CONGENITAL HEART DISEASE

Prenatally diagnosed pulmonary atresia with ventricular septal defect: echocardiography, genetics, associated anomalies and outcome

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Objective: To assess the accuracy of prenatal diagnosis, the association with genetic and extracardiac anomalies, and outcome in fetuses with isolated pulmonary atresia with ventricular septal defect (PA-VSD).

Design and setting: Retrospective study in a tertiary centre for fetal cardiology.

Patients and outcome measures: Echocardiographic video recordings of 27 consecutive fetuses with PA-VSD were reviewed for: (1) intracardiac anatomy; (2) presence of confluence and size of the branch pulmonary arteries; (3) source of pulmonary blood supply; and (4) side of the aortic arch. Postmortem and postnatal data were added. Karyotyping was performed in 25 patients and, in 23 of these, fluorescent in situ hybridisation to identify 22q11.2 deletion.

Results: PA-VSD was correctly diagnosed in 19 of 21 patients (90%) with postnatal or autopsy confirmation of diagnosis. Central pulmonary arteries were correctly identified in 79% (15/19), the source of pulmonary blood supply in 62% (13/21) and major aortopulmonary collateral arteries in 44% (4/9). Aneuploidy was detected in 4 of 25 patients (16%) and 22q11.2 deletion in 6 of 23 patients (26%). Five of 27 patients (19%) had extracardiac anomalies. Eleven pregnancies were interrupted. Eleven of 16 liveborn babies survived. Neonatal survival was 15 of 16 (94%, 95% confidence interval (CI) 70 to 100), one-year survival was 9 of 12 (75%, 95% CI 43 to 95) and two-year survival was 5 of 9 (56%, 95% CI 21 to 86).

Conclusion: PA-VSD can be diagnosed by fetal echocardiography with a high degree of accuracy. However, it can be difficult to determine the morphology of the central pulmonary arteries and to locate the source of pulmonary blood supply. In most liveborn infants, complete surgical repair can be achieved.

Isolated pulmonary atresia with ventricular septal defect (PA-VSD) is a rare form of congenital heart disease, estimated to occur in 10.0/100 000 liveborn infants.¹ The blood supply to the pulmonary arteries is provided by a patent arterial duct or by major aortopulmonary collateral arteries (MAPCAs), which can vary greatly in number and site of origin.²⁻⁴ Echocardiography can be used to assess the presence and size of the central pulmonary arteries in neonates and infants with PA-VSD, and the source of pulmonary blood supply can be determined.⁵⁻⁷ However, no data are available regarding the accuracy of identifying central pulmonary arteries and the source of blood supply during fetal life. An association between conotruncal cardiac abnormalities and 22q11.2 deletion during fetal life has been investigated and reported to occur in 20% of cases of PA-VSD.⁸⁻⁹

The ultimate goal of surgery is to construct completely separated, in-series pulmonary and systemic circulations. This can be achieved as a single or staged procedure, depending on the complexity of the central pulmonary arteries and pulmonary blood supply, as well as the institutional preference. The reported surgical mortality has been relatively low and good functional results have been achieved,¹⁰⁻¹⁴ but data obtained from a surgical series are likely to differ from a series seen from fetal life and thus cannot be simply extrapolated when predicting outcome in prenatal counselling.

The objectives of the current study were: (1) to assess the accuracy of the diagnosis of PA-VSD by fetal echocardiography; (2) to investigate the association with genetic and extracardiac abnormalities; and (3) to evaluate the outcome in patients with prenatal diagnosis of PA-VSD.

METHODS

Study patients

The study group consisted of 27 consecutive fetuses with isolated PA-VSD identified in a single institution during an 11-year period between January 1993 and December 2003. These were all of the patients where no additional cardiac abnormalities beyond a malalignment ventricular septal defect, overriding aorta with either left or right arch and no direct flow from the right ventricle into the pulmonary arteries were identified. Patients with additional cardiac abnormalities, mostly in the context of isomerism of the left or right atrial appendages, were excluded from the study. Confirmation of diagnosis was sought from neonatal echocardiogram reports, as well as from catheter, surgical and autopsy reports. In six cases permission for autopsy was refused and the diagnosis could not be confirmed. All patients underwent a detailed ultrasound examination of the entire fetus by an experienced obstetric sonographer to identify any extracardiac anomalies. Karyotyping was performed in 25 patients and, in 23 of these, fluorescent in situ hybridisation (FISH) to identify 22q11.2 deletion.

Postnatal follow up is sought for all fetuses seen in our unit, whether the fetal echocardiogram is normal or abnormal. This is obtained from questionnaires returned from general practitioners, parents and referring obstetricians when the child is 6-8 weeks of age. Outcome data are available for over 95% of fetuses and to our knowledge there

Abbreviations: FISH, fluorescent in situ hybridisation; MAPCAs, major aortopulmonary collateral arteries; PA-VSD, pulmonary atresia with ventricular septal defect

were no other cases of PA-VSD among the fetuses considered normal at prenatal assessment.

Fetal echocardiography

Fetal echocardiograms were recorded with the Toshiba SSA270 (Toshiba Medical Systems, Crawley, UK) and Hewlett Packard 1000, 2000 and 5500 ultrasound systems (Philips Inc, Andover, Massachusetts, USA). Long- and short-axis images of the intracardiac anatomy, aorta and pulmonary arteries were obtained. Pulsed wave, continuous wave and colour flow Doppler were used in addition to cross-sectional imaging. All scans were recorded on S-VHS videotapes.

Measurements

Prenatal echocardiographic video recordings were retrospectively reviewed by two investigators who were blinded to initial fetal echocardiography reports, as well as to postnatal echocardiography, catheter or autopsy reports. The review focused on: (1) intracardiac anatomy; (2) the presence of confluence and the size of the branch pulmonary arteries; (3) the source of pulmonary blood supply; and (4) the side of the aortic arch. The appearance of the apical four-chamber view was also evaluated and the cardiac axis measured.

The branch pulmonary arteries were considered confluent when the so-called seagull sign was clearly identified. The internal diameters of the left and right pulmonary arteries were measured in the short-axis view of the right ventricular outflow tract and great arteries or in the high transverse views, but only if the particular value was reproducible in more than two different frames. The source of the pulmonary blood supply was considered to be an arterial duct when the retrograde flow from the distal end of the aortic arch or from the transverse arch was seen on colour flow mapping, and was considered to be collaterals when the retrograde flow originated more distally from the descending aorta or aortic arch branches. The side of the arch was evaluated by examination of the crest of the aortic arch in a transverse view of the upper thorax. The cardiac axis was measured from a frozen image of the apical four-chamber view by a hand-held protractor.

Outcome

After PA-VSD in the fetus was diagnosed, all parents received detailed counselling regarding the malformation, associations and possible treatment options. Outcome data were gathered by a review of complete prenatal and postnatal hospital medical documentation for any particular patient.

Data analysis

Descriptive analysis was used, incorporating median and range and percentages for describing numbers of cases. We calculated 95% confidence intervals (CI) to express survival to different ages.

RESULTS

During the study period, 1913 cases of fetal congenital heart disease were identified from a total of 15 861 women referred for fetal echocardiography. Among 1913 fetuses with congenital heart disease, 27 had isolated PA-VSD (1.4%). From our postnatal follow-up information, we identified no additional cases of PA-VSD among those considered normal at prenatal assessment. Table 1 summarises the case details. The reason for referral in all but two cases was suspected congenital heart disease on a routine obstetric ultrasound scan. In the remaining two cases (cases 3 and 16), mothers were referred due to a family history of congenital heart disease. The mother in case 16 was also a diabetic. The

median gestational age at the time of diagnosis was 21 weeks (range 17–38 weeks).

Genetic abnormalities and extracardiac anomalies

Fetal karyotyping was performed in 25 patients. In the remaining two patients, culture of the fibroblasts failed in one (case 1) and karyotyping was declined in the other (case 2). Chromosomal abnormalities were detected in 10 patients (40%). In four of 25 cases (16%), there was aneuploidy, including trisomy 13 ($n = 2$), triploidy 69,XXY ($n = 1$) and 47,XXY ($n = 1$). FISH analysis to identify a 22q11.2 deletion had been performed in 23 patients and confirmed its presence in six of them (26%). Extracardiac anomalies were identified in five of 27 patients (19%). They were present in four of 10 patients with genetic aberrations, but only in one of 13 patients with normal results of genetic studies.

Echocardiographic features and accuracy of prenatal diagnosis

Abnormalities in the four-chamber view of the fetal heart were recognised in all patients but in most they were only minor (for example, leftward shift of the heart axis or ventricular septal defect). The four-chamber view was notably abnormal in two patients. In both (cases 12 and 19), the heart was grossly enlarged. The mean cardiac axis was 66 (SD 11)°, compared with 43 (7)° in normal fetuses.¹⁵ In six of 27 patients (22%), the aorta was overriding the ventricular septal defect by more than 50% and emerged predominantly from the right ventricle. The right aortic arch was documented in seven of 27 patients (26%).

In assessing the accuracy of fetal echocardiography in diagnosing the central pulmonary arteries and the source of pulmonary blood supply, we considered only the fetuses with postnatal or autopsy confirmation of the diagnosis. Of 21 fetuses with postnatal or autopsy confirmation, PA-VSD was accurately diagnosed in 19 (90%) (table 2). In the remaining two fetuses common arterial trunk was diagnosed as part of a differential diagnosis but the autopsy showed PA-VSD in both cases (cases 12 and 19). Confluent central pulmonary arteries were identified in 15 fetuses. In the remaining six fetuses, the central pulmonary arteries were not correctly identified by fetal echocardiography. Postnatal studies or autopsy later showed them to be confluent in an additional four patients, giving an accuracy of prenatal diagnosis of 79% (15 of 19) of those in whom they were actually present. Two of 21 patients in our series had non-confluent central pulmonary arteries.

The source of pulmonary blood supply was identified in 13 of 21 fetuses (62%), in all of them accurately: an arterial duct in nine; and MAPCAs in four. In two fetuses, forward flow across the stenotic pulmonary valve along with a reverse flow in the arterial duct was documented by initial fetal echocardiography, with pulmonary atresia developing during the follow up scans. MAPCAs, which proved to be present in nine of 21 patients (43%), were identified prenatally in four of nine patients (44%). They were particularly common in patients with a right aortic arch (five of seven: cases 1, 5, 11, 15 and 20) and were present in all four patients with 22q11.2 deletion with confirmed pathomorphological features. In eight patients, the pattern of pulmonary blood supply in utero could not be reliably assessed.

Outcome

Eleven sets of 27 sets of parents (41%) opted to terminate pregnancy (fig 1). There were no intrauterine deaths in the continuing pregnancies. In the group of 16 liveborn infants, two did not have surgery: one died unexpectedly at day 6 due to aspiration and in the other the morphology of the non-confluent pulmonary arteries was considered too complex for a unifocalisation procedure to be undertaken. Complete

Table 1 Details of study subjects with pulmonary atresia with ventricular septal defect

Case	Gestation at referral (weeks)	Fetal echocardiographic data				Karyotype; FISH	No of surgeries; type of repair	Outcome
		Pulmonary arteries; L, R (mm)	Source of pulmonary blood flow	Aortic arch	Extracardiac anomalies			
1	20	NPI	NPI	R	0	NA	NA	TOP
2	29	NPI	NPI	L	0	NA	0	NND
3*	18	C; NPM	Ductus	L	0	0	NA	TOP
4	27	C; 2.4, 2.6	Ductus	R	0	0	2; complete repair	Alive
5	20	NPI	NPI	R	Single kidney	22q11; del	0	Alive
6	22	C; NPM	MAPCAs	L	0	22q11; del	1; complete repair	PaedD
7	20	C; NPM	NPI	L	0	0	2; complete repair	Alive
8	25	C; 2.0, 1.8	Ductus	L	Gastric duplication cyst	0	2; complete repair	Alive
9*	17	C; NPM	Ductus	L	0	22q11; del	NA	TOP
10*	17	C; NPM	Ductus	L	0	22q11; del	NA	TOP
11	20	C; NPM	NPI	R	0	NA	1; complete repair	Alive
12	21	C; NPM	NPI	L	Absent stomach, Dandy-Walker syndrome	69,XXY	NA	TOP
13	23	C; 1.3, 1.5	Ductus	L	Oligohydramnion, echogenic bowel	Trisomy 13	NA	TOP
14	23	C; 1.2, 1.7	Forward flow	L	0	0	2; complete repair	Alive
15	21	C; 1.3, 1.4	NPI	R	0	22q11; del	NA	TOP
16	21	C; 1.4, 1.8	Ductus	L	0	NA	1; BT shunt, no follow up	Alive
17*	21	NPI	NPI	L	0	0	NA	TOP
18	21	C; 1.3, 1.4	Ductus	L	0	0	2; complete repair	InfD
19	24	NPI	NPI	R	Hydronephrosis, cardiac ventriculomegaly	Trisomy 13	NA	TOP
20	20	NPI	MAPCAs	R	0	0	2; complete repair	PaedD
21*	20	NPI	MAPCAs	L	0	0	NA	TOP
22	19	NPI	MAPCAs	L	0	22q11; del	1; complete repair	InfD
23*	21	C; NPM	Ductus	L	0	0	NA	TOP
24	38	C; 3.2, 3.2	Ductus	L	0	47,XXY	2; complete repair	Alive
25	21	C; 1.8, 1.7	Ductus	L	0	0	2; complete repair	Alive
26	22	C; NPM	Forward flow	L	0	0	2; complete repair	Alive
27	23	C; NPM	MAPCAs	L	0	0	Surgery planned	Alive

*Autopsy denied.

BT, Blalock-Taussig; C, confluent; FISH, fluorescent in situ hybridisation; InfD, infant death; L, left; MAPCAs, major aortopulmonary collateral arteries; NA, not applicable; NND, neonatal death; NPI, not possible to identify; NPM, not possible to measure; PaedD, paediatric death; R, right; TOP, termination of pregnancy.

surgical repair was performed in 13 patients (81% of live births), with the median age at surgery 12.2 months (range 0.4–30 months). Nine of them had previously undergone arteriopulmonary shunt (eight) or catheter intervention (one) to ensure controlled blood supply to the pulmonary arteries or to promote growth. After complete repair four of 12 patients died (33%): three in early perioperative period and one six months after surgery due to sepsis. One patient had an arteriopulmonary shunt done at the age of 2 days but was later lost to follow up.

Sixteen patients were live born, in whom there was an intention to treat. The overall survival was 11 of 16 (69%, 95% CI 41 to 89). Neonatal survival was 15 of 16 (94%, 95% CI 70 to 100), one-year survival was nine of 12 (75%, 95% CI 43 to 95), and two-year survival was five of nine (56%, 95% CI 21 to 86). Median follow up was 36 months (range 1 to 111). All patients followed up more than one year had complete surgical repair.

DISCUSSION

This study shows that PA-VSD can be diagnosed prenatally with a high degree of accuracy. In all but two cases, the

condition was correctly identified during the first scan, with subsequent scans occasionally providing additional information about the morphology of the central pulmonary arteries and the source of pulmonary blood supply. In two fetuses, the condition could not be differentiated from common arterial trunk. Both these fetuses proved to be genetically abnormal (trisomy 69,XXY and trisomy 13), and the evaluation of the fetal heart was considerably more difficult due to overt cardiomegaly. However, this differential diagnosis often poses a challenge in the diagnosis of PA-VSD prenatally.^{16 17} Apart from the two fetuses who presented with cardiomegaly, the abnormalities in the four-chamber view were minor and unlikely to be recognised during obstetric four-chamber view screening.

Central pulmonary arteries and the source of pulmonary blood supply

Along with the presence of associated extracardiac and genetic anomalies, counselling after prenatal diagnosis of PA-VSD is predominantly influenced by the morphology of the central pulmonary arteries and pulmonary blood supply.

Table 2 Accuracy of diagnosis by fetal echocardiography

Diagnosis	Patients eligible	Correct	Misinterpreted	Not identified	Accuracy (%)
MAPCAs	9	4	0	5	44
Confluent PAs	19	15	0	4	79
Source of PBS	21	13	0	8	62
Aortic arch	21	21	0	0	100
Final diagnosis	21	19	2	0	90

MAPCAs, major aortopulmonary collateral arteries; PAs, pulmonary arteries; PBS, pulmonary blood supply.

Figure 1 Flow diagram of prenatally diagnosed pulmonary atresia with ventricular septal defect (PA-VSD) in 27 fetuses.

Features such as non-confluent or severely hypoplastic central pulmonary arteries and extensive collateral aortopulmonary arterial circulation have a major impact on the proposed surgical treatment and can increase the risks substantially. Patients with relatively normal-sized confluent central pulmonary arteries usually receive pulmonary blood flow from the ductus arteriosus, rarely have incomplete distribution of right and left pulmonary artery, and rarely have large arteriopulmonary collateral arteries.² In contrast, more than 80% of those with non-confluent or hypoplastic central pulmonary arteries have incomplete distribution of one or both pulmonary arteries, with aortopulmonary collateral arteries supplying the non-connected pulmonary arterial segments.¹⁸

The accuracy of correctly identifying central pulmonary arteries and the source of pulmonary blood supply by fetal echocardiography was 79% and 62%, respectively. In our centre, the accuracy for this has improved in the latter part of our series, which is likely to be related to better resolution on ultrasound as well as increasing experience. In all cases where the central pulmonary arteries were identified, they were hypoplastic and measured at least 1 SD below the mean value for gestational age, as published for normal fetuses.¹⁹

MAPCAs have been identified prenatally in 44% of patients in whom they were actually present. The identification of MAPCAs in a fetus is challenging, and a good appreciation of their variability in number, origin and course in the mediastinum is necessary to be successful. Typically, they are from one to six in number and originate from the upper or mid-descending thoracic aorta and occasionally from the aortic arch branches and coronary arteries.^{2-4 18} They generally pursue a somewhat serpiginous course and therefore cannot be visualised in a single plane. In our experience, the identification of MAPCAs was enhanced by using colour flow mapping and by evidence of continuous flow in the aorta to pulmonary direction with spectral Doppler. However, in half of the fetuses in our series the prenatal identification of MAPCAs failed and the diagnostic accuracy did not improve

substantially during the study period. This may partly be explained by the retrospective nature of the study so that with a meticulous search, prenatal identification of MAPCAs should now be feasible in most patients seen prospectively. In addition, the advent of three-dimensional colour flow Doppler technique may enhance the visualisation of such collateral arteries where standard techniques fail.²⁰

In two patients in our series forward flow across the stenotic pulmonary valve was documented at the initial study at 22 and 23 weeks, with pulmonary atresia developing in both 11 weeks later. However, both of these fetuses had a reversal of flow in the arterial duct documented even at the initial study, implicating the arterial duct as a predominant source of pulmonary blood supply, which is not the usual pattern in patients with tetralogy of Fallot.²¹ The in utero development of pulmonary atresia in the presence of tetralogy of Fallot has previously been reported.²²

Genetic abnormalities

The prevalence of 22q11.2 deletion in our series was 26%, in agreement with other prenatal series.^{8 9} The reported prevalence of 22q11.2 deletion in postnatal and surgical series is slightly higher (23–40%),²³⁻²⁶ which may be explained by biases in referring patients with less favourable morphology of the central pulmonary arteries to the more experienced centres. Identification of 22q11.2 deletion is particularly important in prenatal counselling. Patients with PA-VSD and 22q11 deletion had more severely hypoplastic central pulmonary arteries and more arborisation anomalies than did patients without the deletion.^{23 24 26} In a comparison of five-year survival between patients with and without 22q11.2 deletion, survival was significantly lower (36% v 90%) in patients with deletion even after adjustment for the pulmonary artery size with multivariate analysis.²⁵ As affected children are followed up into adolescence and adulthood, significant neurodevelopmental delay and a high prevalence of psychosis are increasingly appreciated.²⁷⁻³⁰ Among other chromosomal abnormalities, one patients had

the 47,XXY karyotype, which has not usually been linked to conotruncal cardiac malformations.

Outcome

Based on an intention to treat, the overall survival in our series was 69%, which is lower than expected from postnatal series. This may be explained by the fact that the fetal spectrum comprises all cases of PA-VSD, whereas postnatal series reflect the selected fetuses that have survived to reach a paediatric cardiology unit. However, this discrepancy in outcome is important to note in prenatal counselling for this condition. In terms of survival to different ages, 28-day survival was 94%, one-year survival was 75% and two-year survival was 56%. Complete surgical repair has been performed in 13 patients and is planned in an additional patient. After complete repair four patients died: three in the early perioperative period and one, a patient with 22q11.2 deletion, due to sepsis six months after surgery.

After diagnosis of PA-VSD, 11 (41%) pregnancies were terminated. Termination of pregnancy was more common in fetuses with chromosomal anomalies (6 of 10 (60%)) than in those with normal or unknown karyotype (five of 17 (29%)). Thus, the decision to continue the pregnancy was influenced by the results of genetic studies and some of these parents may have continued with the pregnancy if the heart defect had been isolated. In contrast, in four fetuses the gestational age was above 24 weeks at presentation and perhaps termination would have been considered if presentation had been earlier.

Conclusions

During fetal life, PA-VSD can be diagnosed by echocardiography with a high degree of accuracy. However, it can be difficult to determine the morphology of the central pulmonary arteries and to locate the source of pulmonary blood supply. The condition is often associated with chromosomal abnormalities and in particular with 22q11.2 deletion. The findings of our study should help in counselling parents, with information about the prognosis of PA-VSD including total morbidity and mortality rather than information related solely to surgery.

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