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Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction

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KEYWORDS: Doppler; fetal growth restriction; interval to delivery; longitudinal analysis; middle cerebral artery

ABSTRACT

Objective *To study if the duration of individual Doppler abnormalities is an independent predictor of adverse outcome in fetal growth restriction (FGR) caused by placental dysfunction.*

Methods *This was a secondary analysis of patients with FGR (abdominal circumference < 5th percentile and umbilical artery (UA) pulsatility index (PI) elevation) who had at least three examinations before delivery. Days of duration of absent/reversed UA end-diastolic velocity (UA-AREDV), low middle cerebral artery PI (brain sparing), ductus venosus (DV) and umbilical vein Doppler abnormalities were related to stillbirth, major neonatal morbidity and intact survival.*

Results *One hundred and seventy-seven study participants underwent a total of 1069 examinations. The duration of an absent/reversed a-wave in the DV (DV-RAV) was significantly higher in stillbirths (median, 6 days) compared with intact survivors and those with major morbidity (median, 0 days for both;* $P = 0.006$ *and* $P = 0.001$*, respectively). Duration of brain sparing was also longer in stillbirth cases compared with intact survivors (median, 19 days vs. 9 days,* $P = 0.02$*). Stepwise multinomial logistic regression showed that gestational age at delivery was a significant codeterminant of outcome for all arterial Doppler abnormalities when the DV a-wave was antegrade. However, when present, the duration of DV-RAV was the only contributor to stillbirth (probability of stillbirth = 1/(1 + exp − (interval to delivery × 1.03 − 2.28)),* $r^2 = 0.73$*). Receiver–operating characteristics curve statistics showed that a DV-RAV for > 7 days predicted stillbirth (100% sensitivity, 80% specificity, likelihood ratio = 5.0,* $P < 0.0001$*). In contrast, neither neonatal death nor neonatal morbidity was predicted by the days of persistent DV-RAV.*

Conclusions *The duration of absent or reversed flow during atrial systole in the DV is a strong predictor of stillbirth that is independent of gestational age. While prematurity remains the strongest predictor of neonatal risks it is unlikely that pregnancy can be prolonged by more than 1 week in this setting. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

In pregnancies complicated by growth restriction from placental dysfunction, the fetus is at risk for intrauterine deterioration and irreversible compromise. In recognition of this fact, the managing physician is faced with the task of determining the best surveillance approach to allow safe pregnancy prolongation and to identify the threshold that favors intervention[1]. To aid in this management, the clinical characteristics of fetal deterioration and its relationship with fetal and neonatal outcomes should ideally be known. Knowledge of these relationships is most pressing for preterm fetal growth restriction (FGR) where ongoing surveillance and delayed delivery carry the risks of unanticipated stillbirth, while immediate delivery increases the risk of prematurity-related morbidity and mortality[2].

In fetuses with early-onset FGR (before 34 weeks' gestation), a characteristic pattern of clinical progression has been described[3]. In this type of early-onset FGR, early signs of placental dysfunction are arterial Doppler abnormalities, such as elevated umbilical artery (UA)

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and decreased middle cerebral artery (MCA) blood-flow resistance, while late responses are marked by progression to reversed UA end-diastolic velocity and venous Doppler abnormalities[4–6]. Following these late vascular responses, fetal heart-rate parameters and dynamic fetal variables eventually become abnormal[7–9]. This sequence of clinical progression is associated with an increased risk for acidemia and stillbirth[10–13]. However, based on cross-sectional observations, the impact of prematurity on neonatal outcomes appears to be so important that it overrides the contribution of deteriorating fetal status until the late second trimester[11,14]. It is therefore in this setting of preterm FGR that the managing physician is most often forced to tolerate non-reassuring fetal surveillance tests in order to gain gestational age. If outcome was determined solely by this balance of fetal and neonatal risks, the amount of time gained by tolerating fetal deterioration would have to be tailored to gestational age. However, there is incomplete knowledge of whether the number of days with persistently non-reassuring fetal surveillance tests has an independent impact on outcome.

It is possible that longer periods with critical Doppler abnormalities have an impact on neonatal outcome that is independent of the gestational age at delivery. This cannot be evaluated in cross-sectional studies, which only relate the fetal presentation at a fixed point with outcomes. Among the large body of publications examining the relationships between Doppler and outcome in FGR there are only a few longitudinal analyses. To the best of our knowledge, only the study by Bilardo and coworkers provides an indirect suggestion that the progressive deterioration of ductus venosus (DV) Doppler abnormalities independently worsens neonatal outcome[13]. It was the aim of our study to test the hypothesis that, in FGR, the duration of persistent Doppler abnormalities has an impact on stillbirth and neonatal complication rates that is independent of the degree of Doppler abnormality and gestational age.

SUBJECTS AND METHODS

This was a secondary retrospective analysis of patients with FGR studied in a multicenter collaboration[14]. In the original study patients were enrolled if they met the following inclusion criteria: (i) singleton pregnancy; (ii) gestational age determined by sure last menstrual period and confirmed by sonography before 20 weeks; and (iii) FGR diagnosed by an abdominal circumference $< 5^{th}$ percentile and elevation of the UA pulsatility index (PI) > 2 SD. For this analysis we evaluated a subset of patients who had at least three Doppler examinations before delivery. Fetuses with chromosomal abnormalities or structural anomalies were excluded.

Fetal Doppler studies

The secondary analysis of pre-existing information was performed because all patients had received standardized assessment of fetal surveillance parameters that were prospectively predefined. Doppler measurements were obtained from the UA, MCA, DV and umbilical vein (UV) according to uniform standards[14]. Umbilical artery end-diastolic velocity was classified as either present or absent/reversed (AREDV). DV velocity during atrial systole was characterized as forward or absent/reversed (DV-RAV). Pulsations in the UV were noted. The PI for each vessel was converted to its *Z*-score to exclude the effect of gestational age[15]. For the UA, a 2 SD elevation of the Doppler index was considered abnormal. For DV, a 3 SD elevation of pulsatility index for veins (PIV) was considered as abnormal. Brain sparing was defined as a 2 SD decline in MCA-PI[16]. An elevated UA-PI and brain sparing were classified as early Doppler changes. Late Doppler changes were categorized as arterial compromise only (UA-AREDV with normal DV), venous Doppler abnormality (DV-RAV, UV pulsation with positive a-wave in DV and DV-PIV > 3 SD with positive a-wave) and combined abnormality (UA-AREDV with positive a-wave in DV).

Obstetric management and delivery details

The choice of surveillance intervals and timing of delivery were at the discretion of the managing obstetrician and dictated by the local standard of care. Perinatal characteristics and delivery details, such as indication, route, gestational age, birth weight, Apgar scores and UA blood gases were ascertained. Stillbirth was noted. Bronchopulmonary dysplasia[17], Grade 3 and Grade 4 intraventricular hemorrhage[18] and necrotizing enterocolitis[17] constituted major morbidity in neonatal life. Neonatal mortality in the first 28 days was ascertained. Intact survival was defined as the absence of stillbirth and major morbidity in the neonatal period.

Data analysis

The categorical endpoints defined for the analysis were the individually defined Doppler abnormalities. Stillbirth, major morbidity and intact survival were evaluated as endpoints for outcome. The interval between the initial observation of each Doppler abnormality and delivery was calculated in days (duration of Doppler abnormality). The relationship between interval to delivery for each Doppler abnormality and major outcome parameters were analyzed. The effect of the severity of the Doppler abnormality on outcome parameters was independently explored. Continuous variables were analyzed using the Mann–Whitney *U*-test after evaluation for normal distribution using the Kolmogorov–Smirnov test. Categorical variables were analyzed with the chi-square or Fisher's exact test depending on cell size. The combined impact of the interval to delivery and the severity of Doppler parameters was investigated using multiple logistic regression analysis. The probability of intact survival, major morbidity and stillbirth were calculated as: $P = 1/(1 + e^{-z})$, where z is the logistic regression equation. Survival-time analysis was performed using Kaplan–Meier tests. The

comparisons of survival curves in outcome groups were performed using the Mantel–Cox test. SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and MedCalc software (Version 9.4.2.0; MedCalc Software, Mariakerke, Belgium) were used for these analyses.

RESULTS

One hundred and seventy-seven pregnant women were included in the study, in whom 1069 Doppler examinations were performed with a median of 7 (3–26) examinations per patient. There were 18 stillbirths and 125 intact survivors, while 34 neonates experienced major neonatal morbidity. There were no peripartum deaths. At similar maternal background risks, the majority of women were delivered for fetal indications by Cesarean section. Patients with stillbirth and major morbidity had earlier-onset, and more marked, FGR. Gestational age at delivery and delivery weight were significantly lower in stillbirths (Table 1).

Among the categorical Doppler abnormalities only an absent/reversed DV a-wave was significantly more common in fetuses with adverse outcomes. The incidence was highest in stillbirths (61.1%), lower in patients with major morbidity (18.2%) and only 3.2% in intact survivors ($P \leq 0.005$ for all comparisons, Table 2). However, when the Doppler index *Z*-scores were considered for all examinations, stillborn fetuses had a greater number of abnormal Doppler indices in all vessels (Table 3). The median PI *Z*-scores were 3.6, 5.09 and 7.9 in the UA, −1.5, −2.07 and −2.24 in the MCA and 0.69, 2.48 and 2.80 in the DV for intact survivors, cases with major morbidity and stillborns, respectively (all $P \leq 0.02$, Table 3).

Following analysis of the overall prevalence of Doppler abnormalities, we next evaluated the impact of the duration of Doppler abnormalities for individual patients. In this analysis, duration of an absent/reversed a-wave in the DV was significantly longer for stillbirth cases (median, 6 days) compared with intact survivors and fetuses with major morbidity (median, 0 days for both; $P = 0.006$ and $P = 0.001$, respectively). The duration of brain sparing was also longer in stillbirths (median = 19 days) compared with intact survivors (9 days) ($P = 0.02$) (Table 4, Figure 1).

To evaluate the impact of Doppler abnormalities and their duration in the context of gestational age, we performed a stepwise multinomial logistic regression. In this analysis, duration of individual Doppler abnormalities (expressed as days to delivery),

Table 1 Maternal demographics and perinatal characteristics of intact survivors, non-intact survivors and stillbirths

Characteristic	*Intact survival* (n = *125*)	*Major morbidity* (n = *34*)	*Stillbirth* (n = *18*)
Maternal age (years)	28 (14–45)	30.5 (16–40)	29 (20–41)
Parity			
0	94 (75.2)	20 (58.8)	13 (72.2)
1	24 (19.2)	7 (20.7)	2 (11.1)
2	7 (5.6)	6 (17.6)	3 (16.7)
3	0	1 (2.9)	0
Race			
Caucasian	84 (67.2)	26 (76.5)	13 (72.2)
Black	39 (31.2)	8 (23.5)	5 (27.8)
Asian	2 (1.6)	0	0
Antepartum risk factors			
None	91 (72.8)	26 (76.5)	13 (72.2)
Chronic hypertension	23 (18.4)	5 (14.8)	2 (11.1)
Diabetes mellitus	4 (3.2)	1 (2.9)	2 (11.1)
Thrombophilia	4 (3.2)	1 (2.9)	1 (5.6)
Others (pancreatitis, asthma, substance abuse)	3 (2.4)	1 (2.9)	0
Indication for delivery*			
Non-reassuring fetal status	80 (64.0)	22 (64.7)	
Pre-eclampsia	14 (11.2)	10 (29.4)	
Abruption	2 (1.6)	1 (2.9)	
Oligohydramnios	2 (1.6)	0	
Spontaneous onset of labor	19 (15.2)	0	
Elective	8 (6.4)	1 (2.9)	
Mode of delivery†			
Spontaneous vaginal	22 (17.6)	0	18 (100)
Cesarean section	103 (82.4)	34 (100)	0
Gestational age at delivery (weeks)†‡§	32.5 (26.3–40.3)	29.1 (25.5–35.4)	28.1 (24.6–38.1)
Birth weight (g)†‡§	1150 ± 525.0	635 ± 265.6	420 ± 105.0
5-min Apgar score < 7†	5 (4.0)	10 (29.4)	
pH < 7.20	31 (24.8)	11 (32.4)	

Data are given as *n* (%), median (range) or mean ± SD, except for maternal age, which is given as mean (range). *Intact vs. major morbidity ($P = 0.037$). †Intact vs. major morbidity ($P < 0.0001$). ‡Intact vs. stillbirth ($P < 0.0001$). §Major morbidity vs. stillbirth ($P < 0.0001$).

Table 2 Incidence of Doppler abnormalities according to perinatal outcome

Parameter	*Intact survival* (n = *125*)	*Major morbidity* (n = *34*)	*Stillbirth* (n = *18*)
Elevated UA-PI *Z*-score	116 (92.8)	33 (97.1)	17 (94.4)
Brain sparing	83 (66.4)	29 (85.3)	15 (83.3)
UA-AREDV with positive a-wave in DV*	42 (33.6)	21 (61.8)	6 (33.3)
UA-AREDV with DV-PIV < 3 SD	21 (16.8)	9 (26.5)	1 (5.6)
DV-PIV > 3 SD with positive a-wave*	33 (26.4)	17 (50.0)	5 (27.8)
UV pulsation with positive a-wave in DV	18 (14.4)	6 (17.6)	3 (16.7)
DV absent/reversed a-wave*†‡	4 (3.2)	6 (17.6)	11 (61.1)

Data are given as *n* (%). *Intact vs. major morbidity ($P < 0.01$). †Major morbidity vs. stillbirth ($P = 0.005$). ‡Intact vs. stillbirth ($P < 0.0001$). AREDV, absent/reversed end-diastolic velocity; DV, ductus venosus; PI, pulsatility index; PIV, pulsatility index for veins; UA, umbilical artery; UV, umbilical vein.

Table 3 Distribution of Doppler *Z*-scores according to perinatal outcome

Parameter	*Intact survival* (n = *1048*)	*Major morbidity* (n = *1015*)	*Stillbirth* (n = *957*)
UA-PI *Z*-score*†‡	3.60 (−2.97 to 30.73)	5.09 (−1.48 to 33.82)	7.90 (0.99 to 39.30)
MCA-PI *Z*-score*‡	−1.50 (−4.96 to 6.34)	−2.07 (−3.28 to 3.38)	−2.24 (−3.73 to 0.79)
DV-PIV > 3 SD with positive a-wave*‡§	0.69 (−3.45 to 10.25)	2.48 (−2.44 to 17.51)	2.80 (−3.99 to 29.77)

Data are given as median (range). *Intact vs. major morbidity ($P < 0.0001$). †Major morbidity vs. stillbirth ($P = 0.002$). ‡Intact vs. stillbirth ($P < 0.0001$). §Major morbidity vs. stillbirth ($P = 0.02$). DV, ductus venosus; MCA, middle cerebral artery; PI, pulsatility index; PIV, pulsatility index for veins; UA, umbilical artery.

Table 4 Interval to delivery in intact survivors, fetuses with major morbidity and stillbirths according to type of Doppler abnormality

	Interval to delivery (days)		
Parameter	*Intact survival*	*Major morbidity*	*Stillbirth*
Increased UA-PI *Z*-score	19.5 (0–86)	15 (1–58)	21 (8–45)
Brain sparing*	9 (0–45)	7 (0–38)	19 (1–38)
UA-AREDV with positive a-wave in DV	11 (0–52)	14 (0–42)	12 (3–21)
UA-AREDV with DV-PIV < 3 SD	10 (0–45)	7 (1–33)	—
DV-PIV *Z*-score > 3 SD with normal a-wave	2 (0–49)	9 (0–45)	7 (1–18)
UV pulsation with positive a-wave in DV	1 (0–49)	7 (2–38)	7 (2–18)
DV absent/reversed a-wave†‡	0 (0–3)	0 (0–2)	6 (1–45)

Data are given as median (range). *Intact vs. stillbirth ($P = 0.02$). †Intact vs. stillbirth ($P = 0.006$). ‡Major morbidity vs. stillbirth ($P = 0.001$). AREDV, absent/reversed end-diastolic velocity; DV, ductus venosus; PI, pulsatility index; PIV, pulsatility index for veins; UA, umbilical artery.

the gestational age at delivery and Doppler *Z*-scores (for UA, MCA and DV) were used as independent variables, and individual outcome endpoints were used as dependent variables. The duration of Doppler abnormality was a significant contributor of prediction of stillbirth in patients with an elevated UA-PI *Z*-score, brain sparing and an abnormal DV Doppler result. In addition to the duration of Doppler abnormality, gestational age at delivery and elevated UA-PI *Z*-score were codeterminants in patients with an abnormal UA Doppler result (for stillbirth, $z = -$gestational age at delivery $\times 0.61$ + UA-PI *Z*-score $\times 0.11$ + interval to delivery $\times 0.07 + 13.55$; $r^2 = 0.3$). In fetuses with brain sparing, gestational age at delivery was an additional risk factor to duration of brain sparing (for stillbirth, $z = -$gestational age at delivery $\times 0.46$ + interval to delivery $\times 0.08 + 10.58$, $r^2 = 0.30$). However, if the DV a-wave was absent or reversed, the duration of this Doppler abnormality was the only contributor to stillbirth (for stillbirth, z = interval to delivery $\times 1.03 - 2.28$, $r^2 = 0.73$). In other late Doppler abnormalities, the gestational age was the only predictor of stillbirth (Table 5, Figure 2).

Elevated DV-PIV with normal a-wave and gestational age were the important predictors of major morbidity. The duration of other Doppler abnormalities did not contribute to this prediction. The gestational age at delivery was the main predictor of major morbidity for other Doppler abnormalities (Table 6, Figure 3). Gestational age at delivery, elevated DV-PIV *Z*-score and the persistence of DV Doppler index elevation were the

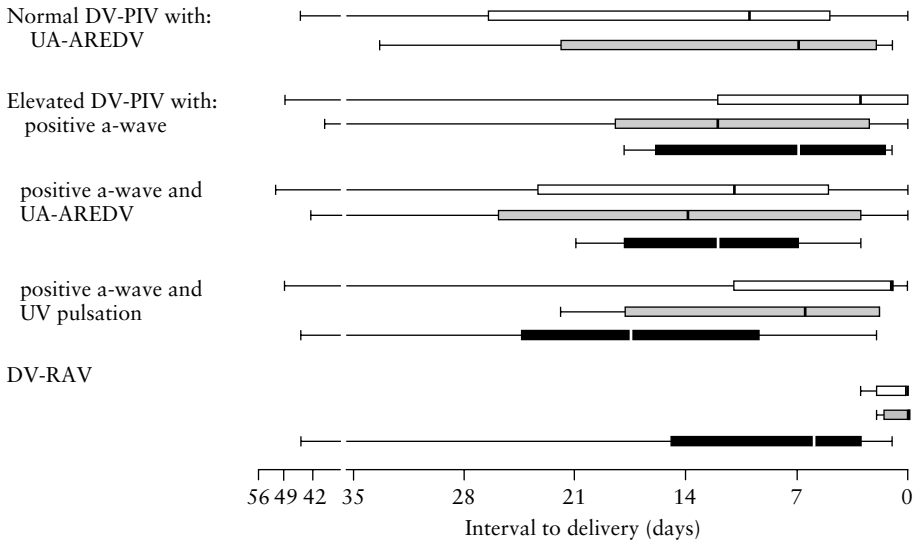

Figure 1 Duration of abnormal Doppler (median, interquartile range and range) in intact survivors (□), fetuses with major morbidity (▩) and stillborn fetuses (■) according to type of Doppler abnormality. The *x*-axis shows interval to delivery. AREDV, absent/reversed end-diastolic velocity; DV, ductus venosus; RAV, reversed/absent a-wave; UA, umbilical artery; UV, umbilical vein.

Table 5 Prediction of stillbirth for Doppler index elevation in the umbilical artery (UA), middle cerebral artery and ductus venosus (DV)

Doppler indices	*Nagelkerke* r^2	*Gestational age at delivery*		*Z-score*		*Interval to delivery*	
		OR (95% CI)	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Elevated UA-PI *Z*-score	0.36	0.54 (0.38–0.78)	0.001	1.1 (1.01–1.2)	0.023	1.07 (1.02–1.13)	0.011
Brain sparing	0.30	0.63 (0.48–0.83)	0.001		NS	1.08 (1.02–1.14)	0.007
UA-AREDV with normal DV-PIV			NS				NS
UA-AREDV with positive a-wave in DV	0.30	0.44 (0.22–0.87)	0.019				NS
DV-PIV > 3 SD with positive a-wave	0.53	0.24 (0.07–0.82)	0.023		NS		NS
UV pulsation with positive a-wave			NS				NS
DV-RAV	0.73		NS			2.79 (1.07–7.26)	0.036

AREDV, absent/reversed end-diastolic velocity; NS, not significant; OR, odds ratio; PI, pulsatility index; PIV, pulsatility index for veins; RAV, reversed/absent a-wave; UV, umbilical vein.

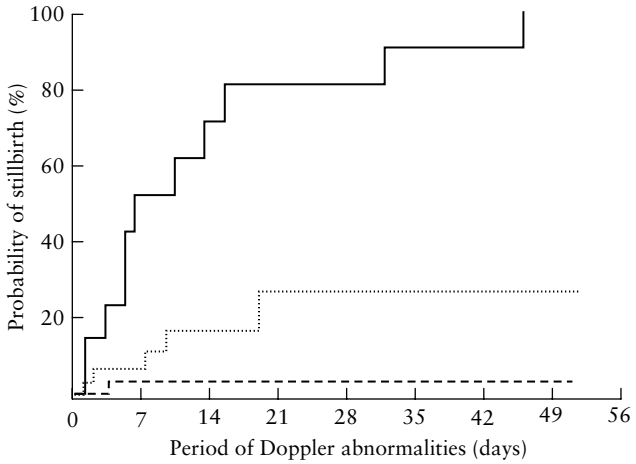

Figure 2 Probability curves for Doppler parameters in stillborn fetuses: absent/reversed a-wave in the ductus venosus (DV) (——); elevated DV pulsatility index for veins (PIV) with positive a-wave, with or without umbilical artery absent/reversed end-diastolic velocity (UA-AREDV) or umbilical vein pulsation (·····); UA-AREDV with normal DV-PIV (- - - -). The *x*-axis shows interval to delivery. The *y*-axis presents probability of stillbirth compared to when Doppler abnormality is not present.

primary contributors to intact survival. This relationship was best described by the following equation: for intact survival, z = gestational age at delivery $\times 1.26$ − DV *Z*-score $\times 1.11$ − interval to delivery $\times 0.18 - 29.16$, $r^2 = 0.66$) (Table 7, Figure 4).

Probability analysis showed that the survival curve related to the degree of elevation of UA indices was significantly different between stillbirths and patients with major morbidity ($P = 0.045$). The survival curves for DV-RAV were also statistically different between the three groups (stillbirths vs. patients with major morbidity, $P = 0.012$; stillbirths vs. intact survivors, $P < 0.0001$; and intact survivors vs. patients with major morbidity, $P = 0.022$, Figures 2–4). Because DV-RAV was the only outcome predictor independent of gestational age we performed receiver–operating characteristics curve statistics to determine the length of time that provided the best prediction of stillbirth risk. In this analysis, DV-RAV for longer than 7 days predicted stillbirth with 100% sensitivity and 80% specificity (likelihood ratio = 5.0, $P < 0.0001$, Figure 5). In contrast, neither neonatal death nor neonatal morbidity was predicted by the duration of DV-RAV.

Table 6 Prediction of major morbidity for Doppler index elevation in umbilical artery (UA), middle cerebral artery and ductus venosus (DV)

Doppler indices	*Nagelkerke* r^2	*Gestational age at delivery*		*Z-score*		*Interval to delivery*	
		OR (95% CI)	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Elevated UA-PI *Z*-score	0.31	0.64 (0.52–0.78)	< 0.0001		NS		NS
Brain sparing	0.28	0.65 (0.53–0.81)	< 0.0001		NS		NS
UA-AREDV with normal DV-PIV	0.42	0.47 (0.25–0.88)	< 0.0001				NS
UA-AREDV with positive a-wave in DV	0.29	0.59 (0.42–0.82)	0.002				NS
DV-PIV > 3 SD with positive a-wave	0.48	0.60 (0.40–0.91)	0.015	2.30 (1.31–4.06)	0.004		NS
UV pulsation with positive a-wave			NS				NS
DV-RAV			NS				NS

AREDV, absent/reversed end-diastolic velocity; NS, not significant; OR, odds ratio; PI, pulsatility index; PIV, pulsatility index for veins; RAV, reversed/absent a-wave; UV, umbilical vein.

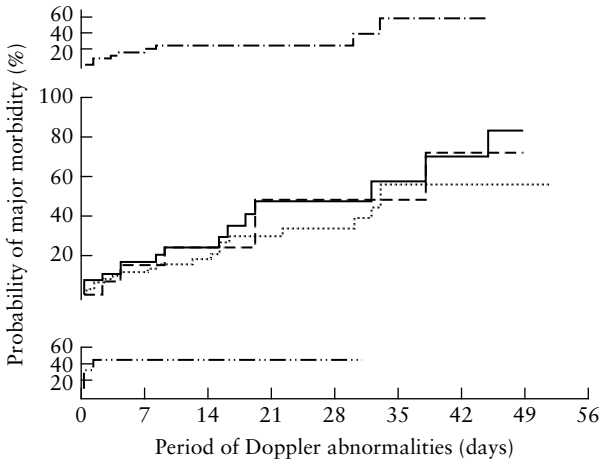

Figure 3 Probability curves for Doppler parameters in fetuses with major morbidity: absent/reversed a-wave in the ductus venosus (DV) (–··–··); elevated DV pulsatility index for veins (PIV) with positive a-wave (——), with positive a-wave and umbilical artery absent/reversed end-diastolic velocity (UA-AREDV) (·····), or with positive a-wave and umbilical vein pulsation (– – –); UA-AREDV with normal DV-PIV (–·–·). The *x*-axis shows interval to delivery. The *y*-axis presents probability of major morbidity compared to when Doppler abnormality is not present.

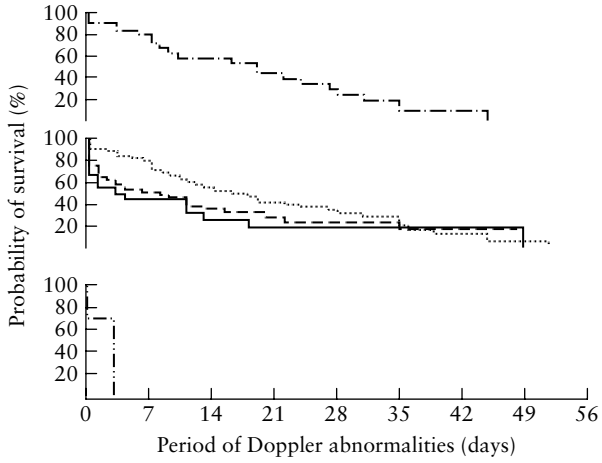

Figure 4 Probability curves for Doppler parameters in fetuses with intact survivors: absent/reversed a-wave in the ductus venosus (DV) (–··–··); elevated DV pulsatility index for veins (PIV) with positive a-wave (——), with positive a-wave and umbilical artery absent/reversed end-diastolic velocity (UA-AREDV) (·····), or with positive a-wave and umbilical vein pulsation (– – –); UA-AREDV with normal DV-PIV (–·–·). The *x*-axis shows interval to delivery. The *y*-axis presents probability of survival compared to when Doppler abnormality is not present.

DISCUSSION

In the preterm growth-restricted fetus, cross-sectional studies have been helpful in estimating the increased perinatal risks that are associated with progressive deterioration of arterial and venous Doppler parameters[1,10,11,14]. Longitudinal studies are more difficult to conduct but are essential to characterize the expected clinical pattern of progression of pregnancies complicated by FGR. A question that remains unanswered by any of these studies is whether the duration of progressive levels of cardiovascular deterioration impacts outcome. This is an important issue because it impacts how long the managing obstetrician may be willing to tolerate specific Doppler abnormalities if delay of delivery is desirable. In this study of patients with FGR caused by placental dysfunction, we evaluated the impact of the time interval of individual Doppler abnormalities on critical perinatal outcomes.

We were able to analyze a representative number of surveillance encounters in a high-risk population. In this group of patients, earlier disease onset, a greater degree of growth restriction and greater deviations of Doppler indices carry the highest risk for stillbirth. In addition we demonstrated here that the time interval between the onset of abnormal DV Doppler and delivery is the primary determinant for stillbirth and an independent predictor of neonatal morbidity. Based on the r^2 value of the regression equation we estimate that together with gestational age, persistent DV Doppler elevation contributes to over 50% of major morbidity. When a-wave velocities become absent or reversed, each day *in utero* doubles the odds of stillbirth independently of gestational age. On the other hand, advancing gestational age in patients in whom a positive DV a-wave is maintained predicts intact survival. To the best of our knowledge, this is the first study to document and provide estimates of increasing risk for adverse outcome that is specifically related to the time interval between the onset of abnormal DV Doppler and delivery.

Table 7 Prediction of intact survivors for each Doppler abnormality

Doppler indices	*Nagelkerke* r^2	*Gestational age at delivery*		*Z-score*		*Interval to delivery*	
		OR (95% CI)	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Elevated UA-PI *Z*-score	0.35	1.54 (1.28–1.86)	< 0.0001		NS		NS
Brain sparing	0.28	1.50 (1.23–1.82)	< 0.0001		NS		NS
UA-AREDV with normal DV-PIV			NS				NS
UA-AREDV with positive a-wave in DV	0.40	1.49 (1.12–1.98)	0.006				NS
DV-PIV > 3 SD with positive a-wave	0.66	3.52 (1.48–8.34)	0.004	0.33 (0.14–0.77)	0.01	0.84 (0.73–0.97)	0.015
UV pulsation with positive a-wave			NS				NS
DV-RAV			NS				NS

AREDV, absent/reversed end-diastolic velocity; NS, not significant; OR, odds ratio; PI, pulsatility index; PIV, pulsatility index for veins; RAV, reversed/absent a-wave; UV, umbilical vein.

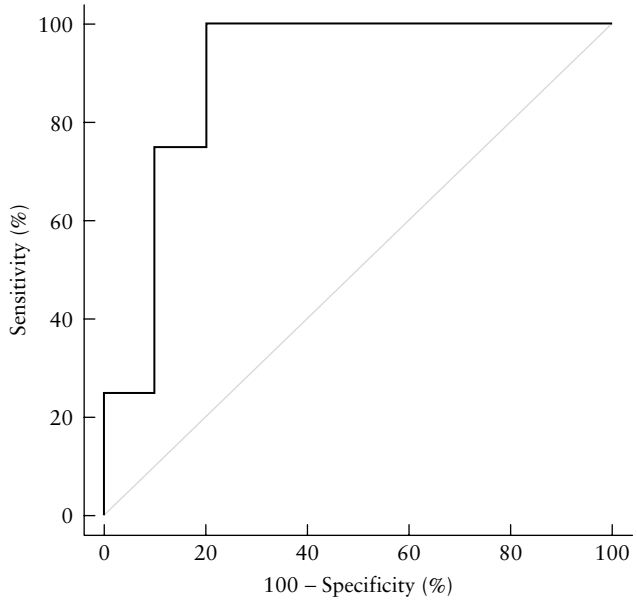

Figure 5 Receiver–operating characteristics curve for the prediction of stillbirth based on duration of reversed a-wave for > 7 days.

Our findings are consistent with several previous cross-sectional and longitudinal studies. As previously observed, progression of Doppler deterioration culminates in abnormal venous Doppler parameters. The worsening of these Doppler parameters is associated with an increased risk for adverse outcome. Despite these relationships, gestational age at delivery remained the primary determinant of neonatal outcomes. While these investigations all showed that the deterioration of venous Doppler parameters escalates fetal risks[10,13], our study examined the duration of these abnormalities. Our results suggest that there is a fundamental increase in stillbirth risk when forward velocities in the DV become absent. From this time onwards fetal survival of longer than 1 week is unlikely. This association is not observed for other Doppler abnormalities, including reversed UA end-diastolic velocity. This unique impact of the DV a-wave flow dynamics is probably a result of the associated abnormalities in central hemodynamics and metabolic derangement.

Decreasing forward flow during atrial contraction in the DV is caused by several mechanisms. Increasing placental blood-flow resistance elevates cardiac afterload and can contribute to elevated end-diastolic intracardiac pressures. Parallel elevation of UA and DV Doppler indices in deteriorating FGR pregnancies is characteristic of early-onset FGR[5,6,8,9]. Cardiac dysfunction with a decrease in ventricular contractility and compliance is a recognized feature of fetal deterioration in severe placental dysfunction[19,20]. High placental afterload and cardiac dysfunction elevate end-diastolic intraventricular pressure, which leads to decreased venous forward flow during atrial systole. Concurrently, the pressure gradient across the coronary vascular bed that is necessary to uphold myocardial perfusion decreases and myocardial oxygen balance may become critical[20,21,22]. In addition, end-stages of placental dysfunction are associated with DV dilation, resulting in increased shunting of umbilical venous blood towards the heart[23]. This deprives the liver further of nutrients and also permits enhanced retrograde transmission of atrial pressure waves. The former is associated with a significant metabolic derangement[24], while the latter is associated with deepening a-wave reversal[25]. Therefore, DV a-wave reversal is associated with concurrent preterminal endpoints of placental dysfunction that are not consistently associated with less severe blood-flow abnormalities. It is therefore plausible that the persistence of Doppler abnormalities only becomes relevant once DV a-wave velocities are absent. The time interval of 1 week observed in our study is consistent with the interval observed to biophysical deterioration[8,9]. Despite the increased risk for stillbirth, the persistence of DV a-wave abnormalities did not override the prematurity-related impact on neonatal morbidity and mortality. This finding is consistent with observations that were based on the degree of venous Doppler parameters without taking their persistence into account[5–7,11,13,14].

There are some limitations to the study design. Owing to the retrospective secondary analysis, monitoring intervals and management approaches were not standardized. Because Doppler parameters and fetal weight-gain change at different rates, we did not consider interval weight gain or estimated fetal weight as a confounding variable. This may raise a concern that because our patient population consists mainly of preterm FGR, the findings cannot be extrapolated to later-onset disease, in which the

development of abnormal venous Doppler parameters is unlikely. Despite these limitations we were able to study a sizeable patient population using a large number of surveillance tests. Doppler variables were well stratified, which allowed us to analyze the impact of independent Doppler abnormalities (such as UA only, MCA only, AREDV with normal DV and UV pulsation with normal DV). We were also able to analyze the impact of the individual categories of DV flow on outcome. Accordingly, our findings do have important implications for further research on the clinical management of pregnancies complicated by FGR.

While it has been assumed that abnormal DV Doppler is one of the vascular endpoints of early-onset FGR, our study quantifies the degree of abnormality and gives an estimate of the time interval when stillbirth is likely to occur. Although UA-AREDV and brain sparing are associated with adverse outcomes, these Doppler abnormalities may have to be tolerated in preterm FGR owing to the important impact of prematurity on outcome. Here, the monitoring intervals need to be adjusted to match the severity of the condition, to avoid unanticipated stillbirth. However, when DV atrial systolic flow becomes absent or reversed, the duration of this finding impacts outcome independently of gestational age. In this setting, preparations for delivery need to be made, as each day of this Doppler abnormality impacts outcome, and fetal survival for more than 1 week is unlikely.

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