Ultrasound Obstet Gynecol 2004; **23**: 119–125
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.965

Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction

C. M. BILARDO*, H. WOLF*, R. H. STIGTER†, Y. VILLE‡, E. BAEZ§, G. H. A. VISSER† and K. HECHER§

**Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, †Department of Obstetrics and Gynecology, University Hospital Utrecht, Utrecht, The Netherlands, ‡Department of Obstetrics and Gynaecology, St George's School of Medicine, London, UK and §Department of Prenatal Diagnosis and Therapy, AK Barmbek, Hamburg, Germany*

KEYWORDS: composite morbidity; ductus venosus Doppler; fetal monitoring; perinatal outcome; severe early growth restriction; short-term variation

ABSTRACT

Objective *To investigate whether pathological changes in the umbilical artery (UA), ductus venosus (DV) and short-term fetal heart variation are related to perinatal outcome in severe, early intrauterine growth restriction (IUGR).*

Methods *This multicenter, prospective, longitudinal, observational study was carried out in the Departments of Fetal Medicine and Obstetrics in Hamburg, Amsterdam, Utrecht and London. In 70 singleton pregnancies with IUGR fetuses, delivered at 26–33 weeks of gestation because of antepartum fetal distress, short-term variation (STV) of fetal heart rate, pulsatility index of the fetal UA (UA PI) and DV pulsatility index for veins (DV PIV) were assessed at least weekly. The final measurement was performed within 24 h of delivery. Standard cut-off levels (2 SD or 3 SD, absent flow or reversed flow) were used and new cut-off levels were calculated by means of receiver–operating characteristics analysis. Adverse outcome was defined as perinatal death, cerebral hemorrhage (≥ Grade II) or bronchopulmonary dysplasia before discharge. The predictive value for adverse outcome was calculated for different cut-off levels of the monitoring parameters, adjusted for gestational age (GA), by multivariate logistic regression analysis. Data were analyzed separately for three different time blocks, namely 8–14, 2–7 and 0–1 days before delivery.*

Results *Adverse perinatal outcome occurred in 18/70 (26%) infants. During the last 24 h before delivery DV PIV and UA PI were significantly higher and STV lower in the adverse outcome group, while 2–7 days before delivery only DV PIV was significantly higher. Adverse perinatal outcome could be predicted at 0–1 days before delivery by DV PIV at a cut-off of three multiples of the SD (odds ratio (OR) 11.3; 95% CI 2.3–57) and GA (OR 0.4; 95% CI 0.3–0.8), at 2–7 days by DV PIV at 2 SD (OR 3.0; 95% CI 0.8–12) and GA (OR 0.5; 95% CI 0.3–0.8) and at 8–14 days by DV PIV at 2 SD (OR 3.9; 95% CI 0.8–20) and GA (OR 0.5; 95% CI 0.3–0.8). Other parameters did not contribute to the multivariate model.*

Conclusions *DV PIV measurement is the best predictor of perinatal outcome. This measurement may be useful in timing the delivery of early IUGR fetuses and in improving perinatal outcome, even when delivery may be indicated at an earlier GA. However, as GA was also an important factor influencing outcome, with poorer outcome at earlier gestation at delivery, this hypothesis needs to be tested in a multicenter, prospective, randomized trial. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

In a previous report on a longitudinal observational study of intrauterine growth-restricted (IUGR) fetuses we demonstrated changes of Doppler and fetal heart rate (FHR) parameters with progressive deterioration of the fetal condition[1]. Pathological changes in short term variation (STV) of FHR and in ductus venosus (DV) flow velocity indices showed a mirror-like trend and were the last to occur and the most closely related to perinatal mortality[1]. DV changes in fetuses delivered before 32 weeks' gestation started to occur on average from 2 weeks before the clinician decided to deliver the

Correspondence to: Dr C. M. Bilardo, Department of Obstetrics and Prenatal Diagnosis H4-205, Academic Medical Center, PO Box 22700, 1100 DE Amsterdam, The Netherlands (e-mail: C.M.Bilardo@AMC.UVA.NL)

Accepted: 14 November 2003

fetus. These trends in monitoring parameters have been confirmed by other studies on longitudinal monitoring of IUGR fetuses[2,3]. In the present analysis the data from the same study were further analyzed with special emphasis on the relationship between the degree and the moment of onset of changes in umbilical artery pulsatility index (UA PI), DV pulsatility index for veins (DV PIV) and STV of FHR and perinatal outcome. The analysis was restricted to the clinically most challenging population, i.e. fetuses delivered at 26–33 weeks of gestation.

METHODS

Included were women with singleton pregnancies, admitted before 33 weeks' gestation because of fetal IUGR, defined as an abdominal circumference < 5th centile for gestational age (GA)[4], with or without pregnancy-induced hypertension. The following monitoring parameters were considered for analysis: (1) UA PI and end-diastolic flow, (2) DV PIV and flow during late diastole (a-wave) and (3) STV calculated from FHR recordings of a minimum of 40 min. The choice of restricting the analysis to these three monitoring parameters was due to the fact that FHR analysis and UA Doppler are the most frequently used monitoring parameters in clinical settings, whereas DV flow studies have shown a potential for being able to predict impending hemodynamic failure in severe and early IUGR fetuses[1–3]. Assessment of the fetal circulation by color Doppler ultrasound and calculation of PIs from blood flow velocity waveforms of the UA and DV were conducted as previously described[5,6]. FHR was analyzed by a computerized system (Oxford Sonicaid System 8002, Oxford Instruments, Abingdon, UK), which fits a baseline to the FHR trace and calculates STV as fetal pulse interval differences averaged over successive periods of 3.75 s, after exclusion of decelerations[7,8]. STV is expressed in milliseconds (ms). The time intervals between monitoring sessions were dependent on the findings of Doppler investigations and FHR recordings. If only the UA PI was > 95th centile for GA, fetal monitoring was performed weekly. In the presence of fetal blood flow redistribution, defined as a PI in the middle cerebral artery < 5th centile, monitoring sessions were scheduled at least twice weekly. If there were abnormal venous flow velocity waveforms with a PI > 95th centile for GA or a suspicious or abnormal FHR recording with a STV < 5 ms, monitoring was scheduled daily. Cases were included for analysis if the last assessment had occurred within 24 h before delivery and when at least three different monitoring sessions had taken place.

The indication for elective delivery or the decision to abstain from intervention was left to the discretion of the attending obstetrician and included considerations such as GA, estimated fetal weight and weight gain, coexisting maternal disease and parental preference. Fetal condition was evaluated by cardiotocography using both visual analysis and computer calculation of STV. STV was classified as < 3 ms, ≥ 3 ms but < 4 ms, ≥ 4 ms but less than the 5th centile, and ≥ 5th centile according to published normal ranges[9]. An STV of < 3 ms or the presence of a recurrent decelerative heart rate pattern was regarded as a high risk for metabolic acidemia or intrauterine death[7,8,10–12].

The UA was classified as showing either reversed diastolic flow, absent diastolic flow, PI > 2 SD or normal, the DV as reversed or absent flow during the a-wave, positive flow during a-wave with DV PIV > 2 SD, or within normal range. Adjustment for GA was performed according to *Z*-scores[5]. DV measurements did not influence clinical management decisions.

Data were classified in three time blocks: 8–14, 2–7 and 1–0 days before delivery. In cases of multiple measurements per period the average of the recordings was considered for the analysis, so that each fetus was included only once in each time block.

The endpoints of the study were adverse perinatal outcome, defined as antenatal death, neonatal death or major neonatal complications before discharge, the latter being defined as intracerebral hemorrhage (ICH) Grade > II according to the Papile criteria or bronchopulmonary dysplasia (BPD)[13].

The population was subdivided into two different GA groups (26–29 and 30–33 weeks). The subdivision was based on the clinical relevance of focusing separately on a more severe group of IUGR fetuses requiring delivery prior to 30 weeks' gestation and a less severe one.

Statistical analysis was performed by *t*-test or Chi-square test as appropriate. The predictive value of the different cut-off points of the monitoring parameters on adverse perinatal or neonatal outcome, adjusted for GA at measurement, was calculated by multivariate logistic regression analysis. Statistical calculations were performed with SPSS statistical software (SPSS, Chicago, IL, USA) and BMDP statistical software (BMDP, Cork, Ireland).

RESULTS

Of the 93 initially investigated fetuses, 70 met the criteria of the present analysis.

Table 1 shows the perinatal data of the study population. The population was subdivided in two groups according to the GA at delivery: 26–29 and 30–33 completed weeks, respectively. Antenatal death, neonatal death, ICH or BPD occurred in 15/33 (45%) infants delivered at 26–29 weeks and in 3/37 (8%) infants delivered at 30–33 weeks.

Table 2 shows the percentage of fetuses in the two groups with UA PI ≥ 2 SD and absent or reversed end-diastolic flow measured at 2–7 and 0–1 days of delivery. In both groups only a few fetuses had an UA PI < 2 SD before birth: 12% and 15%, respectively. These fetuses all had a DV flow within normal ranges (DV PIV < 2 SD) and had a normal outcome. UA PI at a cut-off of 2 SD did not show a significant difference between the subgroups of fetuses with normal or adverse perinatal outcome (Table 2).

Table 1 Perinatal data from the study group, subdivided for women delivered at 26–29 or 30–33 weeks' gestational age*

	GA at delivery (weeks)			
	26–29		*30–33*	
	n *(%)*	*Birth weight (g)*	n *(%)*	*Birth weight (g)*
Total	33	650 (253–1120)	37	970 (469–1700)
Normal outcome	18 (55)	728 (540–1120)†	34 (92)	970 (620–1700)
Adverse outcome	15 (45)		3 (8)	
Antepartum death	6 (18)	480 (253–630)†	—	—
Neonatal death	6 (18)	600 (480–930)	2 (5)	820 (469–1170)
ICH/BPD	3 (9)	665 (502–860)	1 (3)	990
Pre-eclampsia/HELLP syndrome	17 (52)	—	17 (46)	—
Cesarean section	27 (82)	—	36 (97)	—

*Data are presented as numbers with percentages in parentheses or as median values with ranges in parentheses. †$P < 0.05$. BPD, bronchopulmonary dysplasia; GA, gestational age; ICH, intracerebral hemorrhage > Grade II.

Table 2 Number of fetuses with umbilical artery pulsatility index ≥ 2 SD, and with absent or reversed diastolic flow in the groups delivered at 26–29 and 30–33 weeks, specified for outcome and for measurements taken 2–7 and 0–1 days before delivery*

	PI ≥ 2 SD	*Absent/reversed diastolic flow*	*Total* (n)
26–29 weeks' GA			
2–7 days before delivery			
Normal outcome	15 (94)	12 (75)	16
Neonatal death/morbidity	7 (78)	6 (67)	9
Antepartum death	5 (100)	5 (100)	5
0–1 days before delivery			
Normal outcome	15 (88)	12 (71)	18
Neonatal death/morbidity	9 (100)	8 (89)	9
Antepartum death	6 (100)	6 (100)	6
30–33 weeks' GA			
2–7 days before delivery			
Normal outcome	27 (84)	16 (47)	32
Neonatal death/morbidity	3 (100)	3 (100)	3
0–1 days before delivery			
Normal outcome	29 (85)	20 (59)	34
Neonatal death/morbidity	3 (100)	2 (67)	3

*Percentages in parentheses. GA, gestational age; PI, pulsatility index.

Table 3 reports the number of fetuses with abnormal DV PIV in the early and in the late group. In the early GA group at 2–7 days before delivery DV PIV ≥ 2 SD occurred in 11/14 (79%) fetuses with adverse perinatal outcome (missing data for one fetus) and in 6/16 (38%) fetuses with normal outcome (missing data for two fetuses). During the final day before delivery this was observed in 14/15 (93%) fetuses with adverse outcome and in 7/18 (39%) fetuses with favorable outcome. The difference between the normal and adverse outcome group was statistically significant in both time blocks (Chi-square test, $P < 0.05$). When measurements performed within 24 h of delivery were considered, only one-third of the infants (6/19) with a DV PIV ≥ 3 SD and only one-fifth (2/11) of the infants with absent or reversed flow during the a-wave had a normal outcome. In the group of fetuses delivered at 30–33 weeks no statistically significant differences in DV PIV were observed between infants with a normal or adverse outcome.

Box plots of DV PIV, UA PI and STV measured at different time blocks in fetuses with normal and adverse neonatal outcome are presented in Figures 1, 2 and 3, respectively. In the 24 h before birth DV PIV and UA PI were significantly higher in the adverse outcome group than in the normal outcome group, and STV was significantly lower. At 2–7 days before delivery of the three parameters only DV PIV was significantly higher.

Receiver–operating characteristics analysis of DV PIV for neonatal adverse outcome (mortality and morbidity, with exclusion of intrauterine death) is shown in Figure 4. At a cut-off level of 2 SD sensitivity was 83% and specificity 60%, at 3 SD 83% and 68% and at 4 SD 50%

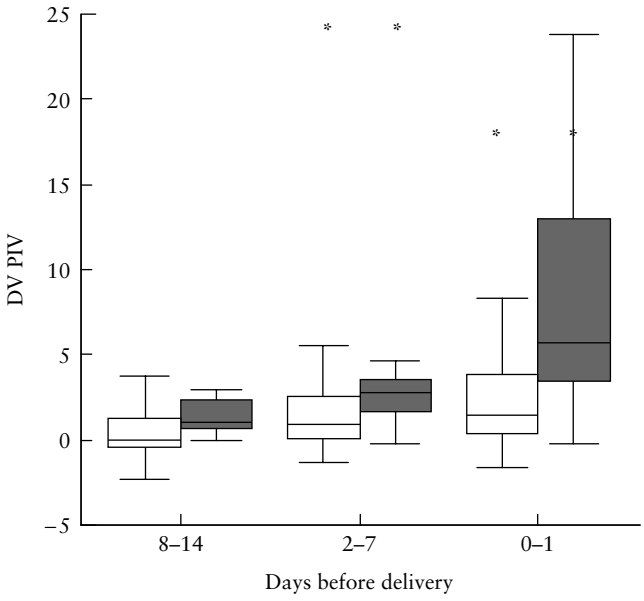

Figure 1 Box plots showing median and interquartile range of serially measured ductus venosus pulsatility index for veins (DV PIV) in fetuses with normal outcome (□) and with adverse outcome (■) in the total study group. DV PIV is expressed as multiples of the SD. *$P < 0.05$.

Table 3 Number of fetuses with ductus venosus pulsatility index ≥ 2 SD, ≥ 3 SD and with absent or reversed a-wave in the ductus venosus in the groups delivered at 26–29 and 30–33 weeks, specified for outcome and the number of days between measurement and delivery*

	PI ≥ 2 SD	*PI ≥ 3 SD*	*Absent/reversed diastolic flow*	*Total* (n)
26–29 weeks' GA				
2–7 days before delivery				
Normal outcome	6 (38)[a]	4 (25)	1 (6)	16
Neonatal death/morbidity	6 (67)	3 (33)	2 (22)	9
Antepartum death	5 (100)[a]	3 (60)	2 (40)	5
0–1 days before delivery				
Normal outcome	7 (39)[bc]	6 (33)[de]	2 (11)[f]	18
Neonatal death/morbidity	8 (89)[b]	8 (89)[d]	4 (44)	9
Antepartum death	6 (100)[c]	5 (83)[e]	5 (83)[f]	6
30–33 weeks' GA				
2–7 days before delivery				
Normal outcome	9 (27)	6 (19)	2 (6)	32
Neonatal death/morbidity	1 (33)	1 (33)	0 (–)	3
0–1 days before delivery				
Normal outcome	14 (41)	10 (29)	5 (15)	34
Neonatal death/morbidity	2 (67)	2 (67)	1 (33)	3

*Percentages or SD values in parentheses. [a–a,b–b,c–c,d–d,e–e,f–f], $P < 0.05$. GA, gestational age; PI, pulsatility index.

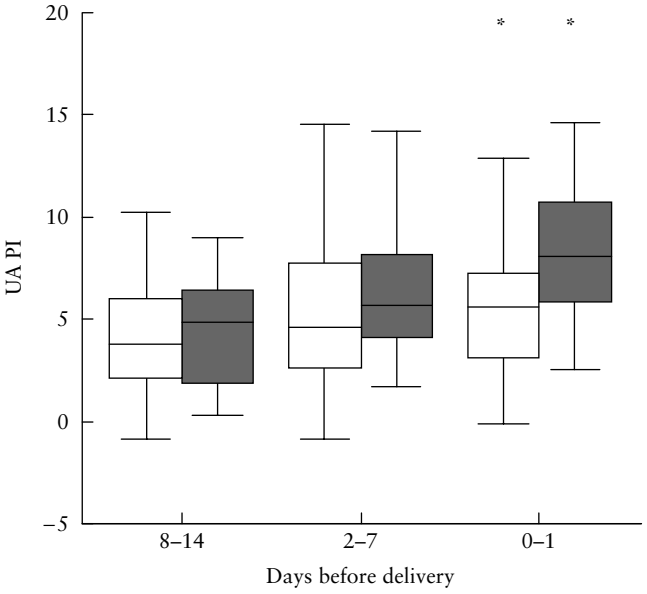

Figure 2 Box plots showing median and interquartile range of serially measured umbilical artery pulsatility index (UA PI) in fetuses with normal outcome (□) and with adverse outcome (■). UA PI is expressed as multiples of the SD. $^{*}P < 0.05$.

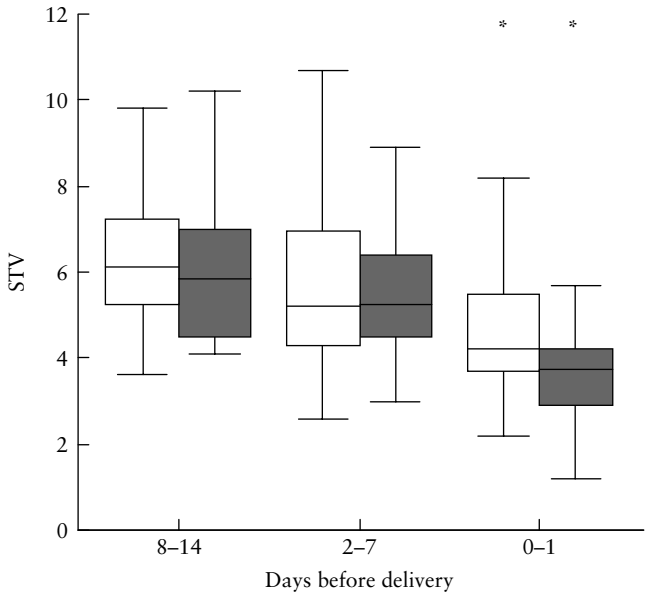

Figure 3 Box plots showing median and interquartile range of serially measured short-term variation (STV) in heart rate in fetuses with normal outcome (□) and with adverse outcome (■), expressed in milliseconds. $^{*}P < 0.05$.

and 77%. For UA PI and STV the area below the graph did not reach statistical significance (Figures 5 and 6).

Logistic regression analysis demonstrated that an abnormal DV flow profile and GA at the time of measurement were both predictive of an adverse perinatal and neonatal outcome, while UA PI and STV did not contribute to the multivariate model in any of the subgroups (Table 4).

DISCUSSION

This longitudinal study shows that in severe early IUGR abnormal DV flow is closely related to adverse perinatal outcome. In the case of a DV PIV value above 2 SD at 2–7 days before delivery the chance of an adverse outcome is increased three-fold, and when the DV PIV deteriorates to above 3 SD on the day preceding delivery the chance is increased 11-fold.

The natural course of placental insufficiency leading to severe fetal IUGR is characterized by a gradual deterioration of the fetal condition, as indicated by the progressive alterations of the biophysical profile, Doppler flow velocity waveforms and FHR variables[1–3,14]. Regarding clinical decisions at a very early GA, abnormal arterial Doppler values are tolerated in view

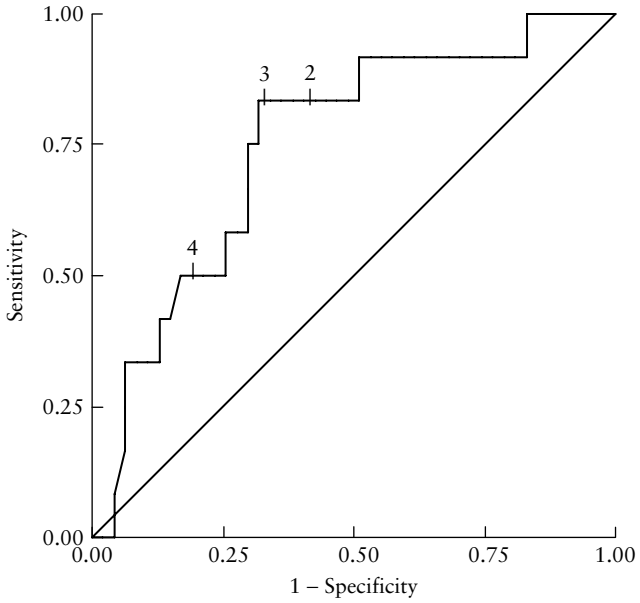

Figure 4 Receiver–operating characteristics analysis for prediction of adverse neonatal outcome by ductus venosus pulsatility index, area under the curve 0.748, $P = 0.008$. Points for a cut-off at 2 SD, 3 SD and 4 SD are inserted in the figure. At a cut-off of 3 SD, sensitivity is 83% and specificity 68%.

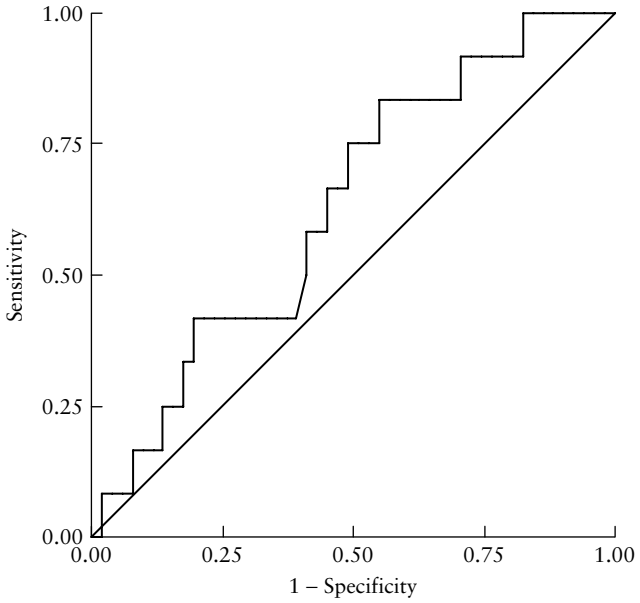

Figure 5 Receiver–operating characteristics analysis for prediction of adverse neonatal outcome by umbilical artery pulsatility index, area under the curve 0.630, $P = 0.164$.

of the high risk of neonatal complications related to very preterm delivery, despite their association with fetal hypoxemia[15,16]. These abnormalities may persist without clear deterioration for a considerable number of weeks[1–3,17]. At early GAs it is generally considered difficult to decide on the optimal timing of delivery[17,18]. Ideally, the clinician would wish to allow the pregnancy to continue in order to gain fetal maturity, just to the point before irreversible fetal damage occurs[17,18]. The GRIT trial has recently addressed the issue of optimal timing of delivery in IUGR fetuses monitored by cardiotocography and UA Doppler measurements, in circumstances where the clinician was uncertain as to whether to deliver the baby or allow the pregnancy to continue[19]. Short-term results from this study did not show a clear benefit for either option[19]. Some infants in the immediate delivery group might have benefited from a longer delay as complications of preterm birth and neonatal death occurred more often in this group. Conversely, some infants in the delayed delivery group died unexpectedly before birth. However, cardiotocography and UA velocimetry may not be the most effective tools for recognizing impending deterioration of fetal condition. The use of more sophisticated monitoring techniques, such as venous Doppler, may allow some infants to benefit from a delay of delivery in cases of normal venous flow, while those at high risk of fetal death may be delivered in a timely fashion. In view of these problems, in tertiary referral centers the standard of surveillance of the early and severely IUGR fetus is increasingly relying upon additional monitoring techniques such as computerized FHR analysis and Doppler investigation of the central venous circulation[1–3,20–22]. A decrease of

Table 4 Odds ratios with 95% confidence limits for adverse perinatal outcome (perinatal death, neonatal intracerebral hemorrhage (ICH) or bronchopulmonary dysplasia (BPD)) and for adverse neonatal outcome (neonatal death, ICH or BPD) of the parameters that contributed significantly to the predicting model as calculated by multivariate logistic regression analysis

	Days before delivery		
	0–1	*2–7*	*8–14*
Perinatal death, ICH or BPD			
DV PIV ≥ 2 SD	—	3.0 (0.8–12)	3.9 (0.8–20)
DV PIV ≥ 3 SD	11.3 (2.3–57)	—	—
GA	0.4 (0.3–0.8)	0.5 (0.3–0.8)	0.5 (0.3–0.8)
Neonatal death, ICH or BPD			
DV PIV ≥ 2 SD	—	—	—
DV PIV ≥ 3 SD	10.0 (1.7–57)	—	—
GA	0.5 (0.3–0.9)	0.5 (0.3–0.8)	0.6 (0.3–1.0)

BPD, bronchopulmonary dysplasia; ICH, intracerebral hemorrhage; GA, each gained gestational week; PI, pulsatility index.

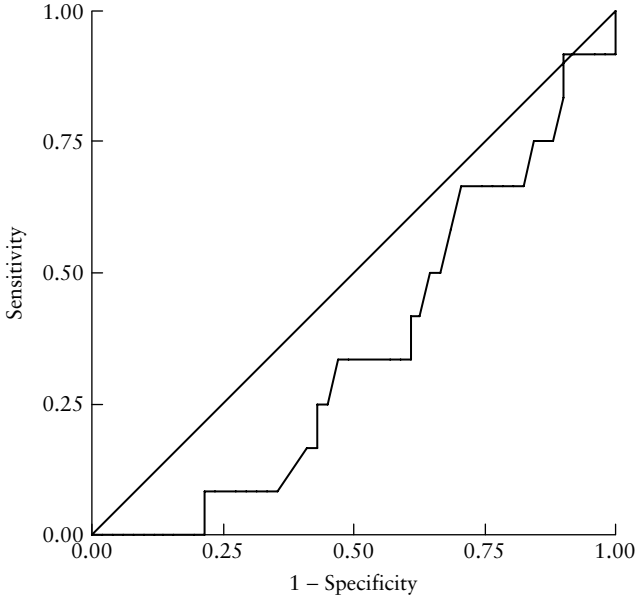

Figure 6 Receiver–operating characteristics analysis for prediction of adverse neonatal outcome by short-term variation in fetal heart rate, area under the curve 0.355, $P = 0.121$.

STV below 3 ms and an increase of DV flow velocity indices are known to occur late in the process of fetal deterioration and are related to hypoxemia, acidemia and intrauterine death[1–3,10,12,14,18,22]. However, in the case of increased DV PIV, once this becomes abnormal it is not yet known which degree of abnormality may be tolerated.

Reduction of STV may be caused by disturbance of the autonomic nervous system[23]. Interpretation of heart rate changes is sometimes difficult because other factors, such as maternal administration of steroids or anticonvulsive drugs, may also influence STV[24].

Hemodynamic failure is clinically recognized by abnormal venous Doppler waveforms, which may reflect increased pressure in the right atrium and decreased contraction force of the heart during the terminal stage of fetal malnutrition[1–3,25]. Therefore abnormal venous Doppler waveforms may represent a more reliable sign for impending multi-organ failure than FHR[17,20]. The present study shows that in the group of severely and early IUGR fetuses requiring delivery before 30 weeks' gestation, abnormal DV PIV is an ominous sign that may have a great impact on early neonatal morbidity and mortality. This hypothesis is supported by the observation that abnormal DV PIV was not only related to antenatal death, but also to adverse neonatal outcome. In all cases of intrauterine death DV PIV was ≥ 2 SD already at 2–7 days before death occurred. Moreover, DV PIV ≥ 3 SD within 24 h of delivery was the best predictor for neonatal mortality and severe morbidity. This is in agreement with the results of another study in which the perinatal mortality was the highest in the group of IUGR fetuses showing abnormal venous Doppler. In this study abnormal venous Doppler values were particularly associated with intrauterine death[22].

In contrast to other authors[26–29] we failed to find a significant relationship between absent or reversed UA end-diastolic flow and adverse fetal outcome, after adjustment for GA. The time interval between onset of reverse flow and fetal heart rate abnormalities prompting delivery varies depending on GA and concomitant maternal disease, being much shorter at later gestation and in the presence of severe pre-eclampsia[28,29]. Due to the nature of our population, absent or reversed end-diastolic flow was observed frequently and for a considerable duration of time in both adverse and normal outcome groups (Table 2) and did, therefore, not contribute to the risk assessment.

Similarly, we were unable to show a significant correlation between STV and fetal and neonatal outcome in this study. Although fetuses with poor perinatal outcome had a lower STV 0–1 days before delivery, this parameter could not discriminate between different outcome groups.

A number of contributing factors may have influenced the outcome of this longitudinal, observational study. In some patients it was decided to abstain from intervention after counseling of the parents due to the very low estimated fetal weight. In other cases concomitant maternal disease may have prompted delivery. However, in most cases the decision to deliver the infant was made because of abnormalities in the FHR pattern, such as the onset of repetitive late decelerations.

As a conclusion, from the results of this study one may speculate that infants delivered on the basis of mild FHR abnormalities, but in the presence of a normal DV PIV, might have benefited from prolongation of pregnancy, whereas the fetuses with severe DV abnormalities, such as negative or reverse flow during atrial contraction, were delivered at a stage where multi-organ damage was already irreversible. However, this is an arbitrary and retrospective categorization that has to be tested in a prospective manner. The only other significant prognostic factor for perinatal outcome was GA, showing a 50% reduction in the incidence of adverse outcome for every additional week of gestation at delivery. This emphasizes the important influence of fetal maturity on outcome in IUGR.

It is obvious that the dilemma of the optimal timing of delivery in severe, early IUGR can only be solved by a randomized trial with different management protocols. Other groups have also advocated the desirability of such a study[1–3,17]. The high rate of adverse outcome described in this study justifies a randomized trial investigating the additional value of DV PIV in planning delivery, especially at a GA below 30 weeks. Based on the present observations, a cut-off value for DV PIV of 2–3 SD seems to be most appropriate for delivery. Presently a multicenter, prospective, randomized trial with the acronym of TRUFFLE (trial of umbilical and fetal flow in Europe) is being designed.

REFERENCES

1. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackeloer BJ, Kok D, Visser GHA. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol* 2001; **18**: 564–570.
2. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. *Ultrasound Obstet Gynecol* 2001; **18**: 571–577.
3. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galan HL. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. *Ultrasound Obstet Gynecol* 2002; **19**: 140–146.
4. Snijders RJM, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
5. Harrington K, Carpenter RG, Nguyen M, Campbell S. Changes observed in Doppler studies of the fetal circulation in pregnancies complicated by pre-eclampsia or the delivery of a small-for-gestational-age baby. I. Cross-sectional analysis. *Ultrasound Obstet Gynecol* 1995; **6**: 19–28.
6. Hecher K, Campbell S, Snijders R, Nicolaides K. Reference ranges for fetal venous and atrioventricular blood flow parameters. *Ultrasound Obstet Gynecol* 1994; **4**: 381–390.
7. Street P, Dawes GS, Moulden M, Redman CWG. Short-term variation in abnormal antenatal fetal heart rate records. *Am J Obstet Gynecol* 1991; **165**: 515–523.
8. Dawes GS, Moulden M, Redman CWG. Short-term fetal heart rate variation, decelerations, and umbilical flow velocity waveforms before labor. *Obstet Gynecol* 1992; **80**: 673–678.
9. Nijhuis IJM, ten Hof J, Mulder EJH, Nijhuis JG, Narayan H, Taylor DJ, Westers P, Visser GHA. Numerical fetal heart rate analysis: nomograms, minimal duration of recording and intrafetal consistency. *Prenat Neonatal Med* 1998; **3**: 314–322.
10. Guzman ER, Vintzileos AM, Martins M, Benito C, Houlihan C, Hanley M. The efficacy of individual computer heart rate indices in detecting acidemia at birth in growth-restricted fetuses. *Obstet Gynecol* 1996; **87**: 969–974.
11. Visser GHA, Sadovsky G, Nicolaides KH. Antepartum heart rate patterns in small-for-gestational-age third-trimester fetuses: correlations with blood gas values obtained at cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 698–703.
12. Ribbert LSM, Snijders RJM, Nicolaides KH, Visser GHA. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses. *Br J Obstet Gynaecol* 1991; **98**: 820–823.
13. Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, Davies J, Hanlon-Lundberg K, Simpson L, Stone J, Wing D, Ogasawara K, Muraskas J. Single vs. weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. *JAMA* 2001; **286**: 1581–1587.
14. Visser GHA, Stigter RH. Monitoring of the growth retarded fetus (Chapter 18). In *Asphyxia and Fetal Brain Damage*, Maulik D (ed.). Wiley-Liss, Inc.: New York, NY, 1998; 333–344.
15. Bilardo CM, Nicolaides KH, Campbell S. Doppler measurement of fetal and uteroplacental circulations: relationship with umbilical venous blood gases measured at cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 115–120.
16. Pardi G, Cetin I, Marconi AM, Lanfranchi A, Bozzetti P, Ferrazzi E, Buscaglia M, Battaglia FC. Diagnostic value of blood sampling in fetuses with growth retardation. *N Engl J Med* 1993; **328**: 692–696.
17. Romero R, Kalache KD, Kadar N. Timing the delivery of the preterm severely growth-restricted fetus: venous Doppler, cardiotocography or the biophysical profile. *Ultrasound Obstet Gynecol* 2002; **19**: 118–121.
18. Visser GHA, Stigter RH, Bruinse HW. Management of the growth retarded fetus. *Eur J Obstet Gynecol Reprod Biol* 1991; **42**: S73–S78.
19. The GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG* 2003; **110**: 22–27.
20. Hecher K, Hackeloer BJ. Cardiotocogram compared to Doppler investigation of the fetal circulation in the premature growth-retarded fetus: longitudinal observations. *Ultrasound Obstet Gynecol* 1997; **9**: 152–161.
21. Senat MV, Schwärzler P, Alcais A, Ville Y. Longitudinal changes in the ductus venosus, cerebral transverse sinus and cardiotocogram in fetal growth restriction. *Ultrasound Obstet Gynecol* 2000; **16**: 19–24.
22. Baschat AA, Gembruch U, Reiss I, Gortner L, Weiner CP, Harman CR. Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction. *Ultrasound Obstet Gynecol* 2000; **16**: 407–413.
23. Malik M, Camm AJ. Components of heart rate variability – what they really mean and what we really measure. *Am J Cardiol* 1993; **72**: 821–822.
24. Derks JB, Mulder EJ, Visser GH. The effects of maternal betamethasone administration on the fetus. *Br J Obstet Gynaecol* 1995; **102**: 40–46.
25. Hecher K, Campbell S, Doyle P, Harrington K, Nicolaides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation. Arterial, intracardiac, and venous blood flow velocity studies. *Circulation* 1995; **91**: 129–138.
26. Reuwer PJHM, Sijmons EA, Rietman GW, van Tiel MWM, Bruinse HW. Intrauterine growth retardation: prediction of perinatal distress by Doppler ultrasound. *Lancet* 1987; **ii**: 415–418.
27. Bekedam DJ, Visser GHA, van der Zee AGJ, Snijders RJM, Poelmann-Weesjes G. Abnormal velocity waveforms of the umbilical artery in growth-retarded fetuses: relationship to antepartum late heart rate decelerations and outcome. *Early Hum Dev* 1990; **24**: 79–89.
28. Arduini D, Rizzo G, Romanini C. Changes of pulsatility index from fetal vessels preceding the onset of late decelerations in growth-retarded fetuses. *Obstet Gynecol* 1992; **79**: 605–610.
29. Arduini D, Rizzo G, Romanini C. The development of abnormal heart rate patterns after absent end-diastolic velocity in umbilical artery: analysis of risk factors. *Am J Obstet Gynecol* 1993; **168**: 43–50.

