Foetal echocardiographic assessment of tetralogy of Fallot and post-natal outcome

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Aims
Outcome of foetuses diagnosed with tetralogy of Fallot (TOF) or pulmonary atresia with ventricular septal defect (PA-VSD) and the reliability of foetal echocardiography to predict post-natal surgical outcome.

Methods and results
Outcome of 218 foetuses having been diagnosed with TOF (n = 153) or PA-VSD (n = 65) was reviewed. Abnormal karyotyping, 22q11 deletion, and extracardiac anomalies were found, respectively, in 11, 18, and 46%. Pregnancy was terminated in 75 cases (34%), and in three cases foetuses died in utero. Presence or absence and confluence of PA branches were confirmed after birth or pregnancy termination in all but five (5%) cases. Main pulmonary trunk (MPA) was incorrectly described in 11 (10%) cases and major aorto-pulmonary collateral arteries in 16 (13%) cases. Among live born infants, 110 (88%) were operated and 92 (74%) underwent complete repair in the first year of life. Size of confluent PAs and presence of MPA were related to the probability of having a complete repair in the first year of life.

Conclusion
Foetal diagnosis of TOF and PA-VSD has a major impact on pregnancy outcome, as associated anomalies are frequently found. Pre-natally determined size of PA branches and presence of MPA are good predictors of complete repair in the first year of life.

Keywords
Tetralogy of Fallot • Foetus • Heart defects • Congenital • Echocardiography • Outcome

Introduction
Over the past two decades, the detection rate of structural heart defects has considerably increased.¹ Nevertheless, the impact of pre-natal diagnosis on the outcome of newborns with CHD has been hard to evaluate mostly because of selection bias, as cases that are more likely to be diagnosed pre-natally tend to be the more severe cases.² As a result, various studies found overall poorer outcome in CHDs diagnosed pre-natally compared with those diagnosed after birth. In fact, the impact of pre-natal diagnosis varies considerably between CHDs because of differences in peri-natal physiology and postnatal management.³ Thus, improved outcome has been reported for pre-natally diagnosed coarctation of the aorta or transposition of the great arteries.⁴⁻⁵ Furthermore, recent studies have reported possible strategies to predict early neonatal outcome in specific defects such as transposition of the great arteries or to indicate foetal interventions in hypoplastic left heart syndrome.⁶⁻⁷ On the other hand, a great variety of echocardiographic techniques have improved the precision of the diagnosis of foetal CHDs and have led to a more accurate assessment of their anatomic features.⁸ Identifying in utero parameters able to predict post-natal mid-term outcome will certainly become the new challenge in foetal diagnosis of CHD.

In a recent Parisian population-based study, pre-natal diagnosis rates of tetralogy of Fallot (TOF) showed a constant increase over time reaching ~70% in 1995–2000.¹ In addition, associated extracardiac anomalies (ECAs) are frequent and have been identified as important prognostic factors in TOF and pulmonary atresia with ventricular septal defect (PA-VSD).⁹ Therefore, confirmation of these diagnoses leads to proposing a detailed anatomical scanning for extracardiac malformations and to performing karyotype analysis with fluorescent in situ hybridization (FISH) for 22q11 deletion.¹⁰⁻¹³ However, in a series of patients recently published, most chromosomal anomalies were not related to a poorer
post-natal outcome in opposition to syndromes affecting multiple-organ systems. Moreover, surgical outcome of TOF and PA-VSD is strongly dependent on the anatomy of pulmonary arterial tree. Therefore, both pulmonary artery anatomy and presence of associated anomalies should be taken into consideration to ensure a valid pre-natal counselling.

In this study, we assessed the characteristics and outcome of a series of foetuses diagnosed with either TOF or PA-VSD. We also evaluated the accuracy of the diagnosis by foetal echocardiography and the influence of the pre-natal description of pulmonary arterial tree anatomy on post-natal surgical outcome.

Methods

Patients

All consecutive foetuses diagnosed with TOF or PA-VSD between January 1997 and December 2003 in a single institution were included in this study. Foetuses with TOF and either absent pulmonary valve or other additional intracardiac abnormalities were excluded. Pre-natal data were gathered by a review of all available medical documentation. Foetuses were screened for ECAs within a period of 1 month before or after echocardiography. Foetal karyotyping and FISH for the detection of 22q11 deletion were proposed in all cases. Following pre-natal diagnosis, parents received a detailed counselling regarding the CHD, associated abnormalities, and possible therapeutic options from three specialized paediatric cardiologists in our institution.

Post-natal outcome was evaluated by reviewing the hospital medical records of all newborns. This study was approved by our institutional review committee and informed consent was given by parents to review files and echocardiography reports.

Foetal echocardiography and anatomy of the pulmonary arteries

Detailed foetal echocardiography by transabdominal approach was performed by two of us (L.F. and J.L.) using Acuson Sequoia (Mountain View, CA, USA), and from 2004, using GE Vivid 7. Standard views (four chamber, outflow tracts, great vessels) were obtained. Anatomy of the pulmonary arterial tree was described only using two-dimensional imaging (maternal obesity, foetal position, late gestational age) were obtained. Anatomy of the pulmonary arteries (MAPCAs) that were analysed using colour Doppler imaging. Measurements of pulmonary artery branches. (Figure 1), except for the major aorto-pulmonary collateral arteries (MAPCAs) that were analysed using colour Doppler imaging. All foetal echocardiographies were retrospectively reviewed by two of us (F.K. and A.B.) to identify pulmonary artery anatomy. Neonatal diagnosis and outcome data were unknown to both reviewers. Following information was retrieved from echocardiogram reports: presence or absence of the main pulmonary artery (MPA) and pulmonary artery branches (PAs) and presence or absence of MAPCAs. MPA and PAs sizes were classified as normal, small, or absent on the basis of previously established age-specific standards of foetal heart dimensions. Foetal examinations with poor quality imaging (maternal obesity, foetal position, late gestational age) were noted.

Post-natal pulmonary artery anatomy in live born infants was analysed using echocardiography, angiography, and surgical findings. All patients with PA-VSD underwent catheterization for angiography before surgery, whereas in patients with TOF, catheterization was performed only if PAs were not confluent or prior to complete repair following a palliative surgery. Foetuses that had undergone termination were submitted to foetopathological examination after informed consent by parents.

Finally, foetal echocardiographic data and neonatal or autopsy findings were compared to determine the accuracy of foetal echocardiography regarding CHD diagnosis and pulmonary artery anatomy.

Outcomes

Foetal outcome was determined by the total number and reasons for the termination of pregnancy (TOP) and intrauterine death (IUD). Assessment of post-natal outcome was limited to the first year of life and was determined by the total number and reasons for post-natal death (vital outcome) and the total number and type, palliative and/or complete repair, of surgery performed (surgical outcome).

Statistical analysis

Results are presented as numerical values and percentages for categorical variables and median and range for continuous variables. Comparisons of characteristics between groups were made using the χ² or Fisher’s exact test when appropriate. All tests were two-sided and the criterion for statistical significance was a P-value ≤ 0.05. All statistical calculations were performed using SAS software version 9.1 (SAS Inc., Cary, NC, USA).

Results

During the study period, 238 foetuses had a diagnosis of TOF or PA-VSD. Twenty foetuses were further excluded because their outcome remained unknown at the time of study analysis. Thus, our study is limited to 218 foetuses, 153 TOF and 65 PA-VSD, as diagnosed in utero. Median maternal age at diagnosis was 31 years (range 17–45). Median gestational age at diagnosis was 24 weeks (range 14–39.5), with 97 cases (44.5%) diagnosed before 24 weeks of gestation. One hundred and fourteen were female foetuses, 77 male, and for the remaining 27, gender was unknown. Principal reasons for referral in our tertiary reference centre after obstetric routine scan included the following: suspicion for CHD in 124 (57%) cases, diagnosis of TOF or PA-VSD in 75 (34%) cases, positive family history of CHD in eight cases (4%), presence of extracardiac abnormalities in eight cases (4%), and other (normal karyotyping, teratogenic drugs, non-immune foetal hydrops) in three cases (1%). One hundred and twelve foetuses had a second foetal echocardiography (median gestational age 31 weeks gestation) and 30 had a third foetal echocardiography (median gestational age 32 weeks gestation).
Associated chromosomal and extracardiac anomalies

Foetal karyotyping results were available in 185 of 218 pregnancies, and abnormalities were identified in a total of 20 (11%) foetuses (Table 1). FISH for 22q11 deletion results was available in 152 of 218 cases. Twenty-eight of 152 foetuses had 22q11 deletion, with a higher prevalence in PA-VSD (12/46, 26%) than in TOF (16/106, 15%). ECAs were detected in a total of 101 of 218 (46%) cases (70 TOF, 31 PA-VSD), with 25/101 anomalies being detected only after birth or autopsy. Therefore, the pre-natal detection rate of ECA was 75%.

On the basis of available data, 44/101 foetuses with ECA presented with a chromosomal anomaly (karyotyping abnormality \(n = 18\) or a 22q11 deletion \(n = 19\)) or a specific syndrome affecting multiple-organ systems: Alagille syndrome \((n = 2)\), CHARGE association syndrome \((n = 2)\), and VACTERL association syndrome \((n = 3)\). Moreover, 72 foetuses presented more than one associated ECA. Details on types of ECA associated with TOF and PA-VSD are presented in Figure 2. Differences between TOF and PA-VSD foetuses regarding karyotyping abnormalities, 22q11 deletion, and presence of ECA did not reach statistical significance.

Finally, echocardiography identified the presence of polyhydramnios in 22 cases, intrauterine growth restriction in 33 cases, and both of these conditions in six cases. Polyhydramnios was significantly associated with the presence of a 22q11 deletion in the foetus \((P = 0.03)\).

Pregnancy outcome

Seventy-five of 218 sets of parents opted for TOP and 34/75 refused foetal autopsy. In addition, TOP was more frequently considered after a pre-natal diagnosis of PA-VSD compared with that of TOF \((38/65\) vs. \(37/153; P < 0.0001)\). Overall, factors determining parents’ choice were complexity of the cardiac defect in 34% of TOP, associated chromosomal anomalies in 29%, severe ECA in 20%, complexity of the cardiac defect and chromosomal anomalies in 12%, and complexity of the cardiac defect with severe ECA in 5% of TOP. In fact, the majority of TOP in TOF was motivated by the presence of either a chromosomal anomaly or an ECA (79%), whereas in PA-VSD it was the complexity of the cardiac defect that mostly influenced the decision for TOP (50%).

In addition, there were three IUD in the continuing pregnancies: one occurred 7 days after an amniocentesis had been performed (direct relation to the procedure was unclear), and the other two concerned foetuses presenting severe associated ECA. Standard karyotype analysis and FISH for 22q11 deletion were normal in these three foetuses.

Accuracy of pre-natal diagnosis

To assess the accuracy of foetal echocardiography, we based our analysis only on foetuses with post-natal or autopsy confirmation of diagnosis. This was possible in 125/140 newborns, as 13 were lost to follow-up and two died soon after birth without confirmation of pre-natal diagnosis. This was also possible for 41/75 TOP and 2/3 IUD. Therefore, data from 168 cases were available for analysis.

Post-natal diagnosis was TOF in 114 cases and PA-VSD in 51 cases. Therefore, we noted that foetal diagnosis was erroneous in 3/168 (2%) cases: two patients presented a truncus arteriosus and one patient presented a double-outlet right ventricle with transposed great arteries, pulmonary atresia, and disconnected PAs.

Pre-natal diagnosis was partially exact in 27 cases (16%). In 11 foetuses with pulmonary atresia at birth, a patent pulmonary outflow tract had been detected at foetal echocardiography.

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**Table 1** Chromosomal abnormalities and 22q11 deletion in foetal tetralogy of Fallot and pulmonary atresia with ventricular septal defect

<table>
<thead>
<tr>
<th>Karyotyping abnormalities</th>
<th>TOF (screened (n = 132))</th>
<th>PA-VSD (screened (n = 53))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21 ((n = 7))</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Trisomy 13 ((n = 3))</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rare anomalies ((n = 10))</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trisomy 20 in mosaic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triploidy 69 XXX in mosaic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47 XXY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 XXY + 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 XX del (16q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 XX inv (9)</td>
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<tr>
<td></td>
<td></td>
<td>46 XX inv (5p)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46XY trisomy 1p monosomy 1p</td>
</tr>
<tr>
<td>22q11 microdeletion</td>
<td>TOF (screened (n = 106))</td>
<td>PA-VSD (screened (n = 46))</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Total of karyotyping anomalies and 22q11 microdeletions</td>
<td>31</td>
<td>17</td>
</tr>
</tbody>
</table>

TOF, tetralogy of Fallot; PA-VSD, tetralogy of Fallot with pulmonary atresia.
(performed at a median gestational age of 32 weeks; range 22–37 weeks). Six of them had had sequential echocardiographies, with the last follow-up scan occurring between 32 and 35 weeks gestation, and all of these examinations had showed a forward pulmonary flow. On the other hand, two foetuses described as presenting PA-VSD were diagnosed with TOF at birth. In addition, foetal echocardiography failed to document the presence of multiple VSD in eight cases and coronary artery anomalies in six cases. Finally, pre-natal diagnosis was fully exact in 138 out of 168 (82%) foetuses. Poor quality imaging was noted in 41/168 (24%) scans: in 2/3 erroneous diagnoses, 6/27 partially exact diagnoses, and 33/138 fully exact pre-natal diagnoses.

Accuracy of pre-natal echocardiographic description of pulmonary artery anatomy was based on the analysis of available data: in 94 cases for the description of PAs, 112 cases for that of MPA, and 126 cases for that of MAPCAs. Foetal echocardiographic evaluation was always consistent for the presence of PAs (89/89 cases). However, it was discordant for the absence of PAs in three cases where post-natal examinations confirmed the presence of PAs, and for the confluence of PAs in two cases (disconnected left PA arising from ductus arteriosus not visualized antenatally). Consistency between foetal evaluation of MPA and post-natal or autopsy findings was correct in all but 11 cases of PA-VSD (11/112) where MPA was pre-natally described as present but was actually absent. Finally, when foetal echocardiography detected MAPCAs (n = 9), this finding was confirmed in all but two cases. Conversely, when MAPCAs were not reported (n = 117) in foetal scans, they were in fact present in 14 cases.

**Post-natal outcome**

Both vital and surgical outcomes in the first year of life of the 140 newborns pre-natally diagnosed with TOF or PA-VSD are presented in Figure 3. Among the 10 infants who died before surgery (six TOF, four PA-VSD), seven presented severe ECA: diaphragmatic hernia (n = 3), tracheal malformation (n = 1), DiGeorge syndrome (n = 1), exomphalos (n = 1), and trisomy 13 (n = 1). Among the remaining, two neonates deceased because of respiratory distress complicating prematurity, and one neonate died of cardiac arrest at 3 months of age while presenting severe mitral stenosis.

In addition, five patients were not proposed for surgery in their first year of life because of extracardiac conditions (all scheduled for surgery soon after their first anniversary), and two moved abroad and were lost to follow-up.

Overall, 92 of 125 infants followed up to 1 year of life (74%) underwent complete surgical repair of their CHD, and 109 of 125 (87%) were alive in the same period of time. Unsurprisingly, complete repair rate was more elevated in TOF than in PA-VSD (85 vs. 37%; P < 0.0001). Survival rates in the two groups were not significantly different: 91% of survival for patients with TOF and 81% for those with PA-VSD.

**Prediction of reparability**

Among patients who had available pre-natal echocardiographic data on PAs size and were followed up to 1 year of life, we noted 66 complete surgical repairs in the first year of life among foetuses with normal size PAs (n = 77) and 20 among those with small or absent PAs (n = 36) (86 vs. 56%; P < 0.001). Among patients with present MPA, 79% (90/114) underwent complete repair vs. only 17% (1/6) of patients with absent MPA (P < 0.001). Finally, among patients with absent MAPCAs, 76% (89/117) underwent complete repair vs. 50% (3/6) with existing MAPCAs (P = 0.15).

**Discussion**

Pre-natal diagnosis of TOF is currently performed in many institutions in developed countries. Because of the French policy of pre-natal surveillance for congenital anomalies, foetal diagnosis of this defect is proportionally high in our area. There is certainly a
positive impact of the pre-natal diagnosis of TOF. First of all, it allows the search and identification of chromosomal anomalies as well as that of associated extracardiac malformations. Our series confirms the high prevalence of chromosomal anomalies, 22q11 deletions, and extracardiac malformations in TOF foetuses. It is of particular interest that the presence of associated anomalies accounted for 80% of TOP among TOF, whereas 50% of TOP in PA-VSD cases had been influenced by professionals’ uncertainty about cardiac prognosis.

Overall survival of foetuses with TOF or PA-VSD at 1 year of age was 87%. The high number of TOP was related to chromosomal malformations or ECAs in overall 67% of the cases. Post-natal mortality rate of patients who underwent surgery was low (5%) and principally related to the presence of ECAs. Furthermore, 74% of patients had already undergone complete repair of their defect at 1 year of age, and most of the remaining patients were suitable for complete repair within a short period of time. Thus, we believe that when ECAs are not life threatening or do not lead to TOP, the overall prognosis of foetal TOF, with or without pulmonary atresia, is satisfactory. Termination rate in this series is certainly high in specific cases, particularly in PA-VSD because parents consider that the prognosis of PA-VSD is much worse. Our results show that vital and surgical outcomes of both TOF and PA-VSD are satisfactory (and not comparable because the vital outcome is comparable but the surgical outcome is quite different, 85% vs. 37%) when pulmonary arteries are present. In the absence of major ECA, we should revise our attitude and tailor our pre-natal counselling essentially according to pulmonary artery anatomy.

However, interpretation of our results is subject to limitations. Classification of the defect in TOF or PA-VSD was based on pre-natal description and not on the verified post-natal or post-mortem diagnosis. This is probably the reason why the difference in the proportion of 22q11 deletions between TOF and PA-VSD was not significant, whereas this difference became significant when rectified post-natal or post-mortem diagnoses were considered (presence of 22q11 deletion in 28% of PA-VSD vs. 6% of TOF, \( P = 0.001 \)). Also, our results concerning the description of chromosomal anomalies and ECA are partially biased since we associated pre-natal and post-natal information available in only 77% of foetuses. Nevertheless, these biases could only lead to an underestimation of the proportion of associated anomalies in isolated TOF and PA-VSD.

Moreover, in a high percentage of cases, foetal echocardiographic evaluation was incomplete. The quality of echocardiography was low in 24% of cases, leading either to erroneous diagnosis or to incomplete analysis of obstruction of the right ventricular outflow tract. When technical conditions were adequate, complete diagnosis was possible in almost all cases, with the only persisting difficulty being the one of correctly differentiating a right outflow tract stenosis or atresia. The reason might be that some TOF progressed during the last weeks of gestation and presented as PA-VSD at birth. In six foetuses that presented...
this peri-natal evolution, we were able to review sequential echocardiograms that confirmed forward flow during the third trimester. Notwithstanding this hypothesis, we recommend that neonates with foetal diagnosis of TOF should be screened rapidly after birth to detect patients dependent on the ductus arteriosus for sufficient pulmonary blood flow.

Further, we did not evaluate the impact of foetal diagnosis of TOF and PA-VSD on pre-operative neonatal haemodynamics or on early mortality. Need for prostaglandin E1 infusion is difficult to predict, and since the year 2000, it is our policy to deliver foetuses with TOF or PA-VSD in our institution. However, we could not find any case in Paris Registry for Congenital Malformations that died during the first week of life without having been diagnosed as having TOF or PA-VSD prior to death. This is probably because congenital heart disease was easily suspected when neonates presented heart murmur and/or because duct-dependent cases were rapidly treated with prostaglandin E1 infusion at the presence of cyanosis in the first days of life. Therefore, the only additional benefit from early diagnosis for PA-VSD in the absence of obvious cyanosis would be to anticipate and plan surgical repair strategies.

Finally, the major challenge when diagnosing TOF and PA-VSD is to predict reparability of the defect. In our institution, repair is never done during the neonatal period. When necessary, palliation is provided by a modified Blalock shunt or a right ventricle connection to pulmonary artery without the closure of the ventricular septal defect. In patients with MAPCAs, the usual strategy is staged unfo- localization. We have shown that foetal echocardiography was overall reliable in describing PA anatomy. Size of PAs and the presence of MPA in foetal echocardiography were predictive of surgical outcome at 1 year of life, even though we acknowledge the limitations of our statistical analysis. Prediction of surgical outcome was satisfactory in our series, as echocardiographic description of the pulmonary vessels corresponded to anatomical findings in the large majority of cases. In the remaining cases, anatomy of the pulmonary arteries was less correctly evaluated.

In our opinion, efforts have to be made to further assess pulmonary vessel anatomy in foetuses with TOF and, particularly, in foetuses with PA-VSD since the main reason for TOP in the latter was uncertainty about cardiac prognosis.

**Conclusion**

Foetal diagnosis of congenital heart diseases influences neonatal care and planning of the birth conditions in specific defects such as the transposition of the great arteries, hypoplastic left heart, or suspected coarctation of the aorta since immediate or early neonatal interventions reduce mortality and morbidity. In TOF, foetal diagnosis certainly leads to a high rate of TOP because of associated anomalies. Foetal echocardiography is only partly reliable to differentiate TOF and PA-VSD but this issue did not strongly influence outcome in live born infants. All patients with either diagnosis must undergo a careful evaluation shortly after birth to detect those dependent on ductus arteriosus for sufficient pulmonary blood flow. Finally, reliability of foetal echocardiography in predicting the possibility of a complete repair within the first year of life is satisfactory. Efforts should be made to accurately define PA anatomy in order to inform parents on cardiac prognosis and thus potentially allow reducing the rate of therapeutic abortion in cases of PA-VSD with present pulmonary branches.

**Conflict of interest:** none declared.

**References**


**Clinical Vignette**

**Ventricular septal defect as casual finding in non-invasive CT-angiography**

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A 69 year-old man with history of diabetes, hypertension, and dyslipemia was admitted to emergency department for evaluation of chest pain with non-diagnostic ECG and negative myocardial markers. Multidetector CT angiography was performed without showing any significant coronary stenoses. Moreover CT showed small ventricular septal defect (arrows) (Panel A, volume rendering reconstruction) (Panels B and C, maximum intensity projection reconstruction). No interventricular shunt was demonstrated with colour doppler echocardiography. Only with Ultrasound contrast (Sonovue®) the shunt became patent (Panel D). Patient remains asymptomatic on medical therapy with ACE inhibitors and statins.

This case illustrates the importance of using reconstructions protocols not only for the study of coronary arteries morphology but also for other cardiac structures that are included in the same acquisition.

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