"Y Sign" at the Level of the 3-Vessel and Trachea View

An Effective Fetal Marker of Aortic Dextroposition Anomalies in the First Trimester

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Objectives—The "Y sign" at the level of the 3-vessel and trachea view corresponds to thinning of main pulmonary artery and arterial duct and a dilated transverse aortic arch. The purpose of this study was to evaluate the Y sign for the diagnosis of aortic dextroposition anomalies at the time of the first-trimester scan and to assess the screening performance of only the Y sign, only abnormal left axis deviation (axis sign), and their combination for the diagnosis of aortic dextroposition anomalies.

Methods—A prospective evaluation of 6025 pregnant women undergoing first-trimester ultrasonography was conducted. The cardiac axis was measured in all examined patients and considered abnormal (positive axis sign) at greater than 57°. The frequency of the Y sign and the axis sign was assessed for this population, and their screening performance for the diagnosis of aortic dextroposition anomalies was calculated.

Results—A total of 5775 patients fulfilled the inclusion criteria. Aortic dextroposition anomalies were diagnosed in 17 cases (tetralogy of Fallot in 8 and Fallot-like double-outlet right ventricle in 9). The Y sign was found in 18 of 5775 (0.3%) fetuses examined, of which 7 of 18 were confirmed with tetralogy of Fallot, 9 of 18 with a Fallot-like double-outlet right ventricle, and 2 of 18 with pulmonary stenosis. A positive axis sign of greater than 57° was found in 20 fetuses, including 4 with normal heart anatomy. The sensitivity values of the Y sign, the axis sign, and their combination were 94%, 76%, and 94%, respectively.

Conclusions—Visualization of the Y sign should increase the suspicion of aortic dextroposition anomalies in the late first trimester. The screening performance of the Y sign alone and in combination with an abnormal cardiac axis was high and may aid in the early diagnosis of aortic dextroposition anomalies in the fetus.

Key Words—double-outlet right ventricle; early fetal echocardiography; first-trimester ultrasonography; obstetrics; prenatal ultrasonography; tetralogy of Fallot

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Abbreviations

CHD, congenital heart defect; US, ultrasonography

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Despite technological advances in ultrasound technology and international efforts to spread the use of prenatal ultrasonography (US) for congenital heart defects (CHDs), recent data have shown unsatisfactory overall prenatal detection rates for this group of anomalies, at the level of 34%.[1] Low detection rates were mainly observed in conotruncal anomalies: tetralogy of Fallot showed a detection rate of 27%; D-transposition of the great arteries,

28%; double-outlet right ventricle, 44%; and common arterial trunk, 41% in North American data from registries collected between 2006 and 2012 in the United States.[1] This group of defects is especially important from the clinical point of view because of the high prevalence of ductal-dependent cases resulting from severe infundibular pulmonary stenosis. For a number of years, we have put stress on early identification of fetuses suspected of having CHDs.[2] On the basis of safety evaluation studies of early cardiac assessment with the use of color Doppler US, we apply this technique with low thermal index values not exceeding 0.5.[3]

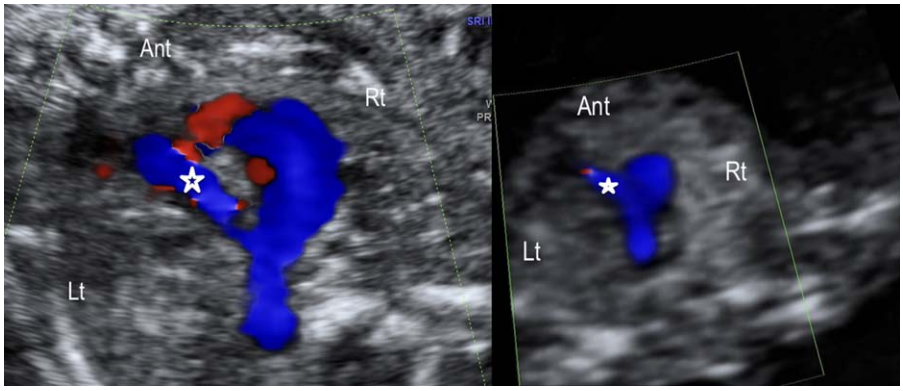
In this article, we focus on aortic dextroposition anomalies, which are potentially caused by infundibular underdevelopment.[4,5] Aortic dextroposition anomalies include tetralogy of Fallot, Fallot-like double-outlet right ventricle, and Eisenmenger complex. The first two are characterized by a narrowing of the right ventricular outflow tract and consequent thinning of a main pulmonary artery and an arterial duct. These features of the infundibular pulmonary stenosis reflect US findings at the level of the 3-vessel and trachea view even at the time of the early cardiac scan in the form of size dominance of the aortic arch over the ductal arch. On the other hand, the normal 3-vessel and trachea view on color mapping reveals the prominent pulmonary arm over the aortic arm.[2] We described this difference between patterns 1 and 3 for 3-vessel and trachea view in our previous study.[2] Whenever main pulmonary artery pattern 3 is observed, the examiner may even conclude that the arterial duct does not join the descending aorta at the level of the aortic isthmus. Therefore, in aortic dextroposition anomalies, instead of the typical "V sign," a shape resembling the letter Y is observed ("Y sign" or main pulmonary artery pattern 3). The shorter arm of the Y sign represents the small main pulmonary artery and arterial duct, whereas the larger arm corresponds to the enlarged and dilated transverse aortic arch (Figure 1).

To date, the available literature has referred to only the first-trimester diagnosis of the above-mentioned anomalies using cardiac axis measurements.[6] Taking the above into account, we planned a prospective study aimed at first-trimester screening for aortic dextroposition anomalies based on color mapping patterns of the main pulmonary artery. The first aim was to evaluate the clinical usefulness of the Y sign as a potential marker of aortic dextroposition anomalies at the time of the first-trimester scans. Our second goal was to assess the aortic dextroposition anomaly screening performance of 3-vessel and trache view pattern 3, abnormal left axis deviation (axis sign), and their combination.

Materials and Methods

This work was a prospective study performed on a population of women referred for a first-trimester screening examination between January 2012 and January 2016. The patients were referred from cooperating physicians and examined at the Ultrasound Laboratory of the Department of Gynecology and Obstetrics of Jagiellonian University. Most referrals were low-risk patients (4049), and because of the tertiary center setting, an important group of high-risk patients (1976) was

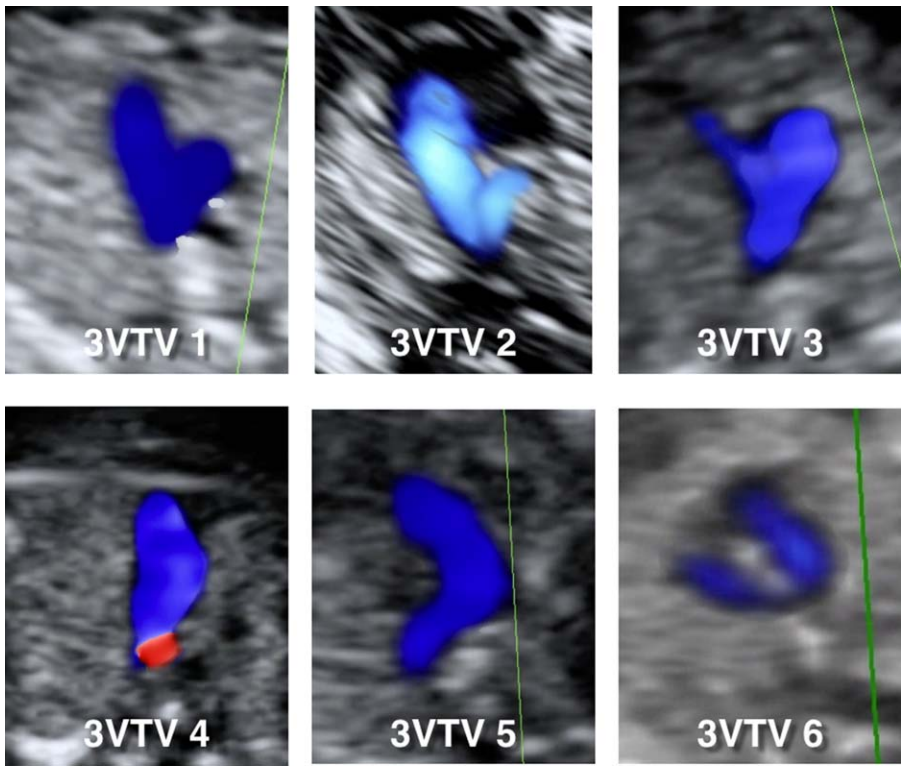
Figure 1. Patten 3 of the 3-vessel and trachea view (Y sign) identified in a case of tetralogy of Fallot in the second trimester (left) and the first trimester (right). Thinning of the main pulmonary artery (stars) and arterial duct in relation to the aortic arm is clearly shown in both images. Ant indicates anterior; Lt, left; and Rt, right.



enrolled in this study as well. Among the high-risk patients, referrals for maternal age older than 35 years (966) and suspicious US findings on initial scans performed by nonqualified obstetricians who were not trained for first-trimester screening (1010) were included. The following inclusion criteria were used in this study: singleton pregnancy and a crown-rump length measurement of 45 to 84 mm. Multiple pregnancies, combined anomalies, patients lost to follow-up, with unknown pregnancy outcomes, or pregnancy terminations, and fetuses with other than a biventricular inflow pattern on the 4-chamber view on color mapping 3-vessel and trachea view pattern 4 or 5 (single vertical or convex arterial arm observed at the level of 3-vessel and trachea view on color mapping; Figure 2) were excluded from the study.[2]

The local Ethics Committee approved the study protocol, and all patients provided oral consent for the use of the images for clinical studies. All patients underwent a detailed US scan performed transabdominally by 4 physicians, who are tertiary center certified examiners (M.P., M.W., A.N., and A.K.) with 5 years of experience in early fetal echocardiography and early anomaly scanning, using a Voluson E6 US system (GE Healthcare, Zipf, Austria) or a WS80 system (Samsung Medison, Seoul, Korea). Transvaginal US (5–9 MHz) was used only if required to complete the scan. The scan protocol consisted of an evaluation of early fetal anatomy (continuity of the calvarium, division of cerebral hemispheres, presence of orbits, continuity of the secondary palate in the axial view, relationships of thoracic organs, position of the stomach in the abdominal cavity, abdominal wall continuity, presence and size of the urinary bladder, number of umbilical arteries, and upper and lower limbs) and markers of chromosomal aberrations according to Fetal Medicine Foundation guidelines. Briefly, they included measurement of nuchal translucency and evaluation of secondary markers for the presence of the nasal bone, tricuspid regurgitation, and flow in the ductus venosus. Next, an early simplified fetal echocardiographic examination was performed, consisting of the following parameters: visceral situs, measurement of the

Figure 2. Classification of the most common patterns at the level of 3-vessel and trachea view in color mapping observed at the time of a nuchal scan by Wiechec et al.[2] 3VTV 1 indicates the normal arrangement of great arteries; 3VTV 2, aortic coarctation; 3VTV 3, infundibular pulmonary stenosis; 3VTV 4, hypoplastic left heart syndrome; 3VTV 5, D-transposition of the great arteries; and 3VTV 6, right aortic arch with left ductal arch.



cardiac axis, 4-chamber view, and 3-vessel and trachea view on B-mode US with color Doppler mapping.[2] Bidirectional power Doppler US was not used in this study because of the application of color Doppler settings optimized by us, mainly in terms of persistence, color balance, line density, line filtering, and better productivity during fetal movements. At the levels of the 4-chamber view and main pulmonary artery, patterns described in our previous study were assigned to each patient.[2] All images were acquired in a standardized position so that the fetal spine was visualized at the 6- or 12-o'clock position to avoid oblique sections with an insonation angle to the interventricular septum of approximately 45°.[7] The cardiac axis was measured according to the traditional method. A normal cardiac axis was defined as 45° ± 10°.[6,8–12] A cardiac axis exceeding 57° was considered abnormal and defined as a positive "axis sign."[6] The positive Y sign was equal to main pulmonary artery pattern 3 (Figure 3).[2]

The color Doppler application was used under the ALARA (as low as reasonably achievable) principle to limit the time of exposure of the fetus.[13,14] All patients included in the study were subsequently examined in the second trimester for cardiac and extracardiac anomalies. Early suspicions of CHD were compared with the postnatal evaluation or with necropsy findings. Karyotyping was offered to all patients with an identified CHD in the fetus together with an analysis for microdeletion 22q11 if indicated.

The data were stored in research databases, and a standard statistical analysis was performed with SPSS version 14.0 software (IBM Corporation, Armonk, NY). Screening performance was evaluated by the detection rate, false-positive rate, screening accuracy, positive predictive value, and negative predictive value.

Results

A consecutive series of 6025 fetuses were examined during the 4-year study period; 97.9% of scans were performed transabdominally, and 2.1% of cases required a transvaginal approach. Of those patients, 251 were excluded for loss to follow-up (221), multiple anomalies/chromosomal aberrations (19), a univentricular inflow pattern (6), and main pulmonary artery pattern 5 (5) detected in the fetus. After exclusion of patients lost to follow-up, the prevalence of CHDs in the study population was 0.69%. Finally, 5775 women were included in the analysis. The median maternal age was 30 years (range, 16–42 years); the median crown-rump length was 62 mm (range, 45–84 mm); and the median body mass index was 23 kg/m^2 (range, 18–34 kg/m^2. Amniocentesis was performed in 405 (7%) cases with positive first-trimester screening results or anomaly findings. The first-trimester prenatal detection rate for CHDs in the analyzed group was 89.7%, including abnormal cases, which were excluded from the analysis. Three patients affected by a trabecular ventricular septal defect and 1 case of a total anomalous pulmonary venous return were not identified either at the early scan or at the second-trimester scan. All cases diagnosed with CHDs during the study period are listed in Table 1.

The prevalence rates for the Y sign and an abnormal cardiac axis in the total population and by the type of anomaly are summarized in Table 2. Overall, the Y sign was found in 18 of 5775 (0.3%) fetuses examined, of which 7 of 18 were fetuses with classic tetralogy of Fallot; 9 of 18 were fetuses with a Fallot-like double-outlet right ventricle; and 2 of 18 were fetuses with pulmonary stenosis. The Y sign was not observed in any of the 5750 fetuses who had normal early basic cardiac scan

Figure 3. Three-vessel and trachea view with color mapping showing a normal V sign (left), a Y sign with a hardly visible pulmonary arm (center), and a Y sign showing a dominance of the aortic arm and an abnormal connection of the arms that is unevenly convergent (right). AoA indicates ascending aorta; Lt, left; MPA, main pulmonary artery; and Rt, right.

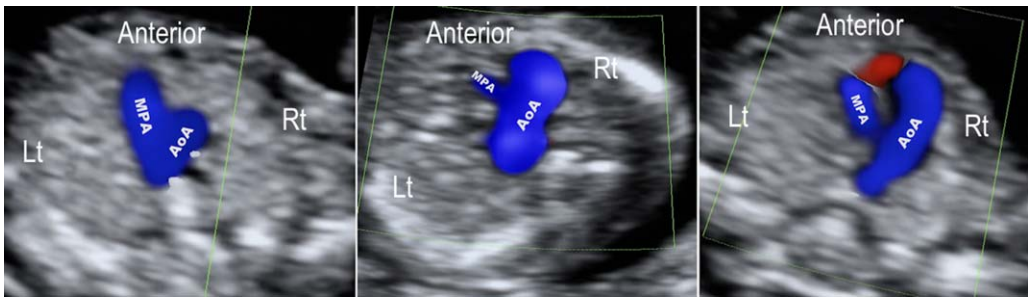


Table 1. Gestational Age and US Findings at the Time of the First-Trimester Scan With Postnatal and Pregnancy Outcome Confirmation in Cases With CHDs

Case	CRL, mm	GA, wk + d	NT, mm	CAx, °	4CVc Inflow Pattern	3VTVc Pattern	Study Status	Early Diagnosis	Final Diagnosis	Mode of Confirmation	Genetic Evaluation	Pregnancy Outcome
1	55	12 + 1	2.1	76	1	3	Included	ToF	ToF	Postnatal ECHO	AMNIO 46,XX	Delivery at term
2	62	12 + 4	1.8	53	1	3	Included	ToF	ToF	Postnatal ECHO	CVS 46,XX	Delivery at term
3	58	12 + 2	2.2	89	1	3	Included	ToF	ToF + RAA	Postnatal ECHO	AMNIO 46,XY; 22q11 microdeletion	Delivery at term
4	71	13 + 2	1.9	66	1	3	Included	ToF	ToF	Postnatal ECHO	Postnatal 46,XX	Delivery at term
5	68	13 + 0	2.3	56	1	3	Included	ToF	ToF	Postnatal ECHO	AMNIO 46,XY	Delivery at term
6	64	12 + 5	1.9	68	1	3	Included	ToF	ToF	Postnatal ECHO	AMNIO 46,XY	Delivery at term
7	62	12 + 4	2.3	77	1	3	Included	ToF	ToF	Postnatal ECHO	Postnatal 46,XY	CD at term
8	63	12 + 5	2.4	54	1	1	Included	Normal	ToF	Postnatal ECHO	Not done	Delivery at term
9	70	13 + 1	3.2	58	1	3	Included	ToF	DORV-FL	Postnatal ECHO	CVS 46,XY	Delivery at term
10	59	12 + 3	1.9	62	1	3	Included	ToF	DORV-FL	Postnatal ECHO	AMNIO 46,XX	CD at term
11	60	12 + 3	2.5	56	1	3	Included	ToF	DORV-FL	Postnatal ECHO	AMNIO 46,XX	Delivery at term
12	65	12 + 6	5.4	63	1	3	Included	ToF	DORV-FL	Postnatal ECHO	Not done	Delivery at term
13	70	13 + 1	1.9	68	1	3	Included	ToF	DORV-FL	Postnatal ECHO	AMNIO 46,XX	Delivery at term
14	72	13 + 2	2.6	88	1	3	Included	DORV-FL	DORV-FL	Postnatal ECHO	AMNIO 46,XY	Delivery at term
15	55	12 + 1	2.8	66	1	3	Included	ToF	DORV-FL	Postnatal ECHO	AMNIO 46,XX	Delivery at term
16	61	12 + 4	3.1	65	1	3	Included	ToF	DORV-FL	Postnatal ECHO	AMNIO 46,XY	Delivery at term
17	68	13 + 0	1.9	69	1	3	Included	ToF	DORV-FL	Postnatal ECHO	Not done	Delivery at term
18	63	12 + 5	3.1	48	1	2	Included	CoA	CoA	Postnatal ECHO	AMNIO 46,XY	CD at term
19	54	12 + 0	2.3	59	1	2	Included	CoA	CoA + LSVC	Postnatal ECHO	AMNIO 46,XX	CD at 36 wk
20	74	13 + 3	1.9	58	1	2	Included	CoA	CoA	Postnatal ECHO	AMNIO 46,XY	Delivery at term
21	72	13 + 2	3.3	63	1	1	Included	EA	EA	Postnatal ECHO	CVS 46,XY	CD at 38 wk/ND
22	60	12 + 3	2.9	56	1	1	Included	TD	EA	Postnatal ECHO	CVS 46,XX	Delivery at term
23	65	12 + 6	3.7	55	1	5	Included	CAT	CAT type I	Postnatal ECHO	AMNIO 46,XX	Delivery at term
24	62	12 + 4	2.7	50	1	3	Included	PS	PS	Postnatal ECHO	Not done	Delivery at term
25	70	13 + 1	2.5	47	1	3	Included	PS	PS	Postnatal ECHO	Not done	Delivery at term
26	58	12 + 2	1.7	46	4	4	Excluded	HLHS	HLHS	Postnatal ECHO	Not done	Delivery at term
27	60	12 + 3	2.8	52	4	4	Excluded	HLHS	HLHS	Postnatal ECHO	Not done	CD at 38 wk/ND
28	71	13 + 2	2.5	53	4	4	Excluded	HLHS	HLHS	Postnatal ECHO	Not done	Delivery at term
29	62	12 + 4	2.6	48	4	4	Excluded	HLHS	HLHS	Postnatal ECHO	Not done	Delivery at term
30	65	12 + 6	3.4	56	4	5	Excluded	TA	PAIVS	Postnatal ECHO	Not done	Delivery at term
31	63	12 + 5	2.7	55	4	5	Excluded	Single ventricle	DILV + TGA	Postnatal ECHO	AMNIO 46,XY	Delivery at term
32	77	13 + 5	2.8	47	1	5	Excluded	D-TGA	D-TGA + VSD	Postnatal ECHO	Not done	Delivery at term
33	60	12 + 3	3.0	48	1	5	Excluded	D-TGA	PA+VSD	Postnatal ECHO	AMNIO 46,XX; 22q11 microdeletion	Delivery at term

(Continued)

Table 1. Continued

Case	CRL, mm	GA, wk + d	NT, mm	CAx, °	4CVc Inflow Pattern	3VTVc Pattern	Study Status	Early Diagnosis	Final Diagnosis	Mode of Confirmation	Genetic Evaluation	Pregnancy Outcome
34	75	13 + 4	1.8	60	1	5	Excluded	D-TGA	L-TGA	Postnatal ECHO	Not done	Delivery at term
35	62	12 + 4	2.6	56	1	5	Excluded	D-TGA	ToF	Postnatal ECHO	AMNIO 46,XY	Delivery at term
36	70	13 + 1	2.7	55	1	5	Excluded	D-TGA	D-TGA	Postnatal ECHO	Not done	CD at 37 wk
37	63	12 + 5	1.7	49	1	1	Included	Normal	VSD trabecular	Postnatal ECHO	Not done	Delivery at term
38	58	12 + 2	1.6	54	1	1	Included	Normal	VSD trabecular	Postnatal ECHO	Not done	Delivery at term
39	61	12 + 4	1.3	48	1	1	Included	Normal	VSD trabecular	Postnatal ECHO	Not done	Delivery at term
40	65	12 + 6	1.5	47	1	1	Included	Normal	TAPVR supracardiac	Postnatal ECHO	Not done	Delivery at term

AMNIO indicates amniocentesis; CAT, common arterial trunk; CAx, cardiac axis; CD, cesarean delivery; CoA, coarctation of the aorta; CRL, crown-rump length; CVS, chorionic villus sampling; DILV, double-inlet left ventricle; DORV-FL, Fallot-like double-outlet right ventricle; EA, Ebstein anomaly; ECHO, echocardiography; 4CVc, 4-chamber view in color; GA, gestational age; HLHS, hypoplastic left heart syndrome; LSVC, left superior vena cava; ND, neonatal death; NT, nuchal translucency; PA, pulmonary atresia; PAIVS, pulmonary atresia with intact interventricular septum; PS, pulmonary stenosis; RAA, right aortic arch; TA, tricuspid atresia; TAPVR, total anomalous pulmonary venous return; TD, tricuspid dysplasia; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; 3VTVc, 3-vessel and trachea view in color; and VSD, ventricular septal defect.

results or in 6 fetuses with cardiac anomalies other than tetralogy of Fallot (coarctation of the aorta in 3, Ebstein anomaly in 2, and a common arterial trunk in 1). One case of tetralogy of Fallot did not show the Y sign in the first trimester and was finally diagnosed in the second trimester with less evident pulmonary stenosis.

The mean cardiac axis in fetuses without CHDs was 46.2° (range, 33°–56°). The mean cardiac axis was 67.4° (range, 53°–89°) in fetuses with tetralogy of Fallot, and it was 66.1° (range, 56°–88°) in fetuses with a Fallot-like double-outlet right ventricle. The differences in the cardiac axis between normal cardiac anatomy and tetralogy of Fallot and normal cardiac anatomy and a Fallot-like double-outlet right ventricle were statistically significant ($P = .001$; $P < .001$). However, there were no statistically significant differences between the cardiac axis in tetralogy of Fallot and a Fallot-like double-outlet right ventricle ($P = .073$).

Levorotation of the heart axis was found in 20 fetuses, including 4 with normal heart anatomy. Compared to the Y sign test, results of the axis sign test were negative in 3 cases of tetralogy of Fallot, 1 case of a Fallot-like double-outlet right ventricle, and all cases of pulmonary stenosis (2), coarctation of the aorta (1), Ebstein anomaly (1), and common arterial trunk (1).

For screening performance of the Y sign and axis sign, the detailed results are shown in Table 3. The Y sign test alone and in combination with the cardiac axis sign achieved sensitivity of 94%. In comparison, evaluation of levorotation of the heart axis had sensitivity of 76% for the diagnosis of aortic dextroposition anomalies.

Discussion

Aortic dextroposition anomalies are cardiac defects that may have similar prenatal US results, and a final differentiation may not be possible until birth. The detection rates for these anomalies are low, at 15% to 40% for tetralogy of Fallot and 44% for a double-outlet right ventricle in prenatal series.[1,15–17] Despite improvements in prenatal detection of tetralogy of Fallot in recent years according a study based on the analysis of 460,467 live births, this anomaly remains the third most common among cases with a delayed postnatal diagnosis.[18] The reason for missing the above-mentioned anomalies is the lack of attention to the outflow tracts. Furthermore, at the time of the first-trimester scan, despite the advancement in US equipment, outflow tracts are not

easy to evaluate. To enhance the prenatal detection of CHDs, Chaoui et al[19] presented upper mediastinal views and called them views 4 and 5. These views were consistent with views described later: the 3-vessel view by Yoo et al[20] 3-vessel and trachea view by Yagel et al.[21] 3-vessel and trachea view in the first trimester was proven to be obtainable in 94% of patients in screening populations.[22,23] At our site, examiners gain reproducibility of the first-trimester 3-vessel and trachea view on color mapping after 2 months of training dedicated to a nuchal scan. The 3-vessel view and 3-vessel and trachea view were applied in the second trimester as indicators of outflow tract and aortic arch anomalies, including tetralogy of Fallot, which is the most common anomaly in the group of aortic dextroposition anomalies.[7] According to Tongsong et al,[24] two-thirds of fetuses with tetralogy of Fallot can be detected in the second trimester by a careful evaluation of the series of axial views, including the 3-vessel view, transverse ductal arch, transverse aortic arch, and 3-vessel and trachea view. After implementation of a national screening program in the Netherlands, which covered the 3-vessel view and outflow tracts despite the 4-chamber view, the prenatal detection rate for tetralogy of Fallot nearly doubled from 22.2% to 41.7%.[25] Wu et al[26] described cardiovascular *z* score formulas for the second- and third-trimester fetuses developed for the prenatal diagnosis of tetralogy of Fallot. These formulas were also based on aortic dilatation and an abnormal main pulmonary artery-to-ascending aorta ratio, which is in line with our first-trimester observation. There are a few theories explaining the pathogenesis of tetralogy of Fallot.[4,27–30] van Praagh et al[4] postulated that it is a "monology" in which underdevelopment of the subpulmonary infundibulum is the main defect, and all others are its sequelae. Anderson and Tynen[27] and Becker et al[28] also highlighted the major role of the anterocephalad location of the outflow part of the interventricular septum in the development of tetralogy of Fallot. In a Fallot-like double-outlet right ventricle, the contribution of the overriding aorta is attributed more to the right ventricle, which causes prenatal US findings that are similar to those for tetralogy of Fallot.

Our investigation showed that the Y sign, which is a valuable marker with sensitivity of greater than 90% and specificity of 99%, improves the diagnosis of aortic dextroposition anomalies at the time of the first-trimester scan. The diagnosis of aortic dextroposition anomalies is not substantially improved when measurement of the fetal heart axis is added. Furthermore, the latter increases the false-positive rate for aortic dextroposition anomalies in early pregnancy. The positive axis sign,[6] did not improve the diagnosis of aortic dextroposition anomalies.

Table 2. Prevalence of the Y Sign, the Cardiac Axis Sign, and Their Combination in the Studied Population With Regard to the Type of Anomaly

	Y Sign		Cardiac Axis		Y Sign + Cardiac Axis	
Anomaly	Present (n=18)	Absent (n = 5757)	>57° (n = 20)	<57° (n = 5755)	Present (n = 25)	Absent (n = 5750)
Normal	0	5750	4	5746	4	5746
ToF (n = 8)	7	1	5	3	7	1
DORV-FL (n = 9)	9	0	8	1	9	0
PS (n = 2)	2	0	0	2	2	0
CoA (n = 3)	0	3	1	2	1	2
EA (n = 2)	0	2	1	1	1	1
CAT (n = 1)	0	1	1	0	1	0

Abbreviations are as in Table 1.

Table 3. Screening Performance of the Y Sign, the Axis Sign, and Their Combination for Aortic Dextroposition Anomalies

Parameter	Y Sign	Axis Sign	Y Sign + Axis Sign
Sensitivity, %	94.11 (69.23–99.69)	76.47 (49.76–92.17)	94.11 (69.23–99.69)
Specificity, %	99.90 (99.96–100.00)	99.87 (99.73–99.94)	99.84 (99.69–99.92)
PPV, %	88.89 (63.92–98.05)	65.00 (40.94–83.69)	64.00 (42.61–81.28)
NPV, %	99.98 (99.88–100.00)	99.93 (99.80–99.97)	99.98 (99.88–100.00)

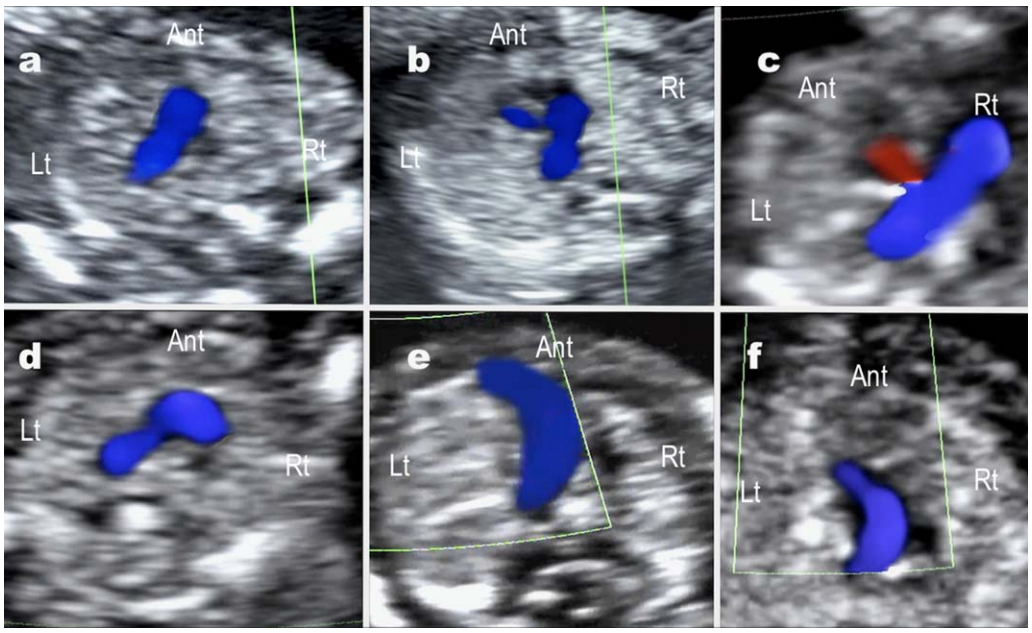
Values in parentheses are 95% confidence intervals. NPV indicates negative predictive value; and PPV, positive predictive value.

We chose cardiac axis assessment as an additional screening method because the 4-chamber view is a basic cardiac screening view highlighted in most US guidelines, including first-trimester guidelines.[31,32] Earlier studies have demonstrated that the cardiac axis establishes its position by the 12th week of gestation and remains unchanged during pregnancy.[11] For the first trimester, it should be at least 30° but less than 60° and is abnormal in 74.1% of fetuses with CHDs such as tetralogy of Fallot, coarctation of the aorta, and Ebstein anomaly.[3,9,10,33] In our study, a positive axis sign was observed in the above-mentioned anomalies, but in 3 of 5 tetralogy of Fallot cases, it was not found, and this method had 73% sensitivity for the detection of a Fallot-like double-outlet right ventricle. Similarly, in a first-trimester study by Sinkovskaya et al,[6] an abnormal cardiac axis did not detect all tetralogy of Fallot cases, as this finding was observed in only 28 of 33 of such cases.

To our best knowledge, our study is the first in the literature that focused on the detection of aortic dextroposition anomalies in the first trimester by adding evaluation of the main pulmonary artery on color mapping to the standard early cardiac assessment. Surprisingly, in only 1 patient from our aortic dextroposition anomaly series was 22q11 microdeletion observed, and no other chromosomal aberrations were found. This finding may be explained by the fact that multiple anomalies were excluded from this analysis.

In tetralogy of Fallot, the caliber of the main pulmonary artery determines the caliber of the aorta. A smaller-caliber main pulmonary artery results in greater aortic dilatation and vice versa.[4] This important feature explains why in some cases of tetralogy of Fallot, the pulmonary arm of the Y sign is hardly visible. Later in pregnancy, the atypical main pulmonary artery in tetralogy of Fallot has been proposed to be defined as a "question mark" sign.[34] It should be emphasized that a Y sign with a small main pulmonary artery in the first trimester is not a specific finding of tetralogy of Fallot. It can be seen in cases of a Fallot-like double-outlet right ventricle, pulmonary stenosis, Ebstein anomaly, and or type IB tricuspid atresia. This hypothesis was confirmed in our observations, and the Y sign was observed in anomalies other than aortic dextroposition anomalies as well.

Figure 4. Difficult first-trimester differential diagnosis at the level of an expected or observed V sign. **a**, A case of tetralogy of Fallot with severe pulmonary stenosis (Y sign absent). In this case, the ductal arm was not visible in the first trimester. **b**, A case of tetralogy of Fallot (Y sign present). The tiny ductal arm was visible in the first trimester. **c**, A case of tetralogy of Fallot with pulmonary atresia. Retrograde flow (red) is shown in the ductal arm of the Y sign. **d**, A case of common arterial trunk type I (Y sign absent). **e**, A case of D-transposition of the great arteries showing the convexity sign, which starts posterior to the sternum. **f**, A case of L-transposition of the great arteries including the short convexity sign, which starts from the center of the heart.



Above all, we did not observe any notable differences between first-trimester images of tetralogy of Fallot and Fallot-like double-outlet right ventricles. A similar image as the Y sign may be also present in cases of a right aortic arch with a right ductal arch and normal-size great arteries. However, we did not encounter cases of this anomaly in our series. Therefore, 100% specificity for the Y sign cannot be observed.

In our study, the Y sign was not observed in 1 case of tetralogy of Fallot. This finding can be explained by the fact that in certain cases without pronounced pulmonary stenosis, the normal size main pulmonary artery may be visible at the level of three-vessel and trachea view, giving the impression of a normal V-shaped configuration.

On the other hand, because of the difficulties in visualization of the ductal arm at the level of the main pulmonary artery in the first trimester in some cases of aortic dextroposition anomalies, examiners may suspect other conotruncal anomalies. First of all, they may be classified as main pulmonary artery pattern 5 according to Wiechec et al[2] and be suspected to be D-transposition of the great arteries or a double-outlet right ventricle with a subpulmonary ventricular septal defect, but in fact they may be tetralogy of Fallot with severe pulmonary stenosis or even pulmonary atresia. In our opinion, this limitation should be accepted in the first trimester, and all of these cases should require a detailed second-trimester cardiac evaluation. In our study, all of these cases were excluded, but we highlight this issue because of its clinical importance. It should be also emphasized that US scanner settings and, above all, a suboptimal insonation angle at the outlet portion of the right ventricle may produce this false first-trimester impression of a singular arterial arm at the level of the main pulmonary artery in cases of aortic dextroposition anomalies with severe right outflow tract obstruction. Another difficulty in differentiation of conotruncal anomalies at the time of the first-trimester scan is the various geometries of great vessels among particular disorders in this group. This observation makes standardization of the level for 3-vessel and trachea view assessment impossible.[35] Particular care should be taken to search for the level of the connection between the arterial arms and sometimes the expected section in a strict axial view. Our collection of these difficult cases observed in this study is shown in Figure 4.

According to published guidelines for first-trimester US, a cardiac evaluation should include the normal position of the heart on the left side of the chest (levocardia), the heart rate, and, optionally, the symmetry of the 4 chambers.[2,3] However, with this approach, many cardiac anomalies, especially conotruncal anomalies, will remain undetected until the second-trimester scan. The published data suggest that early fetal echocardiography before 15 weeks has high specificity and a good negative predictive value for the absence of CHDs.[36,37] Furthermore, a combined approach by evaluating the 4-chamber view and 3-vessel and trachea view with color mapping has high sensitivity for CHDs of 88.57% at the time of the nuchal scan.[2] These views are feasible to obtain in 73% of the scans when performed by sonographers in a low-risk population with the aid of color and power Doppler modes.[38] Therefore, we suggest that the main pulmonary artery in color should be added to the first-trimester US protocol.

In conclusion, because aortic dextroposition anomalies are common conotruncal anomalies, and some of them are ductal dependent in fetal series, a Y sign at the level of the main pulmonary artery may serve as a potential screening tool for defining the population of fetuses at risk for aortic dextroposition anomalies at the time of a nuchal scan. The screening performance of the Y sign alone and in combination with an abnormal cardiac axis is high and may aid in the early diagnosis of aortic dextroposition anomalies in the fetus. We hope that this approach will enhance detection rates for aortic dextroposition anomalies in coming years.

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