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ORIGINAL RESEARCH

Contemporary Outcomes in Tetralogy of Fallot With Absent Pulmonary Valve After Fetal Diagnosis

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BACKGROUND: Tetralogy of Fallot with absent pulmonary valve is associated with high mortality, but it remains difficult to predict outcomes prenatally. We aimed to identify risk factors for mortality in a large multicenter cohort.

METHODS AND RESULTS: Fetal echocardiograms and clinical data from 19 centers over a 10-year period were collected. Primary outcome measures included fetal demise and overall mortality. Of 100 fetuses, pregnancy termination/postnatal nonintervention was elected in 22. Of 78 with intention to treat, 7 (9%) died in utero and 21 (27%) died postnatally. With median follow-up of 32.9 months, no deaths occurred after 13 months. Of 80 fetuses with genetic testing, 46% had chromosomal abnormalities, with 22q11.2 deletion in 35%. On last fetal echocardiogram, at a median of 34.6 weeks, left ventricular dysfunction independently predicted fetal demise (odds ratio [OR], 7.4; 95% CI 1.3, 43.0; P=0.026). Right ventricular dysfunction independently predicted overall mortality in multivariate analysis (OR, 7.9; 95% CI 2.1–30.0; P=0.002). Earlier gestational age at delivery, mediastinal shift, left ventricular/right ventricular dilation, left ventricular dysfunction, tricuspid regurgitation, and Doppler abnormalities were associated with fetal and postnatal mortality, although few tended to progress throughout gestation on serial evaluation. Pulmonary artery diameters did not correlate with outcomes.

CONCLUSIONS: Perinatal mortality in tetralogy of Fallot with absent pulmonary valve remains high, with overall survival of 64% in fetuses with intention to treat. Right ventricular dysfunction independently predicts overall mortality. Left ventricular dysfunction predicts fetal mortality and may influence prenatal management and delivery planning. Mediastinal shift may reflect secondary effects of airway obstruction and abnormal lung development and is associated with increased mortality.

Key Words: congenital heart disease ■ fetal cardiology ■ fetal echocardiography ■ prenatal diagnosis ■ tetralogy of Fallot with absent pulmonary valve

Tetralogy of Fallot with absent pulmonary valve (TOF/APV) is a rare congenital heart defect associated with severe perinatal morbidity and mortality, with a reported survival after initial diagnosis of 14% to 68%.[1–3] The clinical presentation is highly variable. Patients may have perinatal demise, may present with severe postnatal respiratory and hemodynamic compromise, or be born with no respiratory symptoms, with a relatively benign neonatal course, and undergo elective repair later in infancy. Despite improved fetal diagnosis, it remains difficult to reliably predict the clinical course of a patient

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CLINICAL PERSPECTIVE

What Is New?

- This multicenter cohort study of outcomes in fetuses with tetralogy of Fallot with absent pulmonary valve demonstrates that perinatal mortality remains high, with 64% survival among fetuses with intent to treat.
- Right ventricular dysfunction on fetal echocardiogram independently predicted overall mortality; however, left ventricular dysfunction predicted fetal demise and may therefore influence prenatal management and delivery planning.
- Pulmonary artery diameters did not correlate with outcomes; mediastinal shift on fetal echocardiogram may reflect secondary effects of airway obstruction and abnormal lung development and was associated with increased mortality.

What Are the Clinical Implications?

- A comprehensive assessment of the fetal heart and lungs can predict outcomes in tetralogy of Fallot with absent pulmonary valve, guide prenatal counseling and perinatal management, and direct future efforts to further risk stratify and potentially reduce mortality from this disease.

Nonstandard Abbreviations and Acronyms

CTA	cardiothoracic area
GA	gestational age
TOF/APV	tetralogy of Fallot with absent pulmonary valve
VTI	velocity time integral

diagnosed in utero. This ambiguity limits both delivery planning and prenatal counseling. Several studies have attempted to identify fetal predictors of mortality in TOF/APV. However, they have been limited by small study populations and heterogeneous cohorts that included other absent pulmonary valve variants, including those with an intact ventricular septum or tricuspid valve dysplasia.[2,3]

It has been theorized that severe pulmonary artery dilation, a hallmark finding in this defect, develops because of severe pulmonary insufficiency and volume overload. Over time, this can progress and can cause airway compression, resulting in postnatal respiratory distress.[4,5] Magnetic resonance imaging studies in fetuses with TOF/APV suggest that a "ball-valve" mechanism of bronchial obstruction leads to prenatal fluid or postnatal air trapping within the lungs and may cause lung compression or hyperexpansion that worsens respiratory and cardiac compromise.[6,7] From a cardiovascular standpoint, it has been posited that this long-term volume and pressure overload on the right ventricle cannot only cause ventricular dysfunction and dilation but also elevated venous pressures that can lead to fetal hydrops.[5]

To better understand factors affecting perinatal and early postnatal mortality that are identifiable in the fetal period, we designed a large contemporary multicenter cohort study of fetuses with TOF/APV. We sought to assess prenatal clinical characteristics and fetal echocardiographic findings reflecting cardiac morphological features, function, and Doppler evaluation to identify fetal predictors of in utero demise and overall mortality. We hypothesized that findings on fetal echocardiogram, such as the presence of mediastinal shift and cardiac axis deviation, which can reflect both cardiac enlargement as well as lung hyperexpansion or hypoplasia, may be associated with mortality. A secondary aim, in patients with serial fetal evaluation, was to describe fetal echocardiographic data from initial fetal echocardiogram in relation to the appearance of the final echocardiogram.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

This is a multicenter retrospective cohort study of fetuses presenting with TOF/APV over a 10-year period. Each center, located within the United States or Canada, obtained approval from its institutional review board. We included all fetuses with at least one available prenatal echocardiogram and a known perinatal clinical course. We included fetuses in whom pregnancy termination or planned nonintervention was elected for maternal and fetal demographic analysis only. Fetal echocardiography and outcomes were analyzed only in fetuses with an intention to treat. Fetuses with known genetic abnormalities were not excluded. Fetuses were excluded, however, if they had additional associated complex congenital cardiac or extracardiac lesions likely to significantly alter cardiovascular physiological features and prognosis. The primary outcome of this study among fetuses with intention to treat was overall mortality, defined as fetal or postnatal death from time of last fetal echocardiogram until the end of the study follow-up period.

Data Collection

Each study institution retrospectively collected and anonymized demographic and clinical data for each maternal-fetal dyad from hospital medical records. Study data were collected and managed using a secure online Research Electronic Data Capture database hosted at Children's National Hospital.[8] Anonymized fetal echocardiograms were submitted to the lead institution. There, a single observer (A.C.), who was blinded to outcome, reviewed each subject's final available fetal echocardiogram before delivery or demise to assess structural measurements, functional variables, and lung characteristics, as described below. The time point of the final prenatal echocardiogram was chosen for assessment to reflect disease evolution over the course of gestation, and as these findings most directly influence delivery planning. When additional fetal echocardiograms were available, the initial fetal echocardiogram at time of presentation was also analyzed. The echocardiographic variables assessed are listed in Table 1. As these retrospectively reviewed echocardiograms did not follow a consistent protocol, quantitative assessment was limited; therefore, we qualitatively assessed ventricular size and systolic function. Right ventricular (RV) and left ventricular (LV) systolic dysfunction were defined as abnormal motion of the RV and LV free walls, respectively, identified on 4-chamber and/or short-axis views. Given the presence of pulmonary regurgitation and at a minimum mild RV enlargement in all fetuses, significant RV dilation was noted when graded as moderate or severe; this was assessed qualitatively in the end-diastolic 4-chamber and short-axis views, noting septal position bowing into the left ventricle. Any degree of LV dilation was noted; this was assessed qualitatively in end diastole in the 4-chamber and short-axis views. Tricuspid regurgitation was defined as the presence of a holosystolic regurgitant color Doppler jet seen crossing the tricuspid valve on 4-chamber views. The presence of pericardial effusion was also assessed. The pulmonary valve annulus and main and branch pulmonary artery diameters were measured using the 3-vessel view in systole at the largest diameter, and their *z*-scores were calculated using fetal nomograms reported by Krishnan et al.[9] Cardiothoracic area ratio and cardiac axis were measured on axial 4-chamber views, in fetuses with adequate images, using standard techniques.[10,11]

To assess for mediastinal shift on fetal echocardiogram, we used the method described in obstetrical ultrasound by Colombani and colleagues.[12] Mediastinal shift was defined using the axial 4-chamber image of the fetal thorax, which was bisected by a sagittal line connecting the sternum to the spine. The presence of the cardiac 4-chamber view with the heart either more than two thirds in the left hemithorax (left shift) or more than one third in the right hemithorax (right shift) was noted to be significant, suggesting abnormal cardiac position (Figure 1).

Categorical assessments, including ventricular size and function and the presence of mediastinal shift, and quantitative measurements of cardiothoracic area (CTA) ratio and pulmonary artery dimensions were repeated by an additional blinded observer (M.T.D.) in a subset of 20 randomly selected fetuses to assess interobserver variability.

To assess the significance of fetal Doppler findings, a single observer (J.S.C.) who was also blinded to outcome analyzed intracardiac and extracardiac Dopplers, in fetuses who had them performed, from the first and last fetal echocardiograms. Cardiac Doppler measurements included tricuspid inflow duration/cardiac cycle length, peak pulmonary velocity, pulmonary and aortic valve velocity time integral (VTI), pulmonary regurgitation VTI, and calculated pulmonary forward/reverse VTI ratio. Extracardiac Doppler variables included normal versus abnormal ductus venosus Doppler pattern (ie, absent or reversed end-diastolic flow), middle cerebral artery pulsatility index, and the cerebroplacental ratio based on middle cerebral artery and umbilical artery pulsatility indexes.

Table 1. Fetal Echocardiographic Study Variables

Structural	Functional	Cardiopulmonary	Doppler
Moderate or greater RV dilation	RV dysfunction	Abnormal cardiac axis (<30° or >75°)	TID/CCL
LV dilation	LV dysfunction	Presence of mediastinal shift	PV peak velocity (cm/s)
PV annulus (diameter, cm, and *z*-score)	Presence of TR		PR VTI
MPA size (diameter, cm, and *z*-score)			PV forward/reverse VTI ratio
LPA size (diameter, cm, and *z*-score)			Aortic valve VTI
RPA size (diameter, cm, and *z*-score)			Abnormal DV Doppler pattern
CTA ratio			MCA PI
			CPR PI

CPR PI indicates cerebroplacental ratio for pulsatility indexes; CTA, cardiothoracic area; DV, ductus venosus; LPA, left pulmonary artery; LV, left ventricular; MCA PI, middle cerebral artery pulsatility index; MPA, main pulmonary artery; PR, pulmonary regurgitation; PV, pulmonary valve; RPA, right pulmonary artery; RV, right ventricular; TID/CCL, tricuspid inflow duration/cardiac cycle length; TR, tricuspid regurgitation; and VTI, velocity time integral.

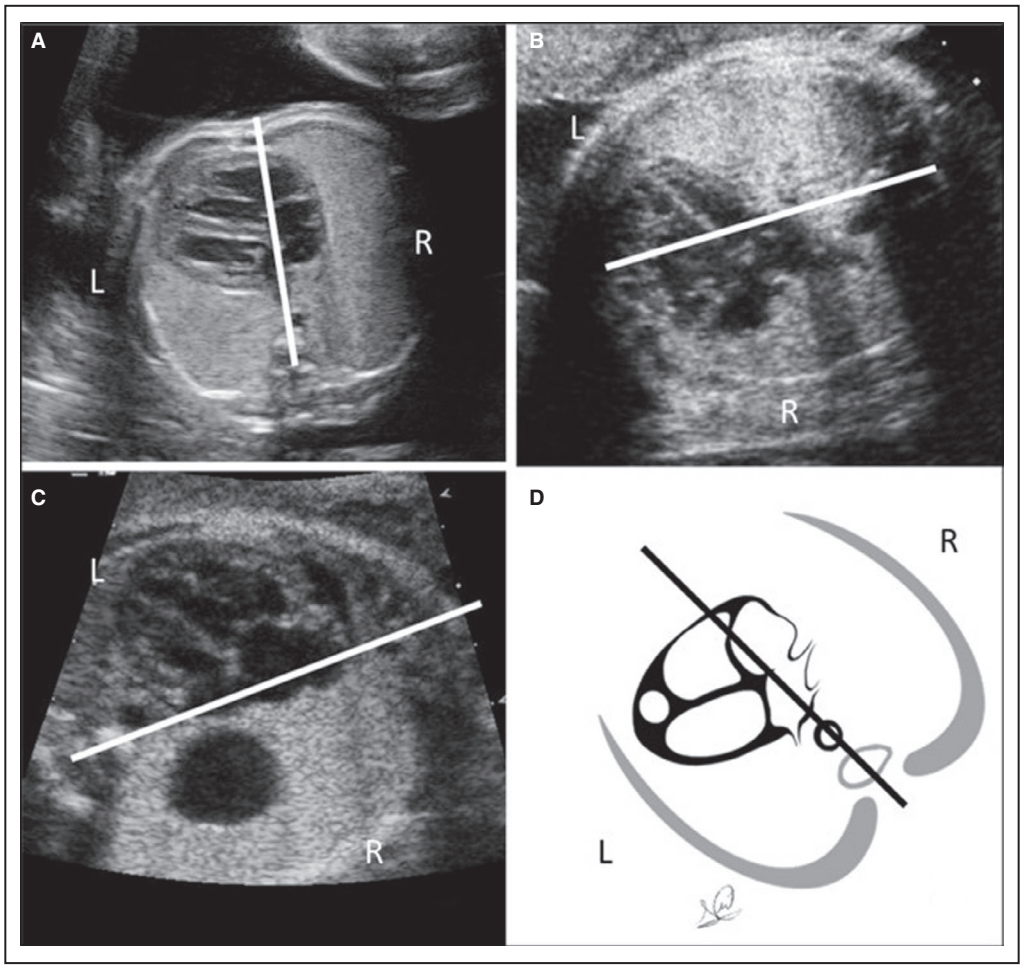

Figure 1. Fetal echocardiographic image and diagram demonstrating assessment of mediastinal shift.
Per the method described by Colombani et al, in the axial 4-chamber view, a line is drawn through the fetal median sagittal plane (**A** and **D**).[12] Rightward mediastinal shift is defined as greater than one third of the cardiac mass within the right (R) chest (**B**). In leftward mediastinal shift (**C**), greater than two thirds of the heart is seen within the left (L) side of the chest. The fetal cardiac axis is also deviated leftward in this example.

In fetuses for whom >1 fetal echocardiogram was available, we described individual differences between the first and last fetal echocardiogram in each patient to assess whether findings are progressive over the course of gestation. We also sought to assess whether variables identified in the primary analysis as fetal predictors of outcome progressed more on repeated echocardiographic assessment among those who died compared with those who lived.

Statistical Analysis

Summary statistics were analyzed, with categorical variables expressed as a frequency (percentage of patients included) and continuous variables expressed as a mean with SD for normally distributed data and median with range for nonparametric data. Kaplan-Meier survival analysis was performed for those with an intent to treat. To test comparisons between groups, χ^2 and Fisher exact tests were used for categorical variables and 2-tailed Student *t*-test was used for continuous variables. Possible fetal predictors of outcomes with $P<0.05$ by univariate analysis were then investigated using a stepwise multivariate logistic regression.

Interobserver variability was calculated in the subset of fetuses with second observer measurements using the Cohen κ (weighted when appropriate), while intraclass correlation coefficients were calculated for continuous variables.

Finally, in fetuses with >1 prenatal echocardiogram available, variables that were found to have a significant association with the primary outcome in the univariate analysis were analyzed for changes between the initial fetal echocardiogram at diagnosis and last follow-up stratified by the primary outcome of survival.

Descriptive analyses were used and included the McNemar test for categorical variables and a paired *t*-test or Wilcoxon signed rank test for continuous variables. Of the variables that appeared to behave differently between the group who survived versus the group who died, a repeated-measures analysis using generalized estimating equations was used to compare the magnitude of change from the first to last examination in the variables identified as predictors of outcome between the group who survived versus the group who died after adjusting for gestational age (GA) at the time of fetal echocardiogram.

The lead author (A.C.) had full access to all the data in the study and takes responsibility for their integrity and the data analysis.

RESULTS

Clinical data and echocardiograms from 108 fetuses with TOF/APV were submitted by 19 centers (range, 1–18 fetuses per center). Of these, 100 fetuses met inclusion criteria. Three were excluded for significant tricuspid valve dysplasia, hypoplasia, or atresia, and 3 for additional complex diagnoses, including double-outlet right ventricle and unbalanced complete atrioventricular septal defect. One was excluded because of a large congenital diaphragmatic hernia, with abdominal viscera occupying the left hemithorax, and one submitted patient was lost to follow-up after the initial fetal echocardiogram and therefore excluded.

Table 2 outlines clinical characteristics of the 100-fetus cohort and their mothers. Of fetuses with available family history information, 20% had a family member with congenital heart disease, with 9 documented to have a parent or sibling with congenital heart disease. Although 6% of fetuses in the cohort were twins, there were no pregnancies with both twins affected. Of the 100 fetuses, 80 had documented amniocentesis, chorionic villus sampling, and/or postnatal genetic testing. The 22q11.2 deletion was the most common genetic abnormality among those tested, affecting 28 of 80 (35%) of those tested. Other findings included 2 fetuses with trisomy 13, 1 with mosaic trisomy 2, 1 with an unbalanced translocation, and 5 with partial gene deletions or duplications. No fetus had trisomy 18 or 21. Nine pregnancies affected by genetic abnormalities were terminated.

Figure 2 depicts the study population. The 20 pregnancy terminations all occurred between 18 and 24 weeks. For 2 fetuses, both with chromosomal abnormalities, postnatal palliative care was planned, and both died within the first 2 days of life. Seven (9%) of the 78 fetuses with intention to treat died in utero, at a median GA of 36 weeks (range, 26–38 weeks). Of the 71 fetuses with intent to treat born alive, 11 died in the neonatal period before an attempt at surgical repair or after a decision was made to redirect goals of care. Of 21 undergoing neonatal repair, 6 died. Thirty-nine of 78 (50%) of those with intent to treat were discharged from the hospital without requiring neonatal surgical intervention after a median length of stay of 7.5 days (range, 3–58 days); 4 of them died before (n=1) or after (n=3) late repair.

Survival from initial diagnosis was 50% among the entire cohort of fetuses diagnosed with TOF/APV, including those for whom pregnancy termination or nonintervention was elected. Overall survival among the 78 fetuses with TOF/APV and an initial intention to treat was 64% (Figure 3). Seventy percent of liveborn babies survived. Five patients were lost to follow-up after initial hospitalization, but among the remaining patients, there were no documented deaths after 13 months of age.

Table 3 demonstrates clinical characteristics of the 71 fetuses born alive with intent to treat. Most fetuses were born at term, and none was delivered before 30 weeks' gestation. Most required respiratory and/or hemodynamic support in the first 24 hours of life.

Table 2. Maternal and Fetal Clinical Characteristics of Cohort With TOF/APV (N=100)

Characteristics	Median (Range) or No. (%)*
Maternal age at first presentation to study center, y	29 (17–45)
GA at presentation to study center, wk	23 (18–37)
Family history of congenital heart disease (n=82)	16 (20)
Twin gestation	6 (6)
Fetal chromosomal abnormality, based on prenatal and/or postnatal testing (n=80)	37 (46)
22q11.2 Deletion	28 (35)
Other aneuploidy, duplication, or deletion	9 (11)
Extracardiac fetal anomaly†	16 (16)
Neurologic	4 (4)
Renal/genitourinary	4 (4)
Gastrointestinal	5 (5)
Musculoskeletal/craniofacial	5 (5)
Abnormal amniotic fluid level (at any time in follow-up)	23 (23)
Polyhydramnios	19 (19)
Oligohydramnios	4 (4)
Fetal hydrops (n=91)	7 (8)
Fetal MRI performed	8 (8)

GA indicates gestational age; MRI, magnetic resonance imaging; and TOF/APV, tetralogy of Fallot with absent pulmonary valve.

*Percentages are based on the number of subjects for which each variable was reported, provided as (n=).

†Two fetuses had multiple anomalies.

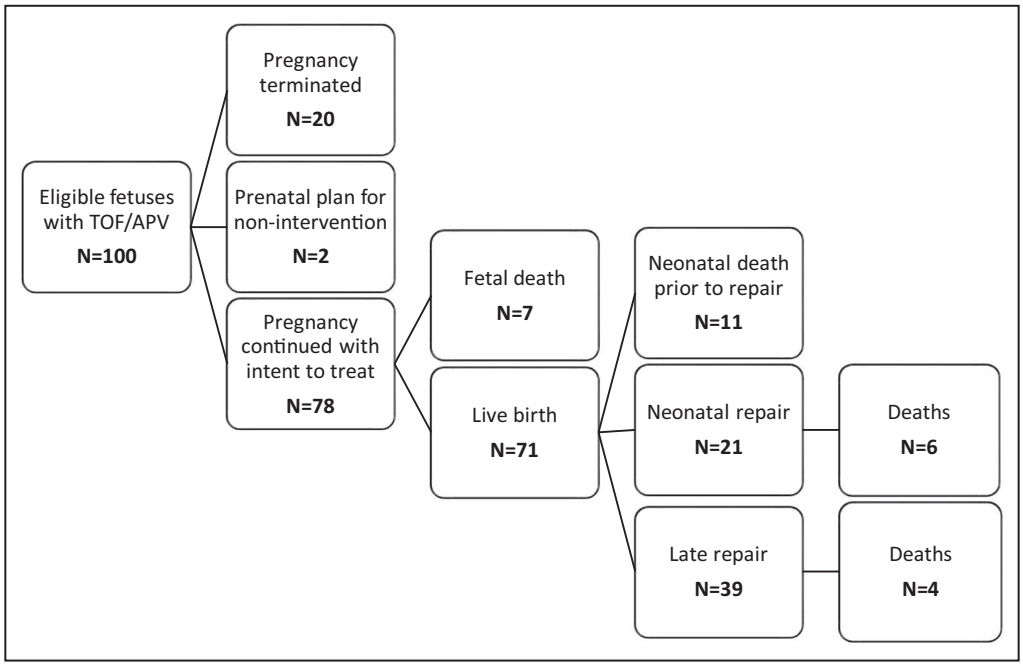

Figure 2. Flow diagram depicting management and outcomes among the fetal tetralogy of Fallot with absent pulmonary valve (TOF/APV) study cohort.

Postnatal echocardiogram demonstrated a patent ductus arteriosus in only 2 patients; in both, the ductus arteriosus supplied a discontinuous left pulmonary artery.

Among patients with intent to treat, fetal clinical characteristics and findings on the last available fetal echocardiogram, performed a median of 9 (range, 2–20) weeks after the initial fetal echocardiogram, were assessed. The last fetal echocardiogram in this cohort was performed at a median gestation of 34.6 weeks, with a range of 19 to 39 weeks, and all but 4 of the final studies were performed in the third trimester. Clinical and echocardiographic findings were compared between the cohort of fetuses who died in utero and those who were liveborn (Table 4). Factors associated with fetal death included fetal hydrops, pericardial effusion, LV and/or RV systolic dysfunction, and tricuspid regurgitation. Only 5 nonterminated fetuses had hydrops; 3

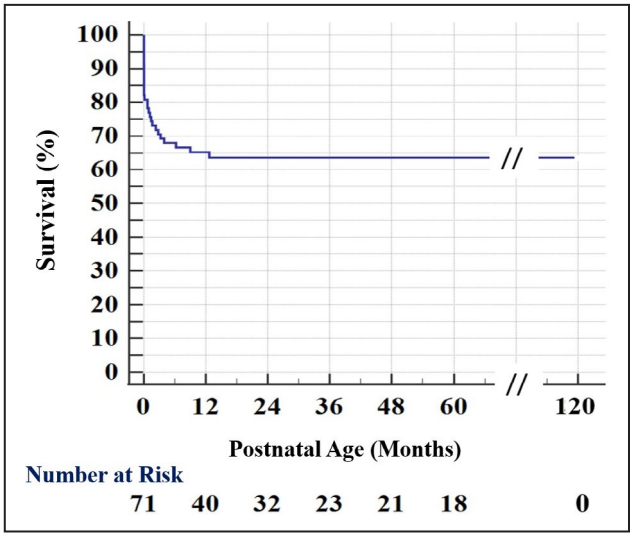

Figure 3. Kaplan-Meier curve demonstrating survival among fetuses with tetralogy of Fallot with absent pulmonary valve with intention to treat (n=78).
Survival at birth reflects fetal deaths but excludes terminations.

Table 3. Postnatal Clinical Characteristics of Liveborn Infants With TOF/APV With Intent to Treat (N=71)

Characteristics	No. (%)* or Mean (SD)
Male sex (n=67)	29 (43)
Cesarean section delivery (n=68)	31 (46)
GA at birth, wk (n=70)	37.5 (2.4)
Birth weight, kg (n=66)	2.8 (0.6)
Need for invasive mechanical ventilation in first 24 h (n=69)	38 (55)
Prone positioning used in first 24 h (n=50)	23 (46)
ECMO cannulation in first 24 h (n=70)	6 (9)
PDA present	2 (3)
Left superior vena cava present	4 (6)

ECMO indicates extracorporeal membrane oxygenation; GA, gestational age; PDA, patent ductus arteriosus; and TOF/APV, tetralogy of Fallot with absent pulmonary valve.

*Percentages are based on the number of subjects for whom each variable was reported, provided as (n=).

Table 4. Fetal Clinical Characteristics and Findings on Final Fetal Echocardiogram Associated With Fetal Death Versus Live Birth (N=78)

Variable	Fetal Death (N=7), No. (%) or Mean (SD)	Live Birth (N=71), No. (%) or Mean (SD)	Unadjusted Univariate OR (95% CI)	*P* Value (Univariate)
Clinical characteristics				
Genetic abnormality (n=67)	3 (75)	25 (40)	4.6 (0.5–46.3)	0.20
Fetal hydrops (n=74)	2 (33)	3 (4)	10.8 (1.4–84.5)	0.02†
Fetal echocardiogram: structural and functional assessment				
Mediastinal shift	7 (100)	38 (54)	NA	NA†
Pericardial effusion	4 (57)	8 (11)	5.9 (1.1–31.3)	0.04†
Abnormal cardiac axis (n=75)	5 (71)	33 (49)	2.7 (0.5–14.6)	0.26
CTA ratio (n=71)	0.41 (0.09)	0.35 (0.08)	2.0 (0.9–4.1)	0.08
RV dilation, greater than mild	7 (100)	37 (53)	NA	NA†
LV dilation	1 (14)	10 (14)	1.0	1.00
RV dysfunction	5 (71)	19 (27)	6.7 (1.2–37.6)	0.03†
LV dysfunction	4 (57)	9 (13)	8.7 (1.7–45.7)	0.01*,†
Tricuspid regurgitation (n=74)	4 (67)	17 (25)	6.0 (1.0–35.7)	0.05†
PV *z*-score (n=75)	–0.4 (2.2)	–1.2 (2.1)	1.4 (0.7–3.0)	0.36
MPA *z*-score (n=73)	4.5 (1.9)	4.5 (1.9)	1.0 (0.4–2.1)	0.95
RPA *z*-score (n=73)	9.8 (6.9)	10.0 (4.5)	1.0 (0.4–2.2)	0.91
LPA *z*-score (n=68)	21.6 (7.5)	18.7 (11.4)	1.3 (0.5–2.8)	0.56
Fetal echocardiogram: Doppler assessment				
TID/CCL (n=58)	0.33 (0.1)	0.43 (0.1)	0.2 (0.1–0.7)	0.008†
PV peak velocity, cm/s (n=55)	222 (35)	252 (57)	0.6 (0.2–1.7)	0.31
PV forward/reverse VTI (n=42)	2.7 (1.4)	1.3 (0.5)	4.6 (1.3–15.9)	0.02†
PI VTI (n=49)	14.5 (7.5)	29.7 (12.1)	0.1 (0–1.3)	0.08
Aortic valve VTI (n=56)	8.9 (3.4)	16.2 (14.1)	0.001 (0.0–0.7)	0.04†
Abnormal DV Doppler (n=48)	2 (40)	12 (28)	0.58 (0.09–3.9)	0.58
MCA PI (n=35)	1.5 (0.4)	1.9 (0.4)	0.3 (0.1–0.98)	0.05†
CPR PI (n=34)	1.4 (0.6)	1.6 (0.5)	0.6 (0.2–1.5)	0.26

Final fetal echocardiograms performed at a median of 35 weeks (range, 20–39 weeks). CPR PI indicates cerebroplacental ratio for PIs; CTA, cardiothoracic area; DV, ductus venosus; LPA, left pulmonary artery; LV, left ventricular; MCA PI, middle cerebral artery PI; MPA, main pulmonary artery; NA, not applicable; OR, odds ratio; PI, pulsatility index; PV, pulmonary valve; RPA, right pulmonary artery; RV, right ventricular; TID/CCL, tricuspid inflow duration/cardiac cycle length; and VTI, velocity time integral.

*Significant variable in multivariate analysis (OR, 7.4; *P*=0.026).

†Significant variable in univariate analysis.

of the 5 hydropic fetuses were assessed as having LV and RV dysfunction, while the other 2 were assessed as having normal biventricular function. Mediastinal shift and moderate or severe RV dilation were found in all 7 patients with fetal demise. In patients with available Doppler findings, fetal demise was associated with decreased tricuspid inflow duration/cardiac cycle length, increased pulmonary valve forward to reverse VTI, decreased aortic valve VTI, and decreased pulsatility in the middle cerebral artery Doppler compared with survivors.

As complete fetal Doppler data were missing for much of the cohort, multivariate regression was performed only on clinical, structural, and functional variables. In multivariate analysis, the only independent predictor of fetal demise was the presence of LV dysfunction (odds ratio [OR], 7.4; 95% CI 1.3, 43.0; *P*=0.026).

When comparing fetuses who died, either in utero or postnatally, with those who survived, clinical factors, including earlier gestation at delivery and lower birth weight, were associated with mortality (Table 5). Genetic abnormalities were not associated with mortality. However, there was a significantly lower incidence of genetic abnormalities in patients with a stable clinical course who were discharged before repair compared with those needing neonatal repair or dying before repair (29% versus 59%; *P*=0.02). Ventricular functional abnormalities, moderate to severe RV enlargement, and any LV enlargement were also characteristic of those who died, and accordingly, CTA ratios were larger. Mediastinal shift was also more

Table 5. Clinical Characteristics and Findings on Final Fetal Echocardiogram Associated With Overall Mortality (Fetal and Postnatal) Versus Survival

Fetal Echocardiogram Findings	Fetal or Postnatal Demise (N=28), No. (%) or Mean (SD)	Survival (N=50), No. (%) or Mean (SD)	Unadjusted Univariate OR (95% CI)	*P* Value
Clinical characteristics				
GA at birth, wk (n=70)	36.5 (2.5)	38 (2.1)	0.5 (0.3–0.9)	0.02†
Birth weight, kg (n=66)	2.57 (0.7)	2.95 (0.54)	0.5 (0.3–0.9)	0.03†
Genetic abnormality (n=67)	11 (52)	17 (37)	1.9 (0.7–5.3)	0.24
22q11.2 Deletion (n=67)	10 (48)	15 (33)	1.9 (0.7–5.4)	0.24
Fetal echocardiogram: structural and functional assessment				
Mediastinal shift	24 (86)	22 (44)	5.9 (1.9–17.9)	0.002†
Pericardial effusion	3 (29)	3 (6)	6.3 (1.5–26.1)	0.01†
Abnormal cardiac axis (n=75)	17 (61)	21 (45)	1.9 (0.7–5.0)	0.18
CTA ratio (n=71)	0.40 (0.09)	0.33 (0.05)	3.7 (1.7–7.8)	0.001†
RV dilation, greater than mild	22 (79)	22 (45)	4.5 (1.6–13.0)	0.006†
LV dilation	8 (29)	3 (6)	6.1 (1.5–25.6)	0.01†
RV dysfunction	17 (61)	7 (14)	9.3 (3.1–27.9)	<0.001*,†
LV dysfunction	11 (39)	2 (4)	14.6 (2.9–72.6)	0.001†
Presence of TR (n=74)	12 (46)	9 (19)	3.7 (1.3–10.7)	0.02†
PV *z*-score (n=75)	−0.41 (2.4)	−1.4 (1.9)	1.7 (1.0–2.7)	0.05
MPA *z*-score (n=73)	5.0 (2.2)	4.2 (1.7)	1.5 (0.9–2.5)	0.11
RPA *z*-score (n=73)	10.1 (4.7)	9.9 (4.7)	1.0 (0.6–1.7)	0.91
LPA *z*-score (n=68)	22.0 (10.9)	17.0 (10.9)	1.6 (1.0–2.7)	0.08
Fetal echocardiogram: Doppler assessment				
TID/CCL (n=58)	0.38	0.44	0.3 (0.1–0.7)	0.005†
PV peak velocity, cm/s (n=55)	213 (46)	266 (52)	0.3 (0.2–0.7)	0.003†
PV forward/reverse VTI (n=42)	1.5 (1.0)	1.3 (0.5)	1.3 (0.7–2.5)	0.37
PR VTI (n=49)	24.8 (11.5)	31.1 (1.8)	0.6 (0.3–1.1)	0.09
Aortic valve VTI (n=56)	13.7 (14.1)	16.4 (13.5)	0.8 (0.4–1.6)	0.5
Abnormal DV Doppler pattern (n=48)	9 (50)	5 (17)	0.2 (0.05–0.8)	0.02†
MCA PI (n=35)	1.7 (0.5)	1.9 (0.3)	0.6 (0.3–1.2)	0.14
CPR PI (n=34)	1.4 (0.5)	1.7 (0.4)	0.5 (0.2–1.0)	0.05†

CPR PI indicates cerebroplacental ratio for pulsatility indexes; CTA, cardiothoracic area; DV, ductus venosus; GA, gestational age; LPA, left pulmonary artery; LV, left ventricular; MCA PI, middle cerebral artery pulsatility index; MPA, main pulmonary artery; OR, odds ratio; PR, pulmonary regurgitation; PV, pulmonary valve; RPA, right pulmonary artery; RV, right ventricular; TID/CCL, tricuspid inflow duration/cardiac cycle length; TR, tricuspid regurgitation; and VTI, velocity time integral.

*In multivariate analysis of clinical, structural, and functional variables, only RV dysfunction was identified as an overall independent predictor of mortality (OR, 7.9; *P*=0.002).

†Significant variable in univariate analysis.

common in fetuses who died. Doppler abnormalities, such as decreased tricuspid inflow duration/cardiac cycle length, abnormal ductus venosus pattern, and a lower cerebroplacentral ratio pulsatility index, were also associated with mortality. Pulmonary artery measurements were not associated with mortality risk. In multivariate analysis of clinical, structural, and functional variables, only RV dysfunction was identified as an overall independent predictor of mortality (OR, 7.9; 95% CI; *P*=0.002).

Interrater variability analysis (Table S1) revealed substantial to almost perfect agreement between observers when assessing RV and LV dilation and dysfunction as well as CTA ratios (κ, 0.8–1.0), and substantial agreement for mediastinal shift and pulmonary valve/artery dimensions (κ, 0.74–0.87).

Data from fetuses with >1 prenatal echocardiogram available are presented in Table S2 and are presented stratified by outcome in Table 6 (survived, n=36; died, n=18). Although for the whole cohort mediastinal shift and pulmonary artery diameters worsened significantly throughout gestation, paired descriptive analyses demonstrate that branch pulmonary artery diameters were the only echocardiographic variables that significantly differed from the first to last fetal echocardiogram among the group

Table 6. Differences in Fetal Echocardiogram Findings, Initial Versus Last Fetal Echocardiograms Before Fetal or Neonatal Death Versus Live Birth Surviving Neonatal Period (n=54)

Parameter	Survived (n=36)			Died (n=18)		
	First Echocardiogram	Last Echocardiogram	*P* Value*	First Echocardiogram	Last Echocardiogram	*P* Value
GA, median (range), wk	26 (23–30)	35.6 (34.4–37)	<0.001	23 (19–26)	34 (29–34.7)	<0.001
Mediastinal shift, n (%)	13 (36.1)	17 (47.2)	0.34	9/18 (50)	14/18 (77.8)	0.06
Abnormal cardiac axis, n (%)	17/34 (50)	19/34 (55.9)	0.48	14/18 (77.8)	13/18 (72.2)	0.31
RV dilation (>mild), n (%)	13/32 (40.6)	14/32 (43.7)	0.74	14/18 (77.8)	16/18 (88.9)	0.15
RV dysfunction, n (%)	4/31 (12.9)	4/31 (12.9)	…	10/18 (55.5)	13/18 (72.2)	0.08
LV dysfunction, n (%)	2/30 (6.7)	1/30 (3.3)	0.31	3/18 (16.7)†	8/18 (44.4)†	0.03†
Tricuspid regurgitation, n (%)	5/29 (17.2)	4/29 (13.8)	0.65	7/15 (46.7)	8/15 (53.3)	0.56
CTA ratio, mean (95% CI)	0.33 (0.05)	0.33 (0.05)	0.97	0.38 (0.04)†	0.41 (0.09)†	0.04†
PV *z*-score, mean (95% CI)	–1.6 (1.9)	–1.5 (1.8)	0.71	0.22 (2.1)	0.20 (2.7)	0.97
MPA *z*-score, mean (95% CI)	4.5 (2.0)	4.3 (1.6)	0.66	4.8 (1.5)	5.4 (2.3)	0.09
RPA *z*-score, mean (95% CI)	8.5 (3.6)	10.7 (4.7)	<0.001	9.2 (4.6)	10.4 (5.1)	0.25
LPA *z*-score, mean (95% CI)	11.4 (6.2)	18.0 (11.3)	<0.001	15.2 (9.2)	22.9 (10.1)	0.01

CTA indicates cardiothoracic area; GA, gestational age; LPA, left pulmonary artery; LV, left ventricular; MPA, main pulmonary artery; PV, pulmonary valve; RPA, right pulmonary artery; and RV, right ventricular.

*For binary variables, the McNemar test was used; for continuous variables, either a paired Wilcoxon rank sum or a paired *t* test was used. Abnormal cardiac axis defined as ≤30° or >75°. RV and LV dysfunction defined as mild or greater dysfunction. Tricuspid regurgitation defined as mild or greater regurgitation.

†Significant variable in univariate analysis.

who survived. In contrast, among those who died either in utero or after birth, the cardiothoracic ratio was significantly higher on the last fetal echocardiogram (0.38 on first versus 0.41 on last) as was the percentage of fetuses with LV dysfunction (16.7% on first versus 44.4% on last). A repeated-measures analysis was performed for these 2 variables to determine if the rate of change from the first to last fetal echocardiogram was significantly different between the group who survived versus the group who died. The odds of LV dysfunction per week increase of GA was marginally higher in the group who ultimately died compared with the group who survived, although our study was underpowered to demonstrate statistical significance. Similarly, there was no statistical difference in the rate of change in CTA ratio from the first to last fetal echocardiogram between the 2 groups, although for every week in GA, CTA ratio increased by 0.002 more in the group who died compared with the group who survived (95% CI, −0.001 to 0.006; *P*=0.32). Finally, it is notable that findings supporting poor prognosis were already present at initial fetal echocardiogram in nearly half, and overall worsening was not necessarily predictable (Table S2).

DISCUSSION

This 10-year, multicenter cohort represents the largest and most comprehensive study to date of clinical and echocardiographic predictors of outcome in prenatally diagnosed TOF/APV. We found that even in the modern era, prenatal and postnatal mortality remains high, with only 64% infancy survival during study follow-up in pregnancies with intention to treat. Mortality occurred mostly in the perinatal period; there were no documented deaths after 13 months of age with median follow-up to 32.9 months (range, 4.8–116.4 months). Our findings highlight the dichotomous clinical presentation and outcomes in TOF/APV.[13] Although there was significant fetal and neonatal mortality among the study population, half of the cohort with intent to treat had a distinctly stable neonatal course: this group was discharged home with plans for later repair, with a low subsequent mortality rate.

Our findings are consistent with those of smaller contemporary cohorts.[2,3,5,14] They are also comparable to those of a recently published multicenter cohort of fetal APV syndrome that included 59 European fetuses with TOF/APV; however, in that study, 26 (44%) pregnancies were terminated or lost to follow-up prenatally, leaving only 33 with intent to treat and documented outcomes.[15] Their study population had a higher rate of fetal death than our cohort, 18% of fetuses with intent to treat compared with our 10%, and similar postnatal survival, with 66% of fetuses with intent to treat surviving beyond a shorter follow-up period of 28 days of age. Unlike our study, in which no fetus presented to a study center before 19 weeks, 15% of their cohort was diagnosed during the first trimester. However, of these first-trimester fetuses, more than half presented with hydrops, and all were terminated, died in utero, or were lost to follow-up. As our cohort was collected entirely from large academic fetal and pediatric cardiology referral centers in North America, it is possible that our findings may not reflect earlier fetal deaths and terminations that may have occurred before pregnant mothers could be referred to study centers.

This study identifies several fetal clinical and echocardiographic findings associated with poor outcome in TOF/APV that can be used to guide perinatal counseling and perinatal management. For overall mortality, qualitative RV systolic dysfunction was found to be the key predictor of poor outcome in multivariate analysis. This finding is consistent with prior work that has suggested a role for RV dysfunction in predicting mortality in TOF/APV.[5,14,16] Nearly all of the fetal echocardiographic measures associated with mortality, including dilation and systolic dysfunction of both ventricles, the presence of tricuspid regurgitation, and increased cardiothoracic area ratio, are indicators of cardiac compromise or failure. The physiologic mechanisms of pulmonary insufficiency and cardiopulmonary interactions that result in RV pressure and volume overload and decreased ventricular compliance in fetuses with TOF/APV are complex and multifactorial. The additional finding of mediastinal shift likely represents the effects of cardiac enlargement as well as the concomitant lung abnormalities, including hyperexpansion and hypoplasia, that have been reported.[6,17–19] The cardiac Doppler findings associated with mortality, such as decreased RV filling time and decreased pulmonary valve velocity, may also reflect underlying ventricular dysfunction, while extracardiac Doppler abnormalities related to cerebral and placental perfusion could reflect altered fetal circulation attributable to inadequate cardiac output.

On the basis of multivariable analysis, fetal demise was best predicted in this cohort by the presence of LV dysfunction. Although prior studies have identified fetal hydrops in association with perinatal mortality,[3,5,20] LV dysfunction was more prevalent in this population than hydrops, a generally later and more ominous finding, and may be an earlier indicator of impending demise. Univariate analysis also demonstrated associations between fetal demise and other indications of fetal cardiac compromise, including LV and RV dysfunction, presence of tricuspid regurgitation, and decreased tricuspid inflow duration, a Doppler finding suggesting diastolic dysfunction and possibly reflecting increased

afterload. Surprisingly, less pulmonary regurgitation, as reflected in increased pulmonary valve forward/reverse VTI, was associated with greater risk of fetal demise. This counters the idea that increased pulmonary regurgitation causes a greater volume load on the fetal RV. However, it is possible that as RV dysfunction and diastolic pressure increase, pulmonary insufficiency may become less apparent by Doppler evaluation. Finally, it is notable that most fetal deaths occurred late in the third trimester, at or close to term. In late-gestation fetuses with TOF/APV who are not anticipated to have a low birth weight, the presence of LV dysfunction even in the absence of hydrops may therefore impact prenatal management and delivery planning.

This study provides further evidence that pulmonary artery dimensions, once hypothesized to correlate directly with severity of airway compromise and outcomes,[13,21] are in fact not independently associated with mortality. Mediastinal shift, however, was more prevalent in those who died, suggesting that the secondary effects of pulmonary artery dilation, including lung compression and fluid trapping, do play a role in the pathophysiological features of TOF/APV. Thus, as Szwast et al have posited, this study supports that linear pulmonary artery dimensions may not reliably reflect their hemodynamic effects.[14] Instead, echocardiography-based lung assessments, whether indirect measures, such as mediastinal shift, or more direct evaluation of lung echogenicity on fetal echocardiogram, as suggested by Tenisch et al, may more reliably reflect the effects of airway compression and fluid trapping than pulmonary artery size.[19]

It is not surprising that clinical factors, such as prematurity and low birth weight, contribute to poorer TOF/APV outcomes, and this finding should be taken into consideration when making decisions to deliver. It is notable, however, that the high incidence of genetic abnormalities, which have been linked to comorbidities, such as heart failure, arrhythmias, and neurodevelopmental differences in patients with congenital heart disease, did not appear to contribute to worse short-term to midterm outcomes in the study population. However, this observation should be observed with caution, considering the high percentage who underwent elective pregnancy termination.

When initial fetal echocardiograms were compared with the latest available fetal echocardiogram, only mediastinal shift and branch pulmonary artery dilation worsened in a significant manner, suggesting that lung pathological features are progressive in these patients. Other variables showed a less predictable propensity for change; however, a high number of fetuses exhibited concerning findings even at presentation. CTA ratio increase and development of LV dysfunction were more commonly seen in fetuses who did not survive. Although findings supporting poor prognosis were already present at initial fetal echocardiogram in nearly half of fetuses, overall worsening throughout the cohort was not predictable. Our findings underscore the importance of repeated echocardiographic assessments throughout pregnancy for development of worsening findings, including evidence suggesting abnormal heart-lung interactions, to identify fetuses at higher risk for poor outcomes.

Given our findings and the extent to which respiratory morbidity can affect survival and long-term neurodevelopmental and functional status in these patients, future investigation into the role of lung findings should also include additional imaging modalities, such as fetal magnetic resonance imaging, which in a small number of cases have been shown to demonstrate abnormalities in lung volumes and echogenicity in fetuses with TOF/APV.[6,7] Incorporation of this additional testing will serve to further refine predictive modeling and perinatal care in these patients.

Limitations

There were some significant limitations to this retrospective study. Fetal echocardiograms were assessed by a single reviewer but had been performed at 19 centers over several years without a standardized protocol, with several missing clinical and echocardiographic data points. Because Doppler data were particularly incomplete, they were not included in multivariate analysis. Fetal echocardiogram timing and follow-up frequency also varied widely, which is important given some variables change with GA. Although indexing of several parameters to fetal weight, most importantly cardiac outputs, would be ideal, we did not have reliable fetal weights recorded for a large segment of the study population. Center-specific practice variations in perinatal and surgical management may have also affected outcomes, which were not adjusted by center. Exclusion of the fetuses subject to pregnancy termination is a limitation in that these may have represented the more severely affected or those with genetic abnormalities, thus artificially improving the outcomes in the remaining cohort.

The most significant limitation of this study is that given the retrospective design of this study measurements of cardiac chamber size and function were of necessity qualitative given inconsistent reproducible images for quantitative measurement. In addition, fetal echocardiographic assessment of mediastinal shift, although standardized and based on similar measures reported by other investigators, was also qualitative,[12,19,22] and the cohort was not large enough to analyze implications of the direction of mediastinal shift. Regardless, interobserver variability assessment

demonstrated substantial interrater agreement for most of the subjective variables used in clinical practice. Future studies using quantitative, reproducible measures of ventricular size and function, such as 3-dimensional volumes or strain analysis, as well as fetal cardiac magnetic resonance imaging, may provide additional insight and could potentially be more sensitive to subtle abnormalities. In addition, a prospective study to determine in utero factors that influence postnatal care, including the timing of surgery, would enable creation of recommendations for detailed prenatal assessment and improved counseling for these high-risk patients.

CONCLUSIONS

In the modern era, fetal and postnatal mortality in TOF/APV remain high. The fetal echocardiographic findings of RV dysfunction, predictive of overall mortality, and LV dysfunction, associated with a high risk of in utero demise, suggest that diminished cardiac output is the primary cause of mortality. Fetuses with mediastinal shift, likely attributable to ventricular enlargement as well as the secondary effects of lung fluid trapping or hypoplasia, have worse postnatal outcomes, highlighting the importance of lung abnormalities in the postnatal care of this high-risk population. Our findings demonstrate that a comprehensive assessment of the fetal heart and lungs can predict outcomes in TOF/APV, guide prenatal counseling and perinatal management, and direct future efforts to further risk stratify and potentially reduce mortality from this disease.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

REFERENCES

1. Galindo A, Gutiérrez-Larraya F, Martínez JM, Del Rio M, Grañeras A, Velasco JM, Puerto B, Gratacos E. Prenatal diagnosis and outcome for fetuses with congenital absence of the pulmonary valve. *Ultrasound Obstet Gynecol*. 2006;28:32–39. DOI: 10.1002/uog.2807.
2. Wertaschnigg D, Jaeggi M, Chitayat D, Shannon P, Ryan G, Thompson M, Yoo SJ, Jaeggi E. 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. DOI: 10.1002/uog.11193.
3. Gottschalk I, Jehle C, Herberg U, Breuer J, Brockmeier K, Bennink G, Hellmund A, Strizek B, Gembruch U, Geipel A, et al. Prenatal diagnosis of absent pulmonary valve syndrome from first trimester onwards: novel insights into pathophysiology, associated conditions and outcome. *Ultrasound Obstet Gynecol*. 2017;49:637–642. DOI: 10.1002/uog.15977.
4. Donofrio MT, Jacobs ML, Rychik J. Tetralogy of Fallot with absent pulmonary valve: echocardiographic morphometric features of the right-sided structures and their relationship to presentation and outcome. *J Am Soc Echocardiogr*. 1997;10:556–561. DOI: 10.1016/S0894-7317(97)70010-5.
5. Moon-Grady AJ, Tacy TA, Brook MM, Hanley FL, Silverman NH. Value of clinical and echocardiographic features in predicting outcome in the fetus, infant, and child with tetralogy of Fallot with absent pulmonary valve complex. *Am J Cardiol*. 2002;1:1280–1285. DOI: 10.1016/S0002-9149(02)02326-3.
6. Chelliah A, Berger JT, Blask A, Donofrio MT. Clinical utility of fetal magnetic resonance imaging in tetralogy of Fallot with absent pulmonary valve. *Circulation*. 2013;12:757–759. DOI: 10.1161/CIRCULATIONAHA.112.139758.
7. Sun HY, Boe J, Rubesova E, Barth RA, Tacy TA. Fetal MRI correlates with postnatal CT angiogram assessment of pulmonary anatomy in tetralogy of Fallot with absent pulmonary valve. *Congenit Heart Dis*. 2014;9:E105–E109. DOI: 10.1111/chd.12091.
8. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381. DOI: 10.1016/j.jbi.2008.08.010.

9. Krishnan A, Pike JI, McCarter R, Fulgium AL, Wilson E, Donofrio MT, Sable CA. Predictive models for normal fetal cardiac structures. *J Am Soc Echocardiogr*. 2016;29:1197–1206. DOI: 10.1016/j.echo.2016.08.019.
10. Paladini D, Chita SK, Allan LD. Prenatal measurement of cardiothoracic ratio in evaluation of heart disease. *Arch Dis Child*. 1990;65:20–23. DOI: 10.1136/adc.65.1_Spec_No.20.
11. Comstock CH. Normal fetal heart axis and position. *Obstet Gynecol*. 1987;70:255–259.
12. Colombani M, Rubesova E, Potier A, Quarello E, Barth RA, Devred P, Petit P, Gorincour G. Management of fetal mediastinal shift: a practical approach. *J Radiol*. 2011;92:118–124. DOI: 10.1016/j.jradio.2010.12.002.
13. Lakier JB, Stanger P, Heyman MA, Hoffman JIE, Rudolph AM. Tetralogy of Fallot with absent pulmonary valve: natural history and hemodynamic considerations. *Circulation*. 1974;50:167–175. DOI: 10.1161/01.CIR.50.1.167.
14. Szwast A, Tian Z, McCann M, Soffer D, Combs J, Donaghue D, Rychik J. Anatomic variability and outcome in prenatally diagnosed absent pulmonary valve syndrome. *Ann Thorac Surg*. 2014;1:152–158. DOI: 10.1016/j.athoracsur.2014.03.002.
15. Axt-Fliedner R, Kurkevych A, Slodki M, Respondek-Liberska M, Zych-Krekora K, Stressig R, Ritgen J, Rizzo G, Krapp M, de Catte L, et al. Absent pulmonary valve syndrome – diagnosis, associations, and outcome in 71 prenatally diagnosed cases. *Prenat Diagn*. 2017;37:812–819. DOI: 10.1002/pd.5094.
16. Inamura N, Kado Y, Nakajima T, Kayatani F. Left and right ventricular function in fetal tetralogy of Fallot with absent pulmonary valve. *Am J Perinatol*. 2005;22:199–204. DOI: 10.1055/s-2005-866603.
17. Madan A, Parisi M, Wood BP. Radiological case of the month: absent pulmonic valve presenting with congenital lobar emphysema. *Am J Dis Child*. 1992;146:113–114.
18. Fink AM, Edis B, Massie J. The CT appearances of delayed amniotic fluid clearance from the lungs in an infant with absent pulmonary valve and congenital lobar emphysema. *Pediatr Radiol*. 2005;35:891–894. DOI: 10.1007/s00247-005-1469-8.
19. Tenisch E, Raboisson M-J, Rypens F, Déry J, Grignon A, Lapierre C. Significance of lung anomalies in fetuses affected by tetralogy of Fallot with absent pulmonary valve syndrome. *Cardiol Young*. 2017;27:1740–1747. DOI: 10.1017/S1047951117001147.
20. Volpe P, Paladini D, Marasini M, Buonadonna AL, Russo MG, Caruso G, Marzullo A, Arciprete P, Martinelli P, Gentile M. Characteristics, associations and outcome of absent pulmonary valve syndrome in the fetus. *Ultrasound Obstet Gynecol*. 2004;24:623–628. DOI: 10.1002/uog.1729.
21. Hiraishi SMD, Bargeron LMMD, Isabel-Jones JB, Emmanouilides GCMD, Friedman WFMD, Jarmakani JMMD. Ventricular and pulmonary artery volumes in patients with absent pulmonary valve: factors affecting the natural course. *Circulation*. 1983;67:183–190. DOI: 10.1161/01.CIR.67.1.183.
22. Rubesova E, Barth RA. Advances in fetal imaging. *Am J Perinatol*. 2014;31:567–576. DOI: 10.1055/s-0034-1371712.

SUPPLEMENTAL MATERIAL

Table S1. Interrater Agreement Analysis.

Fetal Echocardiogram Parameter	Cohen's kappa or ICC (95% confidence interval)*
RV dilation, greater than mild	1.00 (1.00-1.00)
RV dysfunction	0.90 (0.71-1.00)
LV dilation	0.80 (0.54-1.00)
LV dysfunction	0.80 (0.54-1.00)
Mediastinal shift	0.79 (0.58-1.01)
CTA ratio	0.91 (0.77-0.96)
PV diameter	0.83 (0.63-0.93)
MPA diameter	0.77 (0.1-0.92)
RPA diameter	0.87 (0.70-0.95)
LPA diameter	0.74 (0.44-0.89)

*****Cohen's kappa used for categorical variables and ICC for continuous. Cohen's kappa interpretation: almost perfect agreement (0.81-1.0), substantial agreement (0.61-0.80), moderate agreement (0.41-0.60).

RV=right ventricle; OR = odds ratio; LV= left ventricle; CTA = cardiothoracic area; MPA = main pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery; LPA = left pulmonary artery

Table S2. Differences in fetal echocardiogram findings between initial and last fetal echocardiograms prior to fetal death, pregnancy termination or birth (n=54).

	Initial Echocardiogram	Final Echocardiogram	Change from Initial to Final*	P-value†
Median GA, weeks (range) ‡	25 (18-33)	35 (22-39)	9 (2-20)	-
Mediastinal shift‡	23 (47%)	31 (58%)	+ n=13 - n=4	0.05
Pericardial effusion‡	8 (15%)	8(15%)	+ n=4 - n=4	NS
Abnormal cardiac axis (n=52) ‡	23 (44.2%)	28 (53.8%)	+ n=8 -n=3	0.23
RV dilation, greater than mild (n=50) ‡	23 (46%)	20 (40%)	+ n=4 - n=7	0.54
RV dysfunction (n=49) ‡	14 (29%)	17 (35%)	+ n=3 - n=0	0.25
LV dysfunction (n=48) ‡	5 (10%)	9 (19%)	+ n=5 - n=1	0.22
Tricuspid regurgitation (n=44) ‡	12 (27%)	12 (27%)	+ n=4 - n=4	NS
CTA ratio (n=48)	0.35 (0.05)	0.36 (0.08)	0.01 (0.06)	0.15
PV z-score (n=47)	-0.95 (2.1)	-0.87 (2.3)	0.08 (2.2)	0.81
MPA z-score (n=43)	4.6 (1.8)	4.8 (2.0)	0.2 (1.8)	0.55
RPA z-score (n=47)	8.8 (3.9)	10.6 (4.8)	1.8 (3.4)	<0.001
LPA z-score (n=47)	12.9 (7.7)	19.9 (11.0)	7.0 (9.0)	<0.001

*Change from initial to final, where + indicates new or worsening, and – indicates no longer present or improved

† McNemar test for categorical, Wilcoxon signed rank for continuous variables

‡ Initial fetal echocardiographic variables associated with poor prognosis in univariate analysis

RV=right ventricle; LV= left ventricle; RPA = right pulmonary artery; LPA = left pulmonary artery