Title: **Absent pulmonary valve syndrome - diagnosis, associations and outcome in 71 prenatally diagnosed cases**

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What's already known about this topic?

Absent pulmonary valve syndrome (APVS) is a rare congenital heart anomaly and is frequently associated with Tetralogy of Fallot. Risk factors for poor outcome include karyotype abnormalities, presence of hydrops fetalis and respiratory failure in live born patients.

What does this study add?

The current study is the largest study to date analyzing fetal outcome. The results reflect the outcome of APVS diagnosed from the first trimester onwards providing valuable new data for parental counselling.

Ethics statement

Informed parental consent to anonymized analysis of the data was given and the study was approved by the local research ethics committee.

Abstract

Objective

To analyze the spectrum of prenatally diagnosed absent pulmonary valve syndrome (APVS) and the outcome from diagnosis onwards. Fetuses with APVS and tetralogy of Fallot (TOF/APVS) and with APVS and intact ventricular septum (APVS/IVS) were included.

Method

Multicenter retrospective study of the International Prenatal Cardiology Collaboration Group (IPCCG). Clinical and echocardiographic databases of nine referral centers were reviewed from 2012-2016.

Results

The cohort included 71 cases, 59 with TOF/APVS and 12 with APVS/IVS. In 18.3% of cases diagnosis was achieved within first trimester. Association with hydrops fetalis was high within first trimester (69%). No fetus with known outcome survived after first trimester diagnosis. Karyotype anomalies occurred in 45% of cases with known karyotype. Intrauterine fetal demise occurred in 14.3%.

Overall survival after initial diagnosis in the total cohort was 28.1% (28.8% TOF/APVS, 25.0% APVS/IVS). Survival to birth was 50% in TOF/APVS and 44.4% in APVS/IVS. Survival of subjects born alive beyond neonatal period was 84.6% in TOF/APVS and 100% in APVS/IVS.

Conclusion

Diagnosis of APVS is feasible within first trimester. Outcomes remain guarded, especially if first trimester diagnosis is included into the analysis due to associated karyotypic anomalies, the presence of hydrops fetalis and patent Ductus arteriosus (DA).

Introduction

In absent pulmonary valve syndrome (APVS) the pulmonary valve leaflets are absent or severely undeveloped with a restrictive ring of thickened tissue in the position of the pulmonary valve annulus[1-7]. This may lead to marked pulmonary insufficiency with to-and-fro blood flow over the dysplastic valve, aneurysmal dilation of the main and branch pulmonary arteries and concomitant cardiomegaly causing significant compression of the bronchi. Absence of ductus arteriosus is common in APVS and it has been postulated that absence of the arterial duct plays an important etiologic role in APVS[2,6,7]. APVS carries a significant perinatal mortality and morbidity and postnatal presentation may be aggravated by severe respiratory symptoms including long-term obstructive lung disease[8-11]. APVS occurs with tetralogy of Fallot (TOF/APVS) and with intact ventricular septum (APVS/IVS) in the setting of „isolated APVS" or associated with tricuspid atresia, Ebstein´s anomaly or in combination with absent aortic valve[12-15]. In the majority of cases the ductus arteriosus is absent[2,6]. Connection of a discontinuous left pulmonary artery to the patent arterial duct has been described in rare cases[6].

In postnatal series APVS accounts for 2-6% of all cases with TOF and 0.2%-0.6% of all congenital heart defects. In prenatal series the association of APVS with TOF is probably higher[4,13,16]. Intrauterine demise due to cardiac failure, hydrops fetalis, extracardiac and chromosomal associations as well as termination of pregnancy (TOP) might account for different incidences in pre- and postnatal series and the potentially better outcome in recent postnatal series with reported survival rates from 72%- 86%[3,10,15,17].

Most studies dealt with cases diagnosed from the second trimester and few cases have been described within the first trimester[18,19].

The purpose of the study was to describe the spectrum, associated anomalies and the perinatal course from first trimester diagnosis onward in a large contemporary cohort of prenatally diagnosed APVS.

Methods

This was a multicenter retrospective analysis of all subjects with a diagnosis of APVS from 2012 to 2016. Data from nine European referral centers from the International

Prenatal Cardiology Collaboration Group (IPCCG) were included. The anatomic survey and fetal echocardiography were performed in a standardized fashion according to international guidelines of ISUOG by a segmental approach and defined anatomical planes with color Doppler and pulsed-wave interrogation[20,21]. Cardiovascular analysis was performed by two-dimensional, color and pulsed-wave Doppler echocardiography and was followed by postnatal echocardiography, surgery and/or autopsy. Spectral Doppler interrogation of the umbilical artery, middle cerebral artery and the Ductus venosus was performed in a standardized manor. 5MHz, 7.5Mhz or 9MHz sector or curved array-probes were used for all ultrasound examinations (Toshiba Aplio 500, Toshiba Aplio XG, Toshiba Medical, Neuss, Germany; Philips IU22, Philips Epiq7, Hamburg, Germany; Voluson 730 Expert, Voluson E8, GE Healthcare Solingen, Germany; Acuson Sequoia 512, Siemens, Germany). In the first trimester transvaginal sonography was part of the study whenever appropriate. Fetal karyotyping was offered and included chromosome analysis and fluorescent in-situ hybridization for microdeletion 22q11.2. Parental counselling by pediatric cardiologists and geneticists was part of the prenatal work-up. Data were collected from medical files, from stored ultrasound images and video loops, whenever available. Echocardiographic parameters included presence or absence of arterial duct (DA), aortic arch position and the cardiothoracic ratio (CTR), maximum diameters of pulmonary annulus and the diameter of the right or left branch pulmonary artery either prospectively or retrospectively. Z-scores of PV annulus, branch pulmonary arteries and DA were generated by the use of previously published normative data for fetal pulmonary artery diameters[22-24]. Clinical variables included indication for referral, gestational age at diagnosis, gestational age at birth, maternal age, associated extracardiac anomalies including karyotype abnormalities, presence of hydrops fetalis, the notification of an increased nuchal translucency (NT) within the first trimester, and pregnancy outcome. For subjects born alive postnatal diagnosis and survival beyond the neonatal period was documented. Statistical analysis was performed using X2, Student t-test or Fisher´s exact test. All values are given in mean +/- standard deviation (SD) unless otherwise stated. Survival analysis was performed by Kaplan-Meier analysis. A p value <0.05 was considered significant. Institutional review board approval of the main side (Justus-Liebig-University, Giessen, Germany) was obtained.

Results

During the study period 71 cases with APVS were diagnosed antenatally. Fifty-nine fetuses (83.1%) were classified as having TOF/APVS (figure 1), 12 (16.9%) of the cases presented with APVS/IVS. One case of the latter group additionally had a membranous tricuspid atresia and a non-compaction of the right ventricle. In all cases confirmation of the prenatal diagnosis by necropsy or postnatal echocardiography/surgery was obtained neither encountering false positive nor incorrect diagnoses.

Table 1 details general information on the total study cohort. Eight cases of the total cohort were lost to follow up. Mean gestational age at diagnosis was 21.5 weeks of gestation (wks) for the whole cohort, without significant differences among fetuses presenting with TOF/APVS (22.3 wks) and APVS/IVS (20.2 wks). Hydrops fetalis was found in 11 cases (16.9%). Seven cases with TOF/APVS presented with hydrops (13.2%), in contrast to 4 cases with APVS/IVS (33.3%, $p<0.04$). A patent DA was found in 5 fetuses with hydrops fetalis (31.3%). Among those 5 fetuses two had TOF/APVS and 3 had APVS/IVS. Patency of DA was registered in 14 of 53 cases (26.4%) without hydrops. In 2 cases with absent DA hydrops fetalis occurred in the group of TOF/APVS.

Information on intrauterine fetal demise (IUD) was obtained in 61 cases (85.9%). IUD occurred 9 times (14.7%) in the total cohort. IUD was registered in 6 of 54 cases with TOF/APVS (11.1%) in contrast to 3 of 9 (33.3%) in APVS/IVS. In 4 of those 9 cases DA was patent (44.4%). Information on both IUD and presence/absence of DA was obtained 50 cases (70.4%). In 6 IUDs patency of the DA was observed in 4 cases (66.6%). Of the latter 4 fetuses two presented with TOF/APVS and APVS/IVS each.

In 23 of 61 cases with ascertained information on termination of the pregnancy parents opted for TOP (37.7%). TOP was performed in 21 cases with TOF/APVS (39.6%) and 2 cases with APVS/IVS (22.2%). Among TOPs there were 7 cases (30.4%) presenting with aneuploidy, 4 cases (17.4%) with hydrops fetalis and 10 cases with extracardiac anomalies (43.5%).

Overall survival after initial diagnosis in the total cohort was 28.1% (20/71), with seventeen (28.8%) of 59 TOF/APVS cases and three of 12 (25%) APVS/IVS cases. Of initially 59 subjects in the TOF/APVS cohort, 5 (8.5%) were lost to follow-up. Subsequently survival to birth was 50% (27/54) in the TOF/APVS cohort.

Four babies died within the neonatal period, and all showed severe respiratory failure and one was lost to follow up after live birth. Consequently, of subjects born alive in the TOF/APVS cohort, survival was 84.6% (22/26).

Of initially 12 fetuses in the APVS/IVS cohort, 3 (25.0%) were lost to follow-up. Subsequently, survival to birth in the APVS/IVS cohort was 44.4% (4/9). Of four live births in the APVS/IVS cohort one subject is lost for follow up. Consequently, of subjects born alive in the APVS/IVS cohort, survival was 100% (3/3, table 1, figure 2).

Figure 3 illustrates the current survival for subjects of both groups born alive. In figure 4 current survival is displayed for each group separately.

Extracardiac anomalies were frequent in both cohorts occurring in 36 of 71 fetuses (50.7%). Anomalies predominantly included the central nervous system, urogenital anomalies and gastrointestinal anomalies. Agenesis of the thymus occurred in 5 cases, 4 of them presenting with TOF/APVS (table 2).

Information on prenatal karyotype results were retrieved in 29 fetuses (40.8%). Sixteen of 29 fetuses (55.1%) presented with a normal karyotype. There were 5 cases with trisomy 13 (17.2%) and 2 cases of trisomy 18 (6.8%) respectively. The 2 fetuses with trisomy 18 occurred in the APVS/IVS group, whereas all 5 trisomy 13 cases occurred within the group of TOF/APVS. All 6 fetuses with microdeletion 22q11.2 (20.6%) occurred within the TOF/APVS cohort (table 3).

Table 4 summarizes information on echocardiographic details of the cohort. Assessment of cardiac axis was available in 49 (69%) cases of the cohort. Counterclockwise leftward rotation of the cardiac axis was found in 44 fetuses (89.8%) whereas a normal cardiac axis was seen in 5 fetuses (10.2%) all of them having TOF/APVS. All 7 cases with APVS/IVS with known information on cardiac axis showed abnormal leftward rotation. The vast majority (88.1%) of TOF/APVS cases showed abnormal leftward rotation of the cardiac axis compared to only 5 fetuses (11.9%) with TOF/APVS having a normal cardiac axis. Laterality of the aortic arch was ascertained in 31 cases (43.7%). All cases with right aortic arch (RAA) occurred within the group of TOF/APVS (p=0.1). Although no case of RAA was found in the group of APVS/IVS, the comparison between both groups was statistically not significant.

In 50 of 71 cases (70.4%) information on patency of the DA was retrieved. In 32 fetuses (62.7%) the DA was absent, whereas in 18 (37.3%) a DA was present. All cases with absent DA occurred in the TOF/APVS group. In contrast to 9 of 41 TOF/APVS with patent DA (21.9%), all 9 cases with APVS/IVS had a patent DA ($p<0.001$). In 1 pregnancy with APVS/IVS and membranous TA a narrow duct with z-scores ranging from -2.34 at 23+4 wks to -3.09 at 25+6 wks was diagnosed. All 7 cases with RAA occurred in the TOF/APVS group ($p=0.1$). The pulmonary artery valve-to-aortic valve annular ratio was higher in APVS/IVS cases compared to TOF/APVS cases ($p<0.02$). However, in TOF/APVS the pulmonary artery valve-to-aortic valve annular ratio did not differ significantly in survivors from non-survivors ($p=0.29$, table 4).

Z-scores of main and branch pulmonary arteries in TOF/APVS with ascertained information revealed persistently increased diameters in MPA and branch pulmonary arteries after the first trimester from time of diagnosis onwards. In four cases with information on PA measurement in the first trimester diameters were already markedly increased at this time in gestation, however a correlation of the presence of the DA with the size of the main and branch pulmonary arteries could not be established in those four cases. In one case with APVS/IVS with membranous tricuspid atresia and patent arterial duct with a patent arterial duct significant pulmonary regurgitation was present. However z-scores of the arterial duct were -2.34 at 23.4 wks and -3.09 at 25+6 wks indicating a significant narrowing of the arterial duct. Of note the right and left PA branches and the MPA were of normal size (z-scores 1.15, 1.75 and 0.61 respectively).

First trimester diagnosis was achieved in thirteen fetuses (18.3%) of cases, second trimester was achieved in 62% of fetuses and the diagnosis was made within the third trimester in 16.9% of fetuses. In 2.8% no information on time of diagnosis was obtained. Detailed information on patients with a first trimester diagnosis is shown in figure 5. Nine of 13 cases (69.2%) were diagnosed as having TOF/APVS whereas 4 fetuses presented with APVS/IVS (30.8%). Within the group of first trimester diagnosis hydrops fetalis was present in 9 cases and in all 9 fetuses an increased NT was measured. Of those, 5 cases presented with TOF/APVS (55.5%) and all 4 cases with APVS/IVS and first trimester diagnosis presented with hydrops fetalis. Abnormal Doppler profiles with reversal of flow at the level of the pulmonary annulus, the main

pulmonary trunk or to-and-fro blood flow within the umbilical artery was detected in all of those 9 fetuses (figure 6a, b).

Discussion

The findings of our study revealed important differences between the two main entities occurring with APVS, fetuses with TOF/APVS and APVS/IVS.

First, the distribution with 83.1% of cases presenting with TOF/APVS and only 16.9% having APVS/IVS reflects previous reports with much lower numbers included[10,14,15,17]. In 18.3% of cases of our cohort the diagnosis was made within the first trimester. Differences in health care systems with established detailed anomaly scan together with first trimester screening vs. second trimester screening might in part account for this high number of first trimester diagnosis in our cohort compared to results from the Toronto group with reported diagnosis ranging from 20 to 37 wks in 12 cases or 18 to 39 wks in 21 cases in a report from Philadelphia[15,17]. Results from Gottschalk et al. and Galindo et al. underline the feasibility of first trimester diagnosis in those cases[10,14,25].

The high number of aneuploidies associated with APVS and the distribution of aneuploidies in our cohort with microdeletion 22q11.2 as the most common aneuploidy being very frequently associated with TOF/APVS is in line with previous series and underlines that parental counselling should include chromosomal testing including microdeletion 22q11.2 [10,14,17].

Second, all fetuses with a first trimester diagnosis with known outcome died or were terminated prior 24 weeks due to presence of hydrops or chromosomal anomalies. Nine of those 13 cases presented with TOF/APVS. In 5/9 subjects hydrops was present at the time of diagnosis and in 2 fetuses patency of the DA was ascertained on first trimester ultrasound. Further 4 cases of APVS/IVS were diagnosed with hydrops fetalis and in one of them patency of DA was diagnosed. We do not have the information about the DA in the remaining 3. In older series, a patent arterial duct in APVS has been described in a few second and third trimester fetuses, whereas Zach et al. proposed that intrauterine closure of the DA would be essential for survival in the condition of APVS as patency of the arterial duct would result in important aorto-pulmonary shunting and right sided cardiac failure[26].

No fetus survived after first trimester diagnosis of APVS in our series and this further underlines this statement. In TOF/APVS with patent DA hydrops fetalis is likely to develop early in gestation due to diastolic runoff via the DA into the pulmonary branch arteries and the right ventricle thus increasing the risk of right ventricular overload and fetal heart failure. This may result in high venous pressure and subsequent evolution of hydrops fetalis as was the cases in 9 of the 13 cases in our cohort. Yeager et al. speculated that in APVS/IVS with a normal sized patent duct the end-diastolic RV pressure would equal the aortic diastolic pressure and the authors hypothesized that the consequence would be RV dysfunction[27]. In line with this theory the live born three cases with APVS/IVS in our cohort had a restrictive DA well below the normal size probably preventing the RV from severe dysfunction.

Third, absence of DA only occurred in fetuses with TOF/APVS, fetuses presenting with APVS/IVS had a patent DA.

Previously, absence of DA has been reported to be associated with TOF/APVS and it has been speculated that absence of DA might be in part responsible for the constantly observed aneurysmatical dilatation of the branch pulmonary arteries in this condition[2,6,7]. Further Fischer et al. hypothesized that absence of DA and consecutive absence of right-to-left shunt through the duct also might contribute to maldevelopment of the pulmonary valve[8]. However, there are a few cases with TOF/APVS and a patent arterial duct and patency of the arterial duct is more commonly observed in patients with the rare entity of APVS/IVS. It has therefore been speculated that aneurysmatical dilation of branch pulmonary arteries results from both primary underdevelopment of the pulmonary valve leaflets with an obstructive „ring“ and high right ventricular stroke volume with severe pulmonary insufficiency[2,6,7,27].

Interestingly, in contrast to Gottschalk et al. who speculated that first trimester diagnosis of APVS would rely on the presence of a typical to-and-fro blood flow within the DA, umbilical artery or middle cerebral artery besides the presence of a large VSD or a RAA, we describe four first trimester cases of TOF/APVS with already marked dilatation of PA branches and MPA. Although we could not ascertain information on patency of the DA in those cases hydrops was present and it might be speculated that the observed severe pulmonary regurgitation lead to enlarged PA dimensions early in pregnancy.

Marked dilatation of the PA branches was a constant finding at the time of the second trimester anomaly scan in cases of TOF/APVS and absent DA in our cohort whenever assessed. This is in keeping with observations by Galindo et al. and support the assumption that a combination of volume load and high pulmonary vascular resistance in the fetus might contribute to enlargement of PA branches in case of absent DA[10]. This effect might be further enhanced by pulmonary regurgitation resulting in higher right ventricular stroke volume. Again in cases of APVS/IVS with a narrow, however patent DA massive dilatation of the PA branches was not seen in our cohort as in the series by Gottschalk et al.[14].

From a clinical perspective survival increased after exclusion of cases with associated anomalies and karyotypic anomalies, respectively, leading from an over-all survival after initial diagnosis in the total cohort of 28.1% with 28.8% of TOF/APVS cases and 25% APVS/IVS cases to 50% liveborns in TOF/APVS and 44.4% liveborns in APVS/IVS and resulting in 84.6% survival of subjects born alive in the TOF/APVS cohort and 100% in the APVS/IVS cohort. These numbers favourable compare to data from Gottschalk et al. and is much higher than the reported 14% by Galindo et al.[10,14]. Both series included also first trimester diagnosis. The results are comparable to the 50% survival reported by Wertaschnigg et al. from the initial diagnosis and comparable to the 86% on an intention to treat basis, as well as the 71% survival to birth for TOF/APVS and 83% for APVS/IVS with survival from subjects born alive being 80% by Szwast et al.[15,17] However, the latter two reports are from Northern America with different health care systems and did not include cases with first and early second trimester diagnosis. This might constitute a selection bias in favour of less unfavourable cases.

There have been different notions on survival of actively managed patients in the last decade ranging from 25% to 80%, significantly depending on the underlying lesion[15,17,28-31]. In APV/IVS survival rate was 100% being higher as previously reported. However, we only had three patients with intention-to-treat and in those patients APV/IVS occurred as „isolated APVS“ with a biventricular physiology with a normal tricuspid annulus and a normal or dilated ventricle. Recently one fetus with APV/IVS and a non-compacted RV, were a single ventricle physiology is expected, has been

diagnosed in our cohort. This constitutes a significant risk factor with consideration for heart transplantation.

Prediction of outcome by echocardiographic parameters showed inconsistent results including a higher pulmonary artery valve-to-aortic valve annular ratio and severe left ventricular dysfunction as the most accurate variables[7,10,15,31]. PV/AV ratio was higher in APVS/IVS cases in our series, however pulmonary artery valve-to-aortic valve annular ratio was similar in TOF/APVS who survived or did not survive. This is in contrast to findings by Szwast et al. In their report of 15 fetuses with TOF/APVS a higher pulmonary artery valve-to-aortic valve annular ratio and severe left ventricular dysfunction were more common in non survivors and this might be due to the smaller number of individuals included in their study. Due to the retrospective character of our study, we did not assess left ventricular dysfunction.

Limitations

The study is limited by its retrospective multicenter design. First, there might have been a counselling bias in selected cases in different centres and second, some subjects were lost to follow up and data on postnatal outcomes were difficult to ascertain due to the multicenter approach. The strength of the study is its large cohort, to date, to the best of our knowledge the largest contemporary series of APVS with a prenatal diagnosis.

In conclusion we report on a large contemporary cohort of APVS with prenatal diagnosis. Two main subtypes, TOF/APVS and APVS/IVS were diagnosed. The anomaly can be accurately diagnosed by fetal echocardiography in the first and early second trimester. The outcomes of APVS rely significantly on the underlying lesion. Outcomes remain guarded, especially if first trimester diagnosis is included into the analysis due to associated karyotypic anomalies and the presence of hydrops fetalis. Higher survival rates >80% are achieved in isolated cases of APVS/TOF and APVS/IVS.

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Parameter	TOF/APVS	APVS/IVS	level of significance (p-value)
Number of fetuses (n)	59	12	
Lost for follow up	5	3	
Mean GA (weeks)	22	21	0.48
Hydrops (n)	7/54 (13.0%)	4/9 (44.4%)	0.02*
IUD (n)	6/54 (11.1%)	3/9 (33.3%)	0.08
TOP (n)	21/48 (43.8%)	2/6 (33.3%)	0.63
Live birth (n)	27/33 (81.8%)	4/7 (57.1%)	0.16
Postnatal survival >28 days (n)	22/26 (84.6%)	3/4 (75.0%)	0.63

Table 1 General information of study population according to type of APVS and additional level of significance, expressed by p-values.

(GA, gestational age; IUD, intrauterine demise; TOP, termination of pregnancy)

	TOF/APVS (n)	APVS/IVS (n)
Thymic agenesis	4	1
SUA	2	
ARSA	1	
Holoprosencephaly	3	
Polyhydramnios	2	1
Oligo-/Anhydramnios	2	
Renal agenesis	1	
Anencephaly	1	
Omphalocele	3	2
Polydactyly	2	1
Gastroschisis		1
Enlarged Cisterna magna		1
Cystic hygroma		1
Cleft palate		1
Agenesis of corpus callosum		1
Agenesis of DV	1	
Hyperechogenic bowl	1	
Agenesis of cerebellar vermis	1	

Table 2 Extracardiac anomalies according to type of APVS.

(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum; SUA, single umbilical artery; ARSA, absent right subclavian artery; DV, ductus venosus)

	TOF/APVS	APVS/IVS
normal	11	5
trisomy 18	0	2
trisomy 13	5	0
del22q11.2	6	0

Table 3 Distribution of fetuses with known karyotyping according to type of APVS

(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum)

Parameter	TOF/APVS	APVS/IVS	level of significance (p-value)
CTR	0.55	0.57	0.72
Abnormal heart axis	37/42 (88.1%)	7/7 (100%)	0.34
Patency of DA	9/41 (22.0%)	9/9 (100%)	<0.001*
RAA	7/24 (29.2%)	0/7 (0%)	0.1
PV/AV ratio	0.92	1.42	0.02*
Heart dimensions (Z-scores)			
MPA	3.7 (1.8 – 9.1)		
RPA	5.9 (2.6 – 9.2)		
LPA	5.7 (2.1 – 7.7)		

Table 4 Fetal echocardiographic findings according to type of APVS and additional level of significance, expressed by p-values.

(CTR, cardiothoracic circumference ratio; DA, ductus arteriosus; RAA, right aortic arch; PV, pulmonary valve; AV, aortic valve)

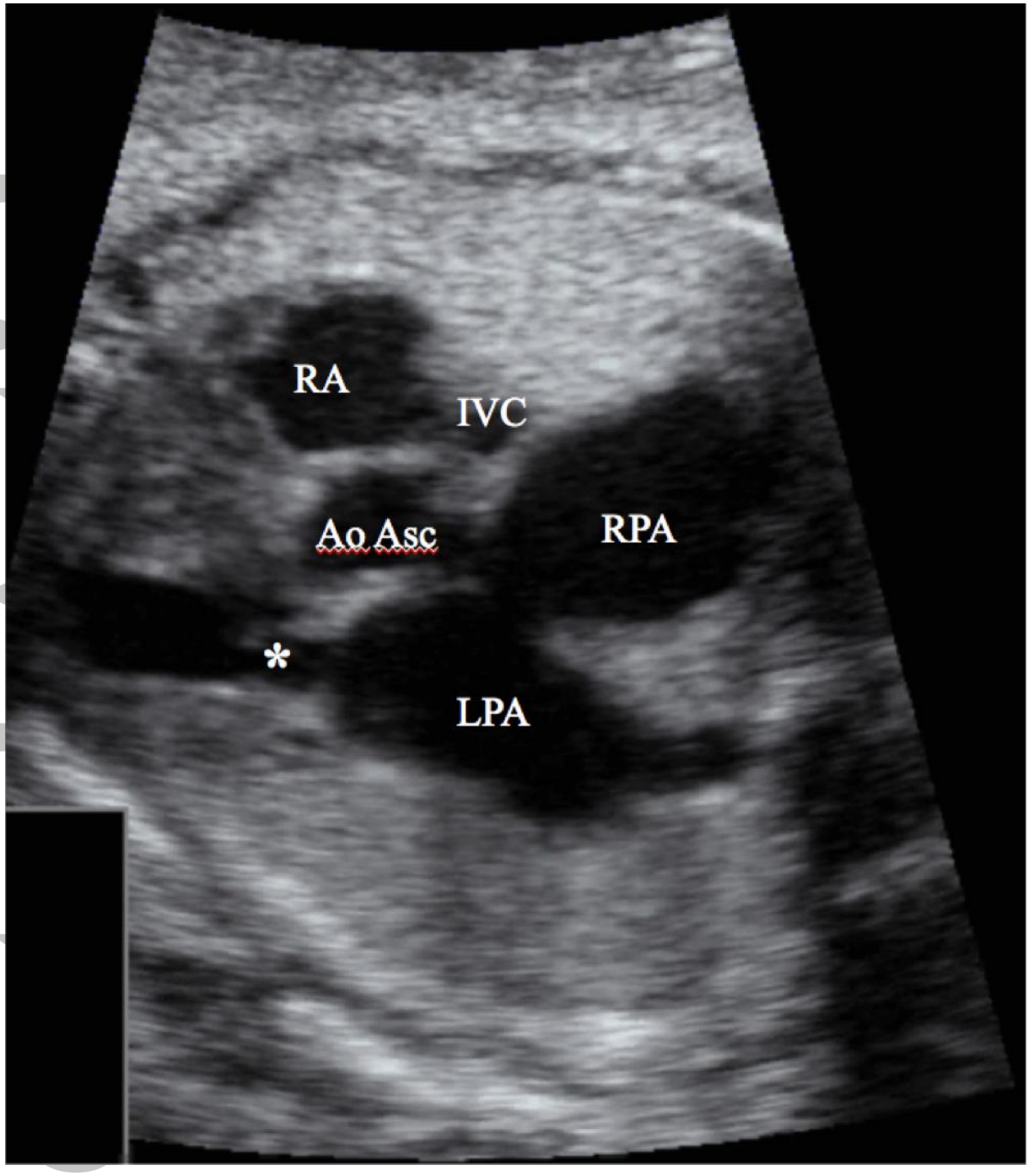

Figure 1

Fetus with TOF/APVS and dilated RPA and LPA. (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; RPA, right pulmonary artery; LPA, left pulmonary artery; RA, right atrium; IVC, inferior vena cava; Ao Asc, ascending aorta; *, pulmonary fibrous annulus)

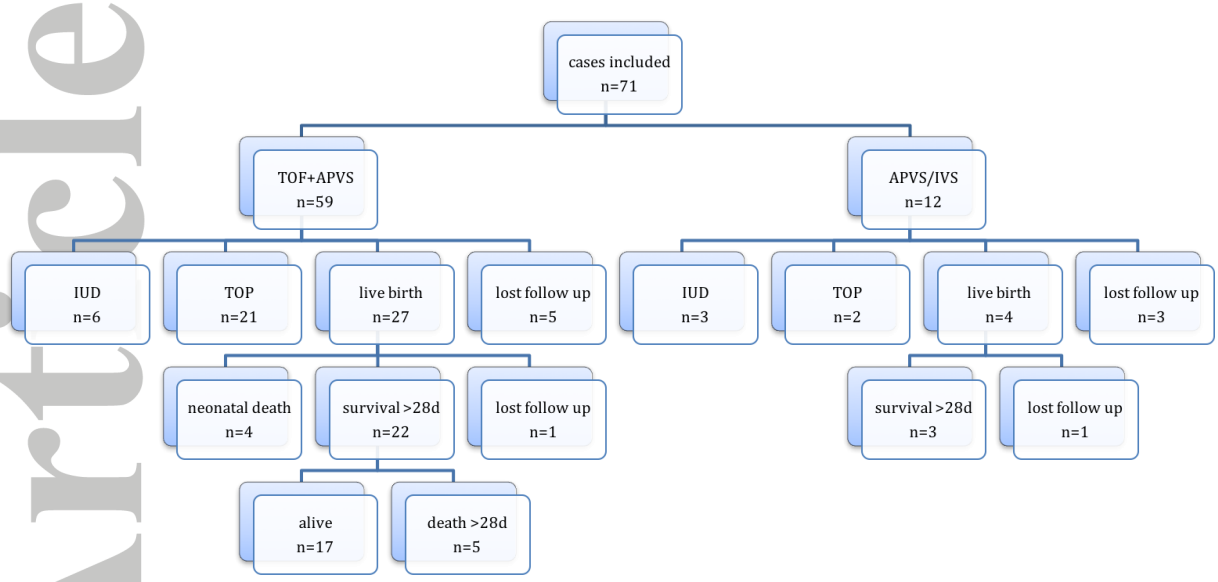

Figure 2

Flowchart of overall study population and outcome according to the type of APVS. (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum; IUD, intrauterine demise; TOP, termination of pregnancy)

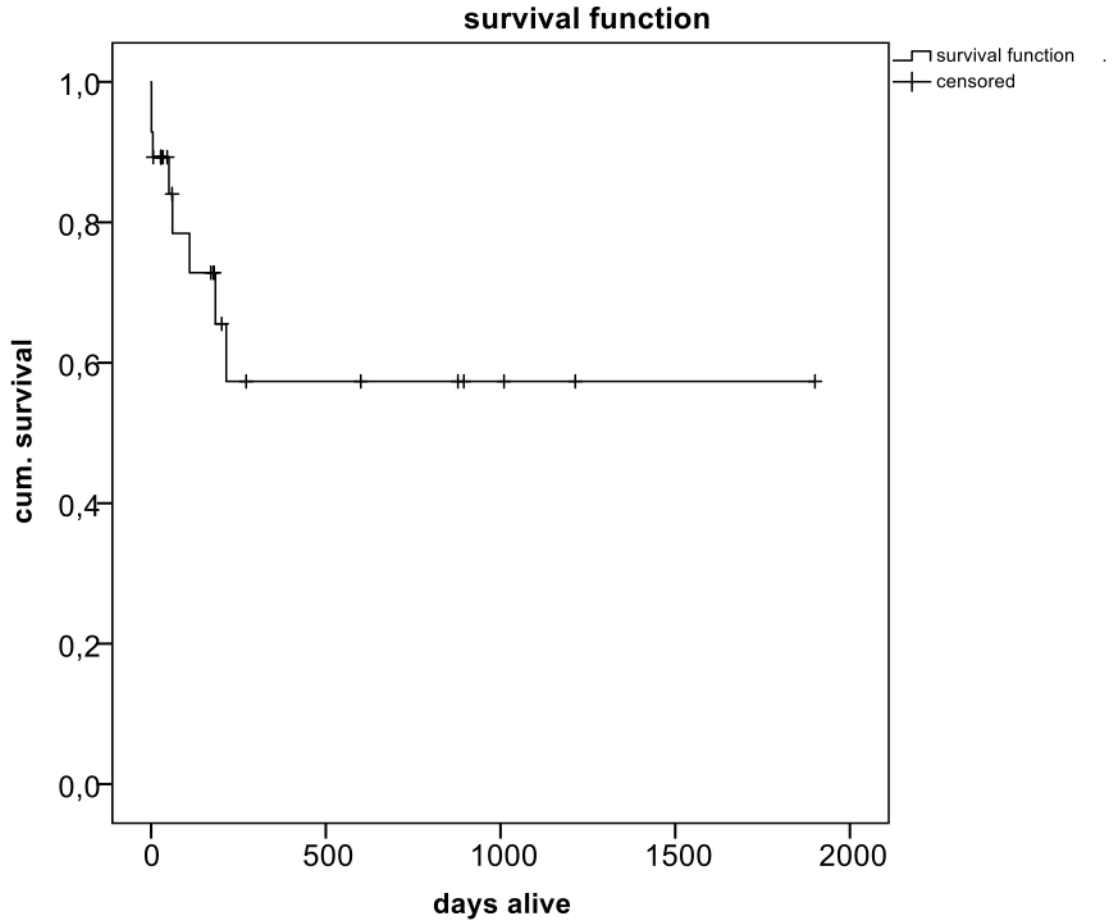

Figure 3

Kaplan-Meier survival curve for the whole cohort (TOF/APVS and APVS/IVS). (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum)

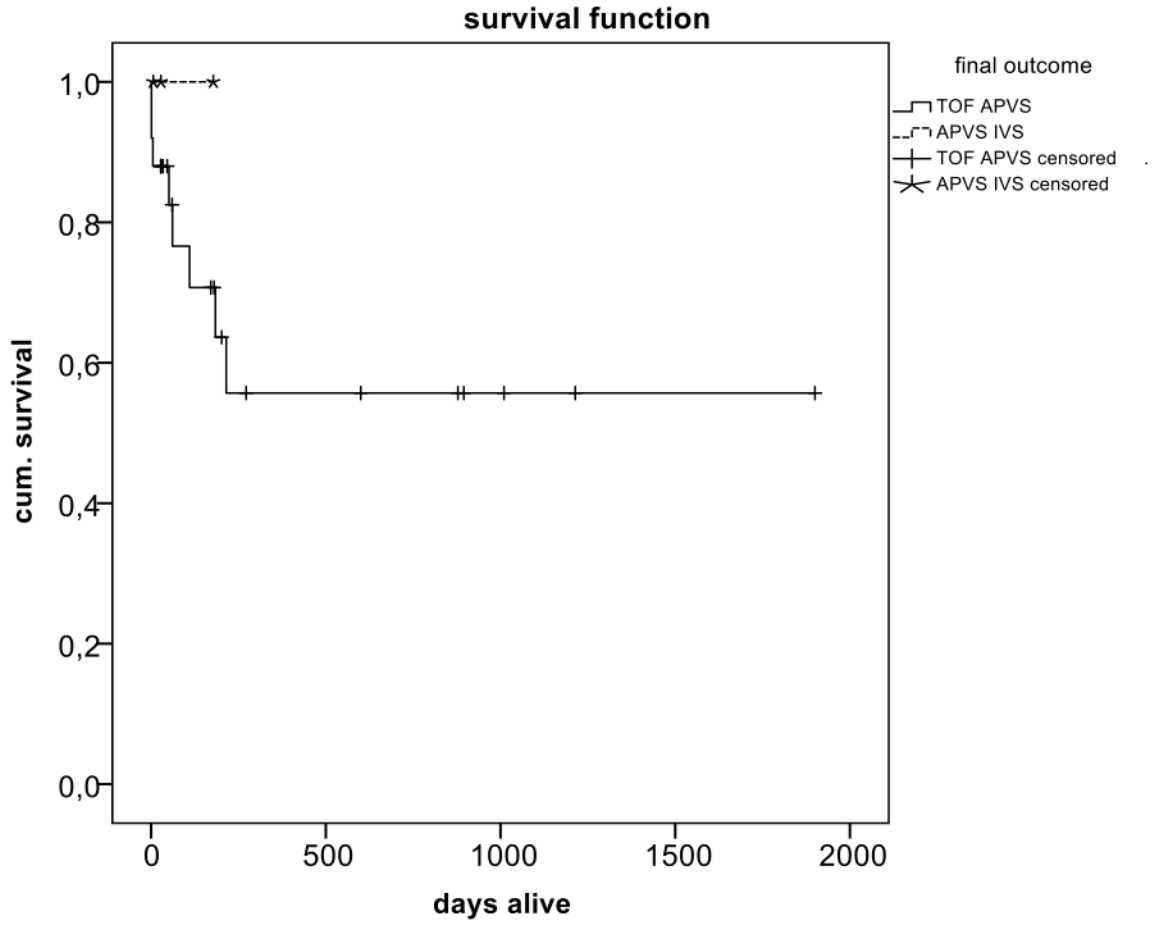

Figure 4

Kaplan-Meier survival curve for both cohorts (TOF/APVS and APVS/IVS) separately. (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum).

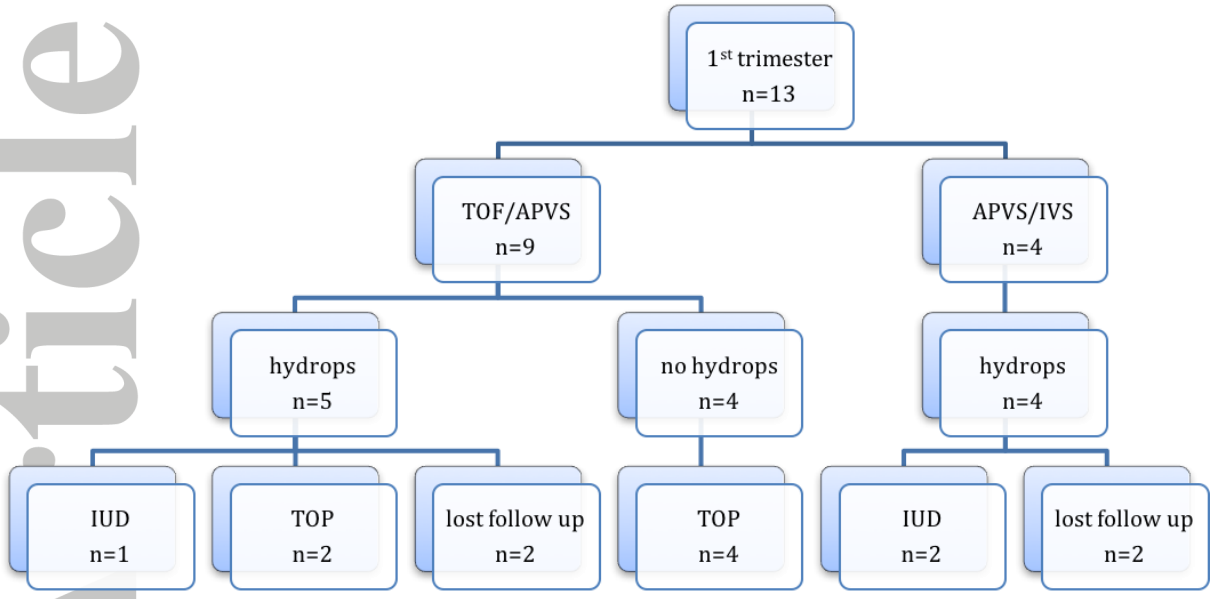

Figure 5

Flowchart of thirteen APVS cases diagnosed in first trimester and outcome according to the type of APVS (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum; IUD, intrauterine demise; TOP, termination of pregnancy)

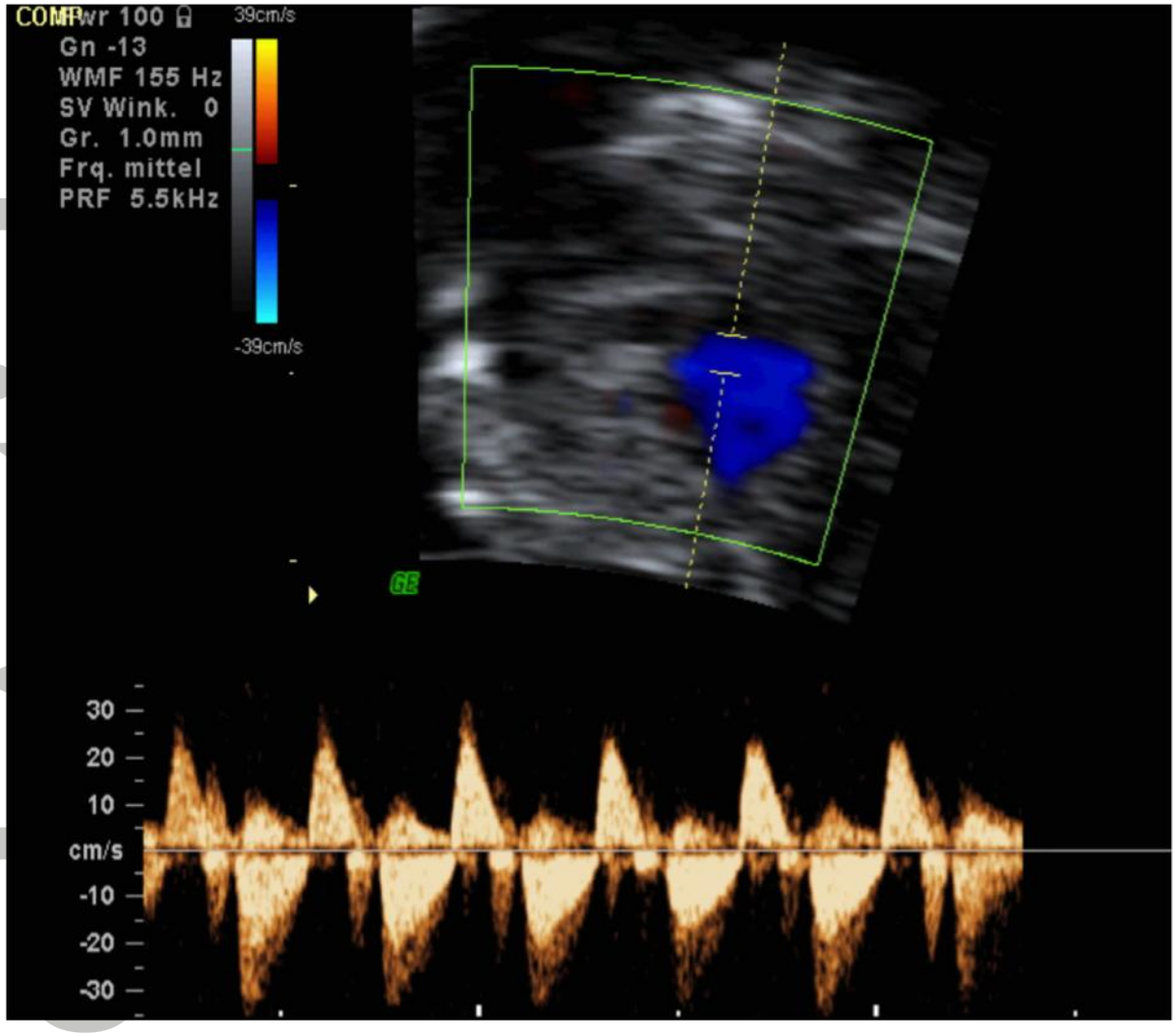

Figure 6a

Blood flow across pulmonary fibrous annulus in fetus of 13 weeks of gestation with TOF/APVS. Continuous wave Doppler recording demonstrates pulmonary to-and-fro-flow. (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome)

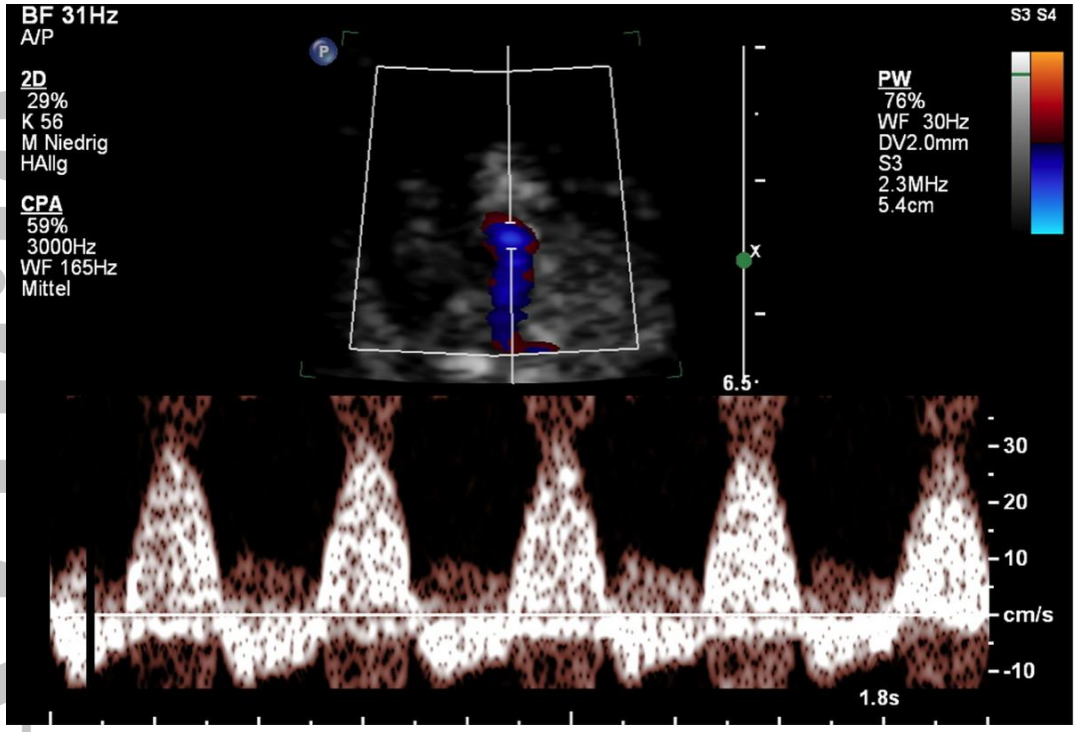

Figure 6b

Fetus (13 weeks of gestation) with TOF/APVS and cystic hygroma; to-and-frow-flow in the umbilical artery. (TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome)