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Extracardiac Doppler indices predict perinatal mortality in fetuses with Ebstein anomaly and tricuspid valve dysplasia

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What's already known about this topic?

- Ebstein anomaly and tricuspid valve dysplasia carry a high perinatal mortality rate. Intracardiac findings such as larger TV annulus and presence of PR predict mortality.

What does this study add?

- This is the first large multicenter study to describe extracardiac findings in this rare group. Abnormal umbilical artery pattern and low umbilical vein velocity are independent predictors of perinatal mortality and provide additive value in prenatal prediction of mortality.

Data Availability Statement:

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

Keywords: circular shunt, ductus venosus, middle cerebral artery, pulmonary regurgitation, pulsatility index, tricuspid regurgitation, tricuspid valve, umbilical artery, umbilical vein

Abstract

Objectives: Ebstein anomaly and tricuspid valve dysplasia (EA/TVD) carry high perinatal mortality. Past studies have focused on cardiac predictors of mortality; we sought to describe the fetal echo (FE) extracardiac Dopplers in this cohort and determine their association with perinatal mortality.

Method: Fetuses with EA/TVD at 23 centers from 2005-2011 were included for retrospective study. Doppler pattern and velocity of the umbilical artery (UA), umbilical vein (UV), ductus venosus (DV), and middle cerebral artery (MCA) were collected. Bivariate and multivariate analyses were performed. The primary outcome measure was perinatal mortality, defined as fetal demise or neonatal death.

Results: Of 190 cases that met eligibility criteria, alterations were seen in 50% of UA, 16% of UV, 48% of DV, and 8% of MCA Doppler indices on the last FE (median 27.4 weeks). Independent predictors of perinatal mortality included abnormal UA Doppler pattern of absence or reversed end diastolic flow (OR 9.7) and UV velocity z-score <1 (OR 2.5), in addition to diagnosis <32 weeks (OR 4.2) and TV annulus z-score ≥6 (OR 5.3).

Conclusion: Abnormal UA Doppler pattern and decreased UV velocity are independent predictors of perinatal mortality in EA/TVD fetuses and should be used to refine mortality risk and guide perinatal management.

Introduction

Ebstein anomaly and tricuspid valve dysplasia (EA/TVD) are rare but potentially serious congenital tricuspid valve malformations, occurring in approximately 1 to 5 in 20,000 live births and accounting for less than 1% of congenital heart disease (CHD).[1, 2] While EA and TVD are morphologically distinct, they carry the same hemodynamic burden of tricuspid regurgitation (TR) that can lead to heart failure. Severe cases are often diagnosed *in utero* and carry a poor prognosis with perinatal mortality rates of 38 to 79 percent.[3-5] In 2015, Freud *et al* reported a 45% perinatal mortality rate in a large multi-center study of prenatally diagnosed EA/TVD with contemporary medical and surgical management. The strongest predictors of mortality were earlier gestational age (GA) at diagnosis, larger tricuspid valve (TV) annulus z-score, presence of pulmonary regurgitation (PR), and presence of a pericardial effusion on fetal echocardiography (FE).[6]

Extracardiac Doppler indices reflect the uteroplacental environment and can be used in the evaluation of fetal disease states and the risk for disease severity to progress *in utero*. Abnormal umbilical artery (UA) Doppler indices, such as increased pulsatility index (PI), and their relationship to middle cerebral artery (MCA) Doppler indices, have been associated with adverse perinatal outcomes in fetuses with and without CHD.[7-9] Examination of the umbilical vein (UV) and ductus venosus (DV) has also been used to provide important physiologic and prognostic information.[10-11] As in other fetal conditions, these Doppler indices may have important value with regard to risk stratification and prognostication in EA/TVD. The aim of this study was to understand the usefulness of extracardiac Doppler indices in a multi-center cohort of fetuses with EA/TVD that were previously evaluated primarily based on the cardiac findings.[6] Our investigation sought to describe the Doppler findings in the context of the known

pathophysiologic aberrations of EA/TVD and to assess their value as risk factors for perinatal mortality in affected fetuses.

Methods

We conducted an ancillary analysis of a previously evaluated multi-center cohort of prenatally diagnosed EA/TVD patients.[6] This cohort was identified retrospectively from 23 centers in the United States and Canada and included 243 fetuses diagnosed with EA/TVD from January 2005 to September 2011. Each center obtained IRB approval with a waiver of informed consent and de-identified FE studies were sent to a core lab at Boston Children's Hospital which were then shared with Children's Hospital Los Angeles (CHLA). Details regarding the cardiac and clinical findings in this cohort have previously been described, however the analysis did not include extracardiac Doppler measurements.[6]

De-identified DICOM images were independently evaluated and measurements of extracardiac Dopplers were performed by two reviewers (SW, JP) at our institution's core lab (CHLA), who were blinded to clinical outcome. For study inclusion, a patient must have had at least one FE with extracardiac Doppler waveform obtained at high enough quality for adequate interpretation. In accordance with guidelines on Doppler interrogation,[12] we used measurements acquired at an insonation angle of 20 degrees or less for pulsed-wave Doppler. If multiple FEs with Doppler indices were available, the first and last FE were analyzed. The Doppler waveform patterns were noted, with an abnormal pattern defined as absence or reversal of end diastolic flow (AREDF) for the UA, AREDF or increased diastolic flow for the MCA, notching for the UV, and absence or reversal of flow during atrial systole (A wave) for the DV. The following measurements were performed where possible: peak systolic velocity (PSV), end diastolic

velocity (EDV), and time averaged max velocity (TAMAX) for the UA for those without AREDF; the mean velocity for the UV; the S wave velocity, A wave velocity, and TAMAX for the DV for those without absence or reversal of the A wave; and the PSV, EDV, and TAMAX for the MCA.

For the UA and MCA, the PI was calculated as (PSV – EDV) / TAMAX. Of note, PI was not calculated when there was AREDF. The cerebroplacental ratio (CPR) was calculated as MCA PI/UA PI. For quantitative assessment of the DV, the PI of veins (PIV) was calculated as PIV = (S wave velocity – early diastolic A wave velocity)/TAMAX.[13] To adjust for the wide distribution of GA at the time of the examination, all velocities and PIs with available published normal values were converted to z-scores for GA.[13-16]

The primary outcome was perinatal mortality, defined as fetal demise or neonatal death before hospital discharge, in accordance with the primary study.[6] Cases with elective terminations or loss to follow-up were excluded. Clinical variables collected included GA at diagnosis, at the time of the FE, and at birth. In addition, the presence of PR was noted and tested for association with abnormalities in Doppler parameters. Doppler data were reported as median (range) for continuous variables or counts with frequencies for categorical variables.

Two analyses were conducted. The first used data for the last FE, and the second used data for the first FE if performed prior to 24 weeks of gestation. Bivariate analyses to explore associations between Doppler indices and perinatal mortality were performed using a Wilcoxon rank sum test, or chi-square or Fisher's exact test where applicable. Multiple logistic regression modeling was performed for the outcome of perinatal mortality using variables that were not missing in 15 or more cases for the last FE or 10 or more cases for the FE prior to 24 weeks of gestation and that had a p-value <0.10 on bivariate analysis. Forward, backward, and stepwise

variable entry techniques were used to identify the most parsimonious models where the criterion for inclusion was a p-value < 0.05. Upon identification of these models, all potential interaction terms were tested for inclusion in the models. Continuous variables were converted to categorical variables for interpretability where possible, using receiver operating characteristic (ROC) curves to determine optimal cut-point values, specifically for TV annulus and UV velocity Z-scores. For the analysis of the last FE, data-splitting (randomization into training and testing groups, 75% and 25% respectively) was performed *post hoc* to correct for over-optimism of the final model's c-statistic. Odds ratios (OR) and their 95% confidence intervals (CI) were reported. Analyses were performed on SAS v. 9.4 (SAS Institute, Cary, NC) statistical software.

Results

Of 243 patients in the cohort, 215 had at least one extracardiac Doppler index available for review. The median GA at diagnosis among this cohort with available Doppler indices was 26.1 (14.0-40.0) weeks. Of this group, 13 pregnancies were terminated, 10 were lost to follow-up in the prenatal period and 2 were lost to follow-up in the postnatal period, resulting in 190 patients for analysis. As shown in Figure 1, there were 37 fetal demises and 55 neonatal deaths in this sub-cohort of fetuses with EA/TVD, yielding a perinatal mortality rate of 48% (92/190) which was similar to 45% reported in the original cohort.[6] The median GA at the time of the last FE was 27.4 (18.0-40.0) weeks. A FE was performed at or prior to 24 gestational weeks in 82 pregnancies (43%), with 62 having at least one Doppler index available for review.

The Doppler characteristics of the cohort at the time of the last FE are summarized in Table 1 and illustrated in Figure 2. Compared to the general population, fetuses with EA/TVD had higher average z-scores for UA PI with a median of 1.57. Moreover, 49.7% of the cohort had

either an elevated UA PI z-score >2 (the 98th percentile) or an abnormal UA pattern of AREDF. An abnormal finding of UV notching was present in 15.7% of the cohort, but the median UV velocity z-score was 0.63 (-2.91 to +5.73). Quantitative measures of DV A wave reversal revealed a decreased median A wave z-score (-2.38 [-4.82 to + 1.70]) and borderline elevated median PIV z-score of 1.29. Nearly half of the fetuses (47.7%) exhibited an abnormal pattern of A wave reversal or elevated PIV z-score >2. The median MCA PI z-score was normal at -0.30 (-5.17 to + 3.10). As a result of the relatively elevated UA PI z-score and normal MCA PI z-score, the median CPR z-score in our EA/TVD cohort was lower (-1.54 [-4.85 to +1.67]) than in normal fetuses.

The associations of extracardiac Doppler indices at the time of last FE with perinatal mortality by bivariate analysis are summarized in Table 2. Lower UA PSV, EDV, and mean velocity z-scores, higher UA PI z-score, abnormal UA pattern, lower mean UV velocity, and UV notching were all associated with increased perinatal mortality. There were no associations between DV indices, MCA indices, or CPR z-scores and perinatal mortality. Elevated UA PI, abnormal UA pattern, elevated MCA PI, and decreased UV mean velocity z-scores were all associated with the presence of PR ($p=0.003$, $p<0.001$, $p=0.020$, and $p=0.067$, respectively). Specifically, the median UA PI z-score was significantly higher in fetuses with PR than those without (2.31 [-1.67 to + 6.82] vs. 1.36 [2.99 to + 7.54]). Additionally, 24% (20 of 82) of fetuses with PR had an abnormal UA pattern while only 4.6% (6 of 131) of fetuses with no PR had an abnormal pattern ($p<0.0001$). While the median MCA PI z-score fell in a normal z-score range, there was a difference between those with and without PR (0.30 [-3.41 to +3.10] vs. -0.44 [-5.17 to +1.96], respectively). DV Doppler indices were not associated with the presence of PR.

Variables that were eligible for testing in the multiple logistic regression model for perinatal mortality for the last FE were: GA at diagnosis, pericardial effusion, pleural effusion, ascites, skin edema, PR, antegrade flow across the pulmonary valve, left to right ductus arteriosus flow, UA AREDF, abnormal UA pattern or PI, the UA PSV z-score, the UA mean velocity z-score, abnormal UV pattern, the UV mean velocity z-score, and the TV annulus z-score. The final model is presented in Table 3 (c-statistic = 0.81) with the following variables found to be independently associated with perinatal mortality: GA at diagnosis < 32 weeks (OR 4.2, 95% CI 1.7-10.3), abnormal UA Doppler pattern with absence or reversal of diastolic flow (OR 9.7, 95% CI 2.0-48.3), UV velocity z-score < 1 (OR 2.5, 95% CI 1.2-5.3), and TV annulus z-score ≥ 6 (OR 5.3, 95% CI 2.6-11). Data-splitting yielded a bias correction of the c-statistic to 0.74 on the testing dataset. Maximizing Youden's index (sensitivity + specificity-1) yielded an optimal cutoff for the predicted probability of the model of 55%, resulting in 72% sensitivity and 73% specificity of the model.

Of the 62 patients who had a FE at or before 24 gestational weeks with available Doppler indices, the median GA at the time of the FE was 21.0 (18.0-24.0) weeks. On bivariate analysis, lower UA PSV (p = 0.014), lower UA EDV (p = 0.048), lower UA TAMAX (p = 0.016) z-scores, abnormal UA pattern (p = 0.054), and lower UV mean velocity z-score (p = 0.026) were all associated with increased perinatal mortality, but UV notching was not. Additionally, the DV and MCA Doppler indices showed no association with mortality. None of the extracardiac Doppler indices were associated with perinatal mortality in this early GA cohort on multivariate analysis. Rather, the only variable that was associated with perinatal mortality was a TV annulus z score ≥6 (OR 12.5, 95% CI 3.2-49.5; c-statistic=0.76).

Discussion

This study is the first to describe the abnormal extracardiac FE Doppler findings in a large, multi-center cohort of fetuses with EA/TVD. We found that an abnormal UA pattern and UV velocity z-score < 1, in addition to GA at diagnosis <32 weeks and TV annulus z-score ≥ 6 were associated with perinatal mortality by multivariate analysis. The abnormal UA and UV Doppler findings were also associated with the presence of PR, which provides insight into the pathophysiology of EA/TVD *in utero*. Not surprisingly, given the well-established progressive nature of this disease, the extracardiac Doppler findings were not predictive of outcome when assessed at a GA of less than 24 weeks.

The presence of UA AREDF and increased UA PI z-score in our EA/TVD cohort were significantly higher in non-survivors as compared to survivors; in fact, perinatal mortality was 9.2 times more likely in those with an abnormal UA pattern. The etiology of the abnormal UA pattern and elevated UA PI in the EA/TVD cohort is likely multifactorial. In bivariate analyses, both the UA peak systolic and diastolic velocities in non-survivors were lower, suggesting diminished flow to the placenta as a result of decreased cardiac output that has been well-described in EA/TVD.[17,18] Additionally, there was a strong association between elevated UA PI and the presence of PR, suggesting that decreased or reversed diastolic flow due to retrograde ductus arteriosus flow and circular shunt physiology may contribute to the finding.[19] As the presence of PR has been associated with mortality,[6] it is not surprising to see this association with both an abnormal UA pattern and PI. The presence of PR may be at times difficult to discern, particularly if the fetal position or acoustic windows are unfavorable or if the pulmonary valve is not well seen. However, acquisition of the UA pulsed Doppler is usually easier and less

user-dependent which could prove to be a more reliable surrogate for assessing the presence and degree of PR.[20]

It is plausible that the abnormal UA pattern in non-survivors is also influenced by placental dysfunction. Abnormal UA flow has been associated with many placental pathologies,[21] and in particular, the placentas of newborns with CHD have been shown in several studies to be more likely abnormal.[22-23] Furthermore, women carrying fetuses with CHD appear to be at increased risk of preeclampsia and fetal growth restriction.[23-25] The fetus with severe EA/TVD is already in a tenuous hemodynamic state due to cardiac dysfunction, abnormal right atrial pressure and decreased cardiac output.[17,18,26] The addition of placental dysfunction with associated increased resistance in these cases may further compromise the circulation and lead to development of hydrops and fetal demise. As such, the UA Doppler examination is useful in that it identifies not only the intracardiac effects such as PR and circular shunt, but also the effects of the extracardiac environment.

UV velocity z-score <1 was also found to be an independent predictor of mortality in multivariate analysis. Though the median UV velocity z-scores fell within a normal z-score range for both non-survivors and survivors (0.30 vs 0.99), it was significantly higher in the latter, which provides insight into the underlying pathophysiology that contributes to poor outcomes. In severe cases of EA/TVD, there is substantial tricuspid regurgitation, right ventricular dysfunction, and decreased antegrade pulmonary blood flow or even reversal of flow through the right heart in the case of circular shunt physiology. Fetuses with EA/TVD have been shown to have larger right atrial (RA) size and decreased RA reservoir function as compared to fetuses with right heart obstructive lesions.[28] Therefore, a lower UV velocity seen in fetuses with EA/TVD is likely to be associated with elevated right atrial and central venous pressure.

A lower UV velocity may also reflect a state of overall decreased fetal cardiac output leading to decreased UA flow and thereby decreased placental flow. This hypothesis is supported by a recent study using magnetic resonance imaging (MRI) that showed UV flow was decreased in fetuses with EA/TVD compared to UV flow in normal controls.[17] The combination of decreased upstream pressure from the placenta and increased downstream central venous pressure in the more severe EA/TVD cases may lead to a lower pressure differential in the umbilical vein that manifests as a relatively lower UV velocity z-score (Figure 3). As is in the case with the UA, obtaining a UV Doppler waveform is a highly accurate and reproducible measure with low user- and software-dependence.[29]

Although abnormal qualitative and quantitative DV indices were noted in nearly half of the fetuses with EA/TVD who had them measured in our cohort, these findings were not associated with perinatal mortality. The DV Doppler pattern of reversal of flow during atrial systole has been associated with poor prognosis in fetuses with normal hearts [8,13] and has been associated with tricuspid regurgitation.[30] However, several studies have reported that flow reversal in fetuses with right-sided CHD is not associated with worse outcomes.[31-32] It has been hypothesized that in EA/TVD fetuses, a severely dilated RA allows for absorption of elevated RA pressure and creates stretching of the foramen ovale such that the septum primum remains functionally open in atrial systole and thus does not manifest as DV flow reversal.[28] Our findings support those of previous studies; neither quantitative DV measures (e.g., S wave, D wave, A wave, PIV z-scores) nor abnormal qualitative measures of DV flow reversal were associated with perinatal mortality.

We found that MCA PI was not significantly different when comparing survivors and non-survivors. Fetuses with placental insufficiency have been shown to have lower MCA PI and

CPR, known as the "brain sparing" effect.[33] This effect has also been demonstrated in CHD as a presumed cerebral autoregulatory response to hypoxemia;[34-35] however, there has yet to be clarity in the case of EA. For example, in one study it was noted that EA was associated with a decreased MCA PI and CPR.[36] However, another study reported increased MCA PI in EA/TVD which was found to be a risk factor for neonatal death.[37] We found that when fetuses were subdivided into those with and without PR, there was a significantly higher MCA PI z-score in those with PR. While one may expect the MCA PI z-score to be lower in severe EA/TVD to reflect cerebral vasodilation in response to relative hypoxemia and low cardiac output,[38] the complex flow disturbance of circular shunt physiology that occurs often in cases with significant PR may impact MCA PI, resulting in a "normal" PI not suggestive of cerebral vasodilation. Of note, normal appearance of MCA PI does not necessarily imply normal cerebral oxygen delivery *in utero* and thus the effects of this lesion are unknown, particularly with regard to neurodevelopment. Further work is needed to investigate this complex physiology and the effect on the circulation.

As shown by past studies,[6, 39-40] EA/TVD is a progressive disease *in utero*. Many fetuses do not manifest markers of poor hemodynamic status such as PR, ventricular dysfunction, or effusion until later in gestation. Similarly, we demonstrated that extracardiac Doppler indices were not associated with perinatal mortality at GA less than 24 weeks. This is likely due to progressive TR, right heart dysfunction, and circular shunting, which lead to heart failure with low cardiac output and an inability to compensate in the face of changing placental resistance as gestation advances. Regardless of the underlying sequence of events, our findings underscore the need for caution when counseling families earlier in gestation and the need to discuss the full range of possible outcomes. Moreover, ongoing surveillance of extracardiac Doppler findings

throughout later gestation is critical for ongoing counseling, refinement of risk stratification, and perinatal management planning.

Limitations

Due to the retrospective nature of this study, data were missing for some patients. In particular, extracardiac Doppler indices were not performed on all FEs, which decreased the size of our cohort for analysis and limited the variables that were eligible for the logistic regression models. Nevertheless, while this study describes a subset of the original cohort, the perinatal mortality was similar. Variations in fetal Doppler acquisition across multiple institutions using different machines, probe settings, and transducer frequencies could affect the qualitative diagnosis of Doppler patterns such as AREDF. However, the Doppler waveforms for each FE were independently reviewed to ensure adequate waveform tracings with good inter-observer correlation noted between the two core labs, CHLA and Boston Children's (supplemental data). Long term survival was not analyzed to avoid confounding factors such as variable medical and surgical management across the multiple heart centers involved in the study. Such outcomes may be of interest in the future, particularly with regard to understanding the MCA Doppler findings. Finally, we did not perform a comprehensive analysis of maternal, placental, or fetal factors that may have contributed to our understanding of the umbilical Doppler findings, such as maternal comorbidities, placental weights and pathologic evaluation, and fetal growth restriction; such investigations may be of interest prospectively.

Conclusions

Extracardiac Doppler indices in fetuses with EA/TVD provide important hemodynamic insight into the *in utero* physiology of the disease process and were associated with perinatal mortality. In particular, the findings of an abnormal UA pattern and lower UV velocity were both ominous signs in the late gestation fetus. Unlike previous studies of CHD, DV abnormalities and MCA Doppler patterns were not associated with mortality in this EA/TVD cohort. Given the ease of reproducibility and reliability in obtaining umbilical vessel Dopplers, an abnormal UA pattern and UV velocity z-score < 1 should be considered additional risk factors for perinatal mortality in the fetus with EA/TVD.

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Table 1. Extracardiac Doppler indices and Z-scores at time of last fetal echocardiogram.

Doppler Index	Median (range) or N(%)	N
Umbilical artery, N=188		
Systolic velocity Z-score	-2.08 (-7.69 to + 5.24)	188
Diastolic velocity Z-score	-1.75 (-12.31 to + 1.37)	163
Mean velocity Z-score	0.10 (-5.74 to + 4.23)	185
PI Z-score	1.57 (-2.99 to + 7.54)	161
AREDF	24 (12.8%)	188
Abnormal pattern or PI	93 (49.7%)	187
Umbilical vein, N=178		
Mean velocity Z-score	0.63 (-2.91 to + 5.73)	178
UV notching	28 (15.7%)	178
Ductus venosus, N=132		
A wave Z-score	-2.38 (-4.82 to + 1.70)	106
PIV Z-score	1.29 (-2.60 to + 9.00)	102
A wave reversal	25 (18.9%)	132
Abnormal pattern or PIV	63 (47.7%)	132
Middle cerebral artery, N= 108		
Systolic velocity Z-score	-1.34 (-6.94 to + 4.49)	107
Mean velocity Z-score	-1.32 (-7.50 to + 4.45)	105
PI Z-score	-0.30 (-5.17 to + 3.10)	99
AREDF	7 (6.5%)	108
Abnormal pattern or PI	9 (8.3%)	108
CPR Z-score, N=98	-1.54 (-4.85 to+ 1.67)	98

EA/TVD = Ebstein anomaly/tricuspid valve dysplasia; PI = pulsatility index; AREDF = absent/reversed end diastolic flow; UV = umbilical vein; PIV = pulsatility index of veins; CPR = cerebroplacental ratio.

Table 2. Bivariate associations of extracardiac Doppler indices with perinatal mortality at the time of the last fetal echocardiogram.

Doppler Index	**Non-survivors (N=92)**	**Survivors (N=98)**	**p-value**
Umbilical artery, N=188			
Systolic velocity Z-score	N=92 -2.51 (-7.69 to +2.34)	N=96 -1.63 (-5.07 to +5.24)	0.001
Diastolic velocity Z-score	N=70 -2.04 (-12.31 to +0.67)	N=93 -1.56 (-4.76 to +1.37)	0.016
Mean velocity Z-score	N=92 -0.20 (-5.74 to +2.59)	N=93 0.61 (-1.88 to + 4.23)	<0.001
PI Z-score	N=70 2.32 (-1.67 to + 7.54)	N=91 1.27 (-2.99 to +5.34)	0.004
AREDF	N=92 22 (23.9%)	N=96 2 (2.1%)	<0.001
Abnormal pattern or PI	N=92 61 (66.3%)	N=95 32 (33.7%)	<0.001
Umbilical vein, N=178			
Mean velocity Z-score	N=87 0.30 (-2.91 to + 3.47)	N=91 0.99 (-1.88 to + 5.73)	<0.001
UV notching	N=87 19 (21.8%)	N=91 9 (9.9%)	0.039
Ductus venosus, N=132			
A wave Z-score	N=45 -2.19 (-4.34 to +1.70)	N=61 -2.64 (-4.82 to + 0.71)	0.068
PIV Z-score	N=43 1.09 (-2.60 to +3.60)	N=59 1.40 (-1.43 to + 9.00)	0.444
AREDF	N=60 14 (23.3%)	N=72 11 (15.3%)	0.270
Abnormal pattern or PIV	N=60 29 (48.3%)	N=72 34 (47.2%)	1.000

Middle cerebral artery, N= 108			
Systolic velocity Z-score	N=56 -1.35(-5.61 to +4.49)	N=51 -1.13 (-6.94 to + 1.96)	0.926
Mean velocity Z-score	N=56 -1.30 (-6.84 to +4.45)	N=49 -1.40 (-7.50 to +3.41)	0.913
PI Z-score	N=52 -0.26 (-3.77 to +2.48)	N=47 -0.30 (-5.17 to +3.10)	0.547
AREDF	N=57 5 (8.8%)	N=51 2 (3.9%)	0.443
Abnormal pattern or PI	N=57 6 (10.5%)	N=51 3 (5.9%)	0.495
CPR Z-score, N=98	N=52 -1.62 (-4.85 to +0.86)	N=46 -1.40 (-4.21 to + 1.67)	0.261

EA/TVD = Ebstein anomaly/tricuspid valve dysplasia; PI = pulsatility index; AREDF = absent/reversed end diastolic flow; UV = umbilical vein; PIV = pulsatility index of veins; CPR = cerebroplacental ratio.

Table 3. Multiple logistic regression analysis of variables associated with perinatal mortality (c-statistic=0.81).

	Odds Ratio (95% CI)	**p-value**

GA at diagnosis < 32 weeks	4.2 (1.7-10.3)	0.002
Absence or reversed diastolic flow in UA	9.7 (2.0- 48.3)	0.005
UV velocity Z score < 1	2.5 (1.2-5.3)	0.014
TV annulus Z score ≥ 6	5.3 (2.6-11.0)	<0.001

CI = confidence interval, GA = gestational age, UA = umbilical artery, UV = umbilical vein, TV = tricuspid valve

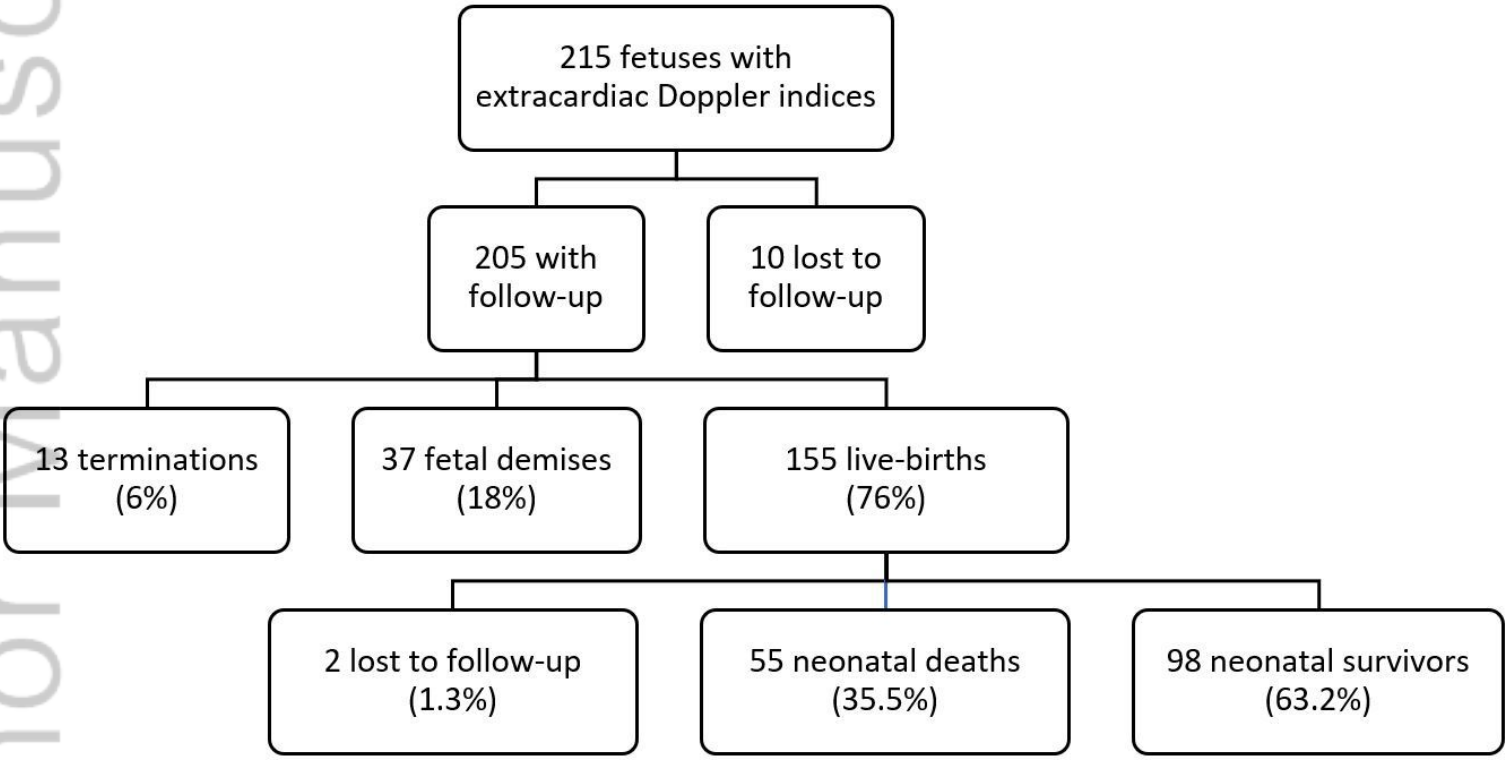
Figure Legend

Figure 1. Perinatal outcome in the cohort of patients with Doppler indices available for analysis.

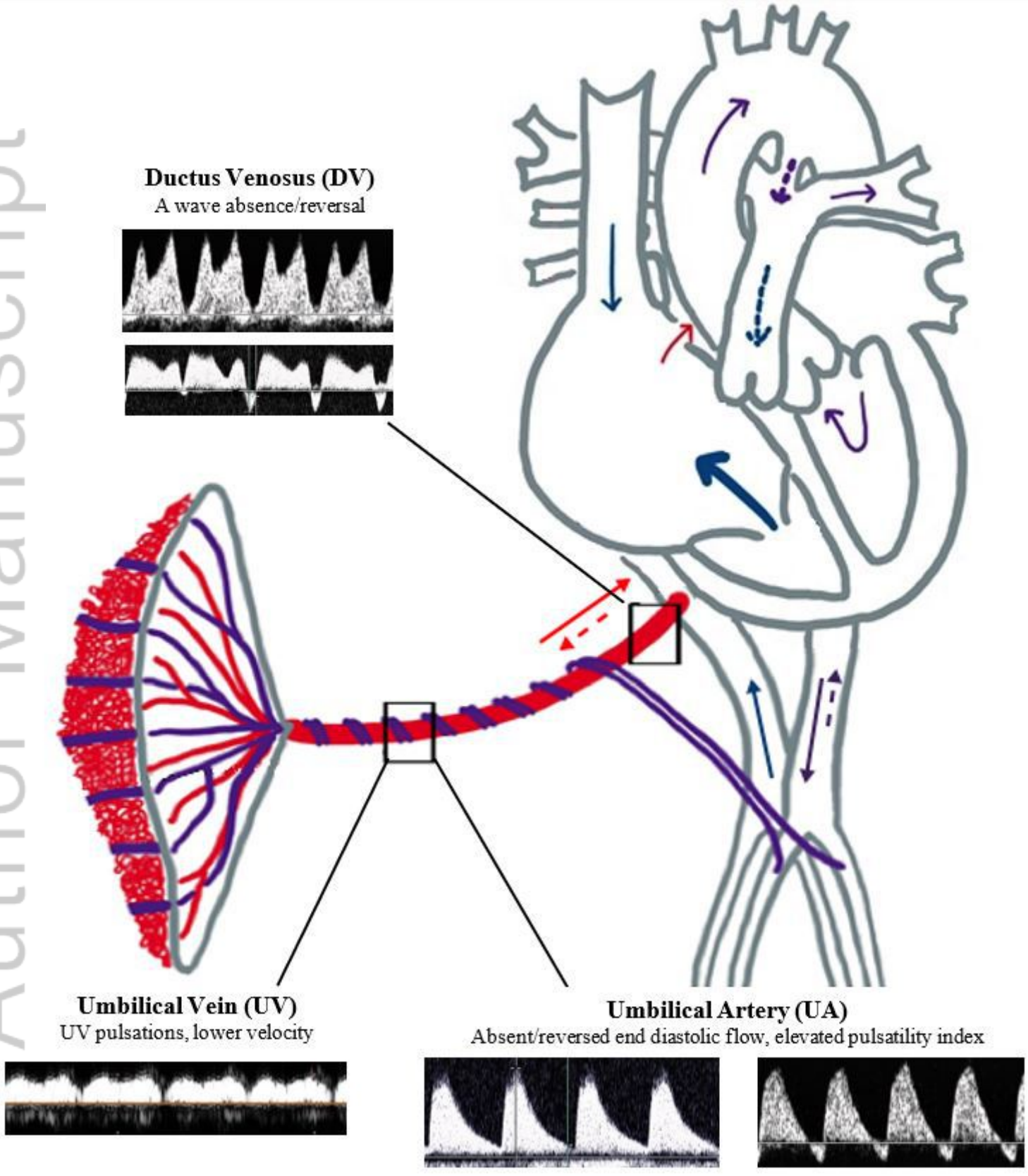
Figure 2. Examples of the abnormal Doppler indices of the ductus venosus (DV), umbilical artery (UA), and umbilical vein (UV) seen in EA/TVD fetuses. Normal DV waveform consists of antegrade flow during ventricular systole, early ventricular diastole, and atrial contraction while abnormal waveforms manifest as diminished, absent, or reversed diastolic flow. UA Doppler waveforms normally show antegrade diastolic flow while abnormal waveforms include absent or reversed diastolic flow. Normal UV waveform consists of constant velocity antegrade flow while abnormal waveform manifests as UV notching or pulsatility.

Figure 3. In severe cases of EA/TVD, the umbilical vein sees decreased upstream flow and pressure from the placenta as well as increased downstream pressure from elevated central

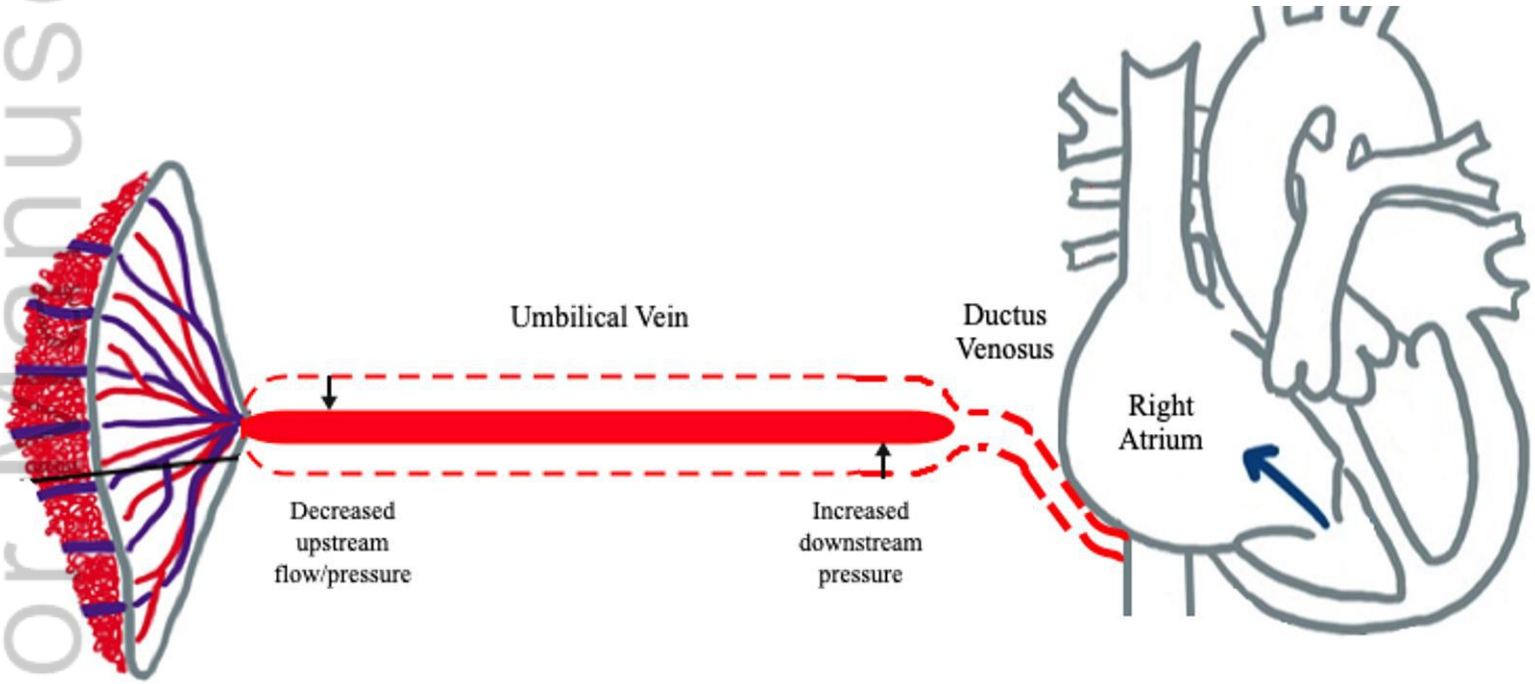
venous pressure which results in a relatively lower pressure differential (red solid line) compared to EA/TVD patients with less severe pathophysiology (red dashed line).



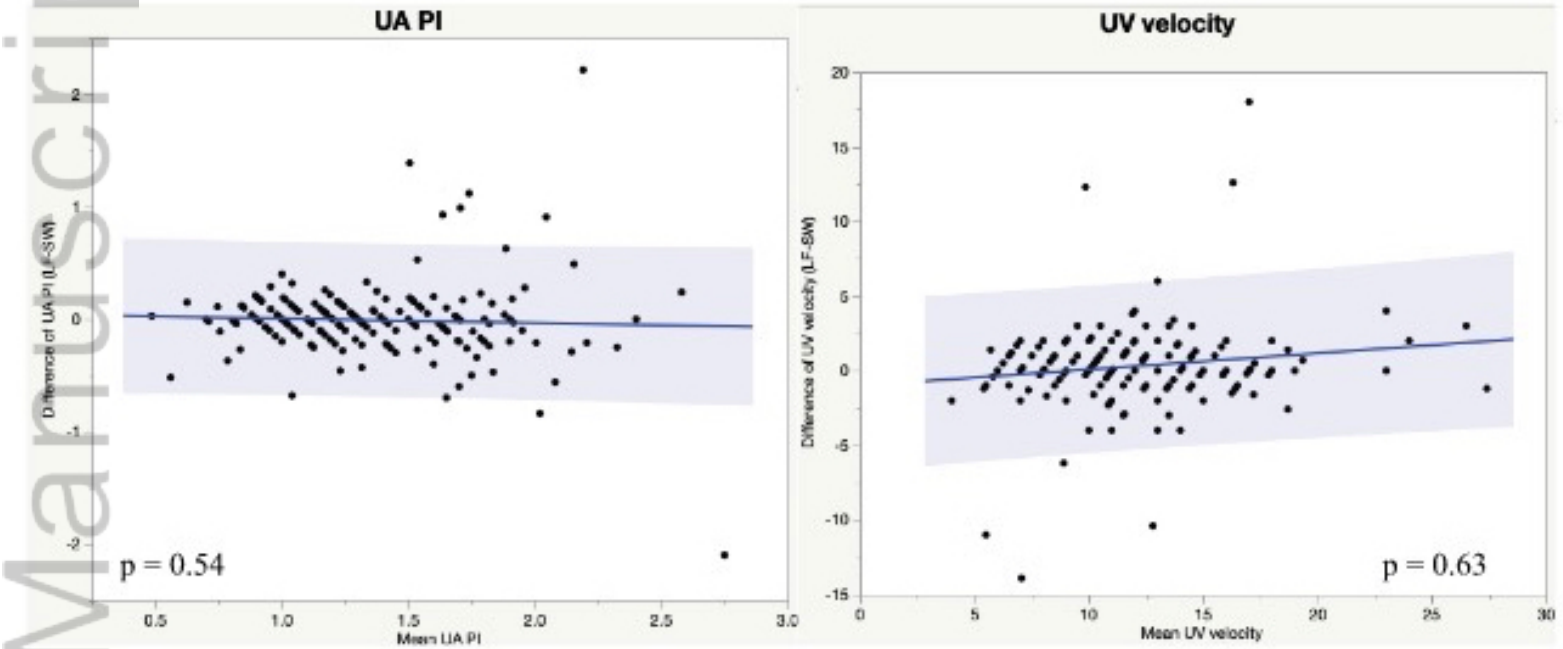
PD_5873_Figure 1.JPG



PD_5873_Figure 2.JPG



PD_5873_Figure 3.JPG



PD_5873_Interobserver Graphs.jpg