Prenatal Findings in Total Anomalous Pulmonary Venous Return

A Diagnostic Road Map Starts With Obstetric Screening Views

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Objectives—Optimal perinatal management of total anomalous pulmonary venous return (TAPVR) involves timely identification followed by surgical correction. Antenatal diagnosis, however, has long been a challenge. We aimed to identify consistent prenatal sonographic features in this condition in a large cohort in whom the diagnosis was made antenatally and confirmed postnatally.

Methods—We conducted a systematic retrospective review of the 2-dimensional and Doppler sonographic features that had helped make the diagnosis of TAPVR at our institution from 2001 to 2012.

Results—Twenty-six patients had prenatal diagnosis of TAPVR (mean gestational age, 24.1 weeks). Four of the fetuses with a prenatal diagnosis represented isolated cases of TAPVR; 22 had heterotaxy syndrome, additional cardiac abnormalities, or both. Prenatally diagnosed abnormal pulmonary venous connections were supracardiac (type I) in 18 cases, cardiac (type II) in 1, and infradiaphragmatic (type III) in 7. Lack of a visible connection of the pulmonary veins to the atrium (100%) and the presence of a visible venous confluence on axial 4-chamber views (96%) were the most consistent findings. Cardiac asymmetry and the presence of additional vertical venous channels on 3-vessel or axial abdominal views were also noted but less consistently. Abnormal pulmonary venous spectral Doppler findings were present in 25 of the 26 fetuses.

Conclusions—The diagnosis of TAPVR can be suspected on standard axial views included in second-trimester obstetric screening examinations of the fetal heart and confirmed on fetal echocardiography with the use of pulsed wave Doppler imaging. Clues recognizable on obstetric sonographic screening have the potential to contribute to increasing the diagnostic yield for prenatal detection of TAPVR.

Key Words—congenital heart disease; Doppler sonography; fetal echocardiography; heterotaxy; obstetric ultrasound

Abbreviations

GA, gestational age; IVC, inferior vena cava; LA, left atrium; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return; 2D, 2-dimensional

The diagnosis of total anomalous pulmonary venous return (TAPVR) is a crucial and notably more difficult diagnosis in the fetus than in the neonate or infant. Although TAPVR only accounts for 0.5% to 2% of all cardiovascular malformations and occurs approximately in 8.7 per 100,000 live births,[1,2] it is the fifth most common cause of critical heart disease.[1] The fundamental characteristic of the malformation is failure of the pulmonary veins to establish normal connections to the left atrium (LA); instead, they either drain directly or through the systemic veins to the right atrium. Abnormal pulmonary venous drainage can be isolated or seen in conjunction with other complex cardiac malformations,

mainly heterotaxy syndromes. Total anomalous pulmonary venous return can be divided into 4 anatomic groups depending on the site of connection to the systemic veins: type I, supracardiac (43%); type II, cardiac (18%); type III, infradiaphragmatic (27%); and type IV, mixed (12%).[1,3]

The unique nature of fetal hemodynamics allows this abnormality to be well tolerated in utero (because pulmonary blood flow is a small portion of the combined ventricular output). However, once postnatal transition occurs, there is complete mixing of the pulmonary and systemic circulations in the right heart, and the infant will be cyanotic and may have difficulty feeding in the first weeks and months of life, even in the absence of other abnormalities. In some neonates, respiratory distress and decompensation may ensue very early in the neonatal period if there is substantial obstruction; obstruction of a pulmonary venous connection results in elevated pulmonary pressures and decreased systemic oxygen delivery. The condition can quickly become life threatening unless the cause is promptly recognized and treated. Early detection along with appropriate stabilization and early surgical repair results in a good long-term prognosis,[4–6] but the high morbidity encountered when not recognized until after birth makes prenatal diagnosis of this condition particularly critical.

Although fetal echocardiography is an established means for prenatal diagnosis of many cardiac defects, TAPVR is rarely detected in the fetus.[1,7,8] The low incidence of the disease and the difficulties in recognition of abnormalities on obstetric screening sonography that might lead to referral for fetal echocardiography have resulted in a relative paucity of information related to this area in the diagnostic ultrasound literature. The small size of the veins and low flow in the pulmonary venous system make the diagnosis quite difficult.[8,9] However, routine antenatal identification of a pulmonary venous connection on the 4-chamber view within the scope of a screening obstetric examination has been successfully reported,[10] and in recent years, an increasing trend in the number of isolated and series reports describing prenatal diagnosis of anomalous pulmonary venous connections has been noted.[1,8,9,11–17] Despite these reports, there is little information in the literature to guide the obstetric ultrasound practitioner in how to systematically assess for TAPVR in a fetus in the setting of second- or third-trimester standard obstetric sonography that includes an anatomic survey. Therefore, the aim of this study was to review a larger series, including all fetuses with a diagnosis of TAPVR prenatally in our institution, to determine the accuracy of specific sonographic features in each case and attempt a compilation of consistent pointers that aid in the establishment of the diagnosis and that might be applied even during second- or third-trimester routine obstetric sonographic screening.

Materials and Methods

We conducted a retrospective cohort review of all fetuses with a diagnosis of TAPVR between 2001 and 2012 at the Fetal Cardiovascular Program and Fetal Treatment Center at the University of California, San Francisco, Benioff Children's Hospital and all neonates with a postnatal diagnosis of TAPVR who had undergone fetal echocardiography at our institution. The study was approved by the University of California, San Francisco, Committee on Human Research (approval number 10-04581), with a waiver of consent.

Our institutional fetal echocardiographic database was searched to identify all cases of prenatally diagnosed TAPVR, both with and without other associated cardiac structural abnormalities. The indications, times of referral, and gestational ages (GAs) at the times of diagnosis were reviewed. All cases with TAPVR, whether in isolation, in conjunction with heterotaxy syndrome, or with other cardiac anomalies, were included in the review. In addition, we searched the neonatal database of the Pediatric Echocardiography Laboratory at our institution for any postnatal diagnoses that included TAPVR and cross referenced these with our fetal echocardiographic database to identify any missed cases.

Fetal echocardiographic examinations were performed with Acuson Sequoia C256 and C512 and Siemens S2000 ultrasound systems (Siemens Medical Solutions, Mountain View, CA) equipped with a combination of curvilinear and phased array probes operating at 6 to 8 MHz. All studies included a complete 2-dimensional (2D) evaluation of cardiac structures and systolic ventricular function with complete pulsed wave and color Doppler examinations, including venous and umbilical cord investigations, and were stored offline in the standard Digital Imaging and Communications in Medicine format.

Although all fetuses had undergone echocardiography as described in current guidelines,[18–20] our main focus was images that would have been included as part of a nonechocardiographic second-trimester obstetric screening examination. Therefore, stored standard 2D axial cardiac views at the abdomen, 4-chamber view, and 3-vessel view similar to those recommended for routine second- and third-trimester obstetric examinations including an anatomic survey and screening views of the fetal heart[21,22] were retrospectively evaluated by a single examiner (S.G.). The 3-vessel view is derived by cranial angulation from an

axial transverse 4-chamber view[23] (see Figure 3A) and is considered in some countries as a component of the recommended evaluation of the fetal outflow tracts done at the time of fetal heart screening in all pregnancies.[21] Additionally, transverse views at the level of the upper abdomen, which should include cross sections of the spine, descending abdominal aorta to the left, and inferior vena cava (IVC) to the right, along with the fetal stomach and liver,[21] were also reviewed. Particular attention was paid to the appearance of the right and left pulmonary venous connections on the axial section through the fetal thorax used to obtain the 4-chamber view (Figures 1 and 2), the 3-vessel view[23] (Figure 3), and the axial images of the abdomen

(Figure 4). In addition, supplemental views only considered part of a fetal echocardiogram as available were also evaluated, including sagittal views of the IVC, superior vena cava (SVC), and atria and at the level of the aortic and ductal arches and short- and long-axis views of the heart.

A systematic analysis of the following was made: (1) the imaging views that had contributed to the TAPVR diagnosis and specifically whether they would have been part of the routine cardiac views incorporated in the second-trimester obstetric anatomic screening examination; (2) findings particular to the standard axial 4-chamber view (asymmetry, lack of a pulmonary venous connection to the LA, and abnormal veins visible behind the LA), outflow
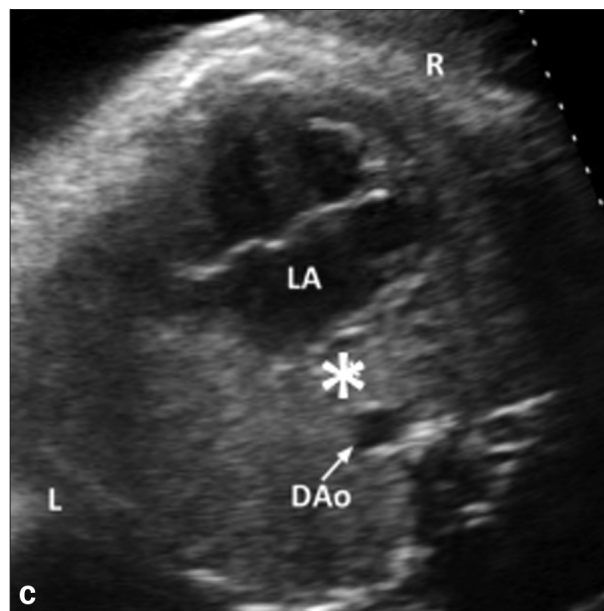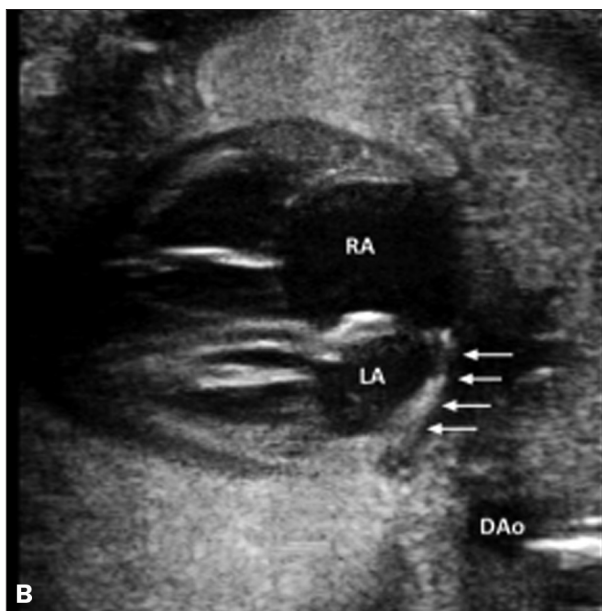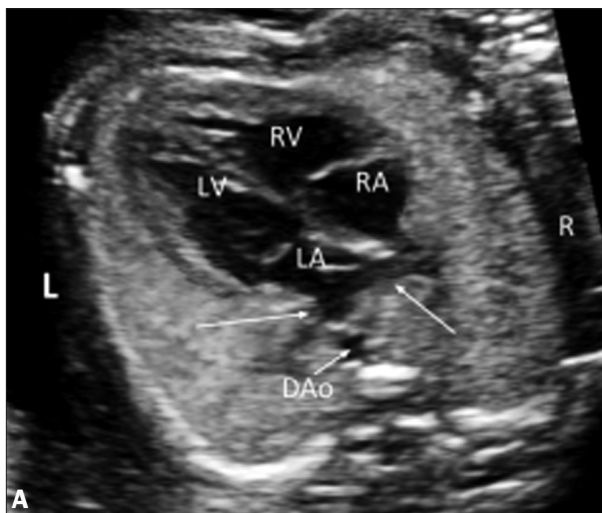
Figure 1. Normal (**A**) and abnormal (**B** and **C**) appearances. **A**, Normal pulmonary venous entry into the LA on an axial 4-chamber view. Note that pulmonary venous connections from the right and left lungs are clearly shown (arrows), and there is close proximity of the descending aorta to the posterior aspect of the LA. **B**, Absence of pulmonary venous drainage into the LA on a 4-chamber view in a fetus with isolated TAPVR. The posterior aspect of the LA is smooth, without visible vein ostia (arrows). **C**, An increased distance (asterisk) between the descending aorta and posterior aspect of the atrium is shown in a fetus with dextrocardia and TAPVR. DAo indicates descending aorta; LV, left ventricle; RA, right atrium; and RV, right ventricle.

tract assessment (including a 3-vessel view assessment of SVC size and the presence of additional vessels), and abdominal views (presence of additional vascular structures) outlined in current accepted guidelines[21,22]; (3) the consistency and reliability (among the entire cohort) of the 2D images that showed the identified key features of the diagnosis; and (4) abnormalities of the pulmonary venous color and pulsed wave Doppler signals and whether particular pulmonary venous Doppler patterns were specific to the site of the anomalous connection.

According to our fetal echocardiographic protocol, the pulmonary venous Doppler waveforms were sampled within the individual pulmonary veins near the entry of the vein into the hilar region, at the site of the evident vertical vein, or both. Normal fetal pulmonary venous flow can be either triphasic or biphasic and pulsatile and dynamically influenced by LA pressure changes[24–27] (Figure 5). With atrial systole, there is a decrease in forward flow to a minimum during the cardiac cycle (biphasic), although atrial reversal of flow ("a" wave, triphasic) is only noted in

Figure 2. **A–D**, Posterior venous confluence (twig sign; arrows) in different patients. The venous structure represents the confluence of the pulmonary veins; the draining vein may ascend (type I), descend (type II), or connect to the coronary sinus and would not be visible in this view. DAo indicates descending aorta; and RA, right atrium.
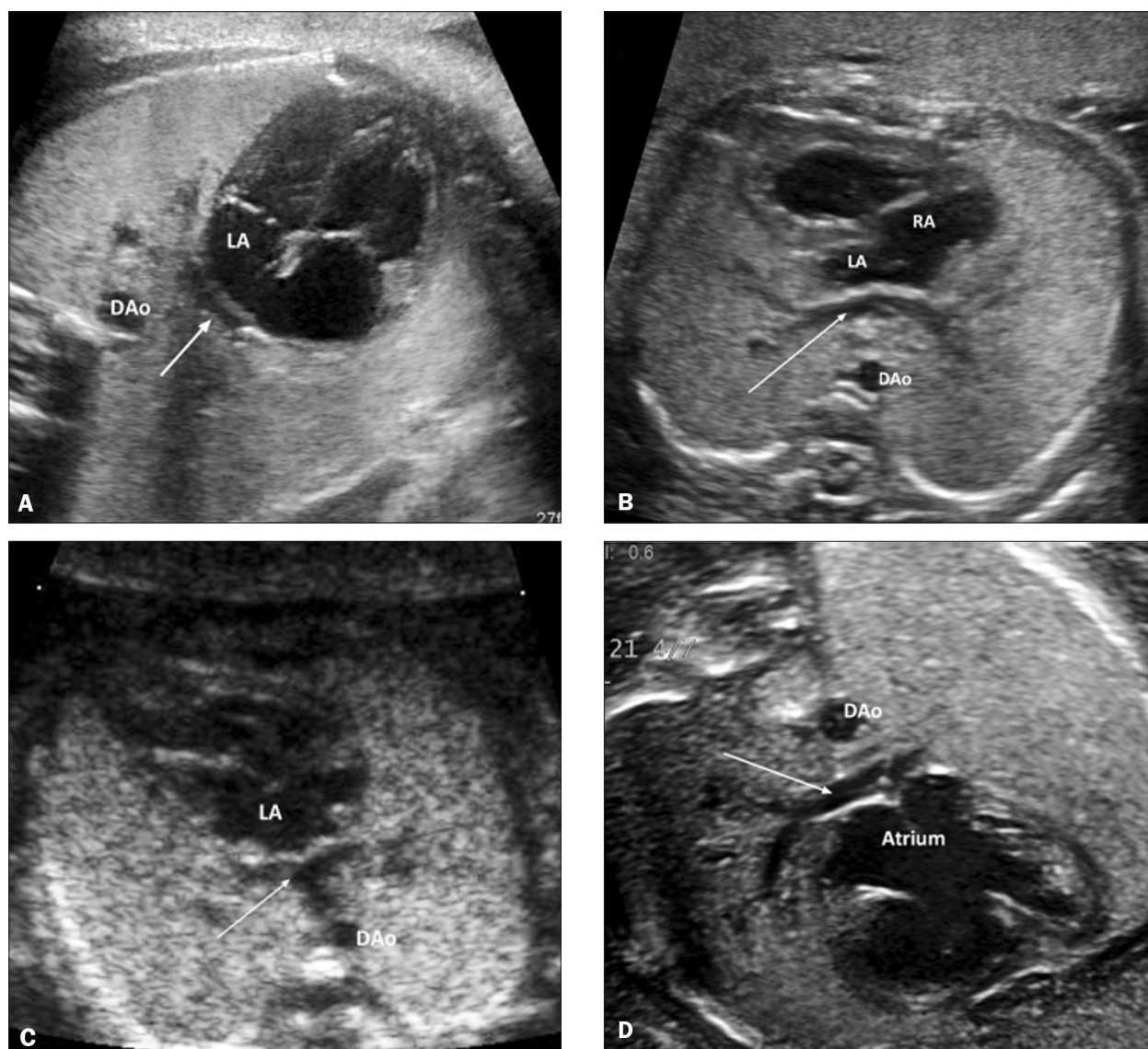
about 10% during the fetal period.[12,25] Abnormal flow waveform profiles in TAPVR were classified on the basis of the phasic nature and the relationship between the "s" and "d" peaks and behavior of the waveform during atrial systole. Waveforms were reviewed retrospectively by an experienced fetal echocardiographer (A.J.M.-G.). The pulmonary venous Doppler waveform patterns were categorized (Figures 5 and 6) as normal (triphasic or biphasic), abnormal s and d appearance but biphasic with normal pulsatility ("pseudonormal"), abnormal with a biphasic waveform but decreased pulsatility, abnormal

with a monophasic pulsatile pattern, or low-velocity monophasic and continuous. The evaluation of the waveforms was repeated by a second observer (N.H.S.), who was blinded to the initial categorization for independent correlation.

For statistical analysis, continuous variables such as GA were described as mean ± standard deviation or range as appropriate. A weighted κ coefficient was calculated with GraphPad software (http://graphpad.com/quickcalcs/kappa2) to compare the independent waveform classifications by the 2 observers.

Figure 3. Normal (**A**) and abnormal (**B** and **C**) 3-vessel views. **A**, Note that the pulmonary artery, aorta, and SVC are the only vessels seen in the mediastinum, and the vena cava is normally smaller than the aorta in this view. **B** and **C**, The SVC is prominent due to of increased venous flow, attributed to anomalous drainage of the pulmonary veins to the innominate vein (type I). Ao indicates aorta; and PA, pulmonary artery.
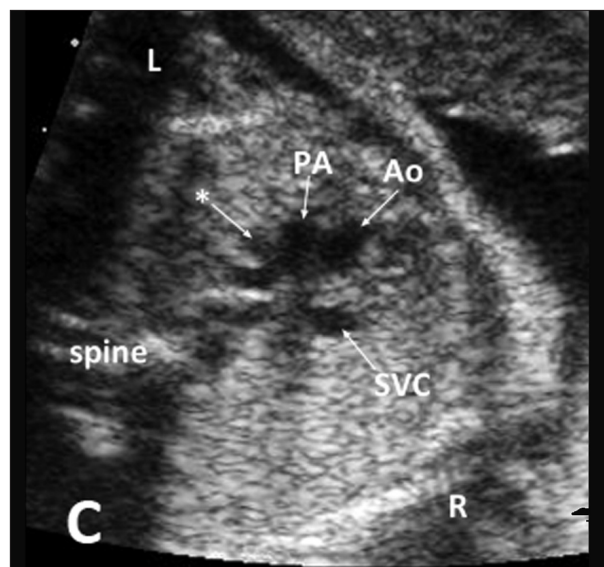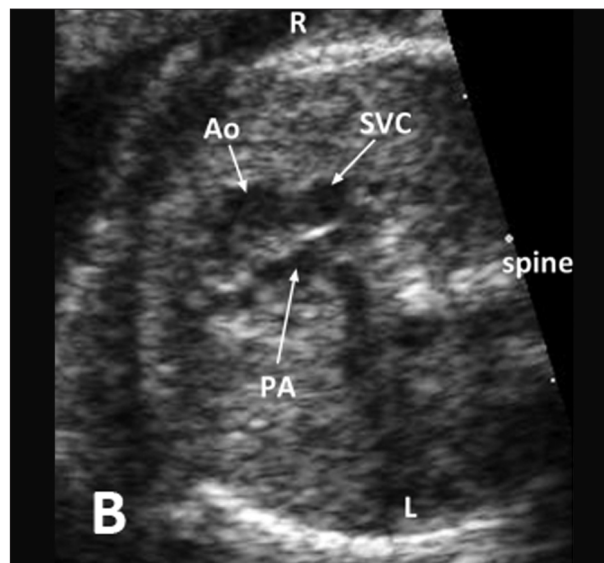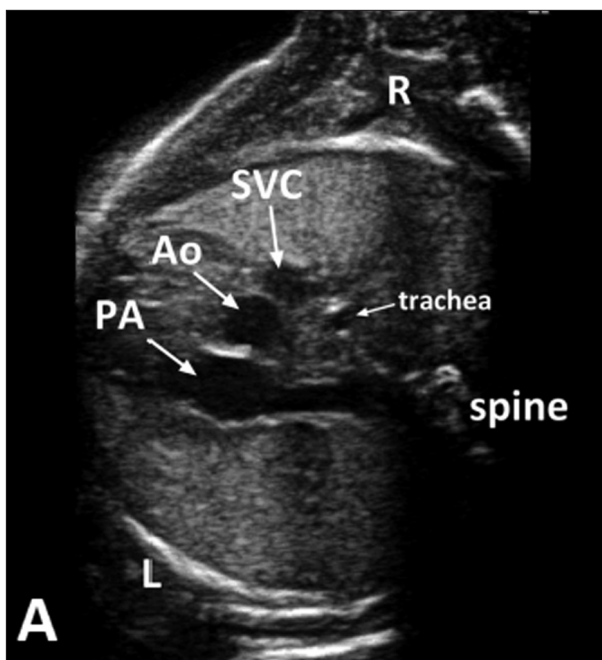
Results

Of the 26 cases of TAPVR diagnosed prenatally at our institution, anomalous connections were identified as supracardiac (type I) in 18 (69%), infradiaphragmatic (type III) in 7 (27%), and directly to the coronary sinus (type II) in 1. One case classified prenatally as supracardiac TAPVR had mixed (type IV) connections with infradiaphragmatic communications diagnosed on the postnatal scan (Table 1).

Figure 4. Normal (**A**) and abnormal (**B**) axial images of the abdomen. The normal relationship of the stomach (St) and descending aorta (DAo) are shown in **A** in contrast with the patient shown in **B**, with an additional vessel (asterisk) between the IVC and aorta in a case of TAPVR with a vertical vein descending to an infradiaphragmatic connection.
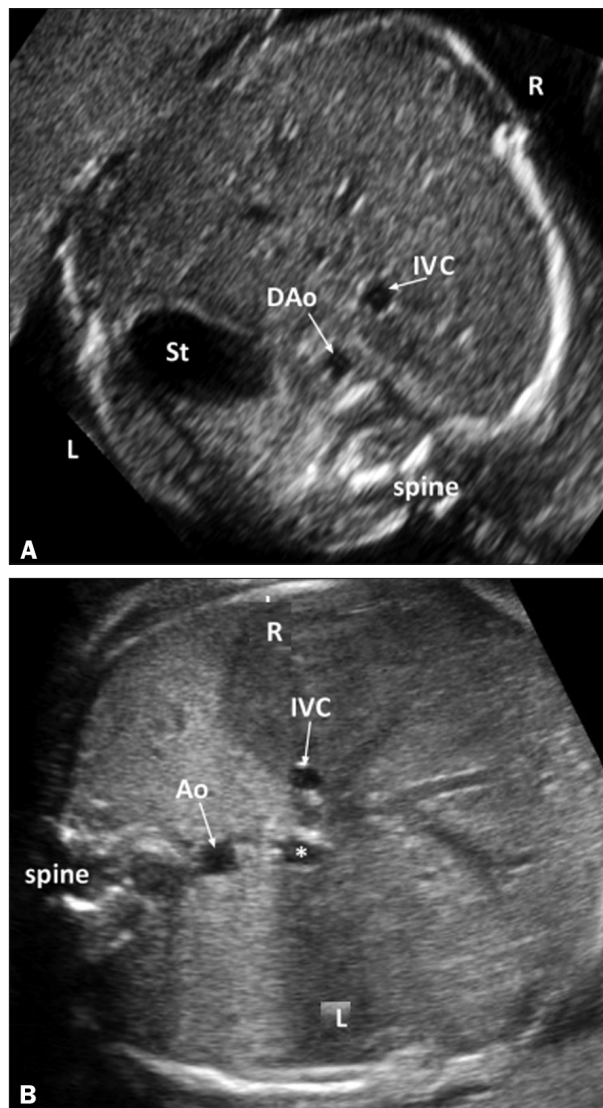
All other live-born neonates had postnatal confirmation of the prenatal diagnosis.

All TAPVR diagnoses were made at our initial echocardiographic evaluation, with no cases of TAPVR suspected before referral. The mean GA at diagnosis was 24.1 weeks (range, 18.0–34.1 weeks). The indications for fetal echocardiographic examinations were a suspected cardiac anomaly (n = 20), a family history of cardiac disease (n = 1), and an abnormal 4-chamber view on the obstetric anatomic survey (n = 5; Table 2). The TAPVR was isolated in 4 cases. One case had other cardiac anomalies, including mitral atresia, a double-outlet right ventricle, malposed great vessels, and a right aortic arch. Anomalous pulmonary veins were associated with visceroatrial heterotaxy in 21 cases: right atrial isomerism with asplenia (n = 18) and LA isomerism (n = 3). Two of the diagnosed cases were part of monozygotic twin gestations with a normal cotwin. Diagnosis was by fetal echocardiography without pathologic confirmation in 5 pregnancies, in which termination was chosen after the diagnosis of heterotaxy, and 1 was lost to follow-up.

Figure 5. Normal pulmonary venous waveforms obtained at the time of fetal echocardiography. The "s", "d," and "a" waves are labeled, corresponding to systolic, early diastolic, and atrial contraction phases of the cardiac cycle. The waveform is pulsatile and biphasic; triphasic waveforms (in which there is brief flow reversal during the "a" phase) are seen in approximately 10% of fetuses and are also normal. The bottom panel also shows simultaneous sampling of the accompanying pulmonary artery (arrow), showing the timing of the "s", "d," and "a" waves with the cardiac cycle better.
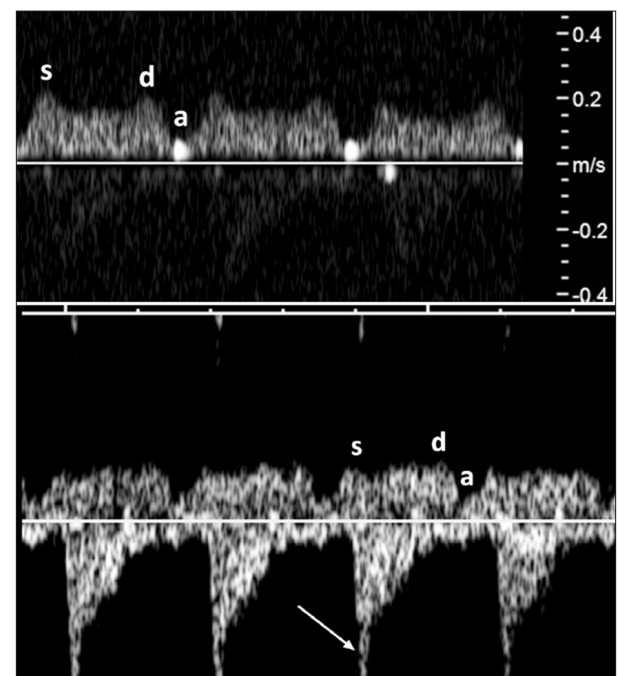
Review of our postnatal database disclosed only 1 case during the study period in which the diagnosis was missed prenatally: a case of heterotaxy and complex heart disease (a right-dominant atrioventricular septal defect and an anterior malposed aorta with pulmonary stenosis) in which the diagnosis of type III TAPVR was not appreciated on the fetal examination. The neonate was asymptomatic, and infradiaphragmatic pulmonary venous drainage was diagnosed incidentally during initial postnatal echocardiography. This patient was not included in the detailed prenatal echocardiographic analysis and scoring of venous waveforms because of a lack of appropriate images (no pulmonary venous Doppler analysis).

Sonographic Features

Our analysis consistently demonstrated that in TAPVR, the pulmonary veins seen in the 4-chamber view failed to connect to the atrium, and in nearly all cases, an abnormal vein behind the heart ("confluence") was shown (Table 2). Additional findings in some patients included a dilated right heart and other less consistent abnormalities, as follows.

Four-Chamber View

Consistent diagnostic signs were noted in this view, including lack of visualization of normal right and left pulmonary veins connecting to the LA (n = 26; Figure 1B). A smooth posterior LA surface and an abnormally wide space between the LA and the descending aorta accompanied absence of normal drainage (Figure 1C). The view also identified a tubular vascular confluence situated posterior to the atria and anterior to the descending aorta (n = 25; supracardiac, 18 [100%]; infradiaphragmatic, 7 [100%]). We describe this as a "twig" sign because of its similar appearance in most cases (Figure 2). Color mapping was not crucial but had aided in determining the flow velocity and direction within this channel. Velocity settings had always been adjusted for low venous flow and maintained at less than 25 cm/s. The one case of anomalous direct cardiac communications with a dilated coronary sinus failed to show a clear confluence on the archived images. Left atrial isomerism was confirmed in this case, with an interrupted IVC and a left SVC connecting to the dilated coronary sinus.

Figure 6. Abnormal pulmonary venous spectral Doppler waveforms obtained at the time of fetal echocardiography and the classification used in the retrospective review. A, Abnormal "s" and "d" appearance but a biphasic waveform with normal pulsatility (pseudonormal). B, Abnormal with a biphasic waveform but decreased pulsatility. C, Abnormal with a monophasic pulsatile pattern. D, Low-velocity monophasic and continuous.
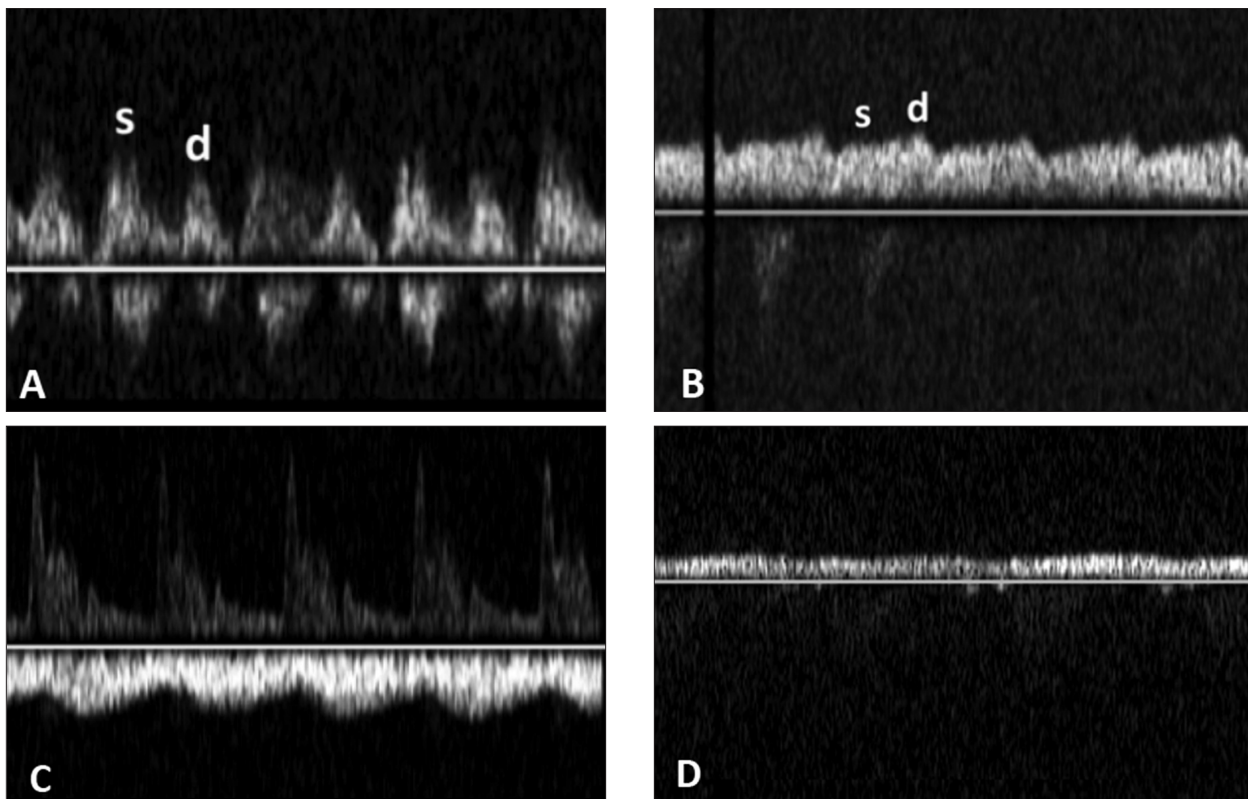
Table 1. Prenatal Diagnosis of TAPVR in 26 Cases, 2001–2012

Patient	GA, wk	Indication for Referral	Type of TAPVR	Site of TAPVR Connection	Other Anomalies on Prenatal Echocardiogram	Obstructed on Prenatal Examination	Postnatal Anatomy
1	34	Suspected cardiac anomaly	I	SVC	AVSD with TOF, severe PS, RAI	No	Confirmed
2	25	Suspected cardiac anomaly	I	SVC via innominate	Right dominant AVSD, DORV, PS, RAI	No	Confirmed
3	18.6	2nd opinion for cardiac anomaly	III	Hepatic veins	Tricuspid atresia, LAI	No	Confirmed
4	27	Abnormal 4-chamber view: asymmetry	I	SVC via innominate	Isolated	Yes	Confirmed
5	28	Suspected cardiac anomaly	I	SVC via innominate	MA/DORV, right aortic arch, PS	No	Confirmed
6	30.2	2nd opinion for cardiac anomaly	III	Ductus venosus	Right dominant AVSD, MGA, PS azygous to right SVC, RAI	No	Confirmed
7	27	Suspected cardiac anomaly	I	Left SVC	Right dominant AVSD, MGV, RAI	Yes	Confirmed
8	20.4	2nd opinion for cardiac anomaly	III	Hepatic and portal veins	Single-ventricle AVSD, MGV, PS left SVC directly to LA, RAI	Yes	Confirmed
9	29.4	2nd opinion for cardiac anomaly	I	SVC	AVSD, L-looped vent, MGV, PA, RAI	Yes	Confirmed
10	18.6	Suspected cardiac anomaly	I	Left SVC	Common AVSD, MGV, PA, RAI	Yes	TOP
11	19.2	Family history of congenital heart disease	I	SVC	Isolated	No	Confirmed
12	21.4	Abnormal 4-chamber view: axis deviation	I	SVC	Isolated	No	Confirmed
13	21.4	2nd opinion for cardiac anomaly	III	Portal and hepatic veins	AVSD, MGV, DORV, PS, RA	Yes	TOP
14	18	Abnormal 4-chamber view: asymmetry	III	Hepatic or portal veins	Isolated	Yes	Confirmed
15	20.3	2nd opinion for cardiac anomaly	I	SVC	Left dominant AVSD, PS, RAI	Yes	Confirmed
16	20	Suspected cardiac anomaly	I	Left SVC	AVSD, MGV, bilateral SVC, RAI	No	Lost to follow-up
17	21.5	Suspected cardiac anomaly	I	SVC	Uncommitted VSD, MGV, PA, RAI	No	Confirmed
18	26.4	2nd opinion for cardiac anomaly	I	SVC via innominate	Common AVSD, MGV, PA, right aortic arch, bilateral SVC, RAI	No	Confirmed
19	29	Suspected cardiac anomaly	I	SVC	AVSD, L-TGA, DORV, RAI	No	Confirmed
20	23	Suspected cardiac anomaly	I	SVC	AVSD, DORV, MGV, large ASD, bilateral SVC, RAI	No	Type IV (mixed TAPVR)
21	30.5	Suspected cardiac anomaly	I	SVC	AVSD, bilateral SVC, IVC to LA, RAI	Yes	Confirmed
22	25	Suspected cardiac anomaly	III	Portal vein	AVSD left dominant, TGA, PS, RAI	No	TOP
23	27	Abnormal 4-chamber view	II	Left SVC to coronary sinus	Right stomach/spleen, ASD, interrupted IVC, LAI	No	Confirmed
24	21	Abnormal 4-chamber view: asymmetry	I	SVC	AVSD, RAI	Yes	TOP
25	21	Suspected cardiac anomaly	I	SVC	Right dominant AVSD, DORV, RAI	No	TOP
26	30.4	Suspected cardiac anomaly	III	IVC	Absent right lung, otherwise isolated	No	Confirmed

ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; DORV, double-outlet right ventricle; LAI, left atrial isomerism (polysplenia); MA, mitral atresia; MGA, malposed great arteries; MGV, malposed great arteries; PA, pulmonary atresia; PS, pulmonary stenosis; RAI, right atrial isomerism (asplenia); TGA, transposition of the great arteries; TOF, tetralogy of Fallot; and TOP, termination of pregnancy.

A sign of lesser note on the 4-chamber view was left-to-right ventricular chamber asymmetry. Although 3 of our referrals were for detection of this sign (right ventricle > left ventricle) on outside obstetric scans (mean GA, 19.3 weeks; range, 18.0–20.2 weeks), we found that a chamber size discrepancy was not a consistent feature until approximately 28 weeks, and as such, it did not prove to be a reliable marker within the early setting of a standard second-trimester obstetric screening examination.

Three-Vessel View
This view showed the presence of an additional cross-sectional vascular channel apart from the normal SVC, aorta, and pulmonary artery, which indicated the possibility of a vertical vein in cross section in several cases with abnormal supracardiac connections (n = 6). The retrospective image review also revealed relative prominence of the SVC, in that it was either as large as or larger than the

aorta (as opposed to the usual relationship, in which the SVC is smaller than the aorta), in 12 of the 18 supracardiac cases (67%; Figure 3, B and C, and Table 2).

Abdominal Views
The descending vertical veins in infradiaphragmatic abnormal pulmonary venous connections were seen passing through the esophageal hiatus as an additional venous channel between the aorta and IVC in all cases with infradiaphragmatic TAPVR (n = 7; Figure 4B). Spectral and color Doppler imaging contributed to identifying the flow direction and morphologic characteristics of the vertical veins.

Sagittal Views or "Ductal and Aortic Arches"
Longitudinal or sagittal views identifying "vertical" venous connections were similar to the sectioning used to obtain the cardiac arches, often beginning as a sagittal sweep and

Table 2. Prenatal Sonographic Signs in Fetuses With a Diagnosis of TAPVR

Patient	GA, wk	Type of TAPVR	4-Chamber Asymmetry	Absent PV-LA Connection	Confluence Behind Atrium	3VV: Additional Vessel	3VV: Prominent SVC	PV Waveform[a]
1	34	I	No	Yes	Yes	Yes	Yes	2
2	25	I	No	Yes	Yes	Yes	Yes	2
3	18.6	III	No	Yes	Yes	No	No	3
4	27	I	No	Yes	Yes	Yes	Yes	4
5	28	I	Yes	Yes	Yes	Yes	Yes	3
6	30.2	III	No	Yes	Yes	No	No	2
7	27	I	No	Yes	Yes	No	Yes	4
8	20.4	III	No	Yes	Yes	No	No	3
9	29.4	I	Yes	Yes	Yes	Yes	Yes	3
10	18.6	I	Yes	Yes	Yes	No	No	4
11	19.2	I	No	Yes	Yes	No	Yes	2
12	21.4	I	No	Yes	Yes	No	Yes	3
13	21.4	III	No	Yes	Yes	No	No	3
14	18	III	Yes	Yes	Yes	No	No	4
15	20.3	I	No	Yes	Yes	No	Yes	2
16	20	I	No	Yes	Yes	No	No	2
17	21.5	I	No	Yes	Yes	No	No	2
18	26.4	I	No	Yes	Yes	No	Yes	1
19	29	I	No	Yes	Yes	No	Yes	2
20	23	I	No	Yes	Yes	No	Yes	2
21	30.5	I	No	Yes	Yes	Yes	Yes	2
22	25	III	No	Yes	Yes	No	No	3
23	27	II	No	Yes	No	No	No	Normal
24	21	I	No	Yes	Yes	No	No	4
25	21	I	Yes	Yes	Yes	No	No	1
26	30.4	III	No	Yes	Yes	No	No	3
Total abnormal, n (%)			5/26 (19)	26/26 (100)	25/26 (96)	6/26 (23)	13/26 (50)	25/26 (96)

PV indicates pulmonary vein; and 3VV, 3-vessel view.
[a]Classified as follows: 1, abnormal "s" and "d" appearance but biphasic with normal pulsatility (pseudonormal); 2, abnormal with a biphasic waveform but decreased pulsatility; 3, abnormal with a monophasic pulsatile pattern; and 4, low-velocity monophasic and continuous.

inclining into a parasagittal plane (supracardiac, 18 [100%]; infradiaphragmatic, 7 [100%]). Extension of the sagittal cut below the diaphragm with application of color Doppler imaging revealed alternate venous channels through the portal and hepatic connections to the IVC in all 7 patients with infradiaphragmatic drainage (Figure 7).

Abnormal Spectral (Pulsed Wave) Doppler Waveform Profile in Anomalous Pulmonary Veins
Twenty-five fetuses had scorable pulmonary venous Doppler images available for review. Four distinct abnormal patterns in the pulmonary venous waveforms, all recog-

nizably different from normal, were observed (Figure 6): (1) pseudonormal, biphasic or triphasic and pulsatile but with an abnormal appearance, seen only in supracardiac connections directly to the SVC (n = 2; Figure 6A); (2) biphasic with decreased pulsatility, seen typically in supracardiac connections (n = 9) but also in 1 case of infradiaphragmatic TAPVR (Figure 6B); (3) monophasic but pulsatile, seen in most cases of infradiaphragmatic connections (n = 5) and in 3 cases of supracardiac connections (Figure 6C); and (4) monophasic and nonpulsatile, seen in both infradiaphragmatic (1) and supracardiac (4) connections in the presence of severe obstruction of the vertical vein (all 3 live-born

Figure 7. Sagittal imaging (although not part of a routine second-trimester sonographic examination) shows normal systemic venous anatomy (**A**) and the course of typical vertical veins (draining the confluence to the systemic circulation) in type I (**B**) and type III (**C** and **D**) TAPVR. **A**, Normal bicaval view. **B**, Ascending vertical vein in a sagittal ductal arch view. **C** and **D**, Descending vertical vein connecting to the portal venous system. St indicates stomach; and vv, vertical vein.
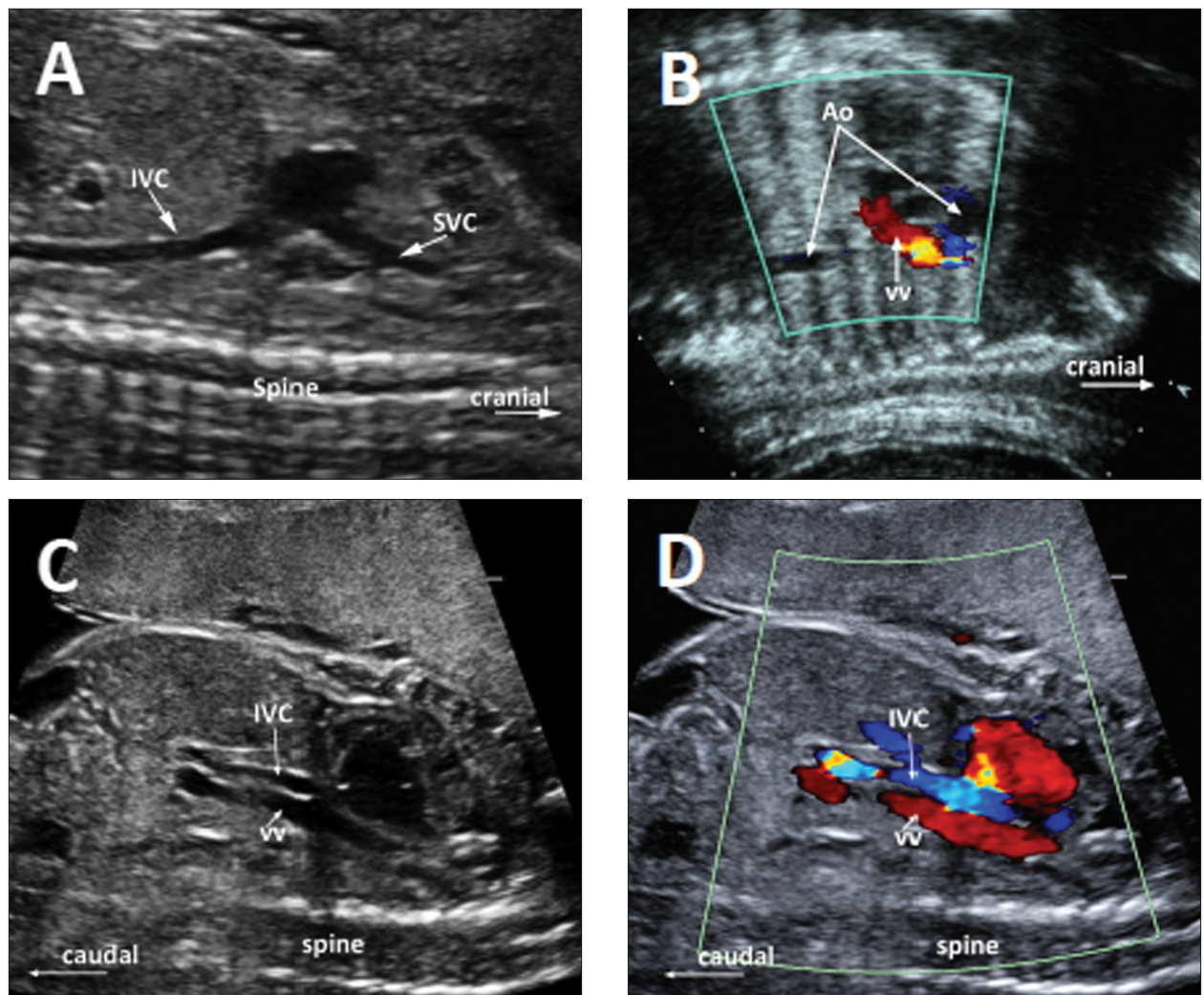
neonates with this pattern underwent emergency surgery at birth for symptomatic obstruction; Figure 6D). The waveform classification was independently repeated by a second blinded author with very good agreement (weighted κ = 0.92; 95% confidence interval, 0.73–1.04).

In addition, spectral Doppler interrogation of the ascending or descending vertical vein was often done at the suspected site of obstruction and showed a continuous high-velocity flow signal (n = 8; supracardiac, 5; infradiaphragmatic, 3), which correlated with severe symptomatic obstruction at birth in only 3 neonates (2 supracardiac and 1 infradiaphragmatic, requiring immediate surgery post-

natally to relieve the obstruction). The junction of the vertical vein to the SVC or IVC was the usual site of obstruction. Flow obstruction was identified as high-velocity turbulence at the site of obstruction (peak velocity, >0.5 m/s).

Postnatal Correlation
Prenatal diagnoses were confirmed by postnatal echocardiography in 20 patients with successful surgical correction. No postnatal autopsy details could be obtained for the 5 pregnancies that underwent termination. One patient was lost to follow-up later in the pregnancy.

Figure 8. Flowchart for assessment of TAPVR within a second-trimester obstetric screening or anatomy scan. This algorithm can be applied to a fetus with no other cardiac structural anomalies or can be modified in cases with additional structural disease in which the 4-chamber view is abnormal. The use of pulsed wave (PW) Doppler imaging for confirmation is then emphasized as a component of fetal echocardiography, performed after the screening examination discloses suspicion of an abnormality.
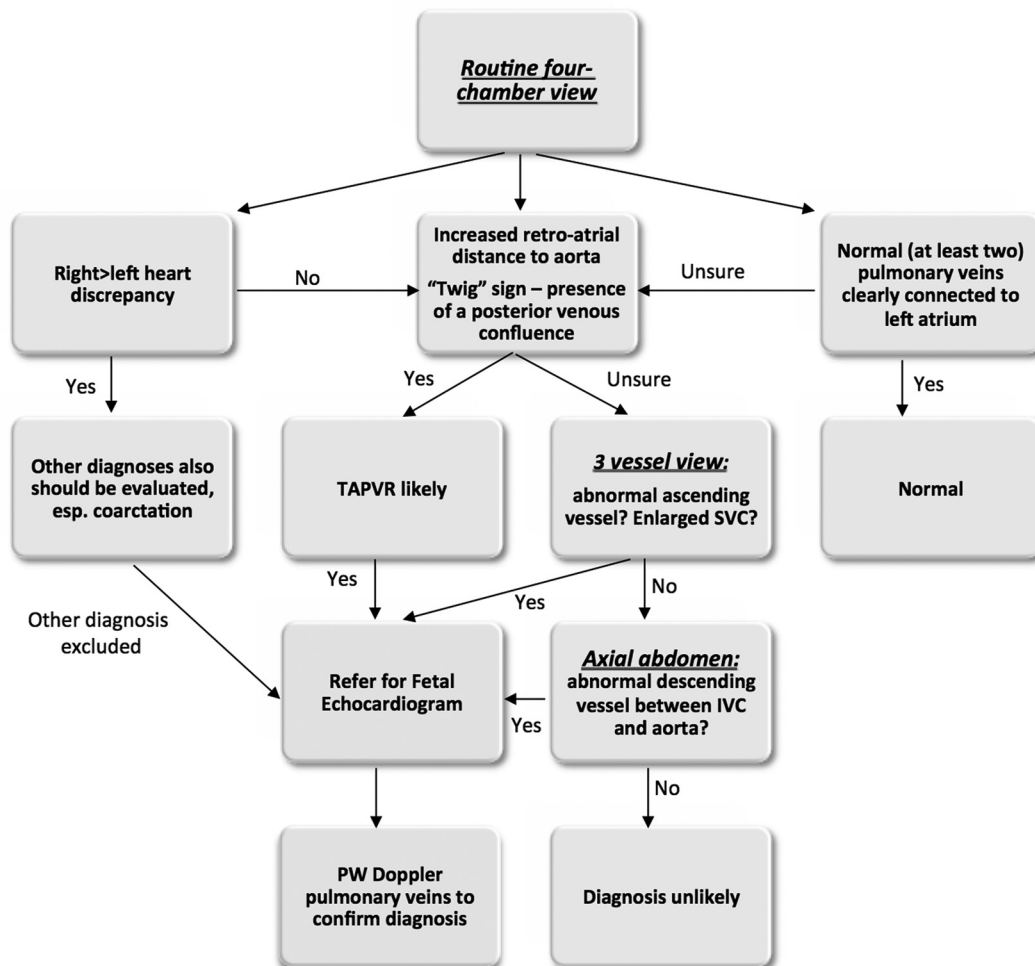
Discussion

Our study suggests that a systematic approach and attention to certain specific features may substantially increase the detection rate of TAPVR in the fetal population (Figure 8). We were able to demonstrate, in a large cohort of fetuses, several consistent sonographic features that were seen in association with TAPVR of all types and irrespective of the presence or absence of other cardiac abnormalities. These features included abnormalities visible on standard axial images that would be expected to be obtained on a routine second- or third-trimester obstetric sonographic examination of a fetus that includes an anatomic survey[22] and screening examination of the fetal heart,[21] including the 4-chamber cardiac view (absence of entry of the veins to the LA on 2D imaging and color Doppler interrogation at a low Nyquist limit, the retroatrial structure twig sign, and increased retrocardiac space), the 3-vessel view (enlarged SVC and extra vessel), and axial abdominal images (descending vein). The addition of pulsed wave Doppler interrogation of a pulmonary vein from the 4-chamber view at the time of fetal echocardiography was also diagnostic in nearly all cases and can even be suggestive of the TAPVR type based on abnormal Doppler patterns.

Prenatal diagnosis of TAPVR has been the subject of very few large studies and traditionally is considered very challenging for an obstetric sonographer or sonologist. It is rarely detected in the fetus on second-trimester obstetric screening because of its low incidence and difficulty in obtaining detailed images.[7] Over the last decade, refinements in sonographic technology and cumulative operator experience have helped improve that somewhat. In 2003, Valsangiacomo et al[17] published a retrospective analysis of 16 cases of prenatally diagnosed TAPVR and partial APVR. More recently, Patel et al[28] reviewed their cohort of 13 patients with a prenatal diagnosis of TAPVR over a 13-year period. The 2 most recent larger series were published by Seale et al[8] from the United Kingdom in 2012 and Laux et al[14] from France in 2013. The former was a multicenter retrospective study reviewing 8 cases of prenatally diagnosed TAPVR, and the latter had 10 cases. Our retrospective review adds to this literature and further demonstrates that reliable 2D signs can be assessed on basic views that would have been obtained at second- or third-trimester obstetric sonography incorporating a screening anatomic scan. Absence of the pulmonary venous connections into the atrium, the posterior venous confluence in the retroatrial area, chamber asymmetry, a prominent SVC, and vertical veins are valuable pointers to the diagnosis.

Additional confirmation was provided at fetal echocardiography by unique spectral Doppler signals, which differ substantially from the normal Doppler waveform expected in the fetal pulmonary veins. In fact, the single missed case during the period under study lacked the Doppler information, but on retrospective review, the 2D signs on the axial 4-chamber views stored were present; had the road map criteria been applied and pulsed Doppler imaging used to confirm suspicions, it is unlikely that the error would have occurred.

Routine obstetric sonographic screening is performed between 18 and 20 weeks and includes assessment of the 4 chambers, outflows, and in some settings the 3-vessel view on 2D views. In a healthy fetus, the axial 4-chamber view shows 2 similarly sized ventricles and at least 2 (1 right and 1 left) pulmonary veins entering the LA. A persistent inability to show normal venous connections on the 4-chamber view may provide the first clue to suspecting this anomaly. A smooth posterior LA surface has also been suggested as a verification of the lack of normal venous connections in cases of TAPVR regardless of the site of abnormal connections.[15] The critical diagnosis of total anomalous pulmonary veins can be excluded if even 1 of the 4 veins connects normally to the LA on 2D imaging in this view. Although not routine practice in the setting of obstetric screening, we also suggest that the addition of color Doppler imaging with appropriate settings to detect low-velocity flow may be a useful adjunct, especially when cases are unclear. An abnormally wide space between the LA and the descending aorta, usually with a visible tubular vascular structure in this position (corresponding to a pulmonary venous confluence) on the 4-chamber view, should also raise the possibility of a venous confluence in anomalous pulmonary venous connections.[17,28] We describe this as the presence of a twig sign on the 4-chamber axial view.

In our series, a right heart-versus-left heart discrepancy was not a consistent finding, although it was present in some of the fetuses. Fetal hemodynamics allow for a proportion of the combined ventricular output to pass through the lungs. The blood returns back to the heart through the pulmonary veins into the LA, accounting for less than half of the left ventricular outflow. In abnormally connected pulmonary veins, this volume returning from the lungs passes through the right heart instead, and it has been hypothesized that this abnormal connection may be evidenced by a right-to-left chamber discrepancy on the 4-chamber view. However the mid second trimester has only about 15% of the combined ventricular output passing through the lungs,[29,30] although this proportion increases

to about 25% to 35% of the cardiac output in the third trimester. The small amount of flow return from the lungs early in gestation, with a flow increase only in later gestation, can be a possible reason for inconsistent evidence of a chamber discrepancy before 28 weeks.[1,8]

Our findings suggest that the 3-vessel view is not a crucial contributor to the diagnosis of TAPVR as much as axial 4-chamber views; however, we encountered some cases in which the 3-vessel view information did provide valuable adjunctive markers. The ascending connecting vessel or "vertical vein," joining the confluence of the anomalous veins to the systemic venous circulation (either right or left SVC or innominate vein) in supracardiac TAPVR, in cross section as a fourth vessel in addition to the pulmonary artery, aorta, and SVC, and an increase in the relative size of the SVC in relation to the aorta may help suggest supracardiac or type I anomalous drainage. When additional vessels were identified on the 3-vessel view, simple (although nonstandard in obstetric screening) techniques such as changing the imaging axis to a longitudinal view may be more likely to confirm and map the course of vertical veins.

Imaging the pulmonary veins using 2D and color Doppler sonography is a recognized part of the fetal echocardiogram.[18–20] However, fetal assessment using 2D and color Doppler imaging sections alone may not allow a conclusive diagnosis of TAPVR. Identifying absent normal pulmonary vein connections, a posterior venous confluence, a chamber discrepancy, or 3-vessel view inconsistencies can be subject to GA, fetal position, maternal bodily habitus, as well as the available equipment. Ambiguity in 2D and color Doppler imaging despite care to decrease the Nyquist limit to a low value capable of detecting the low flow velocities present in the veins can be overcome by identification of the site-specific spectral waveform abnormalities seen in TAPVR. Normal pulmonary venous connections have fairly predictable and uniform-appearing spectral waveforms.[10,25,31] A normal pulmonary venous signal indicates pulsatile flow from the pulmonary vein toward the LA through all the cardiac cycles with biphasic peaks in systole and diastole. There is an initial peak followed by continuous flow during ventricular systole, which corresponds to the atrial filling phase and represented as a recognizable "s." This peak is followed by another peak in early diastole due to atrial emptying across the mitral valve and is seen as a "d." After this peak, there is a period of reduced, no, or negative flow during the atrial contraction "a" phase.[10,31,32] Pulsed Doppler waveforms, then, in normal connections are fairly predictable and uniform in their appearance; the use of pulsed Doppler imaging was very helpful in our cases in raising suspicion or confirming the absence of normal connections, and it can be used at the time of fetal echocardiography for definitive assessment in fetuses with suspected TAPVR on screening cardiac examinations. In abnormally connected veins, unique Doppler waveform patterns likely reflect pathophysiologic alterations due to the lack of LA influences, and may possibly be further affected by resistance to flow within the abnormal pulmonary veins and confluence/vertical vein to connect to the systemic veins, which may be of varying length.

Our findings suggest that abnormal supracardiac connecting waveforms typically retain their triphasicity or biphasicity, showing either an exaggerated pseudonormal waveform or, much more commonly, a damped variation between the "s" and "d" peaks and a lack of a distinct "a" wave phase to the waveform. Infradiaphragmatic connections uniformly showed low velocity and a pulsatile monophasic pattern, and more severely obstructed veins showed a nonpulsatile monophasic pattern similar to that of the umbilical vein. This particular finding, although present only in a small subset of our patients, may be very important prognostically, given that neonates with obstructed veins do especially poorly and require urgent surgery soon after birth.

There were several limitations to our study. Our report is limited in that genetic information was not available for most of the patients. A limitation of any retrospective cohort analysis is that the data are subject to the views and quality of images archived. Our patient population is high risk in a tertiary fetal cardiac referral center, which admittedly provides more operator expertise in this area for a better diagnostic yield than low-risk obstetric scanning centers. Our referral population and operator expertise could be considered somewhat biased toward identifying complex cardiac anomalies such as TAPVR; nonetheless, we believe that this study demonstrates that, with a careful approach to assessment of standard cardiac views, it is indeed possible to determine pulmonary venous connections and to suspect an abnormality within a standard obstetric examination. We excluded patients who did not have a fetal echocardiogram at our institution (the number of missed cases in our region would have undoubtedly been higher than 1 of 27), but it was not our intention to provide a population-based analysis of positive and negative predictive markers but, rather, to specifically evaluate a sample that was enriched for disease with an application of systematic approach to prenatal imaging.

Furthermore, along the same lines, because our primary objective of this descriptive study was to identify and compile reproducible sonographic signs of this anomaly and not to provide numeric predictive values, we did not

apply the diagnostic criteria to a control group; we did not think that process would have been a useful exercise given that, by definition, these sonographic findings would be absent in a normal population. Granted, the most common diagnosis overall reported in our study was heterotaxy (right or left atrial isomerism), which may have extracardiac findings on an anatomy scan that would likely be the first to be noted when examining patients, leading the examiner to think that TAPVR should be considered as a working diagnosis and that the examiner should then apply the other 2D, color flow map, and spectral Doppler analytic methods described to refine the diagnosis. Nonetheless, the effectiveness of the same cardiac views as used in any routine obstetric sonographic examination and the ease and consistency of pointers/abnormalities in those views suggest that it is possible to suspect TAPVR even within a routine obstetric scanning environment, as was the case in our 4 isolated cases. Future efforts to incorporate specific attention to these clues during routine scanning should be made through education and possibly prospective studies in a population-based screening cohort.

In conclusion, the diagnosis of TAPVR remains one of the most challenging in the prenatal period. This study suggests that the frequency of diagnosis of TAPVR may be increased by the systematic application of the specific 2D signs described and visible in views that are part of standard second-trimester screening sonography. At obstetric screening, particular attention should be paid to ensuring normal pulmonary venous connections in the axial 4-chamber view; if normal anatomy cannot be confirmed, or if an abnormality is suspected, the importance of including spectral (pulsed wave) Doppler assessments in conjunction with 2D grayscale imaging at the time of referral for fetal echocardiography is emphasized and in our study was associated with a very high detection rate for this abnormality, as confirmed postnatally. Suspecting this condition in the second-trimester obstetric screening setting may lead to a timelier referral and allow delivery planning at specialized centers equipped to address the cardiovascular implications with this diagnosis in the newborn period.

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