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Prenatal diagnosis and outcome for fetuses with congenital absence of the pulmonary valve

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KEYWORDS: absent pulmonary valve syndrome; nuchal translucency; outcome; prenatal diagnosis

ABSTRACT

Objectives *To analyze fetal echocardiographic findings of absent pulmonary valve syndrome (APVS), its association with chromosomal and extracardiac anomalies including nuchal translucency (NT) and the outcome after diagnosis.*

Methods *Data of 14 fetuses with confirmed APVS retrospectively collected in two tertiary referral centers between 1998 and 2004 were analyzed. The variables examined were: reason for referral, gestational age at diagnosis and associated abnormalities, including first trimester NT thickness. Cardiac evaluation included measurement of cardiothoracic ratio, diameter of pulmonary arteries and Doppler flow in the pulmonary trunk. Information was retrieved from clinical files, recorded videotapes and stored images. Karyotyping including examination for the 22q11 deletion was performed in all cases.*

Results *Mean gestational age at diagnosis was 28 weeks, with 5/14 (36%) diagnosed before 22 weeks. In 13/14 (93%) there was an associated ventricular septal defect (subaortic in 12 fetuses and inlet-type in one) and all 13 had tetralogy of Fallot. Enlargement of the central pulmonary arteries and cardiomegaly were present in all cases diagnosed after 22 weeks. Of the five fetuses in which APVS was detected before 22 weeks, four (80%) had a normal pulmonary trunk diameter, two (40%) had normal pulmonary branches and three (60%) had normal cardiac size. The arterial duct was absent in 11/14 (79%). A correlation between presence of the arterial duct and the size of the central pulmonary arteries or cardiomegaly could not be established. Increased NT was observed in 4/10 cases (40%) for which this information was available. 22q11 microdeletion was diagnosed in three fetuses (21%). There were five terminations of pregnancy, one intrauterine death, five neonatal deaths and one infant death. Of the six neonates with respiratory distress, only one (17%) survived and of the eight babies in whom there was an intention to treat, two survived (25%).*

Conclusions *APVS can be accurately diagnosed by fetal echocardiography but screening ultrasound in the mid-second trimester is likely to have a low detection rate, probably due to the incomplete expression of the disease at this point. Many fetuses with APVS have an increased NT in the first trimester and this may help an earlier recognition of the defect. The most common associated karyotype anomaly is 22q11 microdeletion. Enlargement of the central pulmonary arteries is mainly related to the gestational age at diagnosis. Our results confirm that the outlook for these patients is extremely poor.* Copyright © *2006 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Absent pulmonary valve syndrome (APVS) is a rare congenital heart defect (CHD) characterized by the absence or extremely vestigial development of the pulmonary valve leaflets in association with varying degrees of hypoplasia of the pulmonary annulus. It is almost always associated with a massive enlargement of the pulmonary trunk and its branches[1,2]. APVS has been described as an isolated anomaly[3–5], but it is usually associated with tetralogy of Fallot (TOF)[4–8]. The absence of the ductus arteriosus is also a common but not a consistent feature of this syndrome[9,10].

Prenatal diagnosis of APVS is feasible and has been reported in three case series[4,5,11] and in several case reports[6–8]. Prenatal detection of the defect is usually made in the second half of pregnancy. The perinatal mortality rate is above 60%, closely related to the existence of severe heart failure and/or associated malformations[4,6–8,10].

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This may explain the different levels of incidence reported in pre- and postnatal series; while postnatally APVS accounts for 3–6% of all patients with TOF[12] and for 0.2–0.4% of liveborn infants with CHD[13], its incidence in fetal life is higher, with figures close to 15–20% of all cases with TOF and 1% of all CHD[14].

The aim of this study was to analyze the prenatal characteristics of APVS, its association with chromosomal abnormalities and extracardiac anomalies including increased nuchal translucency (NT), outcome after the prenatal diagnosis and accuracy of the diagnosis with respect to the findings at necropsy or postnatal examination.

METHODS

This was a retrospective study performed at two tertiary referral centers for prenatal diagnosis of fetal pathology. The study period was from January 1998 to December 2004. The prenatal diagnosis of APVS was made on the basis of rudimentary valve leaflets in combination with the concurrent occurrence of pulmonary stenosis and regurgitation. Enlargement of the central pulmonary arteries was also considered a main anatomic feature. With these criteria, 14 cases were retrieved and analyzed.

Ten of the women (71%) were referred for a detailed anomaly scan, counseling and invasive tests for fetal karyotyping from their local hospitals after the finding of an abnormal heart in a routine obstetric scan. The remaining pregnant women were attending our hospitals primarily for standard care and for routine scans.

The following variables were analyzed: reason for referral, gestational age at diagnosis, type of CHD, cardiac axis and associated chromosomal, cardiac and extracardiac abnormalities including review of the NT thickness in the first trimester. We also evaluated the presence of fetal growth restriction and/or amniotic fluid volume disorders and fetal/postnatal outcome. Echocardiographic evaluation included the measurement of cardiothoracic ratio, diameter of the pulmonary trunk and branches (measured immediately after their origin) and Doppler velocimetry in the pulmonary artery. All the data were retrieved from the clinical files of the patients and/or from recorded videotapes and stored images. The cardiac measurements were carried out during diagnostic echocardiography and were recorded in each patient's file. Only calculations of cardiac axis were made afterwards based on printed images. It was possible to obtain high quality images in order to make the cardiac axis calculations in 11 out of 14 cases (79%). These measurements were compared with normal reference ranges[15–19]. We also computed the Z-scores for the main pulmonary artery and branches using the Microsoft Excel™ spread sheet from DeVore[19]. All cases were analyzed together with a pediatric cardiologist. All parents received detailed counseling regarding the diagnosis and therapeutic options after the prenatal echocardiogram.

The thickness of the fetal NT in the first trimester of pregnancy was available in 10 of the 14 cases (71%). This measurement was obtained in a sagittal plane following standard guidelines[20]. Observed values were compared with normal reference ranges for gestational age[21] and those $\geq 95^{th}$ centile of the normal range were considered as abnormal.

Karyotyping was performed in all cases (prenatally in 10 (71%) cases). Chromosomes were analyzed with G-banding and fluorescent *in-situ* hybridization (FISH) for the DiGeorge syndrome critical region (22q11). This was carried out with the probe TUPLE 1 (within 22q11.2)/ARSA (arysulfatase A within 22q13.3), Vysis, Downers Grove, IL, USA). Targeted examination for the 22q11 microdeletion was performed in all cases. Ultrasound examinations were performed with high-quality equipment (Acuson 128XP or Aspen, Acuson Inc., Siemens-Antares, Siemens Medical Solutions, Mountain View, CA, USA; General Electric Logic 500, GE Medical Systems, Milwaukee, WI, USA).

RESULTS

There were 994 cases of fetal CHD detected in the referral centers during the observation period, and APVS was diagnosed in 14 fetuses −1.4% of all CHD. Only one case occurred not in association with TOF. Confirmation of the prenatal diagnosis through necropsy reports or at postnatal echocardiography/surgery was obtained in all cases. There were neither false positive nor incorrect diagnoses.

The mean gestational age at diagnosis was 28 (range, 16–38) weeks, with only 5/14 cases (36%) diagnosed before 22 weeks of gestation, the upper limit for termination of pregnancy (TOP) in our country. In all cases detected in the second half of pregnancy a routine mid-second-trimester scan had been previously performed at the local hospital. The main reason for referral was suspected CHD on a routine obstetric ultrasound scan (11 cases, 79%). The remaining three were referred because of increased NT together with a positive family history (Case 7), fetal chromosomal abnormality (Case 10) and end-diastolic reversed flow in the ductus venosus (Case 11), respectively. The case details are listed in Table 1.

Most fetuses (Cases 1–12) had 'tetralogy of Fallot-type' ventricular septal defects, one had a complete atrioventricular septal defect with aortic override (Case 13), and only in one case (Case 14) was the ventricular septum intact. This case showed a marked reduction in the volume of the right ventricular cavity owing to severe myocardial hypertrophy (Figure 1). Additional cardiovascular anomalies were identified in four patients (29%). There was one case with a right-sided aortic arch together with a muscular ventricular septal defect and left persistent superior vena cava (Case 13). In two fetuses already diagnosed with APVS, the existence of a right aortic arch was overlooked (Cases 2 and 6) and in one of them an ostium secundum atrial septal defect also remained unrecognized (Case 6). In another fetus, an aberrant right subclavian artery was also detected postnatally (Case 9).

Table 1 Data of fetuses with absent pulmonary valve (APV) syndrome

Case	NT (mm)	Reason for referral	GA (weeks)	Diagnosis	CT ratio	Cardiac axis (°)	MPA (cm)/ Z-score	RPA (cm)/ Z-score	LPA (cm)/ Z-score	Arterial duct	Karyotype	Outcome
1	1.7	Suspected CHD	34	TOF–APV	0.66	NA	2.10/6.48	1.80/8.64	1.60/7.73	Yes	Normal	Neonatal death
2	5.1	Suspected CHD	35	TOF–APV	0.61	NA	2.20/6.52	1.90/8.74	1.60/7.55	No	22q11 deletion	Neonatal death
3	NM	Suspected CHD	35	TOF–APV	0.60	67	1.80/5.25	1.40/7.05	1.20/6.08	No	Normal	Neonatal death
4	NM	Suspected CHD	38	TOF–APV	0.59	65	1.70/4.18	1.40/6.49	1.10/5.12	No	Normal	Neonatal death
5	4.3	Suspected CHD	21	TOF–APV	0.70	NA	0.60/2.63	0.90/8.08	0.80/7.22	No	Normal	TOP
6	NM	Suspected CHD	35	TOF–APV	0.60	38	1.62/4.58	1.37/6.93	1.16/5.91	No	Normal	Infant death
7	4.5	Increased NT	17	TOF–APV	0.50	45	0.29/−0.19	0.50/6.27	0.40/5.02	No	Normal	TOP
8	2.1	Suspected CHD	34	TOF–APV	0.58	70	1.60/4.75	1.40/7.25	0.90/4.80	No	22q11 deletion	Alive after surgery
9	2.2	Suspected CHD	29	TOF–APV	0.58	68	1.05/3.43	1.30/7.92	1.20/7.26	No	Normal	Neonatal death
10	1.8	Chromosomal abnormality	21	TOF–APV	0.54	49	0.43/0.51	0.70/6.69	0.60/5.75	No	Chromosome 18 ring	TOP
11	2.1	Reversed flow DV	16	TOF–APV	0.50	39	0.15/−3.86	0.10/−2.25	0.10/−1.66	No	22q11 deletion	TOP
12	NM	Suspected CHD	31	TOF–APV	0.58	42	1.40/4.69	1.20/7.02	1.20/6.84	Yes	Normal	Alive after surgery
13	5.0	Suspected CHD	28	AVSD–TOF–APV	0.62	63	1.20/4.58	0.90/6.12	0.80/5.42	No	Normal	Intrauterine death
14	2.1	Suspected CHD	20	APV	0.48	39	0.53/2.26	0.19/−0.21	0.16/−0.66	Yes	Normal	TOP

Z-scores were computed using Excel spread sheet from DeVore[19]. AVSD, atrioventricular septal defect; CHD, congenital heart defect; CT ratio, cardiothoracic ratio; DV, ductus venosus; GA, gestational age; LPA, left pulmonary artery; MPA, main pulmonary artery; NA, not available; NM, not measured; NT, nuchal translucency; RPA, right pulmonary artery; TOF, tetralogy of Fallot; TOP, termination of pregnancy.

The mean maximum diameter of the ventricular septal defect at diagnosis was 5.8 (range, 2.7–10) mm. Severe pulmonary valve stenosis (peak systolic velocity > 1.5 m/s) and regurgitation were present in all but one case (Figure 2). This fetus (Case 11), in which APVS was diagnosed at 16 weeks' gestation after referral for end-diastolic reversed flow in the ductus venosus seen at 13 weeks, showed a pulmonary valve peak systolic velocity of 0.4 m/sec, within the normal range for gestational age, and only a mild regurgitation was observed. The FISH technique detected 22q11 deletion in this fetus, and the parents opted for TOP. Postmortem findings confirmed the absence of the pulmonary valve.

In 10/14 cases the main pulmonary artery was dilated, being within normal limits in the remaining four cases (Cases 7, 10, 11 and 14) (Figure 3). All cases diagnosed after 22 weeks of pregnancy showed a severely dilated main pulmonary artery, but among those cases detected prior to 22 weeks all but one (Case 5) had a pulmonary artery size within the normal limits for gestational age. The branch pulmonary arteries were markedly dilated in all but two cases (Cases 11 and 14), both diagnosed before 22 weeks. The Z-scores for the central pulmonary arteries are shown in Table 1. All but three fetuses (Cases 7, 11 and 14) had a cardiothoracic ratio > 95th centile, probably related to blood volume overload[22]. These three cases were diagnosed in the first half of pregnancy and also showed a normal pulmonary artery size, and in all but one the branch pulmonary artery sizes were within the normal limits.

All but three fetuses (Cases 1, 12 and 14) showed absence of the arterial duct. A correlation of the presence of the arterial duct with the size of the main and branch pulmonary arteries or with the cardiothoracic ratio could not be established.

The cardiac axis had increased significantly in five of the 11 fetuses for which information was available[18]. In all cases diagnosed before the 22nd week of pregnancy the cardiac axis was within normal limits (4/4, 100%) while its deviation was commonly found among those diagnosed in the second half of pregnancy (5/7, 71%) (Table 1).

No extracardiac anomalies or fetal hydrops were detected in any of our cases. Increased NT was observed in four of the 10 cases (40%) in which this measurement was performed (Cases 2, 5, 7 and 13). Subsequent fetal karyotyping revealed normal results in all these four fetuses although a later analysis, after the diagnosis of the heart defect, showed the 22q11 deletion in one of them (Case 2). There was absence of the arterial duct in all cases with increased NT. In two of the cases with increased NT the heart defect was diagnosed before 22 weeks (one of them previously suspected in the routine second-trimester scan and the other referred for fetal echocardiography because of increased NT with normal karyotype) (Table 1). However, in the remaining two cases fetal echocardiography was not requested by the attending physicians in spite of an increased NT, and the routine scan at 20 weeks overlooked the CHD. In these

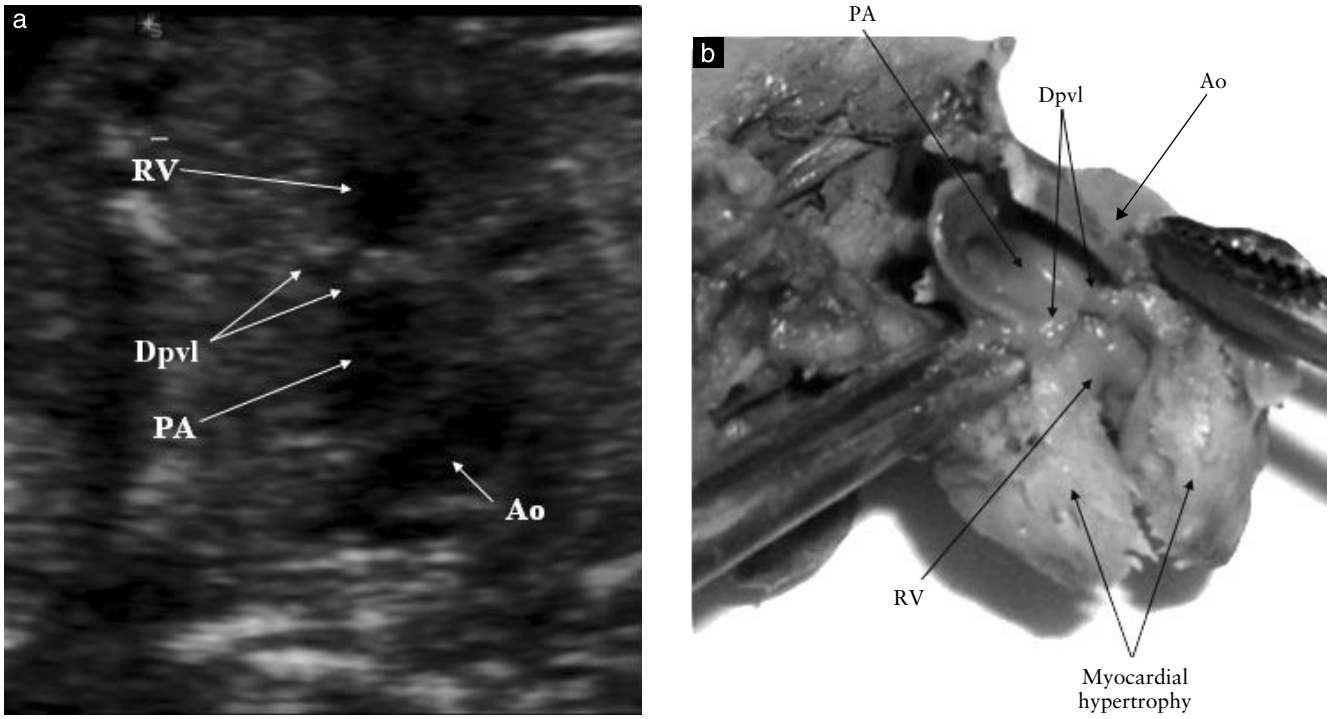

Figure 1 (a) Two-dimensional echocardiographic view at the level of the pulmonary ring and (b) pathological specimen displaying features of absent pulmonary valve in the fetus with intact ventricular septum (Case 14). Ao, ascending aorta; Dpvl, dysplastic pulmonary valve leaflets; PA, pulmonary artery; RV, right ventricle.

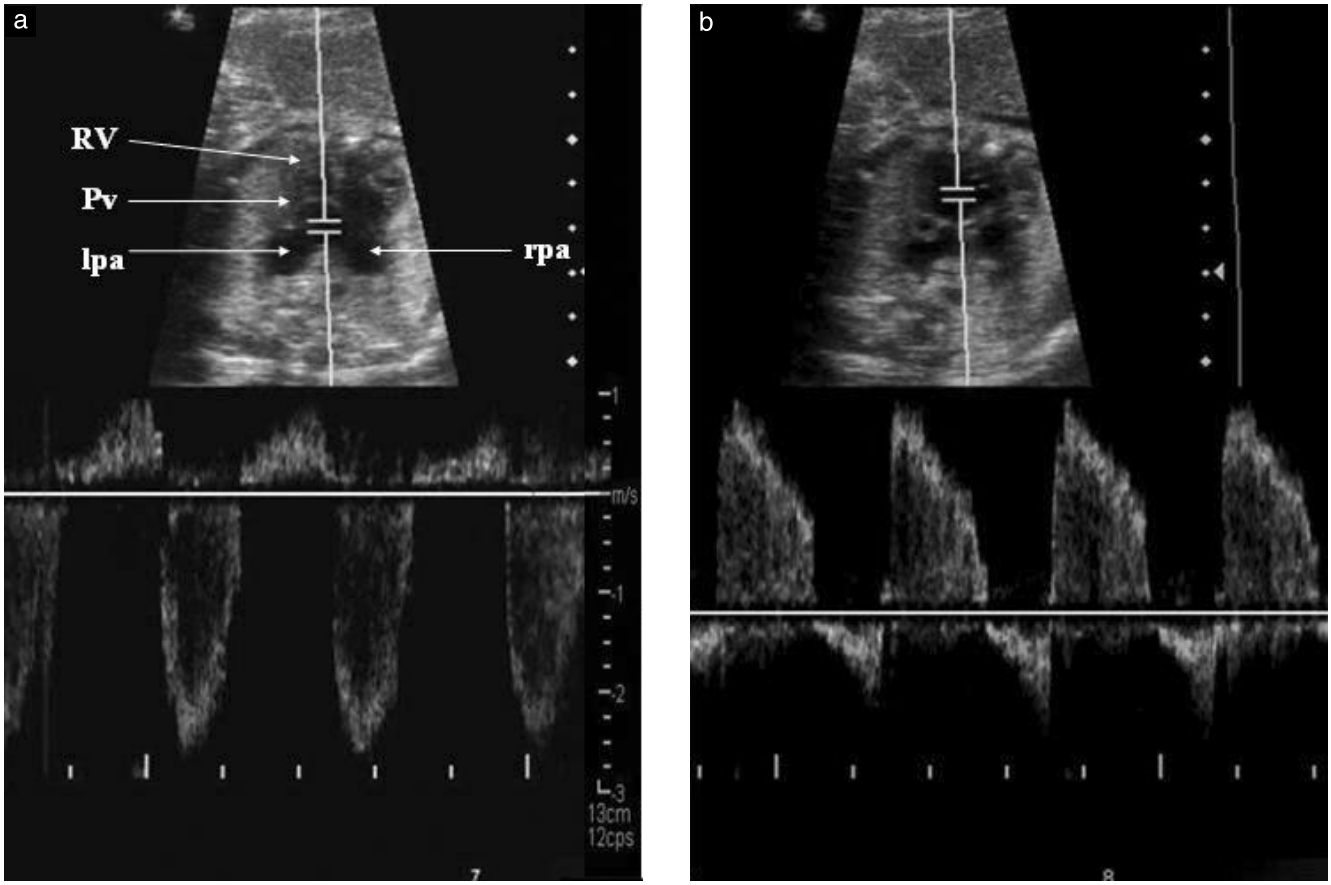

Figure 2 Pulsed Doppler recording showing antegrade and retrograde flow in (a) the pulmonary trunk and (b) the right ventricle. lpa, left pulmonary artery; Pv, pulmonary valve; rpa, right pulmonary artery; RV, right ventricle.

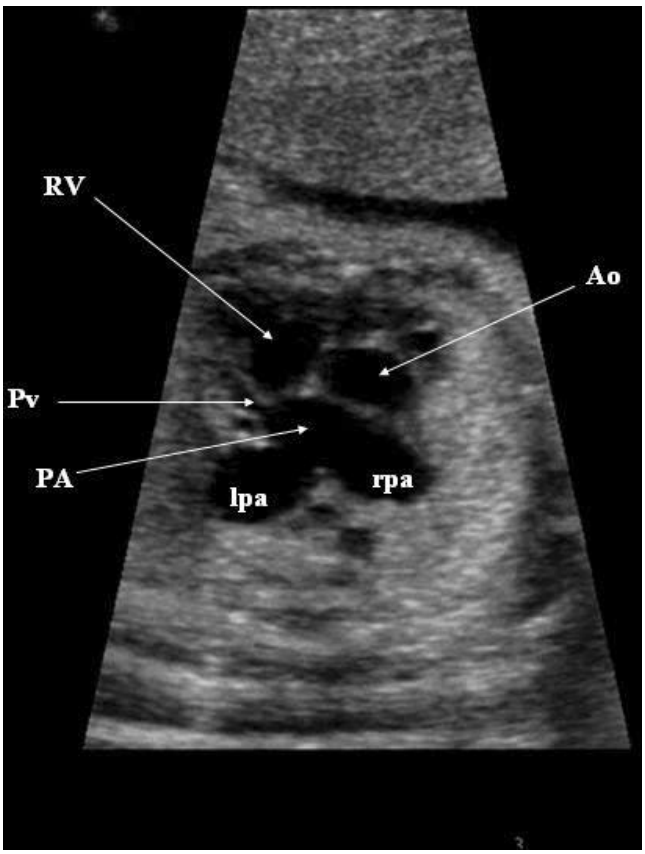

Figure 3 Typical echocardiographic image in the second half of pregnancy of a fetus with absent pulmonary valve displaying the marked dilatation of the central pulmonary arteries. Ao, ascending aorta; lpa, left pulmonary artery; PA, pulmonary artery; Pv, pulmonary valve; rpa, right pulmonary artery; RV, right ventricle.

cases the diagnosis of APVS was not made until the late second half of pregnancy.

A chromosomal abnormality was diagnosed in only one fetus (chromosome 18 ring) and 22q11 microdeletion was detected in three fetuses (21%) (Table 1). There was no significant association between 22q11 microdeletion and the type of aortic arch (left vs. right) or with NT thickness. No genetic anomalies were diagnosed among cases with an arterial duct. Fetal growth and amniotic fluid were within normal limits in all cases.

The outcome for fetuses with APVS was poor. In five of the 14 cases the parents opted for TOP (36% of the total group and 100% of the cases diagnosed before 22 weeks). There was one spontaneous intrauterine death at 32 weeks in the fetus with APVS associated with atrioventricular septal defect and TOF (Table 1). The remaining eight babies were delivered at term in a center with facilities for pediatric cardiac surgery. There were six uneventful vaginal deliveries, and two Cesarean sections were performed for fetal distress. Of the eight newborns, six (75%) had respiratory distress early in the neonatal period requiring intubation and mechanical ventilation, while the remaining two never had any respiratory symptoms. Although the neonates with respiratory distress included those showing the greater degrees of enlargement of the central pulmonary arteries (Cases 1–4), no clear relation between both events was noted as milder degrees of dilatation were associated with respiratory symptoms in some neonates (Cases 8 and 9) and not in others (Cases 6 and 12). Dysmorphic facies and hypocalcemia were observed in two newborns, both with 22q11 deletion (Cases 2 and 8). Five out of the eight newborns (62.5%) died in the neonatal period, all showing severe respiratory distress from the beginning. Four of them died in the first 4 days after birth (Cases 1, 3, 4 and 9) and did not have any surgical or catheter interventions. The fifth (Case 2) underwent neonatal surgery 24 hours after birth, involving a fistula between the left subclavian artery and left pulmonary branch and plication of the pulmonary arteries. The patient died 2 days later. The remaining three babies (37.5%) underwent complete surgical repair beyond the neonatal period. At the time of writing one of them (Case 12), at 5 years of age, is doing well while the other (Case 8), at 14 months, is still dependent on a ventilator because of severe bronchomalacia. The third infant (Case 6) had a full repair at 12 months of age but subsequently the patient deteriorated with multiorgan failure and died 2 days later. Therefore, the overall mortality rate was 86% (12/14) including five TOP, one intrauterine death, five neonatal deaths and one infant death. There were only two survivors and both have survived beyond 1 year of age. Of the six babies who suffered from respiratory distress in the neonatal period, there was only one survivor (17%) and of the eight babies in whom there was an intention to treat, two survived (25%).

DISCUSSION

APVS is characterized by dysgenesis of the pulmonary valve, pulmonary insufficiency, and enlargement of the pulmonary arteries, often reaching aneurysmal proportions. The etiology of the specific absence of the arterial duct is not clear, one hypothesis postulating that it is a primary phenomenon due to a complete failure of the sixth arch artery to develop, while others believe that reduced diastolic pressure due to an absent diastolic closure of the pulmonary valve in combination with a non-restrictive ventricular septal defect may result in an early obliteration and even complete involution and disappearance of a still immature artery[6,23]. Although this issue was not specifically addressed in our paper, both hypotheses seem realistic, as in each of our cases in which the arterial duct could not be seen on ultrasonography the autopsy failed to demonstrate the presence of any remnant of the arterial duct.

The spectrum of physiological derangement in patients with APVS is bimodal. In the most severe cases, newborns have severe respiratory distress due to compression of the central airways by the huge aneurysmal central pulmonary arteries. There are fetuses with APVS whose clinical course resembles closely that of cases with simply TOF and mild degrees of right ventricular outflow obstruction. However most fetal series have reported extremely poor survival rates, probably related to the fact that the more

complex and severe defects are more likely to be detected prenatally[22,24].

It is commonly advocated that the prognosis for patients with APVS is largely dependent on the size of the pulmonary trunk and branches and the degree of bronchial compression[1]. The aneurysmal development of the central pulmonary arteries is attributed to the combination of absence of the ductus and free pulmonary valve regurgitation[9]. However, the differential role of the patency or absence of the ductus arteriosus in the degree of pulmonary artery enlargement is still to be defined. Discussion focuses primarily on the hemodynamic consequences of increased stroke volume associated with severe pulmonary valve regurgitation, the high *in utero* pulmonary vascular resistance and the lack of a ductal pathway for run-off into the systemic circulation, a situation resulting in mechanical enlargement of the pulmonary arteries[1,9,25]. Others invoke poststenotic dilation together with increased pulmonary forward flow secondary to pulmonary insufficiency as possible mechanisms that stimulate growth of the pulmonary vessels[3,10]. Our findings support this last hypothesis as no significant association could be established between the presence of the arterial duct and the size of the central pulmonary arteries. However, pulmonary regurgitation was invariable and we found increased Doppler velocities across the rudimentary pulmonary valve ring in all cases except one. This has also been observed in other series[4,5].

Interestingly, we have also observed that, although enlargement of the central pulmonary arteries is a main anatomic feature in patients with APVS and is a constant feature after 22 weeks, in most of the fetuses in our series in which APVS was diagnosed before 22 weeks the size of the pulmonary arteries was within normal limits. This observation provides evidence that the main features of APVS undergo progression *in utero* and therefore the severity of APVS seen at birth is often not fully realized until late in gestation because the anatomical and hemodynamical abnormalities are still evolving[6,8,10]. The incessant mechanical stimulation caused by volume overload as well as by pulmonary ring stenosis would result in the massive enlargement of the pulmonary arteries commonly observed in these patients when seen in the second half of pregnancy or in the neonatal period. The different sonographic features of APVS in early pregnancy from those observed in the second half of pregnancy have also been observed by Becker *et al.*[6]. Although in the case reported by these authors the diagnosis was not made until 21 weeks, the re-evaluation of a previous scan performed at 13 weeks allowed the observation that there was a pulmonary valve insufficiency as the only sonographic feature, but at this point no enlargement of the central pulmonary arteries was present. In our experience, even the hemodynamically distinctive feature of severe pulmonary stenosis together with regurgitation in APVS may not be evident in the first half of pregnancy, as demonstrated in Case 11, therefore making the early recognition of this CHD very difficult. Late sonographic expression of the main anatomic defect of the heart in fetuses with APVS could be explained, at least in part, by the progressive increase in cardiac output that takes place through pregnancy. This is in agreement with the progressive increase in the size of the pulmonary arteries seen in longitudinal studies of fetuses already diagnosed with APVS[4].

In utero progressive enlargement of the central pulmonary arteries may also provide an explanation for the commonly observed late prenatal diagnosis of fetuses with APVS. Most case reports and the majority of the cases reported in fetal series, including ours, have been diagnosed after 22 weeks' gestation and almost all of them had a scan performed previously at 20–22 weeks[4–8,11]. It is well known that the four-chamber anatomy may seem absolutely normal in many conotruncal malformations[26]. In spite of the recommendation that each screening examination of the fetal heart should include the evaluation of ventriculo-arterial connections to improve the detection rate of conotruncal abnormalities, the four-chamber view still remains the cornerstone of cardiac screening[24]. In the later stages of pregnancy the detection of APVS may be easier owing to the massive enlargement of the pulmonary trunk and branches. Volpe *et al.*[5] have stated that, unlike most conotruncal malformations, APVS can be suspected at routine second-trimester ultrasound scan since the four-chamber view is clearly abnormal in most instances, because of evident cardiomegaly and the fact that the pulmonary trunk is so dilated as to become visible. However, the analysis of our data, even with a lower number of cases diagnosed in the second trimester than in the article by Volpe *et al.*[5], shows that APVS may be missed in the second trimester if the outflow tracts are not directly evaluated. Furthermore although the figures do not allow firm conclusions to be reached, our results show that the deviation from normal of the cardiac axis is usually also diagnosed at a later stage of pregnancy, which may interfere with early diagnosis of APVS. Nevertheless all series have shown the excellent diagnostic performance of fetal echocardiography in terms of accuracy, false positives and missed intracardiac anomalies[4,5,11].

It is now commonly accepted that an increased NT with normal karyotype should constitute an indication for fetal echocardiography, as in this group of fetuses the prevalence of CHD is higher than its prevalence in the general population[27]. Our interesting observation that up to 40% of fetuses with APVS had an increased NT in the first trimester may facilitate the recognition of this heart defect before 22 weeks in a substantial proportion of fetuses that have it. The data of this study are in agreement with other reports and confirm the strong association between increased NT and major CHD in chromosomally normal fetuses[28] and also stress the usefulness of early echocardiography when performed by experts on fetuses specifically at risk for CHD.

The observed prevalence of APVS in our series (1.4% of all CHD) is in agreement with that reported in other prenatal series[4], with the vast majority of the cases seen associated with TOF. With regard to extracardiac

morphological anomalies, in our experience they are rarely associated with APVS, as shown by the thorough anatomical study performed in all our cases. This coincides with other series published[4,22] and explains the low incidence of chromosomal anomalies observed, but it is in contrast to the high number of associated anomalies and chromosomal defects observed by Volpe *et al.*[5]. In their cases none of the anomalies appeared to have a close relationship with the APVS, but in any case, the limited number of cases does not allow firm conclusions to be reached. Furthermore it is possible that the development of fetal hydrops – considered in the article by Volpe *et al.*[5] as an associated anomaly that was present in two fetuses, both of which were diagnosed in the second half of pregnancy – may have been prevented by TOP. As for chromosomal abnormalities, our figure is similar to those reported by others[4,5,11,29]. In all series, including ours, the most common karyotype anomaly was 22q11 deletion, supporting the concept that fetal chromosomal abnormalities should be ruled out whenever an APVS is detected. In accordance with previous reports[4,5], patients with an arterial duct seem to represent a distinct subgroup within APVS since no genetic anomalies or extracardiac anomalies, including increased NT, were observed in our three patients with an arterial duct.

The low survival rate beyond 1 year of age observed in our series shows again that the heart defects seen in fetal life usually represent the more severe forms of the spectrum[4,5,24]. Upon review of the literature, most fetuses with APVS are seen to have severe respiratory difficulty after birth, requiring mechanical ventilation, and signs of right-sided cardiac failure are also a common feature[4,5,22]. Although the small number of liveborn fetuses in our study precludes any statistical analysis, it seems in terms of probability that the greater the enlargement of the pulmonary arteries, the greater the risk of respiratory distress and the poorer the prognosis, as already demonstrated[4,22], but no significant correlation between size and outcome has been noted[22,30]. Moreover, newborns with respiratory difficulty are more likely to need early intervention, both factors – the hemodynamic challenge and respiratory distress – contributing to the poor prognosis of these patients[4,6,10].

To conclude, our study provides further information concerning APVS and that this rare CHD can be accurately diagnosed by fetal ecocardiography. Screening ultrasound scan in the mid-second trimester is likely to have a low detection rate, probably owing to the incomplete expression of the disease at this point. Fortunately, many of the fetuses with APVS had an increased NT in the first trimester of pregnancy and this may be helpful for an earlier recognition of the defect. In contrast with previous studies[4,5,11], the presence of an arterial duct seems not to play a key role in the degree of enlargement of the central pulmonary arteries, which is best correlated with the gestational age at diagnosis. We have also confirmed that the outcome for fetuses with APVS is extremely poor because of respiratory distress, the heart defect itself and/or the associated genetic anomalies.

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