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Ductus venosus Doppler waveform pattern in fetuses with early growth restriction

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Conflicts of interest

None

ABSTRACT

Introduction: We aimed to assess if maximum velocities of the ductus venosus flow velocity waveform are associated with adverse outcomes in early-onset fetal growth restriction. **Material and methods:** Retrospective cohort study from two tertiary referral units, including singleton fetuses with estimated birthweight or fetal abdominal circumference ≤ 10th centile and absent or reversed end-diastolic velocity in the umbilical artery delivered between 26^{+0} and 34^{+0} weeks' gestation. Pulsatility index for veins, maximum velocities of S-, D-, v- and a-waves, were measured in the ductus venosus within 24 hours of birth. Logistic regression was used to describe the relationship between severe neonatal morbidity or neonatal death and clinical independent predictors. **Results:** The study population included 132 early-onset fetal growth restriction fetuses. Newborns with neonatal morbidity or neonatal death had significantly lower values of v/D maximum velocity ratio multiples of the median (0.86 vs. 095; *P*=0.006) within 24 hours of birth. The v/D ratio remained a significant predictor of neonatal death or severe neonatal morbidity after adjusting for gestational age and birthweight (adjusted odds ratio 0.065; 95% confidence interval 0.004 to 0.957). **Conclusions:** Assessment of ductus venosus v/D maximum velocity ratio might help to identify fetal growth restriction fetuses at increased risk for neonatal death or severe neonatal morbidity. Confirmation in prospective studies is necessary.

Keywords

Ductus venosus, maximum velocities, fetal growth restriction, IUGR, cardiac dysfunction, Doppler ultrasound

Abbreviations

aOR adjusted odds ratio
AUC area under the curve
CI confidence interval
DV ductus venosus
DV-FVW ductus venosus flow velocity waveform
FGR fetal growth restriction,
MoM multiples of the median

MPI myocardial performance index

NND neonatal death

NNM neonatal morbidity

PIV pulsatility index for veins

SE standard error

UA umbilical artery

UA-AEDF umbilical artery absent end-diastolic flow

UA-REDF umbilical artery reverse end-diastolic flow

Key message

Evaluation of v/D maximum velocity ratio in the ductus venous might improve identification of growth-restricted fetuses at increased risk for neonatal death or severe neonatal morbidity.

INTRODUCTION

Ductus venosus (DV) Doppler examination is established in the assessment of early-onset fetal growth restriction (FGR), and is typically performed analyzing semiquantitative indices such as the pulsatility index (DV-PIV), or by qualitative analysis focusing on the a-wave[1 2 3, 4]. In FGR, high placental vascular resistance leads to an increase in fetal cardiac afterload and myocardial dysfunction that can be documented as a progressive increase in the DV-PIV manifested initially as deepening and ultimately reversal of the a-wave[5-7], thus reflecting a progressive deterioration of the fetal condition due to worsening chronic hypoxemia[6, 8, 9]. At very early gestations, DV flow profile evaluation is the main cardiovascular parameter affecting neonatal outcome[2, 10-13]. DV flow profiles relate to atrial pressure and volume changes throughout the entire cardiac cycle, producing a multiphasic flow pattern[14]. Although cardiac function might be affected from the early stages of severe FGR, DV-PIV has limitations in assessing the primary underlying cardiac dysfunction[7]. Moreover, overt myocardial dysfunction is not universally present in all cases of FGR with elevated DV-PIV[14]. Other authors have already suggested that velocity ratios of the individual phases of the DV waveform might show relationships with cardiac function that are not detected by the DV-PIV and that might predict adverse outcome in high risk pregnancies [15-17]. In keeping with these findings we hypothesized that a decrease of the forward flow during isovolumetric ventricular relaxation, as demonstrated by a reduced maximum forward velocity of the v-wave, might be associated with worsening myocardial hypoxia and adverse perinatal outcome. Therefore the aim of our study was to assess if maximum velocities of the DV flow velocity waveform recorded within 24 hours of birth were significantly different in early-onset FGR that resulted in neonatal death (NND) or severe neonatal morbidity (NNM), compared to those who survived without severe complications.

MATERIAL AND METHODS

This was a retrospective cohort study performed in two tertiary referral centers. Data were retrieved on singleton pregnancies complicated by early isolated FGR from the prenatal database of the Department of Obstetrics and Gynecology at Spedali Civili hospital in Brescia (January 2011 - June 2017) and the Fetal Medicine Unit at St George's Hospital in London (January 1997 - August 2017). Inclusion criteria were: 1) gestational age determined by a certain last menstrual

period confirmed by ultrasound examination at < 20 weeks' gestation; 2) fetal abdominal circumference or estimated fetal birth weight below the 10th percentile[18]; 3) absent or reversed end-diastolic velocity in the umbilical artery; and 4) delivery between 26^{+0} and 34^{+0} weeks' gestation. We included in our analysis only cases where DV-PIV was measured within 24 hours before delivery. We excluded multiple pregnancies, fetuses with congenital anomalies, chromosomal aberrations or congenital infections, and intrauterine deaths as all of them occurred more than 24 hours after the last ultrasound examination. After the initial diagnosis of FGR antenatal surveillance was performed using fetal Doppler velocimetry and computerized cardiotocography. Appointments were scheduled at least every week, and up to three times a week depending on the severity of growth restriction and Doppler flow changes.

According to our local protocol umbilical artery (UA), middle cerebral artery and DV were assessed at each examination. The DV was identified with color Doppler in a sagittal or oblique view of the fetal abdomen, showing the vessel's typical aliasing due to high-velocity flow at the inlet. The blood velocity curve was subsequently recorded with pulsed Doppler at the inlet of the DV while the insonation angle was kept as low as possible. At each appointment the pulsatility index for the UA, the middle cerebral artery and DV-PIV were determined. UA end-diastolic velocity was classified as present, absent (UA-AEDF) or reversed (UA-REDF). In the same way DV velocity during atrial systole was characterized as forward or absent/reversed. DV flow was considered abnormal in case of DV-PIV ≥95th percentile[19] or if there was absent/reversed a wave. DV assessment was performed following the International Society of Ultrasound in Obstetrics & Gynecology guidelines[20, 21]. According to our local protocol a sequence of at least three successive and symmetric DV waves was required to register measurements during the cardiac cycle using the automatic or the manual trace function. If technically achievable, the intention was to always keep the insonation angle less 30° during DV assessment. In case of abnormal DV flow the finding had to be confirmed before making any clinical decision. Indications for delivery of the fetus were: reduced short term fetal heart rate variation (<3.5 ms at <29 weeks of gestation or <4 ms at ≥29 weeks of gestation); presence of recurrent decelerations of the fetal heart rate at cardiotocography; abnormal DV flow; maternal indication, such as severe preeclampsia; UA-REDF > 30^{+0} - 32^{+0} and UA-AEDF > 32^{+0} - 34^{+0} weeks' gestation[2]. Preeclampsia was defined as blood pressure > 140/90 mmHg and proteinuria as > 0.3 g/L on a 24-h collection of urine [22].

Still images were stored digitally in DICOM format. Images from last examination within 24 hours before delivery were used for analysis. Examinations where the still images were absent or the DV-FVW had a poor signal-to-noise ratio were excluded from the study. Post hoc measurements were performed on one heart cycle only, using the same velocities used for the DV-PIV calculation. Maximum velocities of S-, D-, v- and a-waves, in cm/s, (Figure1) were measured from good-quality waveforms that exhibited a high signal-to-noise ratio and were rounded up or down to the nearest absolute number The following method was used to express the impact of absent and reversed a-wave velocities in statistical calculations: absent a-wave was expressed as 1 cm/s, which is the nearest absolute number close to zero (example: if S = 50 cm/s and a-wave = 0, the a-wave will have the value of 1 cm/s reassigned, with the S/a ratio = 50/1 = 50); if the a-wave was negative, the actual measurement of the a-wave was added to the actual measurement of S, v, and D and divided by 1 (example: if S = 50 cm/s and a-wave= -10 cm/s then the S/a ratio will be = (50 + 10)/1 = 60)[17]. Only ratios of measured velocities were investigated, therefore angle correction was not necessary. DV-FVW velocity ratios were converted into multiples of the median (MoM) adjusting for gestational age[23]. Perinatal records were examined. NND, and severe NNM were recorded at discharge from hospital. For the purpose of this study severe NNM was defined as a composite of one or more of the following severe morbidities: severe germinal matrix cerebral hemorrhage [GMH; intraventricular hemorrhage with dilation of the lateral ventricles (grade III) or intraparenchymal hemorrhage (grade IV)], cystic periventricular leukomalacia (PVL), proven neonatal sepsis (positive blood culture requiring treatment with antibiotics), necrotizing enterocolitis (Bell's stage 2 or greater: presence of pneumatosis or perforation on X-ray or identified by laparotomy) and bronchopulmonary dysplasia, defined as need of supplemental oxygen at discharge. Gestational age at delivery and birthweight were also recorded.

Descriptive statistics were calculated using median and interquartile range and the Mann–Whitney U test was used for median comparisons. The Benjamini-Hochberg procedure was used to control the false discovery rate when conducting multiple comparisons under dependency with false discovery rate cut off set at 0.1. The chi-squared test and Fisher's exact test were used for the analysis of contingency tables of proportions in different groups, as appropriate. *P*-values <0.05 were considered significant. Diagnostic accuracy was assessed by performing receiver–operating characteristics (ROC) curves analysis for quantitative tests in the prediction of NND and severe NNM. Pearson correlation coefficient was used to assess the linear correlation between variables,

where 1 is total positive linear correlation, 0 is no linear correlation, and −1 is total negative linear correlation. *P*-values <0.01 were considered significant. Binary logistic regression was used to describe the relationship between severe NNM or NND at discharge (dependent variable) and a set of clinical independent predictors (gestational age at delivery and birthweight). P-values <0.05 were considered significant. Statistical analysis was performed with Stata 13.1 (StataCorp., College Station, TX, USA).

Ethical approval

The project was classified as a quality improvement study with anonymized data. Therefore ethical committee approval was not required according to local regulations.

RESULTS

One hundred and thirty-two pregnancies complicated by early-onset FGR and assessed within 24 hours of birth constituted our study population (Figure 2, Table 1). Outcomes were comparable between the 2 institutions as the prevalence of the main composite neonatal outcome was not statistically significant during the study period (51% St George's Hospital, 62% Brescia University; p=0.203).

Preeclampsia complicated 97/132 (73%) pregnancies and birth occurred by Caesarean section in 130/132 (98%) cases. Indications for delivery were: reduced short term fetal heart rate variation (5/132; 4%), recurrent decelerations of the fetal heart rate at cardiotocography (76/132; 58%), abnormal DV-PIV (15/132; 11%); maternal indication such as severe preeclampsia (25/132; 19%); UA-REDF> 30^{+0} or UA-AEDF > 32^{+0} weeks' gestation (11/132; 8%).

Among 132 fetuses with absent or reverse flow in the UA at the last ultrasound before birth, 15 (11%) had absent or reversed a-wave velocities in the DV. Neonatal severe morbidity or death at discharge occurred in 12/15 (80%) newborns with absent or reversed a-wave velocities in the DV before delivery and in 60/117 (51%) with positive a-wave velocities (p=0.052). However, FGR newborns with NND or severe NNM at discharge showed significantly lower values of v/D (p=0.006) Maximum velocity ratios in the 24 hours before birth. . In fetuses with intact survival at discharge v/D ratio was significantly higher than in cases with NND (p=0.046) or NNM

(p=0.0263). while it was not significantly different between fetuses with NND and those with NNM (p=1). Differences between newborns with intact survival (n=60), and those with composite adverse outcome (n=72) remained significant after the Benjamini-Hochberg procedure, used to control the false discovery rate. (Table 2). There were no differences in the other DV-FWV Maximum velocity ratios or in DV-PIV between newborns with and without with significant NND or NNM at discharge (Table 2). The v/D ratio was inversely related to DV-PIV (Pearson correlation coefficient -0.4618, p<0.001). Gestation at delivery (*P*=0.0002) and birthweight (*P* =0.0003) were also significantly lower among newborns with significant NND or NNM at discharge (Table 2).

Logistic regression adjusted odds ratio (aOR) with standard error (SE) and 95% confidence interval (95%CI) were calculated to describe the association between NND or severe NNM, v/D MoM, gestational age at delivery , and birthweight.. The dependent variable was NND or severe NNM assessed at neonatal discharge (1=NND or severe NNM; 0=alive without severe NNM). Adjusted odds ratio takes in account the effect of gestational age at delivery (aOR 0.917, SE 0.130, 95% CI from 0.693 to 1.211) and birthweight (aOR 0.988, SE 0.001, 95% CI from 0.996 to 1) on v/D ratio (aOR 0.065, SE 0.0888, 95% CI from 0.004 to 0.957). Binary logistic regression showed that the v/D ratio remained a significant predictor of NND or severe NNM after adjusting for gestational age at delivery and birth weight.

The ROC curves of all the DV indices. for the prediction of neonatal survival without severe NNM are shown in Table 3. The area under the curve (AUC) for v/D was 0.64 (standard error, 0.0489; 95%CI from 0.54383 to 0.73560), while DV-PIV had an AUC of 0.40 (standard error, 0.0507 95%CI from 0.3087 to 0.50745). This difference was statistically significant between these 2 indices (*P*=0.0083), however when all the indices were considered together there were not statistically significant differences (*P*=0.2144).

DISCUSSION

In a cohort of pregnancies complicated by early-onset severe FGR, we observed that neonatal mortality or severe morbidity were associated with lower values of ductus venosus v/D maximum velocity ratios, measured within 24 hours before delivery. Notably DV-PIV was not significantly

different between the two groups and the v/D ratio remained a significant predictor of NND or severe NNM even after adjusting for birth weight and gestational age at birth.
Moreover v/D ratio had an important prognostic value among FGR fetuses with positive a-wave velocities in the DV and among those delivered because of fetal heart rate changes as a reduced v/D ratio significantly decreased the chances of survival without severe NNM at discharge in both groups.

Blood levels of cardiac troponin T, a biomarker of myocardial cell damage, are increased in growth-restricted newborns, as well as in umbilical blood in fetuses with placental insufficiency, confirming that myocardial function is affected during FGR, especially in fetuses with the most pronounced flow abnormalities[24]. While v-wave related ratios are related to fetal cardiac function and to the left ventricular myocardial performance index (MPI), a-wave related ratios and the DV-PIV are not[15]. Moreover, Hernandez-Andrade et al. reported that MPI is an independent predictor of perinatal death in preterm FGR fetuses with a similar accuracy to DV flow[25]. MPI deteriorates with worsening degrees of growth restriction and global myocardial dysfunction in FGR is mainly related to an increase in the isovolumetric relaxation time; some studies on MPI in early-onset FGR, however, found only a modest increase in MPI, with no added clinical utility [6, 25-28].

The v-wave corresponds to the last time of the systole just before the opening of the atrioventricular valves, which in turn seems to fit with the isovolumetric relaxation time[14]. Placental insufficiency characteristic of early FGR results in increased peripheral vascular resistance and increased end-diastolic pressure. As the condition worsens, blood flow during atrial systole decreases and ultimately results in reversal of flow during atrial contraction (a-wave). With increasing myocardial hypoxia and acidosis, the cardiac muscle is less compliant, leading to increased end-systolic intracardiac pressure or residual volume, both of which oppose forward flow during isovolumetric ventricular relaxation (v-wave)[15]. The close relationship between the v-wave ratios and cardiac function can be explained by the absence of other atrial mechanical events during this part of the cardiac cycle[15].

Picconi *et al.* reported an increased risk of fetal demise in FGR fetuses with deep v-waves and developed a DV Doppler index incorporating a direct measurement of the v-wave that, when compared to DV-PIV, seemed to provide a better prediction of adverse cardiovascular outcome in

FGR [29]. A recent study by Dahlback *et al.* showed that an increased S/v ratio was predictive of adverse outcome, and related to umbilical vein pulsations[16]. A high S/v ratio implies a decrease in forward flow during ventricular end-systole (i.e. isovolumetric relaxation time, v-wave) as the pressure in the atria increases. This is in agreement with our findings.

The main strength of our study is that the systematic evaluation of DV-FVW for maximum velocity ratios was performed in a well-characterized cohort of early-onset FGR fetuses with UA-ARED before delivery. Limitations were that we performed a retrospective evaluation on a relatively small sample of FGR fetuses and that the value of short term fetal heart rate variation at the time of delivery was not available, from our database we could only know if short term fetal heart rate variation was above or below a given threshold (<3.5 ms at <29 weeks of gestation or <4 ms at ≥29 weeks of gestation) and if recurrent decelerations of the fetal heart rate were recorded at cardiotocography. Another limitation of our study is given by the fact that clinicians used DV-PIV and qualitative a wave assessment for the clinical management of FGR fetuses, and the v/D ratio was inversely related to DV-PIV; these possible biases of the study prevented us to assess the natural history of v/D ratio changes in all the fetuses, and might also explain the AUC <0.50 observed for the DV-PIV. The v/D ratio only had an AUC of 0.64 for the prediction of neonatal survival without severe NNM, so its clinical usefulness needs to be further evaluated. Although the predictive value of DV parameters might be different with a more active management protocol, computerised CTG and DV assessment are considered the gold standard for monitoring early FGR in many European centers as before 32 weeks, delaying delivery until abnormalities in DV or computerised CTG and/or recurrent decelerations in fetal heat rate occurs likely to be safe and possibly benefits long-term outcome[30, 31]. Therefore, we think that our results are generalizable. However, given the retrospective nature of the study and the relatively small sample size , our results need to be replicated in other centers in order to avoid unrealistic expectations on a new clinical parameter. Finally, it can be argued that accurate information on intrauterine fetal cardiac function can be obtained through fetal echocardiography rather than indirectly assessing the DV. However, while the use of fetal functional echocardiography requires trained operators and seems to be limited to research settings [32], DV assessment has become part of the management of early FGR pregnancies [2, 20].

CONCLUSION

We observed that DV-FWV analysis of v/D maximum velocity ratio, might help to identify FGR fetuses at increased risk for NND or severe NNM, even with positive a-wave velocities in the DV. If this finding will be confirmed in prospective studies, DV-FWV maximum velocity ratios assessment could easily be added to standard DV-PIV evaluation in early-onset and severe FGR.

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Table 1. Characteristics of the study population (n=132).

	Median	**IQR**
Gestational age at delivery (w)	29^{+4}	27^{+6} - 31^{+0}
UA-PI within 24 h before delivery (MoM)	2.32	1.86-3.14
MCA-PI within 24 h before delivery (MoM)	0.61	0.53-0.72
DV-PIV within 24 h f before delivery (MoM)	1.51	1.18-2.13
Birthweight (g)	791	602 - 1036
	N	**%**
UA-AEDF within 24 h before delivery (n)	78/132	59%
UA-REDF within 24 h before delivery (n)	54/132	41%
Absent or reversed DV a-wave within 24 h before delivery (n)	15/132	11%
Delivery indications:		
Maternal indication	25/132	19%
Abnormal DV flow	15/132	11%
Reduced short term fetal heart rate variation	5/132	4%
Recurrent decelerations of the fetal heart rate at cardiotocography	76/132	58%
UA-REDF > 30^{+0} - 32^{+0} and UA-AEDF > 32^{+0} - 34^{+0} weeks' gestation	11/132	8%
Neonatal death (n)	26/132	20%
Severe composite neonatal morbidity	46/132	35%
Severe GMH	2/132	2%
PVL	1/132	1%
Neonatal sepsis	34/132	26%
NEC	14/132	10%
Bronchopulmonary dysplasia	20/132	15%

Abbreviations: IQR, interquartile range; UA-PI, umbilical artery pulsatility index; MoM, multiples of the median; MCA-PI, middle cerebral artery pulsatility index; DV-PIV, ductus venosus pulsatility index; UA-AEDF, umbilical artery absent end diastolic flow; UA-REDF, umbilical artery reverse end diastolic flow; GMH, germinal matrix cerebral hemorrhage; PVL, cystic periventricular leukomalacia; NEC, necrotising enterocolitis;

Table 2. Values of ductus venosus flow velocity waveform (DV-FVW) maximum velocity ratios assessed within 24 hours before delivery, birthweight (g) and gestational age at delivery (w, weeks' gestation) in case of intact neonatal survival , severe morbidity or neonatal death assessed at discharge. The ratios between maximum velocities of S-, D-, v- and a-waves were calculated. DV-FVW are expressed as multiples of the median (MoM).

	Intact survival at discharge (N=60)	**Severe neonatal morbidity (N=46)**	**Neonatal death (N=26)**
DV-PIV(MoM)	1.42 (1.08-1.87)	1.54 (1.21-2.38)	1.63 (1.31-2.32)
D/a (MoM)	1.34 (1.05- 2.33)	1.56 (1.17-3.9)	1.43 (1.17-3.019
v/a (MoM)	1.26 (1.01- 2.02)	1.35 (1.1-2.97)	1.22 (1.00-2.06)
S/a (MoM)	1.36 (1.09- 2.56)	1.57 (1.17-3.55)	1.47 (1.18-3.01)
S/v (MoM)	1.13 (1.04- 1.30)	1.19 (1.06-1.56)	1.28 (1.12-1.45)
S/D (MoM)	1.04 (0.99- 1.09)	1.02 (0.97-1.11)	1.06 (0.96-1.21)
v/D (MoM)*	0.95 (0.81- 1.01)	0.86 (0.75-0.96)	0.85 (0.74-0.93)
Birthweight g*	945 (703-1168)	658 (553-755)	841 (635-1041)
Gestational age w*	30^{+3} (28^{+3}-32^{+0})	28^{+2} (27^{+3}-$29.^{+3}$)	30 (28^{+4}-32^{+0})

Data are reported as median and and interquartile range. Differences between newborns with intact survival (n=60), and those with composite adverse outcome (n=72) are indicated by * when remain significant after the Benjamini-Hochberg procedure, used to control the false discovery rate when conducting multiple comparisons under dependency with false discovery rate cut off set at 0.1.

Abbreviation: DV-PIV, ductus venosus pulsatility index.

Table 3. Receiver–operating characteristics (ROC) curves of all the ductus venosus indices for the prediction of neonatal survival without severe neonatal morbidity are shown.

	AUC	Standard error	95% confidence interval
DV-PIV(MoM)	0.4081	0.0507	0.30870 - 0.50745
D/a (MoM)	0.4022	0.0507	0.30283 - 0.50149
v/a (MoM)	0.4322	0.0512	0.3318 - 0.53263
S/a (MoM)	0.4098	0.0508	0.31035 - 0.50931
S/v (MoM)	0.3873	0.0504	0.28860 - 0.48605
S/D (MoM)	0.4872	0.0521	0.38499 - 0.58935
v/D (MoM)	0.6434	0.0494	0.54656 - 0.74016

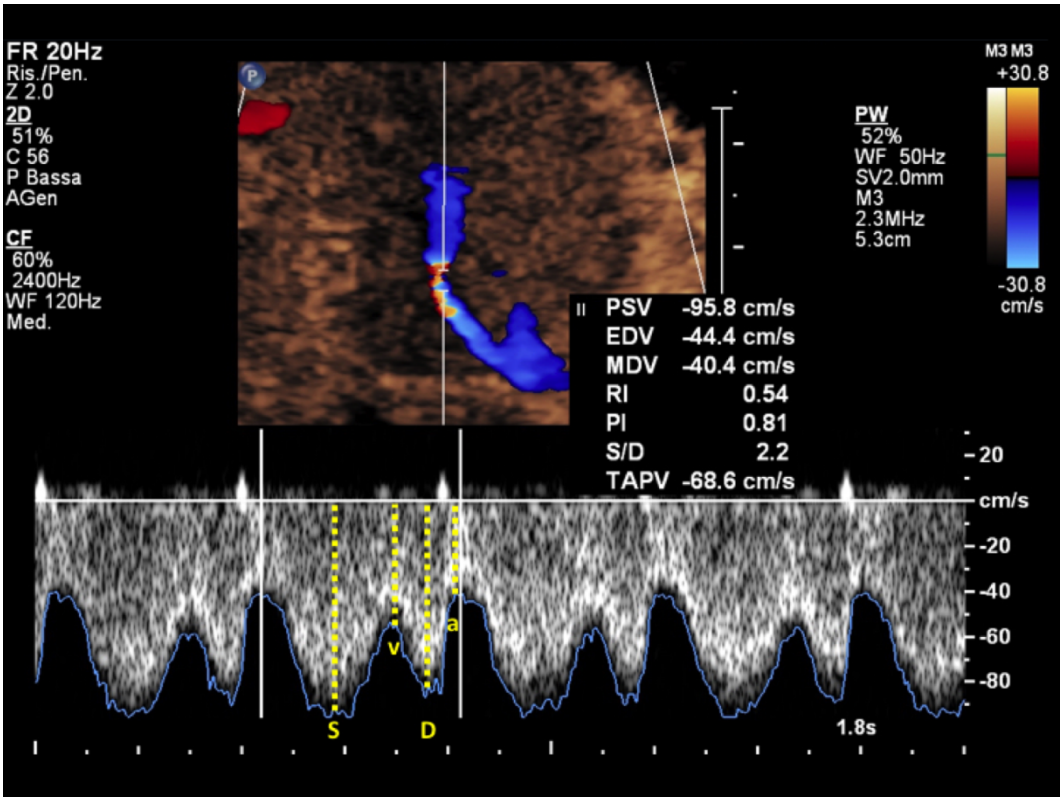
Abbreviations: AUC, area under the curve; DV-PIV, ductus venosus pulsatility index; MoM, multiples of the median; D; a; v; S; maximum velocities of S-, D-, v- and a-waves.

Legends to Figures

Figure 1. Doppler tracings of flow velocity waveform of the ductus venosus showing maximum velocities of S-, D-, v- and a-waves.

Figure 2. Study flow chart. DV, ductus venosus; DV-FVW, ductus venosus flow velocity waveform; FGR, fetal growth restriction; h, hours.

Figure 3. Receiver–operating characteristics (ROC) curves show the diagnostic accuracy of v/D and ductus venosus pulsatility index (DV-PIV), expressed as multiples of the median (MoM), for intact survival at birth. The figure shows that v/D ratio MoM for the prediction of neonatal survival without severe neonatal morbidity had an area under the curve (AUC) of 0.64 (standard error, 0.0489; 95%CI from 0.54383 to 0.73560), while DV-PIV MoM had an AUC of 0.40 (standard error, 0.0507 95%CI from 0.3087 to 0.50745). This difference was statistically significant (P=0.0083).



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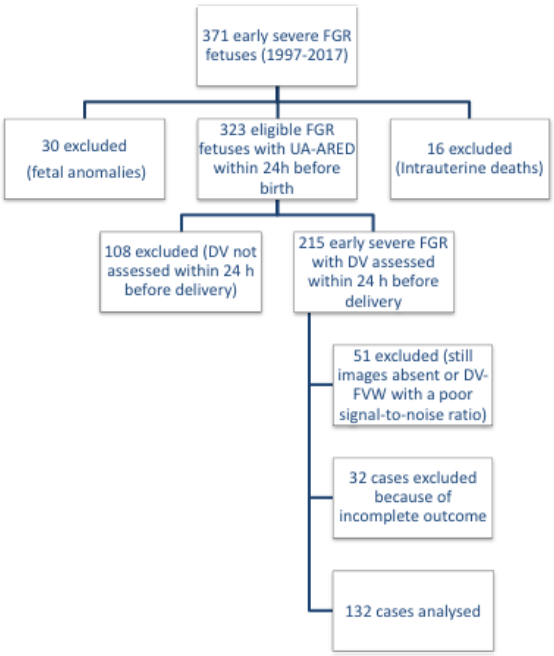

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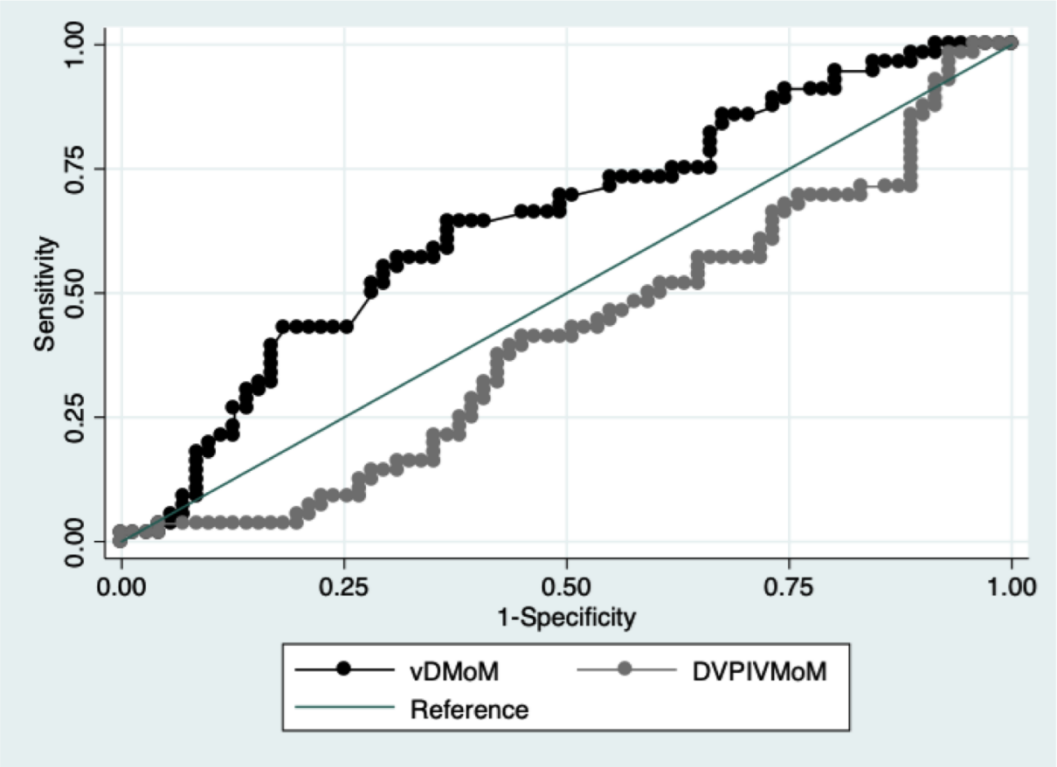

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