Cardiology in the Young (2015), **25**, 684–692
doi:10.1017/S1047951114000638

Original Article

The impact of not having a ductus arteriosus on clinical outcomes in foetuses diagnosed with tetralogy of Fallot

Seth J. Stern, Neelum Wadekar, Luc Mertens, Cedric Manlhiot, Brian W. McCrindle, Edgar T. Jaeggi, Lynne E. Nield

The Hospital for Sick Children, Labatt Family Heart Centre, University of Toronto, Toronto, Ontario, Canada

Abstract *Background*: Foetuses with simple tetralogy of Fallot almost universally have a patent ductus arteriosus. Two recently identified cases had an absent patent ductus arteriosus, requiring emergent intervention at birth. The objective of this study was to determine whether foetuses diagnosed with tetralogy of Fallot and no patent ductus arteriosus have poorer outcomes compared with those with tetralogy of Fallot + patent ductus arteriosus. *Methods*: All foetal cases of tetralogy of Fallot between January, 2000 and 2012 were retrospectively identified from The Hospital for Sick Children (Toronto, Canada) database. Cases – tetralogy of Fallot + no patent ductus arteriosus confirmed on postnatal echo – and controls – tetralogy of Fallot + patent ductus arteriosus, matched for gestational age – were identified from prenatal records, and both clinical and echocardiographic data were reviewed. Optimal outcome was defined as valve-sparing repair with no residual lesions. Student's t-tests and Fisher's exact χ^2 were used to compare groups. *Results*: n = 115 foetuses were diagnosed with tetralogy of Fallot: 11 (9%) had no patent ductus arteriosus, and were matched to 22 controls – mean gestational age at diagnosis 23.2 ± 4.2 weeks, 23.4 ± 6.6 weeks, respectively. Cases had a higher proportion of right aortic arches (64% versus 14%, $p < 0.001$). Foetal and postnatal echocardiographic data did not reveal significant differences in branch pulmonary artery sizes, pulmonary valve sizes, or ventricular function. No differences were identified for cyanosis at birth (2/10 versus 7/20, $p = 0.67$), or catheter intervention (5/10 versus 4/22, $p = 0.12$). Optimal outcome rates were similar between cases and controls (4/11 (36%) versus 5/21 (24%), $p = 0.68$). *Conclusions*: The patent ductus arteriosus does not appear to have an impact on clinical outcome in foetuses with tetralogy of Fallot.

Keywords: Tetralogy of Fallot; ductus arteriosus; foetal echocardiography; outcome

Received: 16 November 2013; Accepted: 26 March 2014; First published online: 28 April 2014

Tetralogy of Fallot is a relatively rare congenital heart defect, occurring in ~3% of foetuses with congenital heart disease.[1] The diagnosis of tetralogy of Fallot by foetal echocardiography is straightforward.[2]

Although this defect is rare, the adult congenital heart population largely comprises tetralogy of Fallot patients' post-surgical repair.[3,4] It is well recognised that the presence of severe right ventricular outflow tract obstruction and hypoplasia of the pulmonary valve, along with abnormal bidirectional or retrograde flow in the ductus arteriosus, is associated with the need for prostaglandins at birth and earlier intervention than those foetuses with milder right outflow obstruction and normal right-to-left flow across the patent ductus arteriosus.[5,6]

In 2011, we identified two cases of tetralogy of Fallot in which the ductus arteriosus was not identified on any serial foetal echocardiograms. These foetuses were born with severe right ventricular outflow obstruction and hypoplastic branch pulmonary arteries, were cyanotic, and required urgent catheter intervention at birth. One foetus died before complete repair.

Correspondence to: L. E. Nield, MD, Labatt Family Heart Centre, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8. Tel: +416 813 6141; Fax: +416 813 5857; E-mail: lynne.nield@sickkids.ca

The aim of the current study was to determine whether foetuses with simple tetralogy of Fallot and no identifiable ductus arteriosus have poorer perinatal outcomes as compared with foetuses with tetralogy of Fallot with a patent ductus arteriosus.

Materials and methods

This study was conducted as a single-centre retrospective case–control study at The Hospital for Sick Children, Toronto, Canada. The study was approved by the hospital's Research Ethics Board; requirement for individual patient consent was waived for a retrospective study.

Inclusion criteria

All prenatally diagnosed cases of tetralogy of Fallot between 1 January, 2000 and 1 January, 2012 were identified from the hospital database. Cases were defined as having no identifiable ductus arteriosus at the first prenatal diagnostic foetal echocardiogram, and confirmed by its absence during the first postnatal echocardiogram. Controls were defined by a diagnosis of tetralogy of Fallot and were matched to cases by gestational age at first diagnostic echocardiography in a 2:1 ratio. Controls were required to have an identifiable ductus arteriosus at the first foetal echocardiogram. Both cases and controls were required to have a full diagnostic postnatal echocardiogram at the Hospital for Sick Children in the first few days of life.

Exclusion criteria

For both cases and controls, all diagnoses of tetralogy of Fallot that resulted in termination of pregnancy were excluded. Concomitant diagnoses of atrioventricular septal defect, pulmonary atresia, or absent pulmonary valve were excluded.

Echocardiographic data

Two-dimensional serial foetal echocardiograms and the first postnatal echocardiogram were reviewed by a single investigator blinded to clinical outcome. All first foetal echocardiograms and first postnatal echocardiograms were reviewed in detail offline. All foetal echocardiographic reports were reviewed. If any follow-up foetal echocardiogram report discussed the presence or suspicion of a ductus arteriosus, that foetal echocardiogram was reviewed by L.N. in detail – no cases demonstrated a ductus arteriosus on follow-up foetal echocardiograms. All first foetal echocardiograms of the cases of tetralogy of Fallot and no identifiable ductus arteriosus were also reviewed by a second investigator (L.M.) blinded to whether this was a case or control. An additional five cases of tetralogy of Fallot with a ductus arteriosus – blinded and randomly selected – were included with the 11 cases to review. Digital echocardiograms were reviewed using SyngoDynamics version 3.1 (Siemens Medical Solutions, Malvern, Pennsylvania, United States of America). Archived videotapes – all echocardiograms between 2000 and 2004 – were reviewed using the Vingmed System Vivid-7 (GE Medical Systems, GE Vingmed Ultrasound AS, Horten, Norway).

Foetal echocardiographic measurements were obtained as per previous published protocols.[6] Two-dimensional measurements were taken for the aortic, pulmonary, tricuspid, and mitral valves, as well as proximal left and right pulmonary arteries. Both foetal and postnatal z-scores were calculated using standardised methods.[7,8] Doppler flow measurements and direction of flow across the pulmonic valve and patent ductus arteriosus were recorded. A peak gradient $\geqslant$100 cm/second was considered clinically important.[9] Valvular regurgitation was qualitatively defined as none, mild, or moderate-to-severe. Ventricular function was qualitatively defined as normal, mildly reduced, or moderate-to-severely reduced, using the 2D four chamber and sagittal views. Uniform global myocardial shortening in both views for the right and left ventricles defined normal ventricular function. Doppler flow patterns across the tricuspid valve (biphasic or monophasic), ductus venosus (normal, increased a-wave reversal), umbilical artery (normal, absent end diastolic flow), and umbilical vein (normal, pulsations) were recorded when available. Foetal hydrops was defined as two or more collections of fluid in the pericardial, pleural, and/or abdominal cavities.

The first postnatal echocardiogram was also reviewed to measure valve and branch pulmonary artery dimensions and z-scores, degree of right ventricular outflow tract obstruction and pulmonary insufficiency, degree of tricuspid regurgitation, and ventricular function. M-mode measurements of chamber sizes were recorded. Additional abnormalities, such as multiple ventricular septal defects, multiple aorto-pulmonary collaterals, mitral valve abnormalities, and coronary abnormalities were also recorded.

Demographic and clinical data

Maternal and postnatal medical charts were reviewed to determine diagnoses and clinical outcomes. Clinical status at most recent follow-up was obtained, if available. Patients' referring physicians were contacted by mail for supplemental information, if not available within hospital records.

Prenatal records were reviewed for maternal health, previous pregnancies, and prenatal testing – including

https://doi.org/10.1017/S1047951114000638 Published online by Cambridge University Press

chromosomal analysis and diagnostic imaging. Foetal outcome, including gestational age at birth, gender, and birth weight were recorded. Cause of intrauterine death was documented, when applicable. Postnatal data were collected to evaluate primary and secondary outcomes. Postnatal information was obtained from the hospital chart and included: cyanosis at birth (oxygen saturation <75% in room air), use of prostaglandins and/or mechanical ventilation, and admission to the intensive care unit versus the cardiac ward.

Primary outcomes. Primary outcomes included the need for early intervention or surgery, length of postoperative intensive care stay, full repair before 4 months of age that is "early", major morbidity – including stroke, cardiac failure, extracorporeal membrane oxygenation requirement, or major arrhythmia – or death.

Optimal outcome. Optimal outcome was defined as full anatomic repair – ventricular septal defect patch closure with pulmonary valve-sparing – with no residual atrial or ventricular septal defect, and no more than mild right ventricular outflow tract obstruction (peak gradient <25 mmHg).[10] Indicators of clinical status at most recent follow-up were documented.

Statistical analysis

Data are presented as mean with standard deviation, medians with interquartile range, or frequencies, as appropriate. Comparisons between cases and controls were made using Student's t-test and Fisher's exact χ^2 analysis. All statistical analyses were performed using SAS v9.3 (The SAS Institute, Cary, North Carolina, United States of America).

Results

Maternal and foetal data

A total of 156 cases were diagnosed with tetralogy of Fallot during the study period. Of these, 41 foetuses were excluded on the basis of concomitant congenital heart disease diagnoses (Fig 1). Of the remaining 115 foetuses, 11 (9%) did not have a ductus arteriosus on first foetal echo or on first postnatal echo. Of those foetal cases, seven were excluded following identification of a patent ductus arteriosus at first postnatal echo. Of those, five had a right aortic arch. One of the cases with a right arch had the patent ductus arteriosus coming off the innominate artery, and one

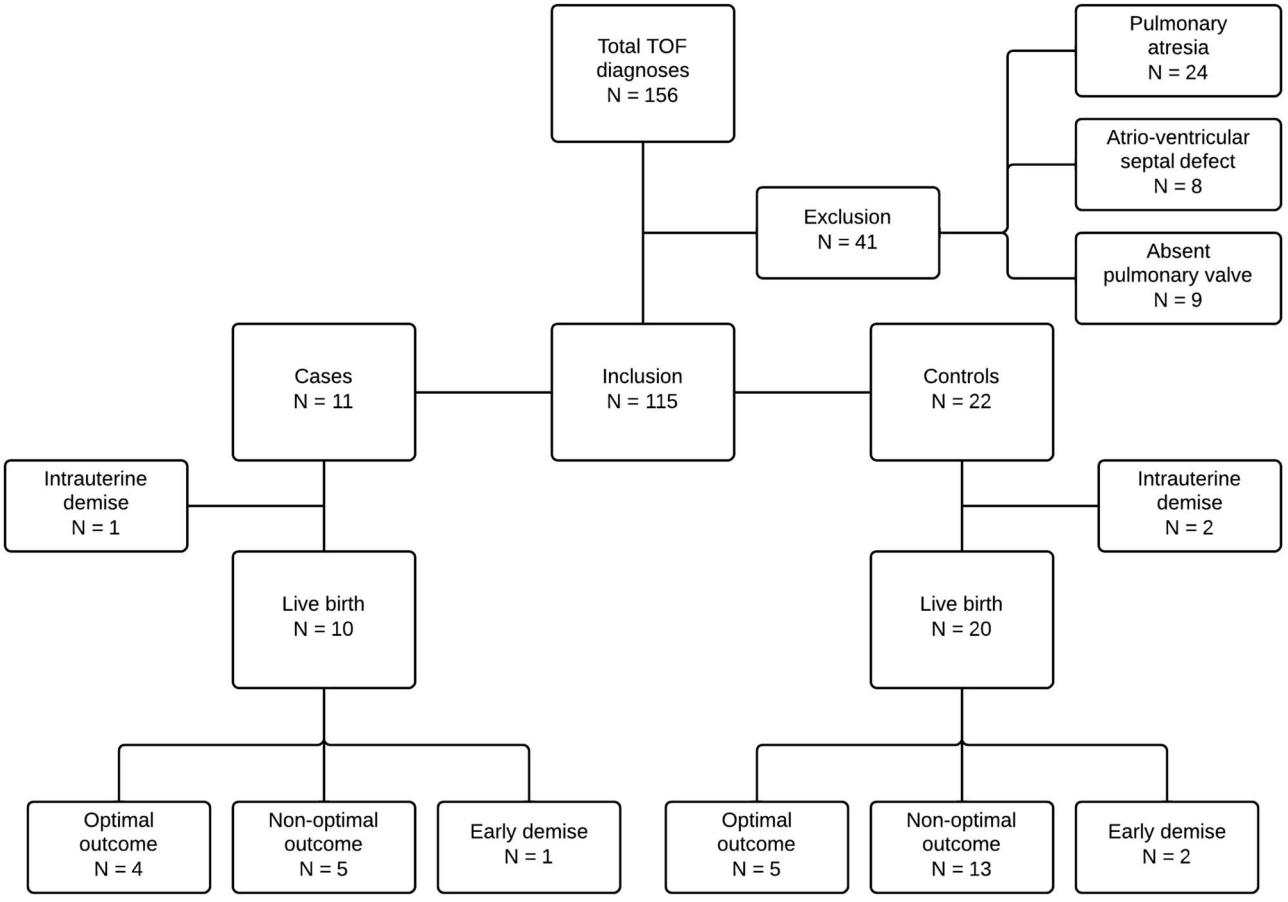

Figure 1.
Flowchart of included and excluded cases of tetralogy of Fallot identified in The Hospital for Sick Children's database.

https://doi.org/10.1017/S1047951114000638 Published online by Cambridge University Press

Table 1. Clinical and demographic data.

	n	Control	n	Case	p
Prenatal data					
Maternal age (years)	22	30.8 ± 6.6	11	32.1 ± 6.5	0.60
Gestational age at diagnosis (weeks)	22	23.4 ± 3.9	11	23.2 ± 4.2	0.88
Multiparity	22	2 (9%)	11	1 (9%)	1.00
Prenatal testing					
Abnormal maternal serum screening	18	3 (17%)	8	1 (13%)	1.00
Abnormal integrated prenatal screening	8	2 (25%)	2	0 (0%)	1.00
Abnormal amniocentesis	14	2 (14%)	5	1 (20%)	1.00
Chromosome testing	22		11		
Normal		11 (85%)		4 (80%)	1.00
Trisomy 21		1 (8%)		0 (0%)	1.00
Trisomy 18		1 (5%)		0 (0%)	1.00
Microdeletion 22		0 (0%)		1 (20%)	0.28
Clinical outcome					
Foetal outcome	22		11		
Live birth		20 (91%)		10 (91%)	1.00
Intrauterine demise		2 (9%)		1 (9%)	1.00
Gestational age at birth (weeks)	21	35.7 ± 4.4	10	37.7 ± 2.0	0.09
Birth weight (g)	19	2781 ± 935	9	3027 ± 587	0.41
Postnatal death	22	2 (9%)	11	1 (9%)	1.00
Birth outcomes					
Cyanosis at birth	20	7 (35%)	10	2 (20%)	0.67
PGE administration	20	6 (30%)	10	1 (10%)	0.37
Mechanical ventilation	20	7 (35%)	10	1 (10%)	0.21
ICU admission	20	9 (45%)	10	2 (25%)	0.25
Catheter intervention	20	4 (20%)	10	5 (50%)	0.12
Age at surgery #1 (days)	18	167.88 ± 28.41	9	149.33 ± 83.44	0.61
Type of surgery	18		9		
Full repair with valve-sparing		8 (44%)		5 (56%)	0.68
Full repair with TAP		10 (56%)		4 (44%)	0.41
Most recent follow-up					
Age (days)	19	727 (191–1160)	10	686.5 (167–1910)	0.39
Clinically well	18	18 (100%)	10	9 (90%)	0.36
Residual pulmonary stenosis	17		9		
None		10 (59%)		5 (56%)	1.00
Yes (mild)		5 (29%)		4 (44%)	0.67
Yes (moderate)		2 (12%)		0 (0%)	0.52
Free pulmonary insufficiency	17	14 (82%)	9	9 (100%)	0.53
Right ventricular end diastolic dimension (z-score)	16	0.44 ± 1.18	9	1.00 ± 0.81	0.19

PGE = prostaglandin E; TAP = transannular patch

had bilateral superior vena cavae. The two cases with a left arch had the usual patent ductus arteriosus from the left. One case was excluded as the infant arrived on day 1 of life in cardiac arrest and died. The echo showed tetralogy of Fallot, severely decreased ventricular function, and an intramural coronary artery.

Mean gestational age at diagnosis was 23.2 ± 4.2 weeks for cases, and 23.4 ± 3.9 weeks for controls (Table 1). Most foetuses (85%) were referred for foetal echocardiography following a suspicion of congenital heart disease on anatomic ultrasound. No significant differences were identified between cases and controls for maternal age, maternal health, previous pregnancies, multiparity, or use of fertility agents. There were three twin pregnancies – one case, two controls. Fertility agents included: clomiphene (one case), in vitro fertilisation (one case), and intrauterine implantation (one control). None of the mothers were using any medications associated with premature closure of the ductus arteriosus – for example non-steroidal anti-inflammatory drugs.

Amniocentesis was conducted in 5 (45%) cases and 14 (64%) controls. Prenatal chromosome testing did not identify any differences in occurrence of genetic abnormalities. Of the controls, two were found to have two separate genetic abnormalities (trisomy 18, trisomy 21), whereas one case was diagnosed with microdeletion 22q11.2. No controls were diagnosed with microdeletion 22q11.2. No significant differences were identified for renal abnormalities (0% of cases versus 5% of controls, p = 1.00) or neurological

https://doi.org/10.1017/S1047951114000638 Published online by Cambridge University Press

abnormalities (27% of cases versus 14% of controls, $p = 0.38$). Additional birth defects were diagnosed in one case (esophageal atresia) and two controls (cleft palate, omphalocele). There was no difference between the groups in terms of clinical status at birth.

Foetal cardiac diagnoses and demise

All foetuses had levocardia. The incidence of right aortic arch was higher for cases than controls (64% versus 14%, $p < 0.001$). One case and four controls had a double-outlet right ventricle (tetralogy-type), and one case had a left superior vena cava. Intrauterine demise occurred in one case – gestational age 26 weeks, associated esophageal atresia – and two controls – gestational age 23 weeks, other gestational age unknown with trisomy 18. The cause of intrauterine demise was unknown for all three foetuses.

Clinical outcomes

A total of 10 cases (91%) and 20 controls (91%) were live births. Clinical outcomes after birth are described in Table 1. Postnatal death occurred in one case (103 days old) and two controls (ages 134 and 154 days old). The case was palliative owing to the presence of central nervous system malformations – chromosome 1p deletion, with agenesis of corpus callosum and microcephaly – although the cause of death was not recorded. Of the controls, one died of respiratory failure and one died of liver failure.

There was no significant difference in the immediate perinatal period between the cases and controls in terms of cyanosis, need for intensive care or prostaglandins, or mechanical ventilation (Table 1).

Age at surgical repair was 4.9 ± 2.9 months for cases and 5.5 ± 0.9 months for controls. Early repair (<4 months old) occurred in two (18%) cases and one (5%) control. The types of surgical procedures and data regarding subsequent surgical procedures are detailed in Table 1. A total of five cases (56%) and eight controls (44%) underwent full repair with valve-sparing surgery ($p = 0.68$). No significant differences were identified for postoperative complications.

Catheter intervention occurred in 50% of cases and 20% of controls ($p = 0.12$). Of these, right ventricular outflow stenting was performed in three cases (days 2, 21, and 25) and two controls (day 4 and 61) because of cyanosis. The other two controls required balloon dilatation of the right outflow tract with a patent ductus arteriosus stent in one (day 10) and left pulmonary artery stent in the other (day 5). A late catheter intervention occurred for branch pulmonary artery stenoses in two cases at days 174 and 341. No controls required a late intervention.

Foetal echocardiography

Foetal echocardiography data are described in Table 2. None of the cases of tetralogy of Fallot without a ductus arteriosus demonstrated a ductus by colour or Doppler on follow-up foetal echocardiograms. Notably, no significant differences were identified between cases and controls for pulmonic valve annulus z-score, aortic valve annulus z-score, or pulmonic valve to aortic valve ratio. In addition, the left pulmonary artery and right pulmonary artery z-scores were similar between groups. Mean pulmonary valve to aortic valve ratio was 0.62 ± 0.18 for cases and 0.60 ± 0.15 for controls ($p = 0.69$).

Postnatal echocardiography

The first postnatal echocardiography was conducted within 48 hours for six cases (range 0–19 days) and for 16 controls (range 0–23 days) (Table 2). Among those that occurred >48 hours, three occurred within 96 hours. The remainder were born at local community hospitals with paediatric cardiologist coverage, and had their first postnatal echocardiogram at the 2–3 weeks of age, with the exception of one case born at our centre who did not receive an immediate echocardiogram because of an initial "do not resuscitate" status. That infant had a prenatally diagnosed severe brain abnormality and the family had elected for compassionate care. However, this child ultimately had a full repair at 6 months of age and was stable from a cardiac standpoint at 9 years of age.

At first postnatal echocardiogram, closure of the ductus arteriosus had occurred in 13 controls (65%), whereas two controls (10%) had a small patent ductus arteriosus and five controls (25%) had a moderate-to-large patent ductus arteriosus. All echocardiograms for controls with a patent ductus arteriosus had occurred within 24 hours. Of those with a patent ductus arteriosus, six demonstrated left-to-right flow, and only one demonstrated bidirectional flow.

No significant differences were identified between cases and controls for sizes of the pulmonary valve, aortic valve, right pulmonary artery, or left pulmonary artery. In addition, rates of pulmonary artery hypoplasia or stenosis were similar between groups. No significant differences were identified for either absent or mild right ventricular outflow tract obstruction. Cases demonstrated an increase in right ventricular end diastolic dimension (1.18 ± 0.18 cm versus 0.94 ± 0.26 cm, $p < 0.001$), with z-scores of 0.76 (0.34, 0.97) and −0.22 (−0.91, 0.52), respectively ($p = 0.01$). Left ventricular ejection fraction and ventricular function were similar between groups.

https://doi.org/10.1017/S1047951114000638 Published online by Cambridge University Press

Table 2. Foetal and postnatal echocardiographic data.

	n	Control	n	Case	p
Foetal echo					
Ductus arteriosus	22		11		
Patent		22 (100%)		0 (0%)	< 0.001
Absent		0 (0%)		11 (100%)	< 0.001
Ductus arteriosus flow	22		11		
Right to left		15 (68%)		0 (0%)	< 0.001
Left to right		3 (14%)		0 (0%)	0.53
Bidirectional		4 (18%)		0 (0%)	0.28
None		0 (0%)		11 (100%)	< 0.001
Pulmonic valve annulus (z-score)	22	−3.39 (−4.42, −2.98)	11	−2.28 (−4.49, −1.80)	0.99
Aortic valve annulus (z-score)	22	2.89 (1.59–3.17)	11	2.39 (1.67–3.35)	0.65
Right pulmonary artery (z-score)	21	−0.52 (−1.00, 0.23)	11	0.31 (−1.80, 0.65)	0.95
Left pulmonary artery (z-score)	21	−0.72 (−1.30, −0.12)	11	−0.66 (−1.80, −0.12)	0.81
Right ventricular outflow tract	22		9		
Laminar		11 (50%)		4 (44%)	1.00
Increased		11 (50%)		5 (56%)	1.00
Right ventricular outflow tract velocity (cm/second)	17	92 (80–120)	9	111 (98–137)	0.20
Postnatal echo					
Ductus arteriosus	20		9		
None		13 (65%)		9 (100%)	0.07
Small		2 (10%)		0 (0%)	1.00
Moderate/large		5 (25%)		0 (0%)	0.15
Ductus arteriosus flow	20		9		
Left to right		6 (30%)		0 (0%)	0.14
Bidirectional		1 (5%)		0 (0%)	1.00
None		13 (65%)		9 (100%)	0.07
Pulmonic valve size (z-score)	20	−2.67 (−3.90, −1.64)	9	−2.76 (−4.20, −1.20)	0.70
Aortic valve size (z-score)	20	4.16 (1.96–4.90)	9	2.57 (2.16–3.23)	0.19
Right pulmonary artery size (z-score)	19	−0.55 (−1.4, −0.32)	9	−0.7 (−1.1, 1.13)	0.63
Left pulmonary artery size (z-score)	20	−0.22 (−0.7, 0.17)	9	−0.57 (−0.8, 0.78)	0.88
Moderate/severe RVOTO	20	7 (35%)	9	6 (67%)	0.23
RVOTO gradient (mmHg)	17	27 (21–42)	9	31 (25–52)	0.30
Right ventricular end diastolic dimension (z-score)	19	−0.22 (−0.91, 0.52)	9	0.76 (0.34, 0.97)	0.01
Mild aortic insufficiency	19	2 (11%)	9	4 (44%)	0.06

RVOTO = right ventricular outflow tract obstruction

None of the infants had mitral regurgitation, and rates of tricuspid regurgitation were similar between groups.

Clinical follow-up data

Most recent follow-up was conducted at ~23 months (range 5–64) for cases and 17 months (range 8–38) for controls (Table 1). No significant differences were identified between groups regarding physician assessment of clinical status being overall well (90% of cases versus 100% of controls, p = 0.36), use of cardiac medication (20% of cases versus 11% of controls, p = 0.60), or occurrence of developmental delay (17% of cases versus 22% of controls, p = 1.00).

Echocardiography carried out at most recent follow-up did not indicate any differences in the occurrence of residual pulmonary stenosis, occurrence of residual septal defects, right or left pulmonary artery size, right ventricular end diastolic dimension, or ventricular function.

Optimal outcome was found to occur in 36% of cases and 24% of controls (p = 0.68).

Discussion

In the 12-year period of 2000–2012, there were 115 cases of simple tetralogy of Fallot diagnosed at this institution. The overall prevalence of foetuses with no identifiable ductus arteriosus was 9%. This subgroup of foetuses who do not have a ductus arteriosus has been intermittently described in the form of case reports,[11,12] but the prevalence has, to the best of our knowledge, not been previously reported in a large tetralogy of Fallot cohort. This is more common than would have been anticipated.

Our original hypothesis was that this subgroup would be more clinically unstable at birth, with a higher incidence of cyanosis and smaller branch pulmonary arteries, and thus potentially require more urgent intervention. We hypothesised that the treatment at birth would be limited, as

https://doi.org/10.1017/S1047951114000638 Published online by Cambridge University Press

prostaglandins would have no effect. Interestingly, our study demonstrated the opposite findings. This led to alternate explanations.

In tetralogy of Fallot, the agenesis of a ductus arteriosus would presumably occur early in gestation, which would thus allow for the foetus to adapt to this physiology. The other two physiological foetal shunts – patent foramen ovale and ductus venosus – plus the large ventricular septal defect would be able to modify flow across the right ventricle and into the pulmonary artery branches, and the presence of a degree of right outflow obstruction would also mediate flow to the pulmonary arteries, thereby ensuring normal growth of the pulmonary vascular bed.

It has been estimated in the lamb foetuses that ~57% of the right ventricular output shunts across the ductus arteriosus in the human foetus, with only 8% diverted into the pulmonary vasculature.[13] The balance of ductal flow and pulmonary flow is felt to be dependent on the intrinsic higher resistance in the pulmonary vascular bed, and has been recently demonstrated in the human foetuses by foetal MRI.[14] This steady physiological state is in distinct contrast to foetuses with tetralogy of Fallot and absent pulmonary valve syndrome and no ductus arteriosus, who develop severely dilated branch pulmonary arteries and bronchial compression.[15–19] The absence of a ductus arteriosus in the absent pulmonary valve group is hypothesised to be caused from either a failure of the development of the 6th branchial arch in early gestation, the involution of the immature ductus in later gestation, or secondary to the decreased diastolic pressure owing to the absent pulmonary valve combined with a large ventricular septal defect.[20,21] We could thus postulate that an absent ductus arteriosus in simple tetralogy of Fallot could be secondary to the first two hypotheses. It is interesting that a small proportion of cases with absent pulmonary valve do have a ductus arteriosus (~16–25%), usually, but not always, in the setting of an intact ventricular septum or tricuspid atresia.[17,18]

A second group of foetuses with an absent ductus arteriosus are those who develop premature closure of the ductus arteriosus.[22–24] This has been shown to occur in the setting of maternal administration of non-steroidal anti-inflammatory medications – for example indomethacin, aspirin – or glucocorticoids.[25,26] Those foetuses develop severe right-sided heart failure, tricuspid regurgitation, and are at significant risk for in utero demise. The treatment of this lesion is delivery. In this setting, the ductus arteriosus closes in the third trimester, and thus the pulmonary vasculature is already well formed, and presumably less amenable to adaptation. In our series, none of the cases developed hydrops or tricuspid regurgitation, implying that the pathogenesis of an absent ductus arteriosus in tetralogy of Fallot is very different from either the tetralogy of Fallot absent pulmonary valve or the premature ductus arteriosus closure groups.

The incidence of a right aortic arch in previous foetal series is approximately one-quarter to one-third of cases.[6,27,28] Our group of foetuses with no identifiable ductus arteriosus had a right arch in two-thirds of the cases, compared with one-third of controls. This could partly be explained by the fact that visualisation of the ductus arteriosus in the setting of a right arch is more technically difficult. The ductus arteriosus can arise from the brachiocephalic artery as opposed to the aortic isthmus, and in the foetus, this area would be superimposed on the transverse arch.[29] The ductal arch view in a sagittal plane is difficult to obtain in patients where the foetal spine is up or anterior, and distinguishing the two arches can be a challenge. Our group routinely will additionally obtain a high three-vessel view – high tracheal view – to identify both the arches. In this view, the two arches are distinct and form a "V" shape. Therefore, it is more reliable, and, if the ductus arteriosus were absent, there would only be one vessel joining the descending aorta. Of the cases without a patent ductus arteriosus on first foetal echo, seven were later found to have a patent ductus arteriosus postnatally, and of these, five had a right arch. Of the seven cases, six were performed before 2005, at the time of transition to digital imaging from videotapes that significantly improved the quality of our foetal echo imaging and offline analysis.

Though not statistically significant, our study did identify a higher rate of early catheter intervention – within 1 month of birth – among neonates born without a ductus arteriosus (3/10 versus 1/20). In each of these cases, intervention was required for right ventricular outflow tract stenting. This may have approached significance in a larger series of cases. In addition, it is possible that the more severe forms of tetralogy of Fallot without a patent ductus arteriosus may demise in utero earlier in gestation, given that the timing of a foetal echocardiogram is usually between 18 and 20 weeks' gestation.

This study was limited by its retrospective nature and small patient numbers. Before 2004, all studies were stored on videotape, and therefore offline analysis was more limited. Not all foetal echocardiograms had obtained a clear three-vessel view or high three-vessel view to image the ductal arch. All foetal echocardiograms had a sagittal view in 2D and colour, but some images were not clear. The ductus arteriosus was therefore not identified but could have still been present. To offset this limitation, all 11 cases plus another five randomly selected controls were reviewed by two independent staff foetal cardiologists to determine whether a ductus

arteriosus was present or not. The inclusion criteria required that each case have a postnatal echocardiogram to confirm no ductus arteriosus at initial assessment. It is well recognised that up to 50% of arterial ducts are not detected by 24 hours after birth, and 90% are not detected by 48 hours.[29] To strengthen any findings of the study, we elected to use a 2:1 ratio of cases to controls. As case–control pairs were not selected on the basis of pertinent confounders, a matched–paired analysis was not utilised.

In conclusion, the presence or absence of a ductus arteriosus does not appear to have an impact on clinical outcome in foetuses with tetralogy of Fallot. Clinical and echocardiographic indices are similar, both prenatally and postnatally. This is likely explained by early haemodynamic adaptations in the foetus, allowing for redistribution of pulmonary blood flow, and consequently, enabling normal growth of the pulmonary vasculature. Therefore, our results do not support a need for increased vigilance surrounding delivery of foetuses with an absent ductus arteriosus. However, in consideration of the limited sample size of the study, further assessment across a larger number of cases is needed to strengthen our conclusion.

Acknowledgements

None.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

None.

References

1. Tennstedt C, Chaoui R, Korner H, Dietel M. Spectrum of congenital heart defects and extracardiac malformations associated with chromosomal abnormalities: results of a seven year necropsy study. Heart 1999; 82: 34–39.
2. Yoo SJ, Lee YH, Kim ES, et al. Tetralogy of Fallot in the fetus: findings at targeted sonography. Ultrasound Obstet Gynecol 1999; 14: 29–37.
3. Hickey EJ, Veldtman G, Bradley TJ, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. Eur J Cardiovasc Surg 2009; 35: 156–164.
4. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. Lancet 2009; 374: 1462–1471.
5. Hornberger LK, Sanders SP, Sahn DJ, et al. In utero pulmonary artery and aortic growth and potential for progression of pulmonary outflow tract obstruction in tetralogy of Fallot. JACC 1995; 25: 739–745.
6. Hirji A, Bernasconi A, McCrindle BW, et al. Outcomes of prenatally diagnosed tetralogy of Fallot: implications for valve-sparing repair versus transannular patch. Can J Cardiol 2010; 26: e1–e6.
7. Schneider C, McCrindle BW, Carvalho JS, Hornberger LK, McCarthy KP, Daubeney PEF. Development of Z-scores for fetal cardiac dimensions from echocardiography. Ultrasound Obstet Gynecol 2005; 26: 599–605.
8. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr 2008; 21: 922–934.
9. Huhta JC, Moise KJ, Fisher DJ, Sharif DS, Wasserstrum N, Martin C. Detection and quantitation of constriction of the fetal ductus arteriosus by Doppler echocardiography. Circulation 1987; 75: 406–412.
10. Van Arsdell G, Maharaj GS, et al. What is the optimal age for repair of Tetralogy of Fallot? Circulation 2000; 102 (Suppl 3): 123–129.
11. Pahl E, Muster AJ, Ilbawi MN, DeLeon SY. Tetralogy of Fallot with absent ductus arteriosus and absent collateral pulmonary circulation: diagnostic and surgical implications during the neonatal period. Pediatr Cardiol 1988; 9: 45–49.
12. Peres LC, Bekhit M, Johki R. A tetralogy of fallot associated with a stenotic pulmonary valve and agenesis of the ductus arteriosus in a 13-week-old fetus: the role of postmortem examination. Pediatr Dev Path 2012; 15: 240–244.
13. Rudolph AM. Congenital Diseases of the Heart. Wiley-Blackwell, Oxford, 2009.
14. Seed M, van Amerom JFP, Al Nafisi B, et al. Feasibility of quantification of the distribution of blood flow in the normal human fetal circulation using CMR: a cross-sectional study. J Cardiovasc Magnet Res 2012; 14: 79–90.
15. Ettedgui JA, Sharland GK, Chita SK, Cook A, Fagg N, Allan LD. Absent pulmonary valve syndrome with ventricular septal defect: role of the arterial duct. Am J Cardiol 1990; 66: 233–234.
16. Razavi RS, Sharland GK, Simpson JM. Prenatal diagnosis by echocardiogram and outcome of absent pulmonary valve syndrome. Am J Cardiol 2003; 91: 429–432.
17. Galindo A, Gutiérrez-Larraya F, Martinez JM, et al. Prenatal diagnosis and outcome for fetuses with congenital absence of the pulmonary valve. Ultrasound Obstet Gynecol 2006; 28: 32–39.
18. Wertaschnigg D, Jaeggi M, Chitayat D, et al. Prenatal diagnosis and outcome of absent pulmonary valve syndrome: contemporary single-center experience and review of the literature. Ultrasound Obstet Gynecol 2013; 41: 162–167.
19. Kohler HG. Premature closure of the ductus arteriosus (P.C.D.A.): a possible cause of intrauterine circulatory failure. Early Hum Dev 1978; 2: 15–23.
20. Bergwerff M, DeRuiter MC, Gittenberger-de Groot AC. Comparative anatomy and ontogeny of the ductus arteriosus, a vascular outsider. Anat Embryol 1999; 200: 559–571.
21. Ettedgui JA, Sharland GK, Chita SK, Cook A, Fagg N, Allan LD. Absent pulmonary valve syndrome with ventricular septal defect: role of the arterial duct. Am J Cardiol 1990; 66: 233–234.
22. Becker R, Schmitz L, Guschmann M, Wegner RD, Stiemer B, Entezami M. Prenetal diagnosis of familial absent pulmonary valve syndrome: case report and review of the literature. Ultrasound Obstet Gynecol 2001; 17: 263–267.
23. Tulzer G, Gudmundsson S, Sharkey AM, Wood DC, Cohen AW, Huhta JC. Doppler echocardiography of fetal ductus arteriosus constriction versus increased right ventricular output. JACC 1991; 18: 532–536.
24. Leal SD, Cavallé-Garrido T, Ryan G, Farine D, Heilbut M, Smallhorn JF. Isolated ductal closure in utero diagnosed by fetal echocardiography. Am J Perinatol 1997; 14: 205–210.
25. Trevett TN, Cotton J. Idiopathic constriction of the fetal ductus arteriosus. Ultrasound Obstet Gynecol 2004; 23: 517–519.

26. Waffarn F, Siassi B, Cabal LA, Schmidt PL. Effect of antenatal glucocorticoids on clinical closure of the ductus arteriosus. Am J Dis Child 1983; 137: 336–338.
27. Moise KJ, Huhta JC, Sharif DS, et al. Indomethacin in the treatment of premature labor: effects on the fetal ductus arteriosus. NEJM 1988; 319: 327–331.
28. Rao BN, Anderson RC, Edwards JE. Anatomic variations in the tetralogy of Fallot. Am Heart J 1971; 81: 361–371.
29. Gentile R, Stevenson G, Dooley T, Franklin D, Kawabori I, Pearlman A. Pulsed Doppler echocardiographic determination of time of ductal closure in normal newborn infants. J Pediatr 1981; 98: 443–448.