Ultrasound Obstet Gynecol 2007; **30**: 750–756
Published online 10 August 2007 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.4101

Computerized fetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid–base status of growth-restricted fetuses

S. TURAN*†, O. M. TURAN*†, C. BERG‡, D. MOYANO†, A. BHIDE§, S. BOWER†, B. THILAGANATHAN§, U. GEMBRUCH‡, K. NICOLAIDES†, C. HARMAN* and A. A. BASCHAT*

**Department of Obstetrics, Gynecology and Reproductive Sciences, University of Maryland, Baltimore, MD, USA, †Harris Birthright Research Centre for Fetal Medicine, King's College Hospital and §Fetal Medicine Unit, St George's Hospital Medical School, London, UK and ‡Department of Obstetrics and Prenatal Medicine, Friedrich-Wilhelm University, Bonn, Germany*

KEYWORDS: arterial Doppler; biophysical profile scoring; computerized CTG; cord pH; fetal growth restriction; non-stress test; venous Doppler

ABSTRACT

Objective *To investigate the performance of non-stress test (NST), computerized fetal heart rate analysis (cCTG), biophysical profile scoring (BPS) and arterial and venous Doppler ultrasound investigation in the prediction of acid–base status in fetal growth restriction.*

Methods *Growth-restricted fetuses, defined by abdominal circumference $< 5^{th}$ percentile and umbilical artery (UA) pulsatility index $> 95^{th}$ percentile, were tested by NST, cCTG, BPS, and UA, middle cerebral artery (MCA), ductus venosus (DV) and umbilical vein (UV) Doppler investigation. The short-term variation (STV) of the fetal heart rate was calculated using the Oxford Sonicaid 8002 cCTG system. Relationships between antenatal test results and cord artery pH < 7.20 were investigated, using correlation, parametric and non-parametric tests.*

Results *Fifty-six of 58 patients (96.6%) received complete assessment of all variables. All were delivered by prelabor Cesarean section at a median gestational age of 30 + 6 weeks. The UA pulsatility index (PI) was negatively correlated with the cCTG STV (Pearson correlation −0.29, $P < 0.05$). The DV PI was negatively correlated with the pH (Pearson correlation −0.30, $P < 0.02$). The cCTG mean minute variation and pH were not significantly correlated (Pearson correlation 0.13, $P = 0.34$). UV pulsations identified the highest proportion of neonates with a low birth pH (9/17, 53%), the highest number of false positives among patients with an abnormal BPS, abnormal DV Doppler and a STV < 3.5 ms, and also stratified false negatives among patients with an equivocal or normal BPS. Abnormal DV Doppler correctly identified false positives among patients with an abnormal BPS. cCTG reduced the rate of an equivocal BPS from 16% to 7.1% when substituted for the traditional NST. Elevated DV Doppler index and umbilical venous pulsations predicted a low pH with 73% sensitivity and 90% specificity ($P = 0.008$).*

Conclusion *In fetal growth restriction with placental insufficiency, venous Doppler investigation provides the best prediction of acid–base status. The cCTG performs best when combined with venous Doppler or as a substitute for the traditional NST in the BPS.*

INTRODUCTION

The role of antenatal surveillance is the detection of preventable fetal damage. This includes stillbirth and deterioration of the acid–base balance, the latter being considered one of the antecedents to adverse neurodevelopment[1]. The term 'small for gestational age' describes a group of neonates with a birth weight below the 10^{th} percentile. This term does not distinguish between constitutionally small infants and growth delay due to underlying pathology. Fetuses suffering from growth restriction due to placental insufficiency (IUGR) are at risk for all of the above complications and, during progressive deterioration, show signs that can be detected in all antenatal surveillance modalities. As the timing of preterm delivery has an independent effect on outcome, identifying

Correspondence to: Dr A. A. Baschat, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Maryland, 405 West Redwood Street, Baltimore, MD 21201, USA (e-mail: aabaschat@hotmail.com)

Accepted: 23 May 2007

surveillance tests that have the highest predictive accuracy for fetal risks is a high priority[2]. The principal surveillance modalities that have evolved for this purpose are fetal heart rate analysis, biophysical profile scoring and multivessel Doppler investigation.

Antepartum fetal heart rate (FHR) monitoring in the form of the non-stress test (NST) is one of the first surveillance tests used in obstetric practice. The importance of assessing FHR control is documented by the high sensitivity to detect fetal hypoxemia. However, observer variability and the relative inability to distinguish between pathologic and physiologic variations of the fetal heart rate limit the specificity of this test[3,4]. This limited accuracy of the traditional NST, particularly in conditions such as preterm IUGR, is one of the factors that led to the development of computerized fetal heart rate analysis. The computerized cardiotocogram (cCTG) not only reduces the inconsistencies of the traditional NST but also determines fetal heart rate parameters, such as the short-term variation (STV), that cannot be visually assessed but provide a more reliable prediction of fetal acidemia[5–7].

Another approach to improving limitations of the traditional NST led to the incorporation of fetal dynamic variables (tone, movement, breathing) and fetal cardiovascular status (amniotic fluid production) into the prediction of acid–base balance. This five-component biophysical profile score provides accurate assessment of fetal acid–base balance from the early mid-trimester onwards[8]. In addition to behavioral responses, many cardiovascular manifestations have been described in IUGR. The evolution of Doppler assessment into a multivessel format incorporating arterial and venous circulations has mirrored the integrated approach utilized in the biophysical profile score. Umbilical artery Doppler allows the diagnosis of placental vascular insufficiency as a cause of growth restriction with greater precision than simple measurement of fetal size. Progressive abnormalities in the cerebral and venous circulation provide evidence of deteriorating fetal condition and acid–base status[9,10].

Previous studies have evaluated the relationship of biophysical and Doppler parameters in IUGR[7]. Doppler parameters, traditional NST and the cCTG have equally been compared with each other in observational studies[11–13]. It was our aim to concurrently evaluate all of these surveillance modalities for their ability to predict acid–base balance at birth in growth-restricted fetuses.

METHODS

We conducted a prospective, multicenter observational study of growth-restricted fetuses between 2000 and 2006. Inclusion criteria for the study were: (a) singleton fetus with normal anatomy documented on a detailed high-resolution sonogram; (b) fetal abdominal circumference $< 5^{th}$ percentile for gestational age; (c) evidence of placental insufficiency documented by an elevated umbilical artery (UA) pulsatility index (PI) by local reference ranges; (d) delivery at a viable gestational age. Exclusion criteria for final analysis were: (a) evidence of fetal infection; (b) chorioamnionitis; (c) fetal anomalies; (d) abnormal fetal karyotype; or (e) patient withdrawal from the study and/or unavailability of follow-up. The study was performed at the Center for Advanced Fetal Care at the University of Maryland, Baltimore, USA, The Harris Birthright Research Centre at King's College, London, UK, the Department for Obstetrics and Fetal Medicine at the University of Bonn, Germany, and the Fetal Medicine Unit at St George's Hospital Medical School, London, UK. The study protocol was approved by the individual institutional review boards.

All study participants underwent uniform antenatal assessment, utilizing traditional NST, cCTG and BPS after Manning *et al.*[14] and multivessel arterial and venous Doppler investigation. The testing methods, including the graded criteria for FHR reactivity, have been described in detail[3]. For the cCTG, the fetal heart rate recorded by the Sonicaid FM 7 monitor was transmitted to the analysis system through a RS 232 port (System 8002; Oxford Instruments Ltd, Medical Division, Abingdon, UK). The system reports the baseline heart rate in beats/min, number of accelerations of 10 and 15 beats/min for 15 s, number of decelerations exceeding 15 beats/min for at least 15 s, duration of episodes of high and low variation (min), and long- and short-term variation (ms). The system has been descried elsewhere[4,15,16]. In patients with normal STV and heart rate parameters, recordings were performed for at least 30 min. In patients with low STV, recordings were always performed over 1 h unless there was an indication for immediate delivery.

The traditional NST was performed over a 30-min interval. Heart rate reactivity was graded by gestational criteria and considered to be present if it fulfilled the following criteria: 24–29 weeks' gestation, two 10-beat accelerations, each sustained for 10 s; 30–36 weeks, two 15-beat accelerations, each sustained for 15 s; after 36 weeks, two 20-beat accelerations, each sustained for 20 s. The NST was considered abnormal (non-reactive) when these criteria for reactivity were not met. For the cCTG, the STV (in ms) was noted. Two methods were used for defining an abnormal STV: first, by using the 2.5^{th} percentile for gestational age as a cutoff (24–28 weeks, 4.4 ms; 28–30 weeks, 5 ms; 30–32 weeks, 5.4 ms; 32–34 weeks, 5.9 ms; > 34 weeks, 6 ms)[4,15]; second, by using a single cutoff of 3.5 ms to define abnormal[16]. For the BPS, a score of 0, 2, 4 or 6 with oligohydramnios (maximal vertical pocket < 2 cm) was defined as abnormal. A score of 6 and 8 with oligohydramnios was defined as equivocal[8]. In the umbilical artery, end-diastolic velocity was classified as either present or absent/reversed (UA-AREDV). In the middle cerebral artery, a PI > two standard deviations (2 SD) below gestational age mean was defined as brain sparing, indicating abnormally reduced cerebral blood flow resistance. The ductus venosus (DV) pulsatility index for veins (PIV)[17] was considered abnormally elevated

when > 2 SD above the gestational mean. Ductus venosus velocity during atrial systole was characterized as forward or absent/reversed (DV-RAV).

The testing intervals and delivery criteria were at the discretion of the managing obstetrician. Delivery indications in Maryland were based on the biophysical profile score. In the three European centers, patients were delivered for venous Doppler abnormalities and/or an abnormal cCTG STV.

To retain a close temporal relationship with acid–base status at birth, antenatal testing results obtained on the day of delivery were related to outcome parameters. Gestational age at delivery as well as indication and route were noted. Umbilical artery pH was obtained from a segment of cord clamped immediately at delivery. The *Z*-score for pH was used as a continuous variable for excluding the gestational age, type of anesthesia and type of delivery[18]. In concordance with several other investigators, we defined an umbilical artery pH < 7.20 as abnormal[19]. This cutoff was chosen for several reasons: first, it corresponds to the 2 SD range below the gestational mean, using many reference ranges for patients delivered in the absence of labor[18,20]; second, this value is abnormal before the onset of labor; finally, the relationship between long-term outcomes in growth-restricted fetuses has been investigated in relation to a similar cutoff. Long-term neurodevelopment and validation of other surveillance tools have been investigated using a similar cutoff[19].

The normal distribution of all Doppler measurements changes with gestational age. To account for this effect, individual measurements were normalized prior to analyses. This was done by expressing the deviation of the individual measurements from the gestational age mean in SDs; this constitutes the *Z*-scores. Relationships between cCTG, Doppler parameters and pH were analyzed using Pearson correlation. Continuous variables were compared using non-parametric or parametric analyses based on their distribution. Proportional distributions of categorical outcome variables were related to cCTG, BPS and Doppler test results, using χ^2 and Fisher's exact tests. Sensitivity, specificity, positive and negative odds ratios were calculated for each categorical value. As a sub-analysis, the BPS was recalculated, substituting the cCTG for the NST and tested similarly. The results were analyzed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant for simple comparisons. For multiple tests, an adjusted *P*-value of < 0.002 was required.

RESULTS

Fifty-eight patients met the study criteria. The predominantly nulliparous Caucasian population, with a median maternal age of 30 years, were all delivered by prelabor Cesarean section at a median gestational age of 30 + 6 weeks . The perinatal characteristics are listed in Table 1. The majority of patients ($n = 56$, 96.6%) had complete fetal assessment using all testing modalities.

Table 1 Maternal demographics, Doppler and perinatal characteristics

Characteristic	*n*	%
Maternal age (years, median (range))	30 (16–41)	
Parity		
Para 0	34	58.6
Para 1	15	25.9
Para 2	6	10.3
≥ Para 3	3	5.2
Maternal race		
Afro-American	8	13.8
Caucasian	50	86.2
cCTG short-term variation		
< 2.5th percentile	33	56.9
< 3.5 ms	15	25.9
Abnormal biophysical parameters		
Absent tone	8	13.8
Absent movement	13	22.4
Absent breathing	24	41.4
Amniotic fluid pocket < 2 cm	13	22.4
Non-reactive non-stress test	46	79.3
Biophysical profile score		
Normal	27	46.6
Equivocal	9	15.5
Abnormal	20	34.5
Abnormal Doppler parameters		
UA-AREDV	30	51.7
Brain sparing	36	62.1
Elevated DV Doppler index	21	36.2
Absent/reversed DV a-wave	3	5.2
Umbilical venous pulsations	10	17.2
Antenatal steroids		
Incomplete course	3	5.2
Completed course	43	74.1
Gestational age at delivery (weeks, median (range))	30.6 (26.0–38.0)	
Birth weight (g, median (range))	1070 (445–2100)	
Indication for delivery		
Non-reassuring biophysical profile score	16	27.6
Non-reassuring Doppler parameters	13	22.4
Non-reassuring fetal heart rate	10	17.2
Abnormal cCTG	4	6.9
Severe pre-eclampsia	7	12.1
HELLP syndrome	5	8.6
Elective Cesarean delivery	3	5.2
Cord artery pH (median (range))	7.23 (7.08–7.40)	
pH < 7.20	17	29.3
5 min Apgar < 7	8	13.8
Neonatal morbidities		
Bronchopulmonary dysplasia	10	17.2
Necrotizing enterocolitis	10	17.2
Grade III/IV intraventricular hemorrhage	3	5.2
Neonatal death	3	5.2
Intact survival	39	67.2

Data are presented as numbers and percentages of all patients or median and range where indicated. AREDV, absent or reversed end-diastolic velocity; cCTG, computerized fetal heart rate analysis; DV, ductus venosus; UA, umbilical artery.

Two fetuses received a modified BPS (maximum amniotic fluid pocket and NST only). The indications for delivery were mainly based on a non-reassuring BPS or Doppler profile (Table 1). A low cord artery pH was present in 17 (29.3%) patients and the 5-min Apgar score was < 7 in eight neonates (13.8%). Nineteen neonates (32.8%) had major morbidities and 39 survived intact (intact survival rate of 67.2%).

A non-reactive NST was the most frequent abnormal surveillance test (46 fetuses, 79.3%), while absent tone was only observed in eight fetuses (13.8%). The five-component BPS was normal in 27 fetuses (46.6%), equivocal in nine (15.5%) and abnormal in 20 (34.5%). Umbilical artery end-diastolic velocity was absent or reversed in 30 fetuses (51.7%). Brain sparing was observed in 36 (62.1%) fetuses and an elevated ductus venosus Doppler index was found in 21 fetuses (36.2%). The ductus venosus a-wave was absent in three fetuses (5.2%) and umbilical venous pulsations were observed in 10 fetuses (17.2%). The cCTG STV was below the 2.5th percentile in 33 fetuses (56.9%) and below 3.5 ms in 15 fetuses (25.9%).

Of all Doppler parameters, only the umbilical artery PI *Z*-score was negatively correlated with the cCTG STV (Pearson correlation −0.29, $P < 0.05$). Other significant correlations were observed between the umbilical artery and middle cerebral artery PI (Pearson correlation −0.38, $P = 0.004$), umbilical artery and the ductus venosus PI (Pearson correlation 0.42, $P = 0.001$). Only the ductus venosus delta PI showed a significant negative correlation with the pH *Z*-score (Pearson correlation −0.30, $P < 0.02$). The cCTG mean minute variation and pH were not significantly correlated (Pearson correlation 0.13, $P = 0.34$).

Among individual testing parameters, umbilical venous pulsations were associated with the greatest odds for a low birth pH (odds ratio 45.0, 95% CI 4.98–406.54). Seven of these 10 fetuses with umbilical venous pulsations had AREDV and nine of these abnormal ductus venosus Doppler parameters. In addition, absent movement, oligohydramnios, an elevated ductus venosus Doppler index and a STV < 3.5 ms were all significantly associated with a cord artery pH < 7.20 (Table 2). As a composite score, an abnormal five-component BPS identified 10/17 (58.8%) neonates with a cord artery pH < 7.20.

We analyzed the ability of individual testing parameters to correctly identify false positive and false negative prediction of a low birth pH, among other testing modalities. Umbilical venous pulsations correctly identified false positives among patients with an abnormal BPS, elevated ductus venosus Doppler index and a STV < 3.5 ms and consistently provided the highest odds ratios. Even in patients with a normal STV (> 3.5 ms) umbilical venous pulsations predicted the birth pH < 7.20 with an odds ratio of 41.25.

In addition, an elevated ductus venosus PI correctly stratified false positives among patients with an abnormal BPS. Umbilical venous pulsations also stratified false negatives among patients with an equivocal or normal five-component BPS (Table 3). The cCTG did not provide any risk stratification for the prediction of a low birth pH. Absent/reversed end-diastolic flow in the umbilical artery had a high false positive (46%) and false negative (35%) rate in predicting acidemia, and accordingly added little precision compared to the other tests. Substitution of the traditional NST by the cCTG more than halved the rate of an equivocal BPS when a cutoff of 3.5 ms was used to define abnormal. The rate of an equivocal BPS with a traditional NST was reduced from 9/56 (16%) to 4/56 (7.1%) with the use of the cCTG. In this patient sample, elevation of the ductus venosus Doppler index in

Table 2 Prediction of pH < 7.20 by individual antenatal testing parameters

Test	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*FPR (%)*	*FNR (%)*	*OR*	*95% CI*	P
Abnormal biophysical parameters									
Absent tone	24	90	50	73	10	76	2.69	0.59–12.4	0.23
Absent movement	41	85	54	77	15	59	3.85	1.05–14.1	0.046
Absent breathing	59	64	42	78	36	41	2.55	0.79–8.19	0.15
Amniotic fluid pocket < 2 cm	41	85	54	78	15	59	4.08	1.12–14.94	0.04
Non-reactive non-stress test	94	27	35	92	73	6	5.87	0.69–49.62	0.09
Biophysical profile score	53	74	47	78	26	47	3.26	0.99–10.76	0.07
Abnormal Doppler parameters									
UA-AREDV	65	54	37	79	46	35	2.12	0.66–6.83	0.26
Brain sparing	71	44	34	78	56	29	1.88	0.56–6.31	0.38
Elevated DV Doppler index	65	76	52	84	24	35	5.68	1.67–19.32	0.006
Absent/reversed DV a-wave	12	98	67	73	2	88	5.33	0.45–63.22	0.20
Umbilical venous pulsation	53	98	90	83	2	47	45.0	4.98–406.54	< 0.0001
cCTG short-term variation									
< 2.5th percentile	71	49	36	80	51	29	2.29	0.68–7.66	0.25
< 3.5 ms	47	83	53	79	17	53	4.32	1.23–15.11	0.025
Biophysical profile score with cCTG < 3.5 ms	47	79	50	78	21	53	3.44	1.01–11.78	0.058

AREDV, absent or reversed end-diastolic velocity; DV, ductus venosus; cCTG, computerized fetal heart rate analysis; FNR, false-negative rate; FPR, false-positive rate; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; UA, umbilical artery.

Table 3 Risk stratification by combination of fetal testing parameters in the prediction of pH

Primary test	*Additional test*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*FPR (%)*	*FNR (%)*	*OR*	*95% CI*	P
cCTG > 3.5 ms	Elevated DV Doppler index	56	79	42	87	21	44	4.82	1.02–22.84	0.088
	Umbilical venous pulsation	56	97	83	89	3	44	41.25	3.8–447.77	0.001
	Biophysical profile score	33	79	30	81	21	67	1.86	0.37–9.36	0.66
cCTG < 3.5 ms	Elevated DV Doppler index	75	57	67	67	43	25	4.00	0.45–35.79	0.32
	Umbilical venous pulsation	50	100	100	64	0	50	—	—	0.077
	Biophysical profile score	75	50	67	60	50	25	3	0.31–28.84	0.58
Normal/equivocal BPS	Elevated DV Doppler index	50	79	40	85	21	50	3.83	0.74–19.99	0.17
	Umbilical venous pulsation	50	97	80	88	3	50	28	2.47–317.68	0.005
	cCTG < 3.5 ms	25	90	40	81	10	75	2.89	0.39–21.29	0.29
Abnormal BPS	Elevated DV Doppler index	78	80	78	80	20	22	14	1.54–127.23	0.023
	Umbilical venous pulsation	56	100	100	71	0	44	—	—	0.011
	cCTG < 3.5 ms	67	70	67	70	30	33	4.67	0.67–32.36	0.18
Normal DV Doppler index	Umbilical venous pulsation	17	100	100	86	0	83	—	—	0.16
	Biophysical profile score	33	74	20	85	26	67	1.44	0.22–9.41	0.65
	cCTG < 3.5 ms	33	87	33	87	13	67	3.38	0.46–24.84	0.25
Abnormal DV Doppler index	Umbilical venous pulsation	73	90	89	75	10	27	24	2.06–279.62	0.008
	Biophysical profile score	64	75	78	60	25	36	5.25	0.7–39.48	0.17
	cCTG < 3.5 ms	55	70	67	58	30	45	2.8	0.46–16.93	0.39
Constant umbilical vein flow	Elevated DV Doppler index	38	78	25	86	23	63	2.07	0.41–10.36	0.39
	Biophysical profile score	50	74	29	88	26	50	2.8	0.59–13.36	0.22
	cCTG < 3.5 ms	50	83	36	89	18	50	4.71	0.94–23.54	0.068
Pulsatile umbilical vein	Elevated DV Doppler index	89	0	89	0	100	11	—	—	1.0
	Biophysical profile score	56	100	100	20	0	44	—	—	1.0
	cCTG < 3.5 ms	44	100	100	17	0	56	—	—	1.0

BPS, biophysical profile scoring; cCTG, computerized fetal heart rate analysis; CI, confidence interval; DV, ductus venosus; FNR, false-negative rate; FPR, false-positive rate; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

association with umbilical venous pulsations predicted a low pH with 73% sensitivity and 90% specificity (odds ratio 24, 95% CI, 2.06–279.62; Table 3).

DISCUSSION

Placental dysfunction as a cause of growth delay predisposes the fetus to progressive deterioration of acid–base balance, irreversible compromise of organ function and stillbirth. The antepartum quantification of these fetal risks and the consideration of concurrent neonatal risks if the fetus is delivered is a fundamental prerequisite for the timing of interventions such as delivery. The accuracy of fetal well-being tests is affected by gestational age, maternal condition or concurrent treatment. Moreover, fetal deterioration may have variable manifestations, even using computerized cCTG analysis[21]. Refining our ability to assess fetal status remains highly relevant for the management of IUGR pregnancies, since inappropriate delay of interventions carries the price of an increased stillbirth rate, while intervening too soon raises risks for prematurity, neonatal morbidity, mortality and neurodevelopmental delay[22]. In this observational study, we analyzed the interaction of concurrent non-stress testing, computerized fetal heart rate analysis, and biophysical and Doppler assessment in the prediction of acid–base status at birth in growth-restricted fetuses with placental insufficiency.

We studied a selected population of fetuses with severe placental insufficiency, as indicated by the high rate of advanced Doppler abnormalities, the preterm gestational age at delivery and the incidence of major morbidities and/or neonatal death. In this group of fetuses, abnormal ductus venosus waveforms and umbilical venous pulsations provided the strongest prediction of low birth pH (< 7.20). As illustrated by the BPS, all testing modalities performed best when used in combination. The substitution of the cCTG for the traditional NST improved the performance of the BPS by reducing the high incidence of equivocal scores. However, it was the combination of umbilical venous pulsations with abnormalities in other testing modalities that provided the overall best prediction of a low birth pH. By clarifying these associations, this study further challenges recent skepticism about the role of venous Doppler surveillance in IUGR[23].

One of the factors that affect the performance of fetal surveillance tests is their ability to distinguish normal and abnormal variations in fetal behavior. In the context of IUGR, the high prevalence of a non-reactive NST and STV below the 2.5th percentile has at least two explanations. On the one hand, it could reflect a deterioration of the fetal condition, with progressive placental insufficiency. Administration of betamethasone in anticipation of delivery may have been a contributor[24]. On the other hand, it may simply represent the typical developmental pattern of fetal heart rate control in IUGR. Both Nijhuis *et al.* and Smith and co-workers have demonstrated higher baseline fetal heart rates, decreased variability and variation and a delayed development of reactivity in growth-restricted fetuses without any evidence of

compromise as defined by acidemia or stillbirth[25,26]. Chronic hypoxemia and/or delayed development of fetal heart rate control have been suggested as possible explanations. Therefore, visual NST analysis and the 2.5th percentile for the STV are inappropriate cutoffs in growth-restricted fetuses, since they include many non-compromised fetuses that exhibit these heart rate patterns as part of their developmental status. Although a STV < 3.5 ms is a better cutoff to use, it performs similarly to the traditional NST. The rate of acidemic neonates does not change in relation to this cutoff. However, almost 80% of neonates with STV > 3.5 ms are not acidemic at birth. This proportion drops to 46% when this threshold is crossed but is mostly confined to fetuses that have deteriorating venous Dopplers. These observations suggest that the fetal heart rate analysis correlates more closely with chronic hypoxemia than with its progression to deepening acidemia.

When evaluation of fetal biophysical parameters is added to fetal heart rate analysis, the prediction of low birth pH is improved. This has been shown in many prior studies and is due to the improved definition of abnormal fetal behavior using multiple parameters. In the context of placental insufficiency, the BPS has several drawbacks. The high rate of a non-reactive NST contributes to frequent equivocal results, which require frequent repeat testing. This could be effectively addressed by incorporating the cCTG into biophysical profile scoring. In the context of placental insufficiency, biophysical profile scoring provides limited prediction of longitudinal progression, which also requires high-frequency testing to minimize the risk of missing progression of fetal disease. Integration of biophysical and Doppler parameters can circumvent this limitation[27]. As shown previously in a larger patient sample, prediction of acid–base balance was most accurate when biophysical and ductus venosus Doppler parameters were abnormal[28].

Despite the high prevalence of venous abnormalities, mostly explained by the severity of placental insufficiency studied, abnormal ductus venosus and umbilical vein waveforms provided strong evidence of a low birth pH. In contrast to fetal heart rate reactivity, venous Doppler parameters consistently become abnormal in advancing placental disease and are therefore associated with progressive acid–base disturbance[10]. Hecher *et al.* reported that persistent abnormalities in the cCTG preceded the occurrence of an abnormal ductus venosus in 52% and simultaneous abnormalities were detected in 5.5%[29]. Similar data were published by Ferrazzi *et al.*[9], who observed that over 50% of fetuses delivered for abnormal fetal heart rate patterns did not have venous Doppler abnormalities. Both explanations can result in a high prevalence of non-reactive NST or a low STV by population-based cutoffs in an IUGR population. Our results support that these fetal heart rate parameters, if used in isolation, do not have sufficient precision to accurately predict fetal status. This association is also reflected in the ability of venous Doppler parameters to stratify the risk for stillbirth, acidemia and perinatal mortality[30]. Bilardo *et al.* studied 70 IUGR pregnancies using UA, ductus venosus Doppler and cCTG STV. They were not able to show a significant correlation between STV and neonatal outcome. In their study the ductus venosus pulsatility index was identified as the best outcome predictor[11]. Our study supports these findings and indicates that the additional presence of umbilical venous pulsations provide even stronger evidence for abnormal acid–base status.

In the clinical management of pregnancies complicated by fetal growth restriction, antenatal surveillance has to fulfill several requirements. The spectrum of fetal manifestation needs to be accurately represented across all gestational ages. The impact of medical management, such as steroid or magnesium administration, should not significantly affect the test accuracy. As IUGR deterioration is manifested in all testing modalities, they all have a potential place in the management[3,6,9–10,19,26]. As one of the traditional testing tools, the NST provides insufficient monitoring. A reactive NST is reassuring. However, a non-reactive test does not predict acidemia, neither does it provide a means for longitudinal monitoring when the assessment of fetal well-being is based on the binary assignment of 'reactive' and 'non-reactive'. The numerical analysis of STV provides a means for objective trend analysis. However, while the cCTG as a stand-alone test does provide this longitudinal monitoring, it appears to have similar limitations in the prediction of acidemia as the NST. A principal difference in fetal heart rate control in growth-restricted fetuses, as well as differential sensitivity to hypoxemia, appears a plausible explanation. Therefore, if acidemia is to be predicted, fetal heart rate monitoring in any form requires the addition of biophysical and/or multivessel Doppler parameters for accurate prediction of acid–base balance. If it is the goal to intervene prior to the development of acidemia, individual investigation of the cCTG makes sense. Identifying which monitoring and management approach results in the best outcome cannot be determined by this observational study and requires randomized comparison of management. In this context, fetal heart rate analysis of any form is likely to be most effective as a complementary rather than a stand-alone surveillance test.

CONCLUSION

Growth-restricted fetuses with placental insufficiency require antenatal testing using multiple surveillance modalities to enhance prediction of birth pH. The incorporation of venous Doppler achieves the best prediction of acidemia. While computerized analysis enhances fetal heart rate assessment, it has limitations as a stand-alone test in fetal growth restriction. The cCTG performs best when combined with venous Doppler or as a substitute for the traditional NST in the biophysical profile score.

REFERENCES

1. Soothill PW, Ajayi RA, Campbell S, Ross EM, Candy DC, Snijders RM, Nicolaides KH. Relationship between fetal acidemia at cordocentesis and subsequent neurodevelopment. *Ultrasound Obstet Gynecol* 1992; **2**: 80–83.
2. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Müller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early-onset placental dysfunction. *Obstet Gynecol* 2007; **109**: 253–261.
3. Baschat AA, Galan H, Bhide A, Berg C, Kush ML, Oepkes D, Thilaganathan B, Gembruch U, Harman CR. Doppler and biophysical assessment in growth restricted fetuses: distribution of test results. *Ultrasound Obstet Gynecol* 2006; **27**: 41–47.
4. Pardey J, Moulden M, Redman CW. A computer system for the numerical analysis of nonstress tests. *Am J Obstet Gynecol* 2002; **186**: 1095–1103.
5. Todros T, Preve CU, Plazzotta C, Biolcati M, Lombardo P. Fetal heart rate tracings: observers versus computer assessment. *Eur J Obstet Gynecol Reprod Biol* 1996; **68**: 83–86.
6. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. 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.
7. Smith JH, Anand KJ, Cotes PM, Dawes GS, Harkness RA, Howlett TA, Rees LH, Redman CW. Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. *Br J Obstet Gynaecol* 1988; **95**: 980–989.
8. Manning FA, Snijders R, Harman CR, Nicolaides K, Menticoglou S, Morrison I. Fetal biophysical profile score. VI. Correlation with antepartum umbilical venous fetal pH. *Am J Obstet Gynecol* 1993; **169**: 755–763.
9. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galan HL. Temporal sequence of abnormal Doppler changes in peripheral and central circulatory systems of the severely growth restricted fetuses. *Ultrasound Obstet Gynecol* 2002; **19**: 140–146.
10. 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.
11. Bilardo CM, Wolf H, Stigter RH, Ville Y, Baez E, Visser GHA, Hecher K. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2004; **23**: 119–125.
12. Guzman ER, Vintzileos AM, Martins M, Hanley 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.
13. Marshall C. The nipple stimulation contraction stress test. *J Obstet Gynecol Neonatal Nurs* 1986; **15**: 459–462.
14. Manning FA. Fetal biophysical profile: a critical appraisal. *Clin Obstet Gynecol* 2002; **45**: 975–985.
15. Street P, Dawes GS, Moulden M, Redman CW. Short term variation in abnormal antenatal fetal heart rate records. *Am J Obstet Gynecol* 1991; **165**: 515–523.
16. Guzman ER, Conley M, Stewart R, Ivan J, Pitter M, Kappy K. Phenytoin and magnesium sulfate effects on fetal heart rate tracings assessed by computer analysis. *Obstet Gynecol* 1993; **82**: 375–379.
17. 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.
18. Gregg AR, Weiner CP. 'Normal' umbilical arterial and venous acid–base and blood gas values. *Clin Obstet Gynecol* 1993; **36**: 24–32.
19. Baschat AA, Guclu S, Kush M, Gembruch U, Weiner CP, Harman CR. Venous Doppler in the prediction of acid–base status of growth-restricted fetuses with elevated placental blood flow resistance. *Am J Obstet Gynecol* 2004; **191**: 277–284.
20. Eskes TK, Jongsma HW, Houx PC. Percentiles for gas values in human umbilical cord blood. *Eur J Obstet Gynaecol Reprod Biol* 1983; **14**: 341–346.
21. 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.
22. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M, GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. *Lancet* 2004; **364**: 513–520.
23. Ghidini A. Doppler of the ductus venosus in severe preterm fetal growth restriction: a test in search of a purpose? *Obstet Gynecol* 2007; **10**: 250–252.
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. Nijhuis IJ, ten Hof J, Mulder EJ, Nijhuis JG, Narayan H, Taylor DJ, Visser GH. Fetal heart rate in relation to its variation in normal and growth-retarded fetuses. *Eur J Obstet Gynecol Reprod Biol* 2000; **89**: 27–33.
26. Smith JH, Dawes GS, Redman CW. Low human fetal heart rate variation in normal pregnancy. *Br J Obstet Gynaecol* 1987; **94**: 656–664.
27. Baschat AA. Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters. *Ultrasound Obstet Gynecol* 2003; **21**: 1–8.
28. Baschat AA, Galan HL, Bhide A, Berg C, Kush ML, Oepkes D, Thilaganathan B, Gembruch U, Harman CR. Doppler and biophysical assessment in growth-restricted fetuses: distribution of test results. *Ultrasound Obstet Gynecol* 2006; **27**: 41–47.
29. Hecher K, Bilardo CM, Strigter RH, Ville Y, Hackeloer BJ, Kok HJ, Senat MV, Visser GHA. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol* 2001; **18**: 564–570.
30. Baschat AA. Doppler application in the delivery timing of the preterm growth-restricted fetus: another step in the right direction. *Ultrasound Obstet Gynecol* 2004; **23**: 111–118.

