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ORIGINAL ARTICLE

Fetal Echocardiographic Measurements and the Need for Neonatal Surgical Intervention in Tetralogy of Fallot

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Abstract
Background This study aimed to evaluate fetal echocardiographic measurements at the time of the first fetal echocardiogram as predictors of neonatal outcome for tetralogy of Fallot (TOF).
Methods The study reviewed all infants with a prenatal diagnosis of TOF from January 2004 to June 2011. Aortic valve (AoV), pulmonary valve (PV), main pulmonary artery (MPA), left and right pulmonary artery diameters, and ductus arteriosus flow were evaluated on fetal echocardiograms, and associations between the fetal echocardiogram and the neonatal echocardiogram measurements and outcomes were assessed.
Results The study identified 67 TOF patients who had an initial fetal echocardiogram at a mean gestational age of 25.0 ± 5.2 weeks. Patients with absent PV syndrome or major aortopulmonary collaterals were excluded from the study, as were those without anterograde pulmonary blood flow at the first fetal echocardiogram. Of the remaining 44 patients, 10 were ductal dependent and required neonatal surgery. Infants who were ductal dependent had lower fetal PV (−5.38 ± 2.95 vs. −3.51 ± 1.66; $p < 0.05$) and MPA (−3.94 ± 1.66 vs. −2.87 ± 1.04; $p < 0.05$) z-scores. A fetal PV z-score of −5 predicted ductal dependence with 78 % sensitivity and 87 % specificity, and a PV z-score of −3 showed 100 % sensitivity and 34 % specificity ($p < 0.001$). Fetuses with a reversed left-to-right flow across the ductus arteriosus (DA) were more likely to be ductal dependent (odds ratio, 25; $p < 0.001$) than those who had normal ductal flow.
Conclusions In TOF, fetal PV and MPA z-scores and direction of the DA blood flow predict neonatal ductal dependence. Patients with fetal PV z-scores lower than −3 or any left-to-right flow at the level of the DA should be admitted to a center where prostaglandin is available.

Keywords Fetal echocardiography · Tetralogy of Fallot · Neonatal outcome

Tetralogy of Fallot (TOF) accounts for 3.5–10 % of all congenital heart disease, [16] and up to 65 % of infants with TOF are diagnosed prenatally [5, 6, 10]. The neonatal presentation of TOF ranges from ventricular septal defect physiology to atresia of the right ventricular outflow with critical need for patency of the ductus arteriosus (DA) [2]. Furthermore, a prenatal diagnosis of TOF provides a unique challenge because the severity of pulmonary outflow tract obstruction may worsen throughout the second and third trimesters [4, 8].

Delivery planning and neonatal management cannot be uniform for all patients because some patients require prostaglandins to maintain ductal patency and a surgical intervention in the neonatal period, whereas others may be discharged from the well-baby nursery [1]. The ability to

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identify prenatally which patients will be ductal dependent can aid in the determination of who should present to a surgical center. Accurate antenatal delivery planning has been shown to improve immediate hemodynamic stability and long-term outcomes [6].

A few small studies have proposed different fetal echocardiographic parameters for the prediction of ductal dependence as well as the type of TOF repair (transannular patch vs. valve-sparing repair). These include the ascending aorta (AAo)-to-main pulmonary valve (MPA) ratio, the aortic valve (AoV)-to-pulmonary valve (PV) ratio, reversal of flow in the DA, and the peak systolic velocity across the PV [4, 7–9, 12]. This study aimed to determine whether measurements taken at the first fetal echocardiogram in TOF fetuses with antegrade pulmonary blood can accurately identify ductal dependence at birth and the need for neonatal surgery.

Methods

We conducted a retrospective review of all TOF infants with a prenatal diagnosis who underwent treatment at the Morgan Stanley Children's Hospital of New York from January 2004 to June 2011. The study protocol was approved by the Columbia University Medical Center Institutional Review Board.

Echocardiographic Assessment

All available fetal echocardiograms and the first complete neonatal echocardiogram were evaluated. The AoV, AAo, PV, left pulmonary artery (LPA), and right pulmonary artery (RPA) were measured on the fetal echocardiograms and the first neonatal echocardiogram. All measurements were made by one investigator (I.W.). Measurements were converted to z-scores based on the gestational age of the fetus [11, 15] and on the body surface area of the neonate [13] using the standard reference z-scores at our institution.

For fetal studies, gestational age-adjusted z-scores were used rather than biometry because although all the fetuses in this study had recorded gestational ages, femur length was not available on all the fetal echocardiograms. The presence of a DA and the direction of blood flow (forward, reversed, bidirectional) were recorded and reviewed by a second reader (S.L.).

Fetal echocardiograms were performed using either a GE Voluson E8 (General Electric, Waukesha, WI, USA), a Philips IE33 (Phillips, Andover, MA, USA), or a Philips IU22 (Phillips, Andover, MA, USA) ultrasound machine. Standard fetal cardiac views were used for the evaluation of cardiac structures [14]. The AoV and AAo measurements were made using a cardiac long-axis view, whereas the PV, MPA, LPA, and RPA were measured using a cardiac short-axis view, and the DA was evaluated with both long-axis (3-vessel view) and ductal/aortic arch views [14].

When atresia of the PV, MPA, RPA, or LPA was documented, the patients were excluded from the respective analyses. Postnatal echocardiograms were performed using the Philips IE33 (Phillips, Andover, MA, USA) device. The AoV and AAo were evaluated using a parasternal long-axis view, and the PV, MPA, LPA, RPA, and DA were evaluated using a parasternal short-axis view as per published guidelines [12].

Postnatal Assessment

The postnatal clinical outcomes included timing of surgery, type of surgery, prostaglandin infusion at birth, prostaglandin infusion at the time of surgery, neonatal mortality, TOF subtype, and chromosomal abnormalities. Prostaglandin infusion was discontinued occasionally in neonates once adequate pulmonary blood flow was documented. For this reason, administration of prostaglandin to sustain adequate oxygen saturations up until the time of surgery was selected as a marker of true ductal dependence and hence the need for neonatal surgery. The infants were divided into two groups, with ductal dependence at surgery used to classify them.

Fetuses with no evidence of antegrade pulmonary blood flow on the first fetal echocardiogram were excluded from the analysis, as were those who had a diagnosis of TOF with absent PV syndrome or TOF with major aortopulmonary collaterals confirmed at birth. Infants who received palliative care and those born prematurely (<32 weeks gestational age) also were excluded from the analysis.

Statistical Analysis

The relationships between fetal and neonatal echocardiographic measurements were assessed using Pearson's correlation coefficient. Student's t test was used to compare differences in fetal echocardiographic measurements between infants who were ductal dependent and those who were not. The relationship between the direction of fetal DA blood flow and neonatal ductal dependence was evaluated using tests of proportions and the χ^2 test. We used receiver operating curves (ROC) to calculate the sensitivity and specificity of fetal echocardiogram z-scores for predicting ductal dependence and the need for neonatal surgery.

Finally, we assessed change in the PV and the MPA z-score over time using paired t tests. Statistics were calculated using SPSS for Windows, version 18 (SPSS Inc., Chicago, IL, USA).

Results

We identified 67 infants admitted to our neonatal intensive care unit during the study period with a prenatal diagnosis of

Table 1 Clinical characteristics of patients ($n = 44$)

Characteristic	Neonatal ductal dependence		p Value
	Yes ($n = 10$)	No ($n = 34$)	
Males (n)	6	21	0.125
Mean gestational age at 1st fetal echocardiogram (weeks)	24.9 ± 53.2	25.5 ± 5.6	0.358
Mean gestational age at birth (weeks)	39.0 ± 1.1	38.2 ± 1.6	0.06
Mean birth weight (kg)	3.018 ± 0.73	3.010 ± 0.58	0.485
Median age at intervention (days)	9.5	106	0.001
TOF subtypes (n)			
Uncomplicated TOF	8	29	
TOF/pulmonary atresia	2	0	
TOF/atrioventricular septal defect	0	5	
Genetic abnormalities (n)			
Trisomy 21	0	6	
VACTERL association	1	1	
22q11 Deletion	0	1	
CHARGE syndrome	0	1	
Alagille syndrome	0	1	
Dandy–Walker syndrome	0	1	

TOF. The initial fetal echocardiogram was performed at a mean gestational age of 25.4 ± 5.1 weeks (range 16–37 weeks). There was an average of two fetal echocardiograms (range 1–5) available for review for each fetus (Table 1). The infants were born at a mean gestational age of 38.4 ± 1.6 weeks.

The exclusion criteria eliminated 23 of these infants from the study including 1 infant with a diagnosis of trisomy 18 who received palliative care, 2 infants born before 32 weeks gestation age, 4 infants with absent PV syndrome, 6 infants with major aortopulmonary collaterals, and 10 infants without antegrade pulmonary blood flow shown on the first fetal echocardiogram. After the exclusion of these patients, 44 patients remained in the analysis.

Ductal Dependence

Of the 44 infants in the final analysis, 10 were ductal dependent and underwent neonatal surgical intervention (Fig. 1). Of the 34 infants who were not ductal dependent, 1 with CHARGE syndrome had neonatal intervention secondary to desaturations of unclear origin.

Relationship Between First Fetal and Neonatal Echocardiograms

The fetal and neonatal MPA diameter z-scores showed a modest correlation ($r = 0.45$; $p < 0.01$). No significant

Fig. 1 Postnatal management

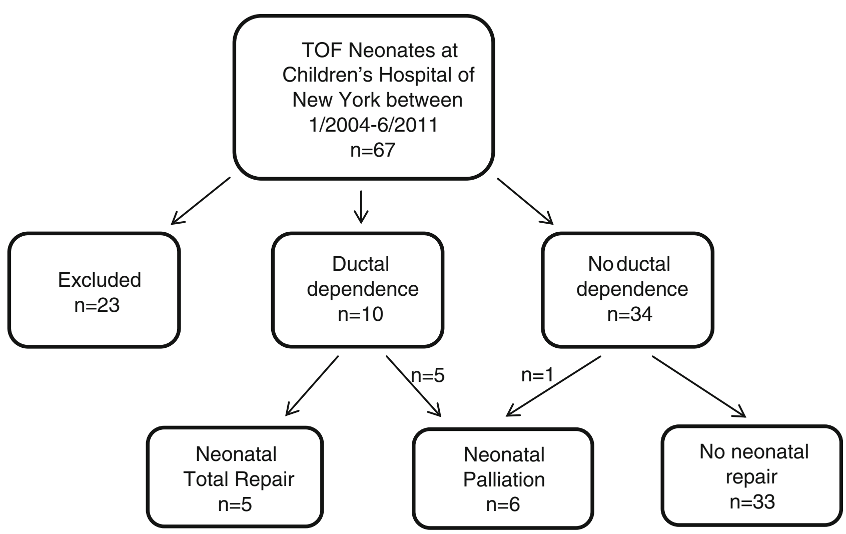

Table 2 Relationship of first fetal and neonatal echocardiogram measurements to neonatal ductal dependence ($n = 44$)

Measurement	Neonatal ductal dependence		p Value
	Yes (mean z-score)	No (mean z-score)	
Fetal			
PV	−5.38 ± 2.95	−3.51 ± 1.66	0.01
MPA	−3.94 ± 1.66	−2.87 ± 1.04	0.02
LPA[a]	−0.31 ± 1.52	−0.41 ± 1.02	0.8
RPA[b]	−1.34 ± 1.52	−0.69 ± 1.17	0.2
AoV	1.97 ± 1.42	2.03 ± 1.13	0.9
AAo	1.73 ± 1.15	1.51 ± 1.38	0.7
Neonatal			
PV	−3.51 ± 0.93	−1.90 ± 0.92	<0.001
MPA	−2.52 ± 1.67	−1.85 ± 1.08	0.1
LPA	−1.23 ± 0.89	−1.06 ± 0.63	0.6
RPA	−1.07 ± 0.70	−1.31 ± 0.61	0.3
AoV	3.07 ± 1.51	2.12 ± 1.19	0.04
AAo	1.50 ± 0.90	0.95 ± 0.93	0.6

PV pulmonary valve, *MPA* main pulmonary artery, *LPA* left pulmonary artery, *RPA* right pulmonary artery, *AoV* aortic valve, *AAo* ascending aorta

[a] $n = 42$

[b] $n = 43$

Table 3 ROC curve coordinates

Pulmonary valve z-score at first fetal echo	Sensitivity	One specificity
−3.15[a]	1.00	0.63
−3.39	0.89	0.59
−4.05	0.78	0.41
−4.59	0.78	0.25
−5.09[b]	0.78	0.13
−5.68	0.67	0.09

[a] Optimized sensitivity with poor specificity

[b] Optimized sensitivity and specificity

association between fetal and neonatal AoV, AAo, PV, LPA, or RPA z-scores was observed.

Relationship Between First Fetal Echocardiogram and Ductal Dependence

The infants with ductal dependence had smaller fetal PV diameters (mean PV z-score, -5.38 ± 2.95 vs. -3.51 ± 1.66; $p < 0.05$) and smaller fetal MPA diameters (mean MPA z-score, -3.94 ± 1.66 vs. -2.87 ± 1.04; $p < 0.05$) at the time of the first fetal echocardiogram than the infants who were not ductal dependent (Table 2). These differences remained when fetal echocardiograms performed at an age younger than 24 weeks gestation and those performed at the age of 24 weeks gestation or older were evaluated separately to account for variation in timing of initial referral. The two groups did not differ significantly with regard to AoV, AAo, RPA, or LPA diameters.

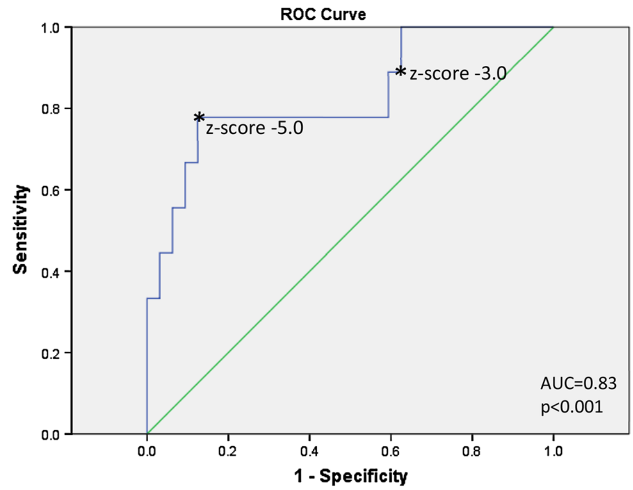

Fig. 2 ROC for fetal PV diameter z-score in predicting neonatal ductal dependence

Table 4 Relationship between fetal ductal flow direction at the first fetal echocardiogram and neonatal ductal dependence

Ductal flow direction	Neonatal ductal dependence		p Value
	Yes ($n = 10$)	No ($n = 34$)	
Normal right-to-left flow	1	20	<0.001
Any left-to-right flow (complete reversal or bidirectional flow)	9	7	<0.001
Only left-to-right flow (complete reversal)	8	0	<0.001

A fetal PV diameter z-score of -5 predicted ductal dependence and the need for neonatal surgery with 78 % sensitivity and 87 % specificity. A fetal PV diameter z-score of -3 provided 100 % sensitivity and 34 % specificity ($p < 0.001$) (Table 3; Fig. 2).

A DA was demonstrated in 37 fetuses at the time of the first fetal echocardiogram. The direction of flow across the DA was classified as normal right to left ($n = 21$), completely reversed left to right ($n = 8$), or bidirectional ($n = 8$). The fetuses with reversed left-to-right flow across the DA were more likely to be ductal dependent and to require neonatal surgery [odds ratio (OR), 25; $p < 0.001$] than those who had normal right-to-left ductal flow (Table 4).

All the fetuses who demonstrated completely reversed left-to-right flow in the DA required neonatal surgery ($p < 0.001$). Fetal complete ductal reversal of flow had a sensitivity of 80 % and a specificity of 100 % for identifying ductal dependence in the neonate. Two neonates who were ductal dependent and required neonatal surgery did not have complete ductal reversal of flow at the time of the first fetal echocardiogram.

A fetus with a diagnosis of VACTERL syndrome had bidirectional flow at the first fetal echocardiogram (gestational age of 28 weeks) and complete ductal flow reversal at birth. A second fetus with an isolated LPA arising from the DA demonstrated a normal ductal flow pattern at the first fetal echocardiogram (gestational age of 23 weeks) and exhibited complete ductal flow reversal by the gestational age of 27 weeks.

The findings showed a significant association between DA flow and fetal MPA *z*-scores. The fetuses with a completely reversed left-to-right DA flow had a smaller mean fetal MPA diameter than the fetuses with normal right-to-left DA flow (mean MPA *z*-score, −4.01 ± 1.85 vs. −2.99 ± 1.06; $p < 0.05$). The fetal PV *z*-score was not associated with the fetal DA flow.

Relationship Between Neonatal Echocardiography and Ductal Dependence

The infants with ductal dependence had smaller neonatal PV diameters (mean *z*-score, −3.51 ± 0.93 vs. −1.90 ± 0.91; $p < 0.001$) and larger AoV diameters (mean *z*-score, 3.07 ± 1.51 vs 1.19 ± 0.20; $p < 0.05$) than the infants who were not ductal dependent. The AAo, MPA, RPA, and LPA diameters did not differ significantly.

Longitudinal Assessment of Fetal PV, MPA, and AoV Growth

The study sought to assess whether fetal PV and MPA diameter *z*-scores change during the course of pregnancy. The change in fetal PV and MPA diameters and *z*-scores from the first to the second fetal echocardiogram was calculated for 36 fetuses who had measurable PV and MPA at the second fetal echocardiogram. The mean gestational age at the second fetal echocardiogram was 30.8 ± 4.9 weeks (range 22–37 weeks) compared with 25.6 ± 5.4 weeks at the first fetal echocardiogram. The PV and MPA *z*-scores did not differ significantly between the first and second fetal echocardiograms, although both PV and MPA *z*-scores became less negative over time (PV *z*-score, −4.7 to −4.2 vs. MPA *z*-score, −3.6 to −3.1).

The ductal-dependent infants had smaller increases in PV *z*-scores between the first and second fetal echocardiograms (+0.3) than the infants who were not ductal dependent (+0.9), although this difference also was not statistically significant ($p = 0.2$). Similarly, the change in mean fetal MPA *z*-score from the first to the second fetal echocardiogram was +0.44 for the ductal-dependent infants compared with +0.86 for the non-ductal-dependent infants ($p = 0.6$). Two neonates in the group with a postnatal diagnosis of TOF/PA had antegrade pulmonary blood flow at the time of the first fetal echocardiogram.

Discussion

A fetal diagnosis of TOF is more common than a postnatal diagnosis [10] in the current era. As prenatal identification increases, pediatric cardiologists are focusing their attention on the ability to predict postnatal outcomes, with the hope of addressing early hemodynamic problems, thereby decreasing neonatal morbidity, improving long-term outcomes, and enhancing cost-effective health care management [6, 10, 17]. Very few studies have evaluated the utility of fetal echocardiographic measurements for identifying TOF patients who will be ductal dependent at birth and thus require neonatal surgical intervention for adequate pulmonary blood flow.

Our study demonstrated that fetal PV and MPA *z*-scores as well as direction of DA blood flow are helpful in predicting neonatal ductal dependence in fetuses with TOF ranging in gestational age from 16 to 37 weeks. We found that a fetal PV *z*-score lower than −3 provided 100 % sensitivity for identification of ductal dependence and the need for neonatal surgery in TOF neonates. Because ultimate determination of the need for neonatal surgical intervention is based on adequacy of pulmonary blood flow at birth [2], it is not surprising that the gestational age-adjusted sizes of the PV and MPA in utero were useful in making this prediction. Conversely, fetal AoV and AAO diameters were not useful in predicting ductal dependence in our study. The presence of reversal or left-to-right flow in the fetal DA, especially without any evidence of bidirectional flow, also was useful for predicting ductal dependence in our cohort.

Longitudinal assessment of PV and MPA *z*-scores did not show a significant difference over time, possibly because our sample size for paired analyses was small. Interestingly, we saw PV and MPA *z*-scores increase from the first fetal echocardiogram to the second one, with smaller increases in fetal PV and MPA *z*-scores over time in infants who were ductal dependent compared with those who were not. Although these changes were not statistically significant, the suggestion of potential accelerated PV and MPA growth in this population of fetuses with right ventricular outflow tract obstruction is perplexing and deserves further investigation.

How the pulmonary outflow track changes over the course of gestation among TOF fetuses could best be addressed in a well-designed prospective study that dictates measurements at specific time points and includes normal fetuses. This would eliminate the variation in intervals between studies that limits our analysis while allowing for direct comparison with normal growth to allow for the calculation of study-specific *z*-scores.

Previous studies have reported the value of fetal echocardiographic *z*-scores for predicting neonatal outcome. In a study of 29 infants, Hirji et al. [7] reported smaller PV *z*-scores for patients who received prostaglandin therapy at birth. However, in their study, the PV *z*-score was useful only when measured at a gestational age of 29–32 weeks.

Our study is the first to show that fetal echocardiographic measurements made as early as the second trimester (mean gestational age, 25.4 $\pm$ 5.1 weeks) can identify neonatal ductal dependence. For one fetus in our study, the PV and MPA measurements at a gestational age of 16 weeks were predictive of neonatal outcome.

The direction of blood flow in the fetal DA also is reported to be associated with neonatal ductal dependence. In a paper by Berning et al. [3], reversal of DA flow in the fetus was reported to be associated with severe right heart obstructive lesions including TOF. Pepas et al. [12] evaluated DA reversal and MPA growth failure over time in 18 TOF fetuses to predict the need for early intervention. Two fetuses in that study had flow reversal in the DA. In both fetuses, progression of PV stenosis developed over time and required neonatal intervention.

In our cohort, the direction of blood flow in the DA was useful for identifying which patients would be ductal dependent at birth. Fetuses with any reversed left-to-right flow in the DA were more likely to require neonatal surgical intervention. Not surprisingly, the likelihood of neonatal ductal dependence became most significant when complete reversal of DA flow (all left to right) was noted on the first fetal echocardiogram.

Only two fetuses with neonatal ductal dependence did not demonstrate complete DA flow reversal. One was a fetus with bidirectional ductal shunt flow related to VACTERL who demonstrated complete ductal flow reversal at birth (only one fetal echocardiogram was available). The second fetus had an isolated LPA from the DA, with normal DA flow shown on the first fetal echocardiogram at the gestational age of 23 weeks and complete DA flow reversal at the second fetal echocardiogram.

We found that fetal MPA *z*-scores were significantly lower for fetuses who had DA reversal, yet interestingly, there was no association with fetal PV *z*-score. The lack of association between the fetal PV *z*-score and the fetal DA blood flow may have been due to the small sample size and limited statistical power.

Although we did not find a significant change in PV or MPA *z*-scores over time, our study confirmed the potential for in utero progression of pulmonary outflow obstruction, first described by Hornberger et al. [8]. We found that two of the ten infants with a diagnosis of TOF and pulmonary atresia after birth had measureable PV and MPA diameters and forward flow during fetal life, with atresia developing over the course of gestation.

Study Limitations

This study was a single-center retrospective investigation. We used strictly anatomic and physiologic variables in our analyses and did not adjust for extracardiac or chromosomal abnormalities. This may have excluded information that could have influenced neonatal management. Because only fetuses who obtained postnatal care at our institution were included in the study, our sample may have been biased toward neonates with more severe forms of TOF who already had been selected for delivery at a tertiary care center. In addition, there may have been confounding due to the exclusion of pregnancies that resulted in abortion (spontaneous or elective).

Conclusions

Among fetuses with TOF and antegrade pulmonary blood flow at the time of the first fetal echocardiogram, use of gestational age-adjusted PV and MPA *z*-scores as well as direction of fetal DA blood flow can identify who will be ductal dependent at birth. A fetal PV *z*-score lower than -3 or evidence of any reversal or left-to-right flow in the DA should prompt prenatal counseling regarding the need for prostaglandin at birth and neonatal surgical intervention.

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