Aus dem Zentrum für Gynäkologie gynäkologische Endokrinologie und Onkologie
Direktor: Prof. Dr. Uwe Wagner

des Fachbereichs Medizin der Philipps-Universität Marburg

ABSENT PULMONARY VALVE SYNDROME PRENATAL DIAGNOSIS, ASSOCIATION AND OUTCOME

Inaugural- Dissertation zur Erlangung des Doktorgrades der gesamten Humanmedizin dem Fachbereich Medizin der Philipps- Universität Marburg

vorgelegt von

Herrn Marios Mamalis aus Athen

Marburg 2019

Angenommen vom Fachbereich Medizin der Philipps-Universität Marburg am: 18.01.2019

Gedruckt mit Genehmigung des Fachbereichs.

Dekan: Herr Prof. Dr. H. Schäfer

Referent: Herr Prof. Dr. R. Axt- Fliedner

1.Referent: Frau Prof. Dr. M. Kühnert

Table of contents

Introduktion

1.1.1 Embryology and anatomy of the heart

The cardiovascular system is the first functional organ system of an embryo. The embryonic development of the heart is a complicated process and it lasts several weeks (27). The heart develops in a modular sequence. Primary cardiac crescent (PCC) forms within the splanchnic layer of the cranial lateral plate mesoderm. Within the embryonic folding, the most cranial portion of PCC comes to lie ventral to foregut endoderm. The primitive heart tube is the result of the fusion of limbs of PCC as lateral body folds move medially. The left ventricle develops from the primary cardiac crescent, the right ventricle and outflow tract originate from the secondary heart field, and cells that form the atria, contribute to the formation of ventricles. The left and right patterning within the heart is established early in the gastrulation. The ballooning model tries to explain the development of the atrial and ventricular chambers; atrial chambers balloon from primitive atrium, atrial septum grows between systemic und pulmonary veins as well as atrial appendages balloon from the initial common atrium. Ventricles balloon from the initially common ventricle.

The contruncus constitutes the outflow tract of the primitive heart tube; the conus arteriosus constitutes the right and the left ventricular outflow tracts. The truncus arteriosus constitutes the ascending aorta and pulmonary trunk. Paired dorsal aortae develop into mesenchym on either side of the notochord, the heart tube is rotated into chest as cranial end of

embryo bends, the dorsal aortae follow in a loop, which is the aortic arch and the paired dorsal aortae fuse from the 4th thoracic to the 4th lumbar vertebrae and to a single midline aorta.

In the fetus main pulmonary artery (PA) trifucates into ductus arteriosus (DA), right pulmonary artery (RPA) and left pulmonary artery (LPA).

Vitelline veins carry blood from the yolk sac to the embryo and give rise to the venous plexus within the developing liver, and they are precursor to sinusoids and hepatic/portal veins. Hepatic sinusoids interrupt cranial portions of UV and VV between the developing liver and heart. Cardinal veins drain the embryonic disc. The sinus venosus of the primitive heart tube is a pair of common cardinals veins via two sinus horns; the right sinus horn eventually drains all systemic venous returns by developing superior/ inferior vena cavae, and it incorporates into the wall of the right atrium.

The umbilical veins drain the chorion; the remaining left umbilical vein becomes the conduit for oxygenated blood returning from the placenta to the embryo. Ductus venosus drived from left umbilical vein acts as a liver bypass to carry umbilical vein blood primarily to the inferior vena cava (IVC) and the heart (21,31).

1.1.2. Fetal circulation

Blood is oxygenated by the placenta in the fetus and returns to the heart via the umbilical vein. This enters the liver to anastomose with the left portal vein. From here, the oxygenated bood is directed across the foramen ovale to the left side of the heart. Deoxygenated blood returns to the right atrium via the superior and inferior vena cavae. This blood flows into the right ventricle and pulmonary artery. Most of the right ventricular output enters the ductus arteriosus to join the descending aorta, which perfuses most of the fetal torso.

1.1.3. Fallot-tetralogy

The tetralogy of Fallot (TOF) is a congenital heart disease and it is defined by an obstruction of the right ventricular outflow tract (RVOT), a ventricular septal defect (VSD), an overriding aorta and a right ventricular hypertrophy. TOF ist the most common cyanotic congenital heart disease. 5% of all liveborn with cyanotic heart disease have TOF. The embryonic mechanism remains uncertain due to its complexity (34). It is supposed to be an incomplete rotation of the conotruncus and a deviation of the conal septum anterior, superior and leftwards.

Concerning the etiology of TOF, diabetic mothers present a high risk (RR 3:1). Mothers with phenylketonuria that use retinoic acids and trimethadione show an increased risk as well. TOF may occur in the CHARGE Syndrom, VACTERL association, 22q11.2 deletion and trisomy

21. ToF ist classified in three groups; The first category of ´´TOF with pulmonary stenosis´´ can be subdivided into two subgroups based on the degree of stenosis, i.e. mild or no stenosis and moderate to severe stenosis. The other categories are ``TOF with the pulmonary atresie`` and ``TOF with absent pulmonary valve``.

The VSD and the overriding aorta are the standard echocardiographic findings. The pulmonary stenosis is the result of the minderperfusion of the valve with a consequent hypertrophy of the right ventricle. The 4-chamber view (4CV) is normal in > 95% of prenatal cases. Concerning the treatment, the prenatal consultation with neonatology and pediatric cardiology is necessary and the delivery plan should be scheduled at a tertiary center. Follow-up for progressive RVOT obstruction is essential, because an early intervention may be required in case of significant RVOT obstruction. The surgical repair includes the VSD closure and the right ventricular outflow tract reconstruction with valve-sparing, infundibular ressection, transannular patch and RV-pulmonary artery conduit (6). The prognosis will be determined by the aneuploid syndrom; if isolated, it has an excellent short -and long- term outcome with definitive repair.

1.1.4 Absent pulmonary valve syndrome

With the 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. This may lead to a marked pulmonary insufficiency with a to- and from- blood flow

over the dysplastic valve, an aneurysmal dilation of the main and branch pulmonary arteries and concomitant cardiomegaly, causing compression of the bronchi. Absence of the ductus arteriosus is common with APVS and it has been postulated that absence of the arterial duct plays an important etiologic role in APVS.

APVS carries a significant perinatal mortality und morbidity and a postnatal presentation may be aggrevated by severe respiratory symptoms including long-term obstructive lung disease.

Absent pulmonary valve syndrome (APVS) occurs with the tetralogy of Fallot (TOF/APVS) and with an intact ventricular septum (APVS/IVS) in the setting of isolated APVS or associated with tricuspid atresia, Ebstein anomaly or in combination with an absent aortic valve. In the majority of cases, the ductus arteriosus is absent. Connection of a discontinuous left pulmonary artery to the patent arterial duct has been described for a few rare cases (12,31).

In postnatal series, it accounts for 2-6 % of all cases with TOF and 0.2-0.6% of all congenital heart defects. In prenatal series, it accounts for approximately 20% of all cases with TOF and 1% of all congenital heart defects (4,13,16). Intrauterine demise due to cardiac failure, hydrops fetalis, extracardiac and chromosomal associations as well as termination of pregnacy (TOP) might acount for different incidents in pre- and postnatal series and the potentially better outcome in recent postnatal series with reported survival rates of 72%-86%.

Most studies deal with cases diagnosed from the second trimester and few cases have been described within the first trimester (3,4).

In Figure 1,2,3,4 and 5 are shown the most common sonographic findings.

Figure 1

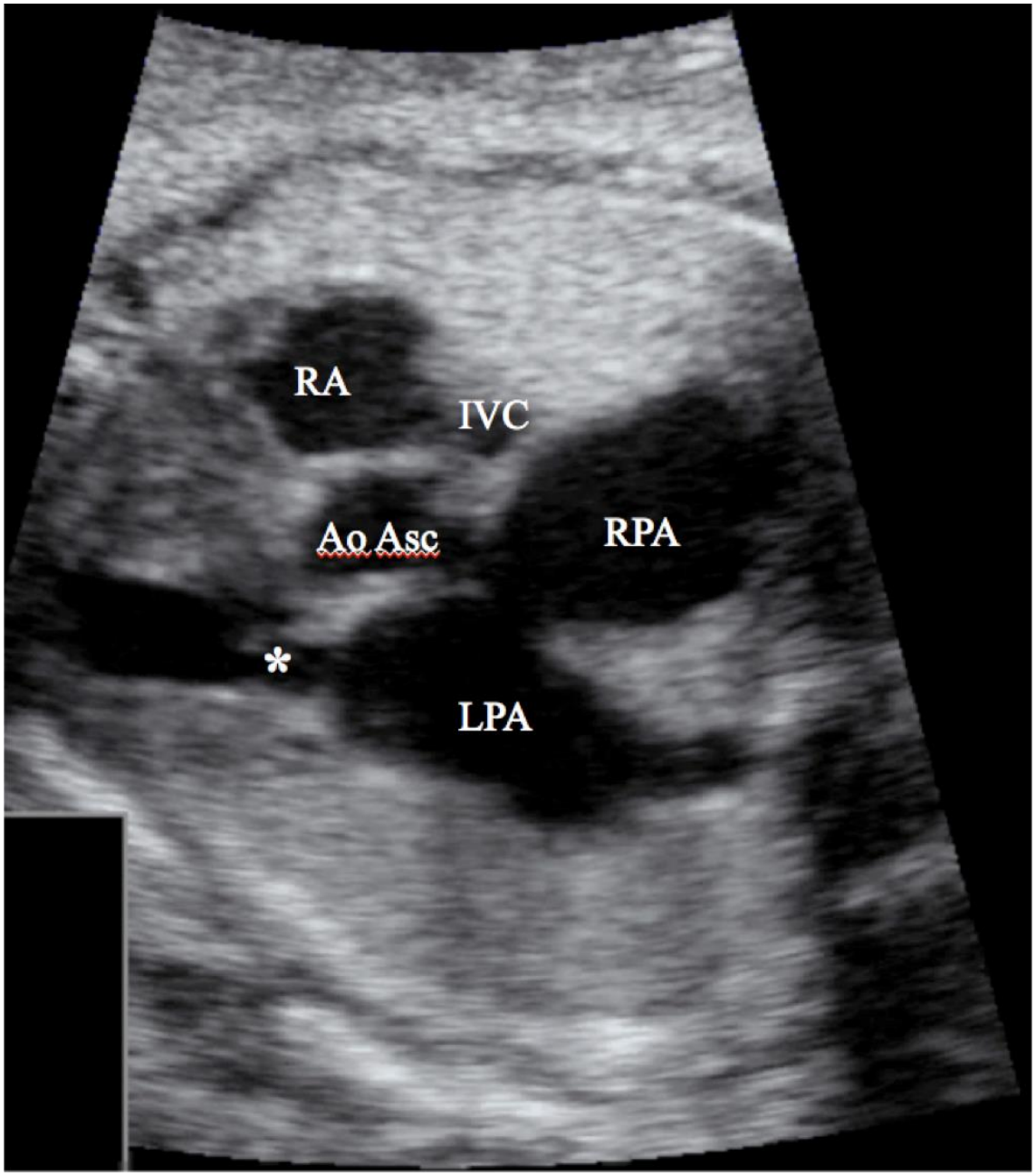

Figure 1 Fetus with TOF/APVS and dilated RPA and LPA.
(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; RPA, right pulmonary artery; LPA, left pulmonary artery; RA, right atrium; IVC, inferior vena cava; Ao Asc, ascending aorta; *, pulmonary fibrous annulus)

Figure 2

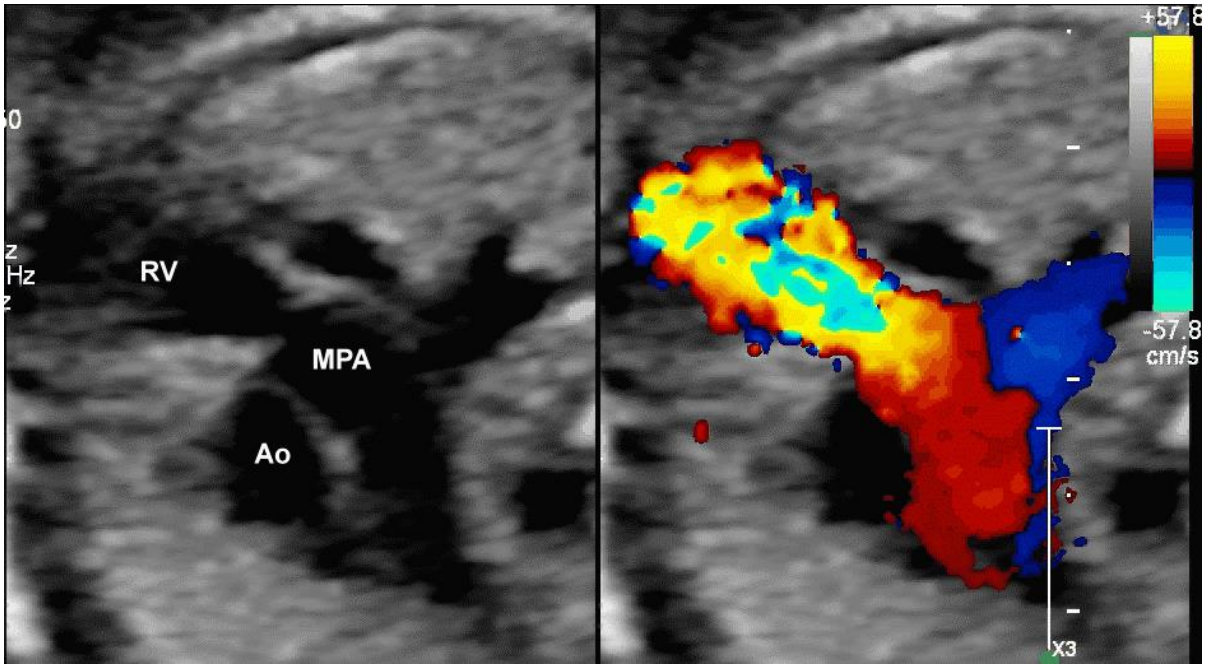

Figure 2 Fetus (21 weeks of gestation) with APVS, ventricular septum defect and right aortic arch. On short-axis view at the level of the great vessels systolic antegrade flow (blue) and diastolic retrograde flow (red) across pulmonary fibrous annulus are visualized.
(APVS, absent pulmonary valve syndrome; RV, right ventricle; Ao, aorta; MPA, main pulmonary artery)

Figure 3

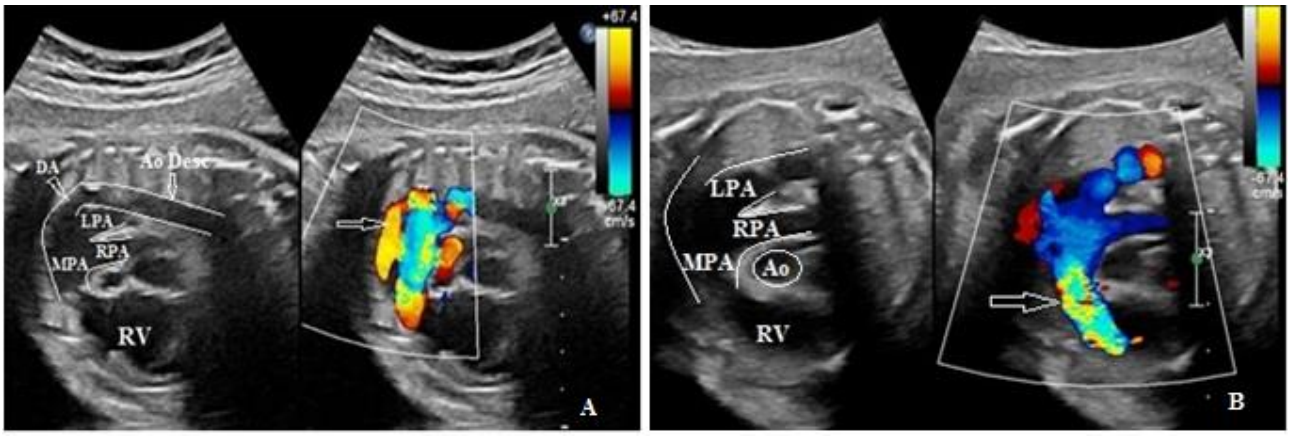

Figure 3 Fetus of 31 weeks of gestation with APVS/IVS. Ductal arch view with color Doppler demonstrates:
A) patent DA with blood flow (big arrow) and dilated LPA and RPA
B) severe pulmonary regurgitation (arrow) across pulmonary fibrous annulus
(APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum; DA, ductus arteriosus; MPA, main pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery; Ao, aorta; RV, right ventricle; Ao Desc, descending aorta.

Figure 4

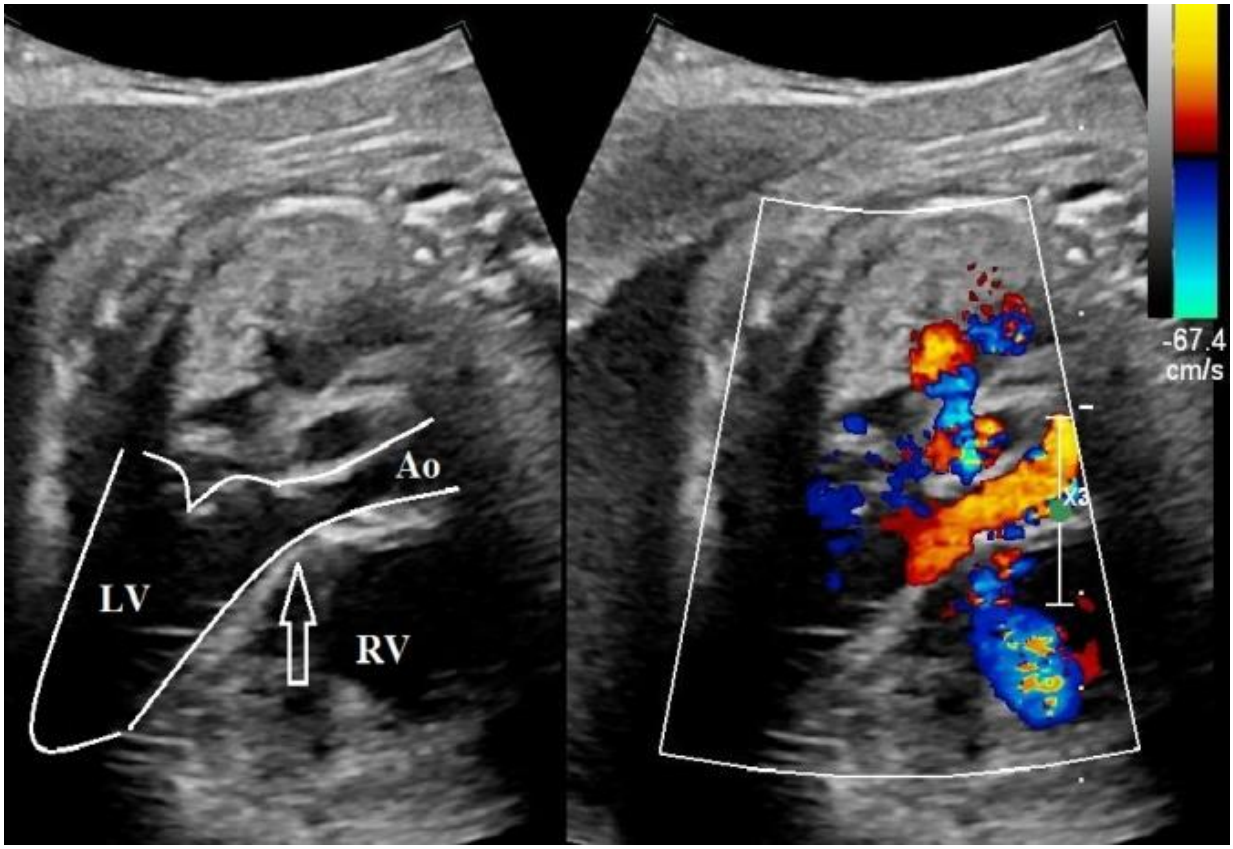

Figure 4 The same fetus of 31 weeks of gestation with APVS/IVS. On long-axis view of the LVOT, IVS (arrow) without any inter-ventricular shunt on color Doppler is visualized.
(APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum; LVOT, left ventricular outflow tract; LV, left ventricle; RV, right ventricle; Ao, aorta)

Figure 5

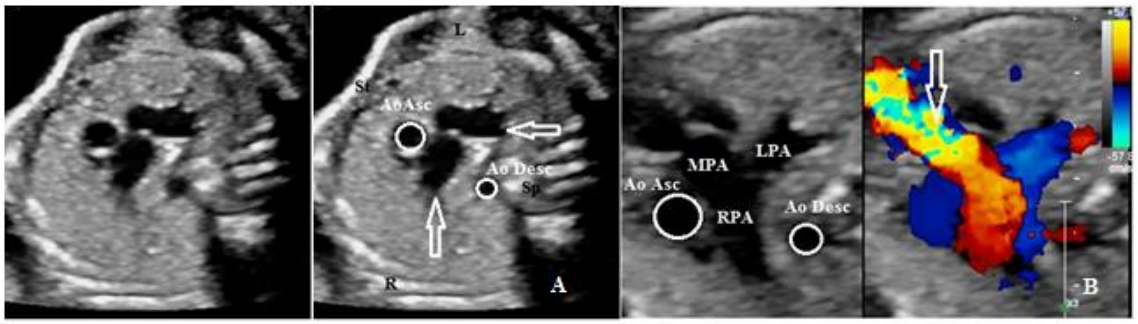

Figure 5 Fetus of 21 weeks of gestation with APVS, ventricular septum defect and right aortic arch.
A) On three vessels view dilated pulmonary arteries (arrows) are shown;
B) B) Short-axis view at the level of the great vessels visualizes dilated main pulmonary artery (MPA), left (LPA) and right (RPA) pulmonary branches and severe pulmonary regurgitation (arrow) across narrow pulmonary fibrous annulus.
(APVS, absent pulmonary valve syndrome; Ao Asc, ascending aorta; Ao Desc, descending aorta)

1.1.5. 22q11.2 Deletion Syndrome

The 22q11.2 Deletion Syndrome is one of the most recognizable chromosome abnormalities causing heart defects (15). It is characterised by conotruncal heart defects, such as a right-sided aortic arch or an interrupted aortic arch, as well as tetralogy of Fallot, cleft palate, micrognathia and hypertelorism. It is an autosomal dominant disease, caused by a haploinsufficiency of 3 genes in del22q11.2.

22q11.2 deletion syndrome or DiGeorge syndrome cannot be diagnosed

by routine karyotype, but requires fluorescence in situ hybridization. It is a rare anomaly (1:3000 live births). Concerning the postnatal signs and symptoms, the phenotype is often quite subtle. The congenital heart disease ist the most common sign (74%). The palatal abnormalities such as velopharyngeal insufficiency, submucosal cleft palate and cleft palate are the second most common sign with 69%. Other characterisitc facial features are the prominent broad nasal bridge, the widely spaced eyes, the downturned mouth, the small recessed jaw and the bulbous nasal tip. These children show learning disabilites, feeding problems, hypocalcemia, hearing loss and suffer from immune deficiency through a thymic hypo/aplasie. In all cases a genetic counselling is required. A prenatal diagnosis by FISH-analysis of amniocytes is unavoidable in high-risk pregnacies based on sonographic findings such as conotruncal heart defect and or cleft palate. Delivery should take place in a tertiary center (31).

2. Goals

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

The goal of this study is to analyze the spectrum of prenatally diagnosed absent pulmonary valve syndrome (APVS) and the outcome from diagnosis onwards of fetuses with APVS and tetralogy of Fallot (TOF/APVS) and with APVS and intact ventricular septum(APVS/IVS).

The current study ist the largest study to date analyzing fetal outcome.

3. Methods

This was a multicenter retrospective analysis of all subjects with a diagnosis of APVS 2012 to 2016. Data from 9 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 colour Doppler and pulsed-wave interrogation (32,6). Cardiovascular analysis was performed by two dimensional, colour 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 9 MHz 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 Heathcare 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). 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 tranlucency (NT) within the first trimester, and pregnacy 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 Fischer's exact test.

All values are given in mean +/- standard deviation (SD) unless otherwise stated. A p –value<0.05 was considered significant. Institutional review board approval of the main side (Justus-Liebig-University, Giessen, Germany) was obtained.

4. Results

During the study period 71 cases with APVS were diagnosed antenatally. 59 fetuses (83.1%) were classified as having TOF/APVS, 12 (16.9%) of the cases presented with APVS/IVS as shown in figures 1-5. 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 encoutering false positive nor incorrect diagnoses.

Table 1 details general information on the total study cohort. Nine 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 TOF/APVS (22.3 wks) and APVS/IVS (20.2 wks). Hydops fetalis was found in eleven cases (16.9%). Seven cases with TOF/APVS presented with hydrops (13.2%), in contrast to four cases with APVS/IVS (33.3%, $p<0.04$). A patent DA was found in five fetuses with hydrops fetalis (31.3%). Among those five fetuses two had TOF/APVS and three had APVS/IVS. Patency of DA was registered in 14 of 53 cases (26.4%) without hydrops. Information on intrauterine fetal demise (IUD) was obtained in sixty two cases (85.9%). IUD occured nine times (14.7%) in the total cohort. IUD was registered in six of fifty three cases with TOF/APVS (11.3%) in contrast to three of nine (33.3%) in APVS/IVS. In four of those nine cases DA was patent (44.4%). Information on both IUD and presence/absence of DA was obtained in fifty cases (70.4%). Six IUDs patency of the DA was observed in four cases (66.6%). Of the latter four fetuses two presented with TOF/APVS and APVS/IV

each.

In twenty three of sixty two cases with ascertained information parents opted for TOP (37.7 %). TOP was performed in twenty one cases with TOF/APVS (39.6%) and two cases with APVS /IVS (22.2%). Among TOPs there were seven cases presenting aneuploidy, four cases (17.4%) with hydrops fetalis and ten cases with extracardiac anomalies (43.5%). Consequently survival to birth was twenty six of fifty three cases (49.1%) within the TOF/APVS group, and three of eight in the APVS/IVS cohort (35%, one ongoing pregnacy).

Table 1

Parameter	TOF/APVS	APVS/IVS	level of significance (p-value)
Number of fetuses (n)	59	12	
Lost for follow up	6	3	
Mean GA (weeks)	22	21	0.48
Hydrops (n)	7/53 (13.2%)	4/9 (44.4%)	0.04*
IUD (n)	6/53 (11.3%)	3/9 (33.3%)	0.08
TOP (n)	21/53 (39.6%)	2/9 (22.2%)	0.32
Live birth (n)	26/53 (49.1%)	3/8 (37.5%)	0.54
Postnatal survival >28 days (n)	18/49 (36.7%)	3/8 (37.5%)	0.97

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)

Four newborns of twenty nine live births (13.7%), all within the cohort of TOF/APVS, died within the neonatal period, and all showed severe respiratory failure. Further four were lost to follow up after live birth. Subsequently, survivals beyond the neonatal period in actively managed cases in TOF/APVS was eighteen of fourty five cases (40 %) compared to

three of eight with APVS/IVS (37.5 %). In total, survival from initial diagnosis beyond the neonatal period was eighteen of fifty three with TOF/APVS (33.9%) compared to three of eight (37.5%, one ongoing pregnacy) in APVS/ IVS (figure 6).

Figure 6

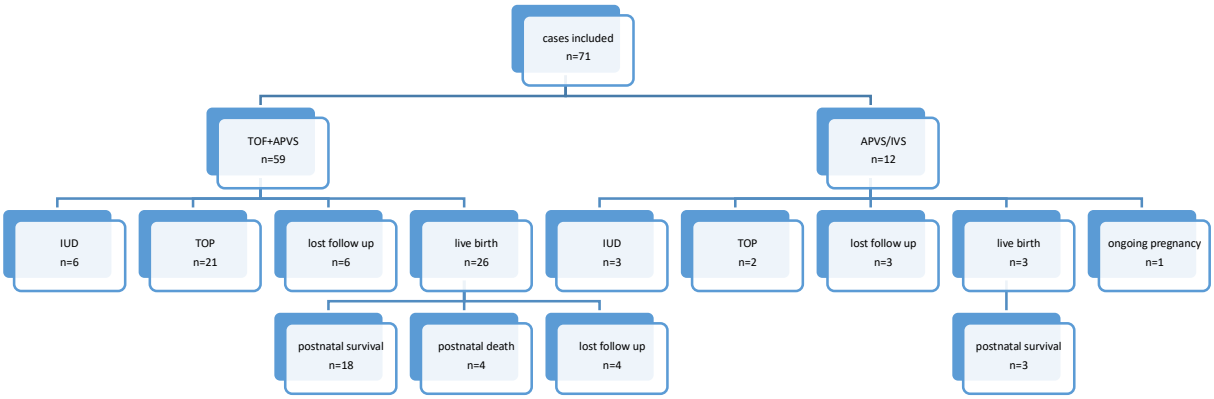

Figure 6

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)

Extracardiac non –chromosomal anomalies were frequent in both cohorts occuring in thirty six of seventy-one fetuses (50.7%). Anomalies predominantly included the central nervous system, urogenital anomalies and gastointestinal anomalies. Agenesis of the thymus occured in five cases, four of them with TOF/APVS (table 2)

Table 2

	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	
Placentomegaly	1	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)

Information on prenatal karyotype results were retrieved in twenty nine fetuses (40. 8%). Sixteen of tweenty- nine fetuses (55.1%) presented with a normal karyotype. There were five cases with trisomy 13 (17.2%) and two cases of trisomy 18 (6.8%) respectively. The two fetuses with trisomy 18 occured in the APVS/IVS group, whereas all five trisomy thirteen cases occured within the group of TOF/APVS. All six fetuses with microdeletion 22q11.2 (20.6%) occured within the TOF/APVS cohort (Table 3).

Table 3

	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

Table 4 summarizes information on echocardiographic details of the cohort. Assessment of cardiac axis was available in fourty nine (69%)

cases of the cohort. Counterclockwise leftward rotation of the cardiac axis was found in fourty four fetuses (89.8%), whereas a normal cardiac axis was seen in five fetuses (10.2%) all of them having TOF/APVS. All seven 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 five fetuses (11.9%) with TOF/APVS having a normal cardiac axis. Laterality of the aortic arch (RAA) occured within the group of TOF/APVS (p=0.1, figure 5). Although no case of RAA was found in the group of APVS/IVS, the comparison between both groups was statistically not significant. In fifty of seventy one cases (70.4%) infomation on patency of the DA was retrieved. In thirty two fetuses (62.7%) the DA was absent, whereas in eighteen (37.3%) a DA was present. All cases with absent DA occured in the TOF/APVS group. In contrast to nine of fourty one TOF/APVS with patent DA was (21.9%) all nine cases with APVS/IVS had a patent DA ($p<0.001$). In one ongoing pregnacy with APVS/IVS and membranous TA (fig. 2) a narrow duct with z- scores ranging from –2.34 at 23+4 wks to -3.09 at 25+6 wks was diagnosed.

All seven cases with RAA occurred in the TOF/APVS group (p00.1, figure 5). The pulmonary artery valve to- aortic valve annular ratio was higher in APVS/IVS cases compared to TOF/APVS cases ($p<0.02$, figure 5). However, in TOF/APVS the pulmonary artery valve to- aortic valve annular ratio did not differ significantly in survivors from non-survivors ($p<0.02$, table 4).

Table 4

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 7-9 display z- scores of main and branch pulmonary arteries at time of diagnosis and throughout gestation in TOF/APVS with ascertained information. In all cases with ascertained measurement after the first trimester persistently increased diameters in MPA and branch pulmonary arteries were measured 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, 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-sores 1.15, 1.75 and 0.61 respectively).

Figure 7

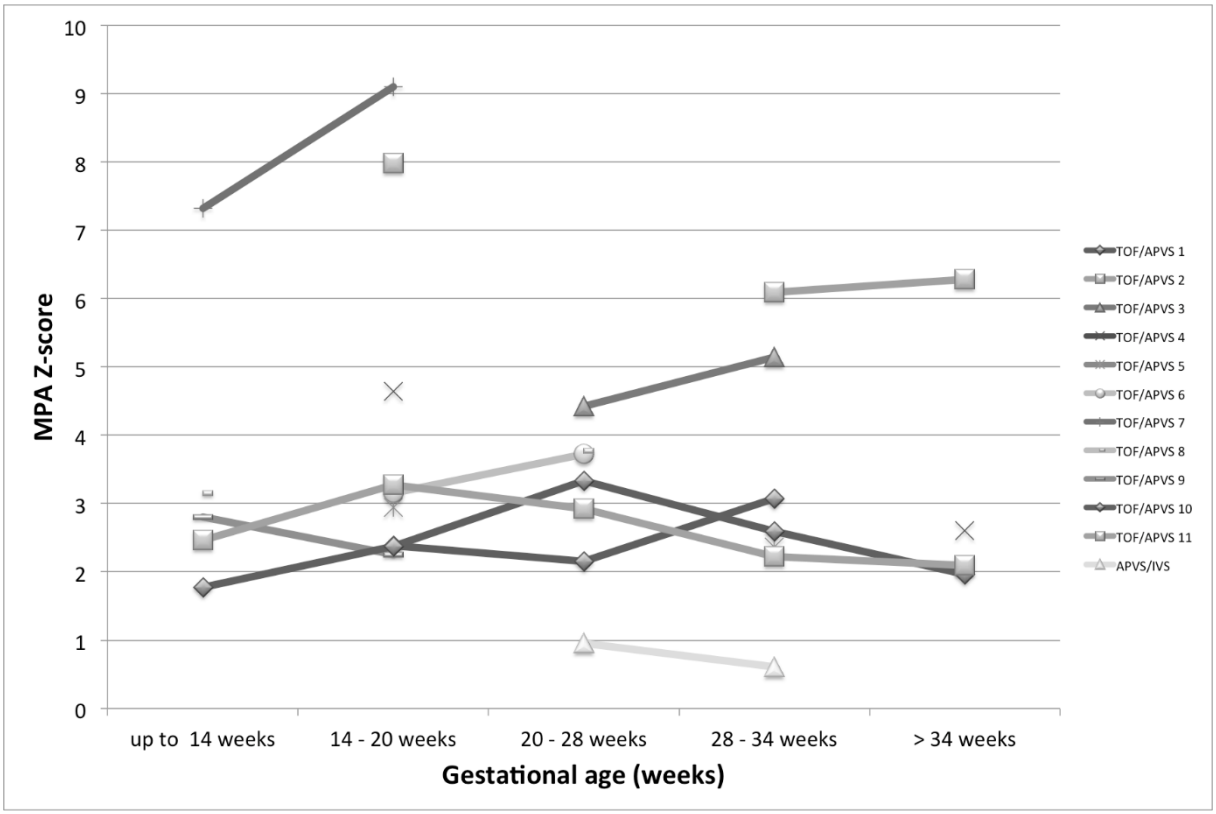

Figure 7 Fetal Z-score values of main pulmonary arteries (MPA) at time of diagnosis and throughout gestation in 11 serially followed cases with TOF/APVS and one case with APVS/IVS.

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

Figure 8

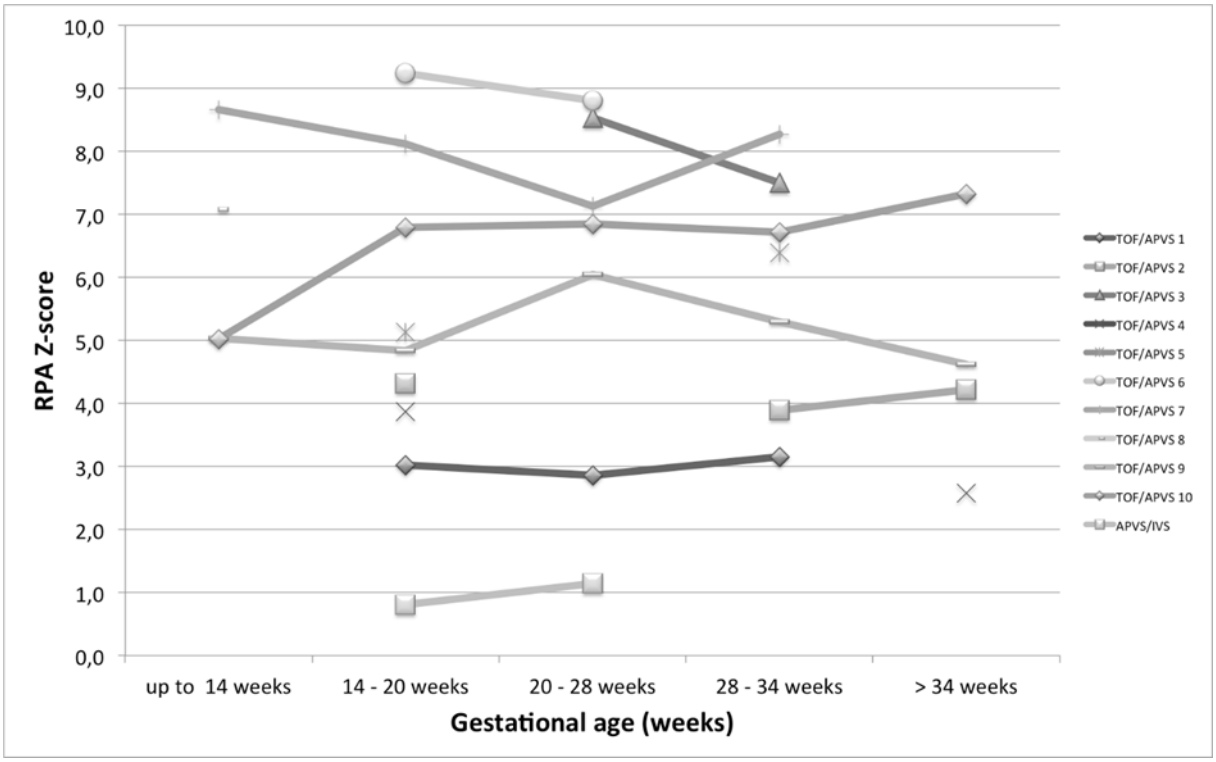

Figure 8 Fetal Z-score values of right pulmonary arteries (RPA) at time of diagnosis and throughout gestation in 10 serially followed cases with TOF/APVS and one case with APVS/IVS.

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

Figure 9

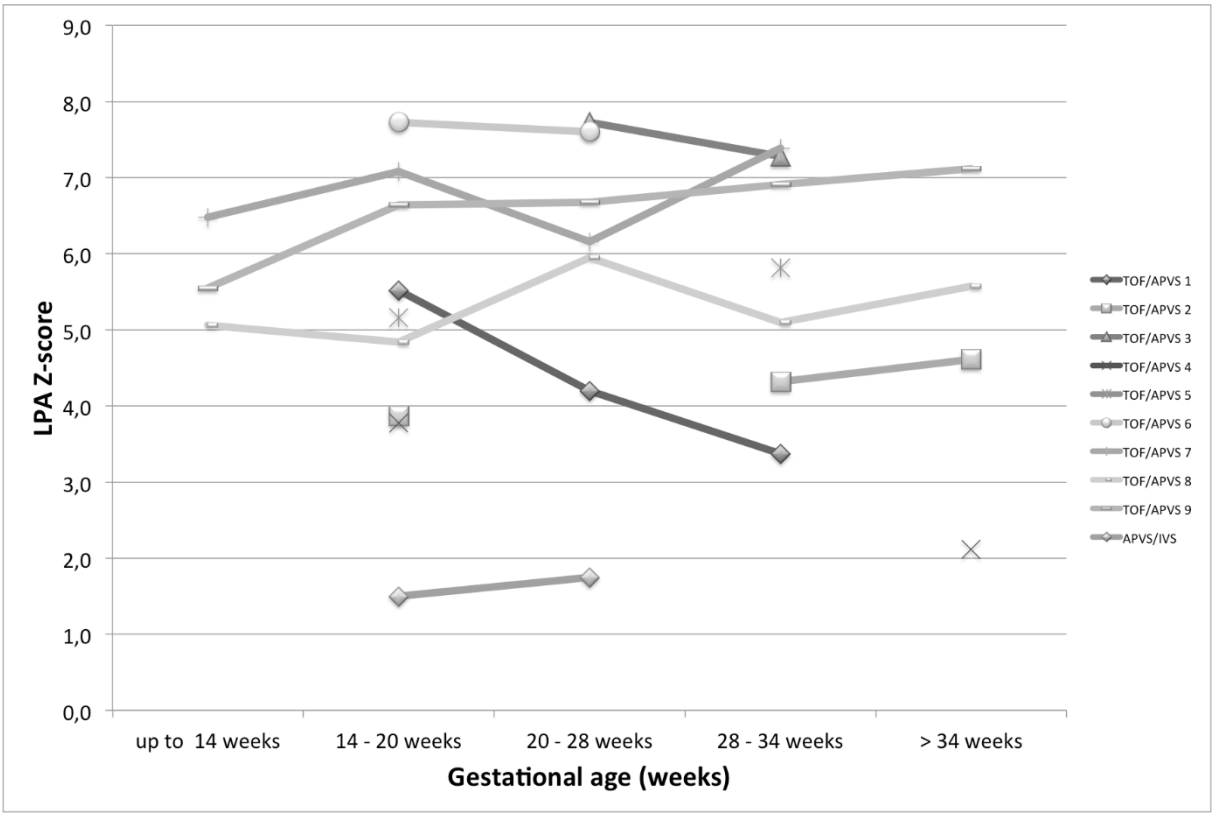

Figure 9 Fetal Z-score values of left pulmonary arteries (LPA) at time of diagnosis and throughout gestation in nine serially followed cases with TOF/APVS and one case with APVS/IVS.

(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome

IVS, intact ventricular septum)

First trimester diagnosis was achieved in thirteen fetuses (18.3%), 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 diagnosis is shown in figure 10.

Figure 10

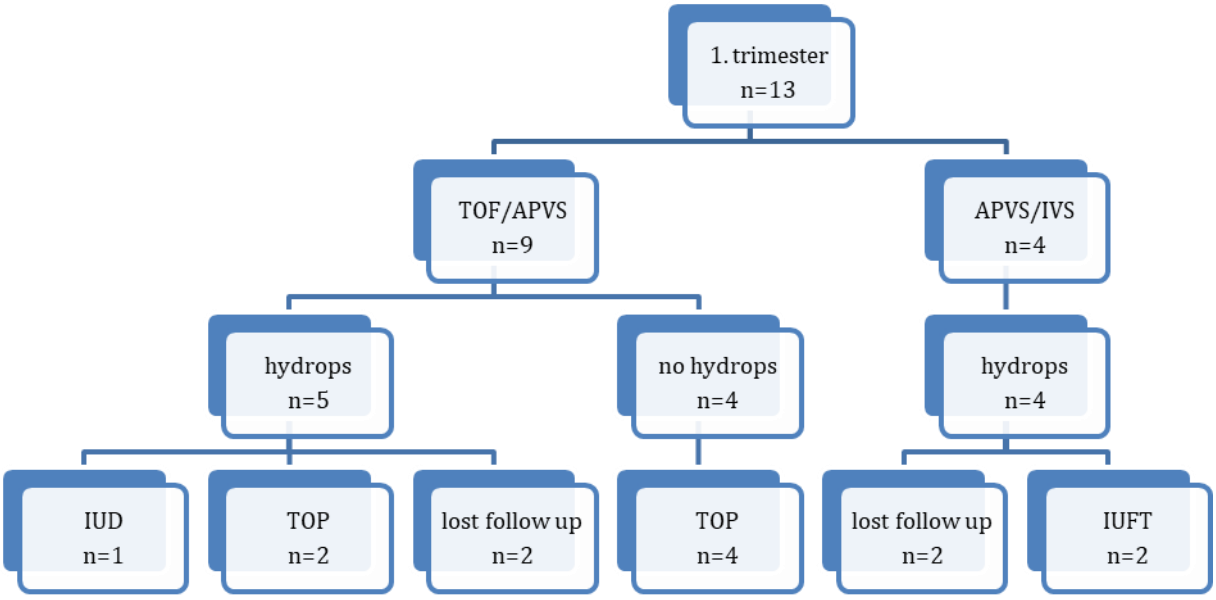

Figure 10 Flowchart of thirteen APVS cases diagnosed in first trimester and outcome according to the type of APVS

(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome; IVS, intact ventricular septum; IUD, intrauterine demise; TOP, termination of pregnancy)

Nine of thirteen cases (69.2%) were diagnosed as having TOF/APVS whereas four fetuses presented with APVS/IVS (30.8 %). Within the group of first trimester diagnosis, hydrops fetalis was present in nine cases and in all nine fetuses an increased NT was measured (figure 11).

Figure 11

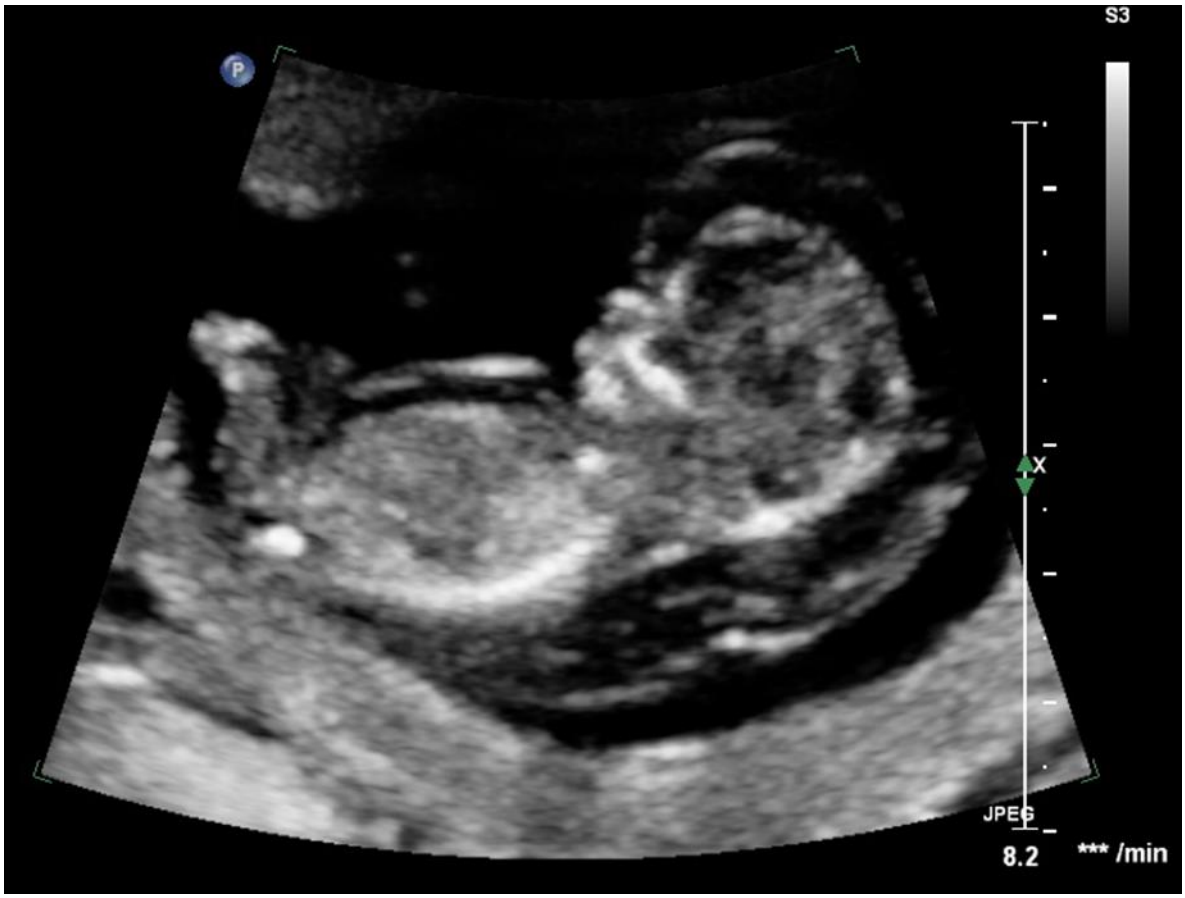

Figure 11 Fetus (13 weeks of gestation) with TOF/APVS and cystic hygroma. (TOF, tetralogy of Fallot; APVS, absent pulmonary valve syndrome)

Of those, five cases presented with TOF/APVS (55,5%) and all four cases with APVS/IVS and first trimester diagnosis presented with hydrops fetalis. Abnormal Doppler profiles with reversal flow at the level of the pulmonary annulus, the main pulmonary trunk or to-and-fro blood within the umbilical artery was detected in all of those nine fetuses (figure 12a, b).

Figure 12a

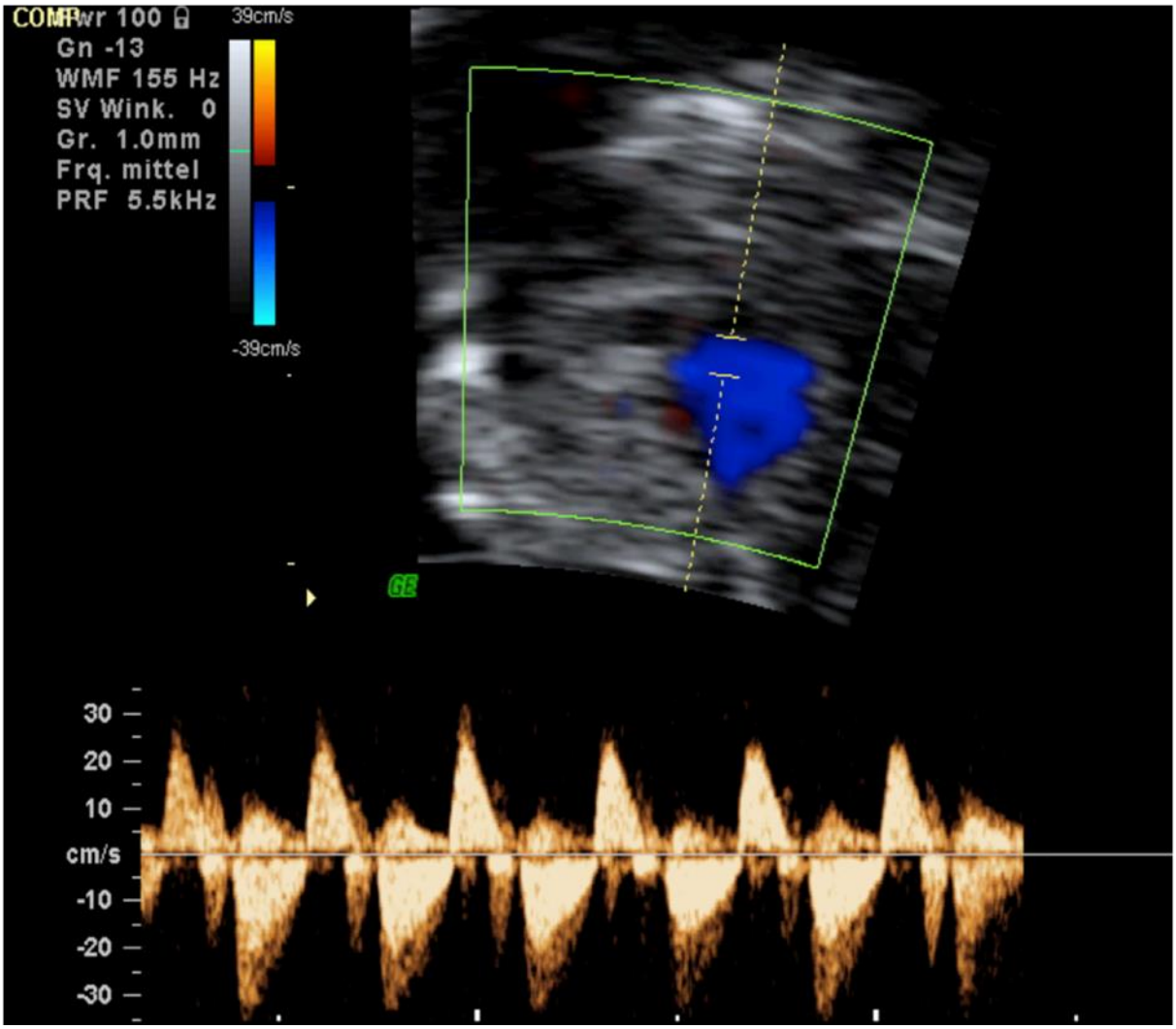

Figure 12a Blood flow across pulmonary fibrous annulus in fetus of 13 weeks of gestation with TOF/APVS. Continuous wave Doppler recording demonstrates pulmonary to-and-fro-flow.
(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome)

Figure 12b

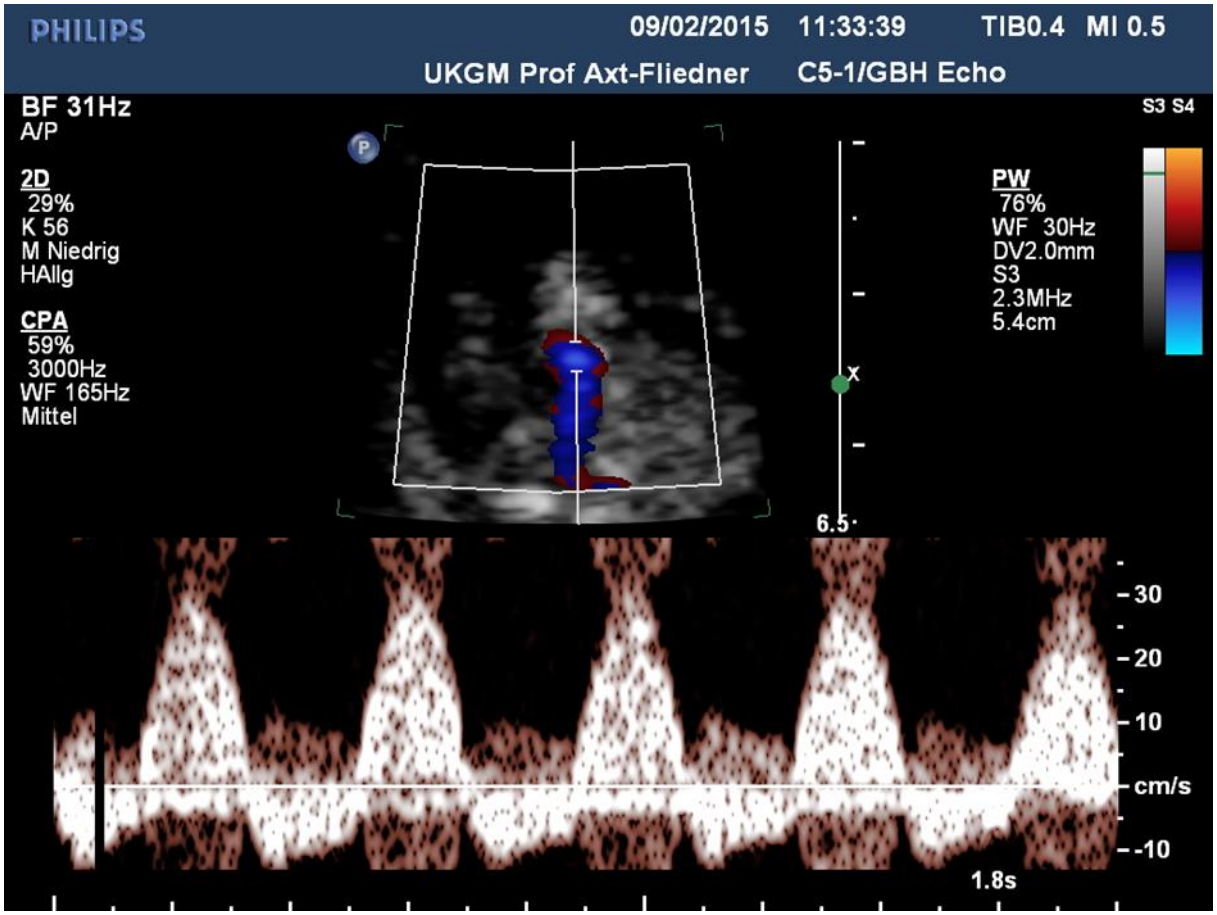

Figure 12b Fetus (13 weeks of gestation) with TOF/APVS and cystic hygroma; to-and-frow-flow in the umbilical artery.

(TOF, Tetralogy of Fallot; APVS, absent pulmonary valve syndrome)

5. Discussion

The findings of our study revealed important differences between the two main entities ocurring 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 (12,13,28,30). 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 versus second trimester screening might account for this high number of first trimester diagnosis in our cohort compared to results from the high number of first trimester diagnosis ranging from 20 to 37 wks in 12 cases or 18 to 39 wks in 21 cases in a report from the Toronto group with reported diagnosis ranging from 20 to 37 wks in 1 case or 18 to 39 wks in 21 cases in a report from Philadelphia (28,30). Results from Gottschalk et al. and Galindo et al. underline the feasibility of first trimester diagnosis in those cases (12,13,5). 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 prenatal counselling should include chromosomal testing including microdeletion 22q11.2(12,13,30).

Second, all fetuses with a first trimester diagnosis died or were terminated prior 24 wks due to presence of hydrops or chromosomal anomalies. Nine of those thirteen cases presented with TOF/APVS, in those four hydrops was present at the time of diagnosis and in two fetuses patency of the DA

was ascertained on first trimester ultrasound. Further three cases of APVS/IVS were diagnosed with hydrops fetalis and in all three cases patency of DA was diagnosed. 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 aortopulmonary shunting and right sided cardiac failure (34).

No fetuses 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 case in nine of the thirteen 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 a RV dysfunktion (33). 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 dysfunktion.

Third, absence of DA only occured in fetuses with TOF/APVS, fetuses presented 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 dilation of the branch pulmonary

arteries in this condition (9,10,20). 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 (11). 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 (9,10,20,33). 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 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 dilation 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 pregnacy.

Marked dilation 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 resistence in the fetus might contribute to enlargement of PA branch 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 narrow,

however patent DA, massive dilatation of the PA branches was not seen in our cohort as in the series by Gottschalk et al. (13). From a clinical perspective, in our series over all survival rate after prenatal diagnosis of TOF/APVS was 49.1% compared to 37.5% in APVS/IVS and reached 0% in actively managed live births in TOF/APVS and APVS/IVS, respectively. These numbers are favourable compare to data from Gottschalk et al. and the reported 14% by Glindo et al. (28,24). Both series included also first trimester diagnosis. The results are comparable to the 50% survival reported by Wertaschnigg et al. from the initial diagnosis but lower than 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. (28,30). 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 (28,30, 2,8). In APVS/IVS survival rate was 100 % being higher as previously reported. However, we only had three patients with intention -to-treat and in those patients APVS/IVS occured 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, where single ventricle physiology is expected, has been diagnosed in our cohort. This constitutes a signifiant risk factor with consideration for heart transplantation. Prediction of outcome by echokardiographic parameters showed inconsistent results including a

higher pulmonary artery valve-to- Ao valve annular ratio and severe left ventricular dysfunktion as the most accurate variables (20,12,28,8). PAV/AoV 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 dysfunktion 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 charachter of our study, we did not assess left ventricular dysfunktion.

6. Limitations

The study is limited by its retrospective milticenter design. Some subjects were lost to follow up and data on postnatal outomes were difficult to ascertain due to the multicenter approach. The strenght of the study is its large cohort, to date, to the best of our knowledge the largest contemporary 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.

7. Summary:

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 und echocardiographic databases of nine referral centers were rewiewed from 2012-2016. Various clinical und echocardiographic parameters were retrieved.

Results:

The cohort included 71 cases, 59 with TOF/APVS and twelve with APVS/IVS. In 3% of cases the diagnosis was achieved within the first trimester. Association with hydrops fetalis was high within the first trimester

(69%). No fetus with known outcome survived after first trimester diagnosis. Karyotype anomalies occured in 44% with microdeletion 22q11.2 beeing the most frequent (21%). Intrauterine fetal demis (IUD) occured in 14.5%. Pulmonary artery dimensions were increased in all cases of TOF/IVS. Survival to birth was 49.1% in TOF/APVS und 37.5% in APVS/IVS. Survival beyond the neonatal period in actively managed neonates was 40% in TOF/APVS and 37.5% in APVS/IVS.

Conclusion:

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

8. Zusammenfassung:

Ziel:

Die Diagnose und das Outcome von pränatal diagnostizierten Fällen mit `absent pulmonary valve syndrome` soll dargestellt werden.

Methode:

Dies ist eine retrospektive Multizenteranalyse aus neun europäischen Zentren. Diese Vorgehensweise wurde aufgrund der Seltenheit der Entität so gewählt. Die Daten wurden zwischen 2012-2016 gesammelt.

Resultate:

Insgesamt konnten einundsiebzig Fälle eingeschleust werden. Davon waren 59 Fälle mit TOF/APVS und zwölf Fälle mit APVS/IVS. In 18.3% der Fälle konnte eine Diagnose im ersten Trimenon gestellt werden. 69% der Feten mit Diagnose im ersten Trimenon entwickelten einen Hydrops fetalis. Alle Feten mit Diagnose im ersten Trimenon kamen nicht lebend zur Welt. In 44% der Fälle mit Information wurde eine chromosomale Anomalie nachgewisen. Davon war mit 21% der Fälle die Mikrodeletion 22q11.2 die häufigste Anomalie. In 14.5 der Fälle wurde ein intrauteriner Fruchttod beobachtet. In den Fällen mit APVS/IVS waren die Durchmesser der Pulmonarterien erhöht. Nach intrauteriner Diagnosestellung überlebten 49.1% der Fälle in TOF/APVS und in 37.5% der Fälle mit APVS/IVS. In Neugeborenen mit Intention to treat überlebten 40% in TOF/APVS und 37.5 in APVS/IVS.

Schlußfolgerung:

Die Diagnose eines APVS kann im ersten Trimester erreicht werden. Die Prognose bei betroffenen Feten muß als zurückhaltend eingestuft werden, speziell im Falle einer Diagnose im ersten Trimester aufgrund von assoziierten Karyotypanomalien und einem gleichzeitig vorhandenen Hydrops fetalis.

9. List of abbreviations

AVV	atrioventricular valve
APVS	absent pulmonary valve syndrome
CTR	cardiothoracic ratio
DA	ductus arteriosus
LPA	left pulmonary artery
IVC	inferior vena cava
NT	nuchal tranlucency
PA	pulmonary artery
PaV	pulmonary valve
PA-V/AoV	Pulmonary valve/Aortic valve
PCC	primary cardiac crescent
RPA	right pulmonary artery

RAA	right aortic arch
RVOT	right ventricle outflow tract
TA	truncus arteriosus
TOP	termination of pregnacy
TOF/APVS	tetralogy of Fallot/ absent pulmonary valve syndrome
UV	umbilical vein
VSD	ventricular septum defect
VV	vitalline vein
Wks	weeks
CNS	central nervous system
4CV	4 chamber view

10. List of tabelles and figures

11. References:

1. Allan LD, Sharland GK, Milburn A et al. Prospective diagnosis of 1006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol 1994; 23:1452-1458.

2. Alsoufi B, Williams WG, Hua Z et al. Surgical oucomes in the tratment of patients with tetralogy of fallot and absent pulmonary valve. European Journal of cardio- Thoracic Surgery 2007; 31:354-359.

3. Aramian A, Gembruch U, Geipel A et al. Ebsteins anomaly oft he tricuspid valve in association with tetralogy of fallot and absent pulmonary valve syndrome. Fetal Diagn Ther 2011; 30: 153-156

4. Berg C, Thomsen Y, Geipel A et al. Reversed end diastolic flow in the umbilical artery at 10-14 wks of gestation is associatd with absent pulmonar valve syndrome. Ultrasound Ostet Gynecol 2007; 30:254-258.

5. Becker R, Schmitz L. Guschmann m et al. Prenatal diagnosis of familal absent pulmonary valve syndrome. Case report and review oft he literature: Ultrasound Obstet. Gynecol 2001; 17: 263-267.

6. Carvahlo JS, Ho SY, Shinebourne EA. Sequential segmental analysis in complex fetal cardiac abnormalities: a logical approach to diagnosis. Ultrasound Obstet Gynecol 2005; 105-111

7. Chen JM, GlicksteinJS, Margossian R et al. Superior oucomes of repair in infants and neonates with tetrallogy of Fallot with absent pulmonary valve syndrom. J Thorac Cardiovas Surg 2006; 1099-1104.

8. Donofrio MT, Jacobs ML, Rychik J. Tetralogy of Fallot with absent pulmonary valve: Echocardiographic morphometric features oft he right – sided structures and their relationship to presentation and outcome.

Journal oft he Amerian Society of echokardiography 1997; 10: 556-561

9. Emmanouilides GC, Thanopoulos B, Siassi B et als Agenesis of ductus arteriosuassociated with the syndrome of tetralogy of fallot and absent pulmonary valve. Am J Cardiol 1976; 37:403-409.

10. Ettedgui JA, Sharland HG, Chita SK et al. Absent pulmonary valve syndome with ventricular septal defect: role oft he arterial duct. Am J Cardiol 1990; 66: 233-234.

11. Fischer DR, Neches WH, Beerman LB et al. Tetralogy of Fallot with absent pulmonary valve syndrom. J thorac Cardiovas Surg 2006; 1099-1104

12. Galindo A, Gutier, Del Rio M et al. Prenatal diagnosis and outcome for fetuses with congenital absence ot the pulmonary valve. Ultrasound Obstet Gynecol 2006; 28:32-39.

13. Gottschalk I, Jehle C, Herberg U et al. Prenatal diagnosis of absent pulmonary valve from the 1st trimester inward: novel insights into pathophysiology, associated conditions and outcome of a rare cardiac defect. Ultrasound Obstet Gynecol; doi: 10.1002/uog.15977

14. Ilbawi MN, Fedorchik J, Muster AJ et al. Surgical approach to severly smpomatik newborn infents with tetralogy of Fallot and absent pulmonary valve. J Thorac Cardiovas Surg 1986; 91: 584-589.

15. Jacobson C. et al: Core neuropschological characteristics of children and adolescents with 22q11.2 deletion. J Intellect Diabil Res. 54(8): 701-13,2010

16. Jordaan HV.Cardiac size during prenatal development. Obstet Gynecol 1987; 69:854-858.

17. Latio K, Gembruch U, Geipel et al. Tricuspid atresia with absent pulmonary valve and intact ventricular septum: intrauterine course and outcome of an unusual congenital heart defect. Ultrasound Obstet Gynecol 2010; 35:243-245.

18. Lev M, Eckner FA. The pathologic anatomy of tetralogy of Fallot and variations. Dis Chest 1964; 45:251-261

19. McDonell BE, Raff GW, Gaynor JW et al. Outcome after repair of tetralogy of Fallot with absent pulmonary valve. Ann Thorac Surg 1999; 67:1391-1396.

20. Moon-Grady AJ, Tracy TA, Brook MM et al. Value of clinical and echocardiographic features in predicting outcome in the fetus, infant and child with tetralogy of fallot with absent pulmonary valve complex. Am J Cardiol 2002; 89:1280-1285.

Nasrallaf A, Williams RL, Nouri S. Absent pulmonary valve in tetralogy of fallot: clinical and angiographic considerations with review oft he literature. Cardiovasc Dis. 1974; 1: 392-299

21. Norgaard et al 2006

22. Pasquinin I, Mellander M, Seale A et al. Z-scores oft he fetal aortic isthmus and duct: an aid to assessing arch hypoplasie. Ultrasound Obstet Gynecol 2007; 29:628-633

23. Rabinovitch M, Grady S, David I et al. Compression of intrapulmonary bronch by abnormally arteries associated with absent pulmonary valves. Am J Cardiol 1982; 50: 804-813.

24. Rao B, Anderson RC, Edwards JE. Anatomic variations in the tetralogy of Fallot. Am Heart J 1871; 81:361-371

25. Razani RS, Sharland G, Simpson JM. Pranatal diagnosis by echocardiogram and outcome of absent pulmonary valve. AM J Cardiol 2003; 91:429-432

26. Schneider C, McCrindle BW, Carvahlo JS et al. Development of z-sores for fetal cardiac domensions from echocardiography. Ultrasound Obstet Gynecol 2005; 26:599-605.

27. Sohn, Cristof, Holzgreve, Wolfgang (2012): Ultraschall in Gynäkologie und Geburtshilfe. 3. Aufl.s.l.: Georg Thieme Verlag KG. Online verfügbar Verlag KG.

28. Szwast A, Tian Z, McCann m et al. Prospective diagnosis of 1006 consecutevive cases of congenital heart diesase in the fetus. J Am Coll Cardiol 1994; 23:1452-1458.

29. Volpe P, Paladini D, Marasini M et al. Characteristics, associations and outcome of absent pulmonary valve syndrome in the fetus. Ultrasound Obstet Gynecol 2004; 24:623-628

30. Wertadchnigg D, Jaeggi M, Chitayat D et al. Prenatal diagnosis and outcome of absent pulmonary valve syndrome: contemprary single-centre experience and review of the literature. Ultraschound Obstet Gynecol 2013; 41:162-167

31. Woodward, PaulaJ.; Kennedy, anne; Sohaey, Roya; Byrne, Janice L.B.; Oh, Karen Y.; Puchalski, Michael D.: Diagnostik **imaging. Third** edition.

32. Yagel S, Cohen SM, Achiron R. Examination oft he fetal heart by five short –axis viwes: a proposed screening method for comprehensive cardiac evaluation. Ultrasound Obstet Gynecol 2001, 17: 367-369.

33. Yeager SB, van der Velde ME, Waters BL et al. Prenatal role oft he

ductus arteriosus in absent pulmonary valve syndrome. Echocardiography 2002; 19:489-493.

34. Zach M, Beitzke A, Singer H et al. The syndrome of absent pulmonary valve and ventricular septal defects-anatomical features and embryonic considerations. Basic Res Cardiol 1979; 74:54-68.

12. Note of thanks

A special note of thanks goes to Prof. R. Axt- Fliedner for all his support. It was a great honour for me to work with him on this project.