found to have some or all pulmonary veins draining to the liver. Three cases had supracardiac connections all diagnosed correctly on prenatal echocardiography. In 2 fetuses, anomalous pulmonary venous return was suspected, but the site was not predicted; both of them had extracardiac connections. Lin et al12 reported a series of prenatally diagnosed cases of heterotaxy syndrome. They reported 6 fetuses with anomalous pulmonary venous connections among 15 fetuses with right isomerism in whom follow-up was available. Valsangiacomo et al13 published a series of 11 fetuses diagnosed with TAPVC. There were 5 with supracardiac connections, 5 with infracardiac connections, and 1 mixed type. Eight fetuses had right isomerism with complex CHD and TAPVC; 1 had hypoplastic left heart syndrome and supracardiac TAPVC; and 2 had isolated infracardiac TAPVC. They were able to identify obstruction in the anomalous pathway in 6 fetuses, 4 fetuses having supracardiac TAPVC, 1 having mixed TAPVC, and another with infracardiac TAPVC.

Prenatal diagnosis of isolated TAPVC is rare. Allan et al14 reported prenatal diagnosis of isolated TAPVC in 4 of 2370 fetuses with diagnoses of
structural heart diseases. There were 2 fetuses with connections to the coronary sinus, 1 with a connection to the right superior vena cava, and 1 with a connection to the inferior vena cava. However, prospective prenatal diagnosis was made only in 1 case. They concluded that ventricular size and great arterial disproportion was seen in fetuses with anomalous pulmonary venous connections above the diaphragm. With an infradiaphragmatic connection, the right heart dilatation may not occur until late in pregnancy. Yeager et al\textsuperscript{11} reported 2 fetuses with isolated TAPVC.

With improvement in sonographic equipment, operator experience, and detailed meticulous attention to the segmental evaluation of the cardiac structures, it is possible to make accurate diagnoses of complex CHD, including anomalies of pulmonary venous connection. The diagnosis of TAPVC can be made reliably in prenatal life by direct examination of the pulmonary veins by color and pulsed Doppler examination of the individual veins with a characteristic damped waveform, identification of the pulmonary venous confluence behind the left atrium, and determination of the site of drainage through the ascending or descending vertical vein. The prognosis remains poor for fetuses with prenatally diagnosed TAPVC, whether it is isolated, in association with right isomerism, or in association with other complex CHD.

References


