

# Doppler and biophysical assessment in growth restricted fetuses: distribution of test results

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**KEYWORDS:** biophysical profile; Doppler; integrated fetal testing; IUGR; test results

## ABSTRACT

**Objective** Multi-vessel Doppler ultrasonography and biophysical profile scoring (BPS) are used in the surveillance of growth restricted fetuses (IUGR). The interpretation of both tests performed concurrently may be complex. This study examines the relationship between Doppler ultrasonography and biophysical test results in IUGR fetuses.

**Methods** Three hundred and twenty-eight IUGR fetuses (abdominal circumference < 5th percentile, elevated umbilical artery (UA) pulsatility index (PI)) had concurrent surveillance with UA, middle cerebral artery (MCA) and ductus venosus (DV) Doppler ultrasonography and BPS (fetal tone, movement, breathing, maximal amniotic fluid pocket and fetal heart rate). Patients were stratified into three groups according to their Doppler examination: (1) abnormal UA alone; (2) brain sparing (MCA-PI > 2 SD below mean for gestational age); and (3) abnormal DV (PI > 2 SD above the mean for gestational age) and BPS groups: (1) normal (> 6/10); (2) equivocal (6/10); and (3) abnormal (< 6/10). Predictions of short-term perinatal outcomes by both modalities were compared for stratification. The distribution and concordance of Doppler and BPS test results were examined for the whole patient group and based on delivery prior to 32 weeks' gestation.

**Results** Abnormal UA Doppler results alone were observed in 109 fetuses (33.2%), brain sparing in 87 (26.5%) and an abnormal DV in 132 (40.2%). The BPS was normal in 158 (48.2%), equivocal in 68 (20.7%) and abnormal in 102 (31.1%). Both testing modalities

stratified patients into groups with comparable acid–base disturbance and perinatal outcome. Of the nine possible test combinations the largest subgroups were: abnormal UA alone/normal BPS (n = 69; 21%) and abnormal DV Doppler/abnormal BPS (n = 62; 18.9%). Assessment of compromise by both testing modalities was concordant in 146 (44.5%) cases. In 182 fetuses with discordant results the BPS grade was better in 115 (63.2%,  $P < 0.0001$ ). Marked disagreement of test abnormality was present in 57 (17.4%) fetuses. Of these, abnormal venous Doppler in the presence of a normal BPS constituted the largest group (Chi-square  $P < 0.002$ ). Stratification was not significantly different in patients delivered prior to 32 weeks' gestation.

**Conclusion** Doppler ultrasonography and BPS effectively stratify IUGR fetuses into risk categories, but Doppler and BPS results do not show a consistent relationship with each other. Since fetal deterioration appears to be independently reflected in these two testing modalities further research is warranted to investigate how they are best combined. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

## INTRODUCTION

Doppler ultrasonography and biophysical profile scoring (BPS) are the principal surveillance tools in pregnancies complicated by placental vascular insufficiency and fetal growth restriction (IUGR). These antenatal testing modalities aim to detect fetal compromise by evaluating fetal manifestations of altered oxygenation and metabolic

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status. Fetal cardiovascular responses are a prominent feature of this form of growth restriction and their assessment reflects disease severity. As placental blood flow resistance worsens, changes in descending aortic and cerebral blood flow resistance are observed in the compensated state. Finally deteriorations in venous Doppler parameters are observed that reflect alterations in cardiac forward function in response to advanced placental insufficiency<sup>1,2</sup>. Multi-vessel Doppler examination is able to accurately depict this progression in IUGR fetuses. Dynamic fetal variables (movement, tone, breathing, heart rate reactivity and amniotic fluid volume) utilized for BPS remain normal longer in the progression of IUGR fetuses<sup>3</sup>. With progressive fetal compromise reduction of global fetal activity is followed by a decline in fetal heart rate reactivity and fetal breathing movement and amniotic fluid volume<sup>4,5</sup>. Finally, fetal tone and movement are lost in response to worsening acidemia<sup>6</sup>. The BPS provides a good correlation with fetal acid–base status throughout the second half of pregnancy<sup>7</sup>.

Previous studies clearly show that cardiovascular and biophysical responses in IUGR fetuses both relate to fetal status. To determine which combination of antenatal tests provides the best reflection of fetal status, it is first necessary to assess the relationship between test results in these principal modalities. If deteriorations in both Doppler and biophysical parameters are closely related then test results should be concordant in the majority of cases. On the other hand, if deterioration in cardiovascular and behavioral status occurs independently of each other a certain degree of disagreement between the test results is to be expected. It was the aim of this study to determine the distribution and relationship of Doppler and BPS test results in a population of IUGR fetuses with placental insufficiency.

## PATIENTS AND METHODS

This report is part of a prospective, multicenter, observational study conducted at academic perinatal centers that investigates relationships between antenatal testing parameters and outcome in IUGR fetuses. Criteria for study eligibility are:

- Singleton fetus with normal fetal anatomy documented on a detailed high-resolution sonogram.
- Fetal abdominal circumference < 5<sup>th</sup> percentile for gestational age.
- Evidence of placental insufficiency documented by an elevated umbilical artery pulsatility index (UA-PI) by local reference ranges.
- Delivery at a viable gestational age.

Patients who give written consent to participate in the study undergo a uniform antenatal assessment protocol that includes umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV) Doppler ultrasound studies as well as a five-component biophysical profile score. Detailed instructions standardizing the examination

technique of all study parameters have been sent to all participating study centers. The results of the last antenatal assessment prior to delivery are used for the final analysis in consecutively submitted pregnancies fulfilling the inclusion criteria. Exclusion criteria for the final analysis are:

- evidence of fetal infection
- chorioamnionitis
- fetal anomalies
- abnormal fetal karyotype
- patient withdrawal from the study and/or unavailability for follow-up.

The study protocol was approved by the institutional review board.

## Doppler and biophysical profile scoring

Ultrasound equipment capable of high-resolution grayscale, pulsed-wave and color-Doppler modes with 4-, 5- or 8-MHz sector probes was used. Pulsed-wave Doppler measurements of the UA, MCA and DV were obtained as previously described using the pulsatility index (PI) to quantify arterial Doppler waveforms and the PI for veins or the systolic:a-wave ratio to quantify the DV waveform<sup>1–3,8</sup>. In the UA absence or reversal of end-diastolic velocities (UA-A/REDV) was noted. In the DV absence or reversal of atrial systolic velocity was assessed. All fetuses had an elevated UA-PI as part of their entry criteria. An MCA-PI greater than 2 standard deviations (SD) below the mean for gestational age was considered as evidence of ‘brain sparing’<sup>9</sup>. A DV Doppler index elevation greater than 2 SD above the mean for gestational age was considered elevated.

A full five-component BPS after Manning<sup>10</sup> was performed during the fetal assessment. Fetal breathing movements sustained for 30 s or more, presence of at least three body/limb movements and at least one vigorous flexion/extension episode of the limbs each yielded 2 points. A maximum vertical amniotic fluid pocket above 2 cm yielded 2 points. Heart rate reactivity was graded by gestational criteria and considered to be present if it fulfilled the following criteria: between 24 and 29 weeks’ gestation, two 10-beat accelerations, each sustained for 10 s; between 30 and 36 weeks’ gestation, two 15-beat accelerations, each sustained for 15 s; after 36 weeks’ gestation, two 20-beat accelerations, each sustained for 20 s. Two points were given if these criteria were met. No points were given for any components if these cut-offs were not met in a 30-min period. When the score was 4 (without oligohydramnios), the testing was immediately extended. When the score was 6, a repeat examination was performed within 12 h. The last test result was used in the analysis.

## Outcome variables and data analysis

Based on the degree of Doppler abnormality we defined three Doppler groups. Group 1 had abnormal UA Doppler

alone. Group 2 had abnormal UA Doppler velocities plus 'brain sparing' but normal venous Doppler. Group 3 had an elevated DV Doppler index. These definitions were based on prior studies that showed significant differences in outcome if IUGR fetuses are stratified in this way<sup>1,2,11</sup>. Biophysical profile scores of 4 or less (6 or less with oligohydramnios) were defined as abnormal. Scores of 8 and 10 (without oligohydramnios) were considered normal, while a score of 6 (8 with oligohydramnios) was defined as equivocal.

At delivery gestational age, indication and route of delivery and Apgar scores assigned by the attending pediatric team were noted. A 5-min Apgar score less than 7 was considered abnormal. Umbilical arterial pH was obtained from a segment of cord clamped immediately at delivery. In concordance with several other investigators we defined an umbilical artery pH < 7.20 as abnormal. The stillbirth, neonatal mortality and perinatal mortality (stillbirth + neonatal mortality) rates were computed.

Proportional distributions of categorical outcome variables were related to Doppler and BPS test results using Chi-square and Fisher's exact tests. Continuous variables were compared using non-parametric or parametric analyses based on their distribution. Results were analyzed with SPSS 10.0 (SPSS Inc., Chicago IL, USA). A *P*-value < 0.05 was considered statistically significant.

## RESULTS

Three hundred and twenty-eight patients agreed to participate in the study. In this predominantly Caucasian population (*n* = 252; 76.8%) with a median maternal age of 29 (range 14–45) years the majority of women were nulliparous (*n* = 238; 72.6%). Chronic and/or pregnancy-induced hypertension was the most common medical condition, observed in 61 women (18.6%). The last examination was performed on the day of delivery in the majority of patients (range 0–3.2 days). UA end-diastolic velocity was present in 195 fetuses (59.5%), absent in 45 (13.7%) and reversed in 88 (26.8%). Brain sparing was observed in over half of the fetuses (*n* = 180; 54.9%). An elevated DV index was measured in 132 fetuses (40.2%). The BPS was 8 or better in 158 fetuses (48.2%). Five fetuses had a score of 8 with oligohydramnios. A score of 6 with normal fluid was given in 63 fetuses (19.2%) and a score of 6 with oligohydramnios in 16 (4.9%). The remaining 86 (26.2%) fetuses had a score of 4 or less. Most (259) were delivered by Cesarean section, predominantly for fetal indications (198/259; 76.4%). The perinatal variables are listed in Table 1.

Based on our assignment of Doppler categories 109 fetuses had an abnormal UA Doppler test only (33.2%), 87 had brain sparing (26.5%) while the largest Doppler group was that with abnormal DV Doppler velocimetry (*n* = 132; 40.2%). As shown in Table 2, the proportions of fetuses with umbilical artery A/REDV increased across the groups in this order. The largest proportion of

**Table 1** Demographics and obstetric outcomes of 328 patients. Percentages are given as percent of total number of patients (328) or the number of live births (304) in the cases of 'delivery indications' and 'Apgar score'

Characteristic	n (%)	Mean or median (SD or range)
Maternal age (years)		29 (14–45)
Maternal race		
Caucasian	252 (76.8)	
African-American	65 (19.8)	
Hispanic	7 (2.1)	
Asian	4 (1.2)	
Total	328 (100)	
Gestational age at delivery (weeks)		31 + 4 (24 + 0 to 41 + 2)
Birth weight (g)		1090 (360–2720)
Mode of delivery (304 live births)		
Spontaneous vaginal	44 (13.4)	
Operative vaginal	1 (0.3)	
Cesarean section	259 (79.0)	
Total live births	304 (92.7)	
Stillbirths	24 (7.3)	
Delivery indications (304 live births)		
Non-reassuring FHR	96 (31.6)	
Non-reassuring Doppler	34 (11.2)	
Non-reassuring BPS	13 (4.3)	
Non-reassuring Doppler & BPS	12 (3.9)	
Oligohydramnios	2 (0.7)	
Pre-eclampsia/eclampsia/HELLP	48 (15.8)	
Placental abruption	6 (2.0)	
Fetal distress/intolerance to labor	27 (8.9)	
Miscellaneous	66 (21.7)	
5-min Apgar score < 7	19 (6.3)	
Cord artery blood gas		
pH		7.25 (± 0.09)
pO <sub>2</sub> (mmHg)		18.6 (± 13.9)
pCO <sub>2</sub> (mmHg)		52.7 (± 10.9)
HCO <sub>3</sub> (mmol/L)		22.1 (± 3.4)
Base excess (mmol/L)		−4.8 (± 4.1)
pH below 7.20	76 (23.2)	
Neonatal death	25 (7.6)	
Perinatal death	49 (14.9)	

BPS, biophysical profile score; FHR, fetal heart rate.

abnormal DV Doppler findings was also observed with UA-A/REDV (92/132 fetuses, 69.7%). The majority of fetuses had a normal BPS (*n* = 158; 48.2%). Sixty-eight (20.7%) had an equivocal score while the second largest group comprised fetuses with an abnormal score (*n* = 102; 31.1%). The distribution of individual test score results is shown in Table 3.

We related outcome parameters to fetal status as assessed by Doppler ultrasonography and BPS. As shown in Table 4, fetuses with more abnormal results in either surveillance modality were delivered significantly earlier. In addition there is significant worsening in acid–base status. Fetuses that had an abnormal DV Doppler or an abnormal BPS had the highest proportion of cord artery

**Table 2** Distribution of Doppler results

	<i>Abnormal UA only (n (%)) (n = 109)</i>	<i>Brain sparing (n (%)) (n = 87)</i>	<i>Abnormal DV (n (%)) (n = 132)</i>
Umbilical artery			
PI high	96 (88.1)	59 (67.8)	40 (30.3)
AEDV	8 (7.3)	11 (12.6)	26 (19.7)
REDV	5 (4.6)	17 (19.5)	66 (50)
Brain sparing		87 (100)	93 (70.5)

A/REDV, absent or reversed end-diastolic velocity; brain sparing, middle cerebral artery pulsatility index more than 2 SD below the mean for gestational age; abnormal DV, ductus venosus index elevation more than 2 SD above the mean for gestational age.

**Table 3** Distribution of biophysical profile score results

<i>Biophysical profile score</i>	<i>Normal score (n (%))</i>	<i>Equivocal score (n (%))</i>	<i>Abnormal score (n (%))</i>
10	62 (39.2)		
8	96 (60.8)		
8 with oligohydramnios		5 (7.4)	
6		63 (92.6)	
6 with oligohydramnios			16 (15.7)
4			49 (48.0)
2			31 (30.4)
0			6 (5.9)
Total	158 (100)	68 (100)	102 (100)

pH below 7.20 and a 5-min Apgar score below 7. Similarly perinatal mortality was highest among these fetuses. Table 4 illustrates that Doppler examination and BPS provided a comparable stratification of risk in this selected population of growth restricted fetuses. According to this stratification Doppler Group 1 and a normal BPS, Doppler Group 2 and an equivocal BPS and Doppler Group 3 and an abnormal BPS carry concordant risks.

Nine different test results are possible when both testing modalities are combined (Table 5). In a significant proportion (146/328, 44.5%) of fetuses the test results were concordant. These include 69 (21.0%) fetuses where a UA Doppler abnormality was associated with a normal BPS, 15 (4.6%) fetuses where brain sparing was associated with an equivocal BPS and 62 (18.9%) fetuses that had an elevated DV Doppler index and an abnormal BPS. In the remaining 182 fetuses (55.5%) the two testing modalities were not in agreement. The Doppler grade was better in 67/182 (36.8%) while the BPS grade was better in 115/182 (63.2%; Chi-square  $P < 0.0001$ ).

The largest subgroups were fetuses in which abnormal UA Doppler ('UA abnormality only') was associated with a normal BPS, or in which an elevated DV index was associated with an abnormal BPS (Table 5). Among fetuses where one testing system was equivocal the other system tended to be decisive. This was the case for 72/87 (82.8%) fetuses with brain sparing and 53/68

(77.9%) fetuses where the BPS was equivocal (Chi-square  $P = 0.46$ ). In the presence of brain sparing the BPS was equivocal in only 15/87 (17.2%), normal in 45/87 (51.7%) and abnormal in 27/87 (31.0%). When the BPS was equivocal brain sparing was present in 15/68 (22.1%), UA Doppler was abnormal in 27/68 (39.7%) and an elevated DV Doppler index was present in 26/68 (38.2%). None of these differences in proportional distribution was significant. Marked disagreement in test abnormality was present in 57/328 (17.4%) fetuses. In 13/109 (11.9%) fetuses with abnormal UA Doppler the BPS was abnormal and in 44/132 (33.3%) fetuses with abnormal DV Doppler the BPS was normal (Chi-square  $P < 0.002$ ).

Because of the wide distribution in gestational ages among the study population concordance of test results was re-examined, stratifying by delivery prior to 32 + 0 weeks' gestation (Table 6). Again, test results disagreed in the majority of fetuses (96/178; 53.9%) prior to 32 weeks and in 86/150 (57.3%) thereafter (Chi-square  $P = 0.57$ ). Among tests in disagreement the BPS grade was better in the majority of patients before (67.7%), and after (59.3%) 32 weeks' gestation (Chi-square  $P = 0.35$ ).

## DISCUSSION

Placental insufficiency places restrictions on the growing fetus that can affect several aspects of organ function and development. A wide variety of fetal responses to placental insufficiency have been described involving virtually every organ system<sup>12</sup>. However, apart from the physical sign of delayed fetal growth only cardiovascular and behavioral responses are currently available for non-invasive assessment. Examination of blood flow dynamics with Doppler ultrasonography permits the detailed study of the cardiovascular system. Limited only by the resolution capability of ultrasound equipment, blood flow in individual vascular beds (organ blood flow), downstream distribution of cardiac output and forward function of the heart can be assessed (venous Doppler). Gray-scale ultrasonography allows examination of fetal behavior and therefore gives insight into the integrity and function of the nervous system. Finally, heart rate analysis records autonomic reflexes and their central integration superimposed on intrinsic cardiac activity. Characteristic changes in any of these fetal testing modalities have been described with deterioration of fetal acid-base status, and these form the basis for antenatal surveillance. The search for better surveillance techniques in IUGR fetuses naturally leads to the question of which antenatal testing modality is best – Doppler ultrasonography, five-component BPS (including fetal heart rate analysis) or a combination of both modalities? The analysis of the distribution of test results is an important first step in initiating investigation of this question. If Doppler examination and BPS are largely in agreement with each other, then a combination

**Table 4** Outcome parameters related to Doppler status and biophysical profile score category

	UA abnormal only (n = 109)	Brain sparing (n = 87)	DV abnormal (n = 132)
Gestational age at delivery (weeks)	34 (24–41.2)	31.1 (24–38.3)*	29.5 (24–39.1)*†
pH	7.26 ± 0.08	7.25 ± 0.06	7.23 ± 0.09*
pO <sub>2</sub> (mmHg)	20.7 ± 10.2	15.8 ± 7.7*	15.8 ± 8.8
pCO <sub>2</sub> (mmHg)	51.2 ± 10	54.1 ± 9.4*	53.1 ± 12.4
HCO <sub>3</sub> (mmol/L)	22.3 ± 2.8	22.9 ± 2.9	21.2 ± 4.2†
BE (mmol/L)	−4.1 ± 3.4	−3.8 ± 3.1	−6.6 ± 4.6*†
pH < 7.20	16/104	17/81	43/109*†
5-min Apgar score < 7	5	1	13*†
Stillbirth	2	2	20*†
Neonatal death	3	4	18*†
Perinatal mortality	5	6	38*†

  

	BPS normal (n = 158)	BPS equivocal (n = 68)	BPS abnormal (n = 102)
Gestational age at delivery (weeks)	33.1 (24–41.2)	31.6 (25.3–39.3)*	30.6 (24–39)*
pH	7.26 ± 0.07	7.26 ± 0.07	7.20 ± 0.09*†
pO <sub>2</sub> (mmHg)	20.5 ± 17.1	19.7 ± 9.7	14.5 ± 9.8*†
pCO <sub>2</sub> (mmHg)	51.3 ± 10.3	49.8 ± 8.8	57.8 ± 12.1*†
HCO <sub>3</sub> (mmol/L)	22.6 ± 2.8	21.8 ± 3.3	21.6 ± 4.3
BE (mmol/L)	−4.1 ± 3.4	−4.5 ± 4	−6 ± 5.2*
pH < 7.20	24/148	13/63	39/83*†
5-min Apgar score < 7	5	3*	11*†
Stillbirth	1	5*	18*†
Neonatal death	9	1	15*†
Perinatal mortality	10	6	33*†

pH comparisons are based on 298 fetuses; complete blood gas comparisons are based on 259 fetuses. \* $P < 0.05$  compared to fetuses with abnormal umbilical artery only (UA only). † $P < 0.05$  compared to fetuses with brain sparing. BPS, biophysical profile score; BE, base excess; DV, ductus venosus.

**Table 5** Distribution of combined Doppler and biophysical profile score test results

	Normal BPS (n (%))	Equivocal BPS (n (%))	Abnormal BPS (n (%))
UA abnormality only	69 (21.0)	27 (8.2)	13 (4.0)
Brain sparing	45 (13.7)	15 (4.6)	27 (8.2)
DV abnormal	44 (13.4)	26 (7.9)	62 (18.9)
Totals	158 (48.2)	68 (20.7)	102 (31.1)

Brain sparing, fetuses with middle cerebral artery pulsatility index more than 2 SD below the mean for gestational age; DV abnormal, fetuses with ductus venosus Doppler index elevation greater than 2 SD above the mean for gestational age; UA abnormality only, fetuses had only Doppler index elevation in the umbilical artery.

of both modalities is clearly redundant. However, if test results are not in agreement then the combination of both modalities may have merit owing to the complementarity of the information gained through their combination.

In this study the distribution of antenatal testing results was evaluated in a large cohort of IUGR fetuses. A comparable proportion of mildly, moderately and severely abnormal test results for each modality was observed, making this a valid cohort to study the research question.

**Table 6** Distribution of combined Doppler and biophysical profile score testing results in patients stratified by delivery before and after 32 completed weeks of gestation. Data are presented as numbers and percentages of the subsets of 178 patients delivered prior to 32 weeks' gestation and 150 patients delivered thereafter

	Normal BPS (n (%))	Equivocal BPS (n (%))	Abnormal BPS (n (%))
<b>Umbilical artery only</b>			
Delivery < 32 + 0 weeks	21 (11.8)	12 (6.7)	7 (3.9)
Delivery > 32 + 0 weeks	48 (32.0)	15 (10.0)	6 (4.0)
<b>Brain sparing</b>			
Delivery < 32 + 0 weeks	19 (10.7)	9 (5.1)	13 (7.3)
Delivery > 32 + 0 weeks	26 (17.3)	6 (4.0)	14 (9.3)
<b>Ductus venosus abnormal</b>			
Delivery < 32 + 0 weeks	23 (12.9)	22 (12.4)	52 (29.2)
Delivery > 32 + 0 weeks	21 (14.0)	4 (2.7)	10 (6.7)

Brain sparing, fetuses with middle cerebral artery pulsatility index more than 2 SD below the mean for gestational age; ductus venosus abnormal, fetuses with ductus venosus Doppler index elevation more than 2 SD above the mean for gestational age; umbilical artery only, fetuses had only Doppler index elevation in the umbilical artery.

Looking at short-term outcomes the three Doppler and BPS categories stratified patients into comparable grades of severity. Abnormal UA Doppler and normal BPS scores

were associated with the least amount of disturbance in acid–base balance. With brain sparing or an equivocal BPS the mean pH remained unchanged while the rate of stillbirths showed a small increase, and patients required earlier delivery. At the worst end of the spectrum a significant decline in acid–base status and increase in perinatal mortality were observed when DV Doppler scan or BPS was abnormal.

Although patients were stratified into groups with similar perinatal outcomes, agreement of testing modalities was not universal. In this study over half of IUGR fetuses did not have the same degree of abnormality when tested with the two different surveillance systems. In a significant proportion of these fetuses the BPS indicated less severe compromise. For example, among 158 fetuses with normal BPS, 21 had AEDV and 24 had REDV in the UA. Test results of intermediate abnormality such as brain sparing and an equivocal BPS dominated this group while absolute disagreement was unusual. However, it is noteworthy that Doppler examination indicated more severe compromise in three times as many fetuses as did the BPS. These findings indicate that the cardiovascular and behavioral manifestations of fetal deterioration in IUGR fetuses are largely independent of each other. They also confirm findings from observational studies that show that cardiovascular deterioration precedes an abnormal BPS. This pattern probably accounts for the higher proportion of abnormal Doppler findings in our study group.

Blood-flow dynamics in IUGR fetuses are related to several factors, including vascular resistance, changes in blood pressure, differential organ autoregulation, vascular reactivity, blood viscosity and cardiac function<sup>12</sup>. Blood-flow resistance may be determined by the histologic properties of a vascular bed. For example, decrease in tertiary villous elaboration in the placenta is associated with a proportional increase in UA blood-flow resistance. Blood-flow resistance may also be modulated as a response to perceived changes in oxygen tension. Examples are the aortic baroreceptor reflex or augmentation of cerebral perfusion through autoregulation<sup>13</sup>. Early Doppler changes observed in IUGR fetuses therefore predominantly reflect modulation in the downstream distribution of cardiac output, and require intact organ autoregulation and normal cardiac function<sup>1,2,14–16</sup>. Late Doppler changes indicate that loss of cardiovascular homeostasis and declining cardiac forward function are the principal factors initiating cardiovascular deterioration. Perinatal outcomes in IUGR fetuses are clearly related to cardiovascular status. While redistribution and brain sparing are generally associated with a normal pH, late Doppler changes such as abnormal venous Doppler indices and umbilical venous pulsations are associated with fetal acidosis and the poorest perinatal outcomes<sup>1,11</sup>. Because flow-velocity waveforms in the fetal circulation are influenced by many parameters in addition to oxygen tension, most Doppler findings are associated with a wide range of pH values<sup>17–20</sup>.

In a parallel but asynchronous way, fetal behavioral responses to placental insufficiency can also be subdivided

into early and late. Early changes are predominantly due to maturational delay in the central integration of fetal behaviors – this delayed acquisition of behavioral milestones is only apparent on computerized analysis. Fetal heart rate control is also affected, causing a delay in the gestational decrease in baseline and delayed development of reactivity<sup>12</sup>. Despite maturational delay, centrally regulated responses to changes in acid–base status are still preserved. Once fetal hypoxemia is perceived a decline in global fetal activity precedes the loss of individual biophysical variables and is often also accompanied by a gradual decline in amniotic fluid volume<sup>3,21</sup>. With worsening hypoxemia fetal breathing movement ceases. Gross body movements and tone decrease and are finally lost when acidemia develops<sup>4</sup>. Abnormal fetal heart rate patterns are generally also observed at this time<sup>4,5,7</sup>. Because the five-component BPS accounts for physiological variation, and central responses to hypoxemia are preserved, a close relationship between the test score and fetal pH is maintained throughout gestation irrespective of the underlying condition<sup>7</sup>.

Doppler and biophysical variables are endpoints reflecting different mechanisms of fetal compromise in IUGR, and as such they have the potential for truly complementing each other. There is plenty of direct and indirect evidence that this is the case. Application of biophysical profile scoring to a population of IUGR fetuses that has been preselected by Doppler examination yields good results<sup>22–24</sup>. One important factor that explains these results is that Doppler and biophysical deterioration can occur independently of each other. This has been previously suggested by Pillai and James based on the concurrent analysis of the umbilical circulation and fetal behavior<sup>25</sup>. We have previously examined arterial and venous Doppler indices in a selected cohort of fetuses delivered specifically for an abnormal BPS<sup>3</sup>. In this cohort abnormal venous Doppler indices preceded an abnormal BPS in the majority of cases. In the study presented here we have related arterial and venous Doppler ultrasound examination to a more general IUGR population that was preselected by small fetal size associated with evidence of abnormal placentation. Our results suggest that even when DV Doppler ultrasonography is taken into account, Doppler and BPS results appear to be independent. This provides strong evidence that Doppler examination and BPS are complementary antenatal modalities. Therefore, pursuit of a combined testing approach has merit. In developing such an integrated fetal testing modality detailed appraisal of the relationships between individual testing parameters and critical perinatal outcomes will be of importance.

## CONCLUSION

Used separately, multi-vessel Doppler ultrasonography and BPS can effectively stratify IUGR fetuses with placental vascular insufficiency into distinct risk categories. When applied together, the pattern of results is not perfectly consistent. Fetal deterioration appears to be

independently reflected in these two testing modalities: their combined use is likely to be complementary. This calls for further research on how this can be achieved.

## REFERENCES

- 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.
- Bilardo CM, Stigter RH, Ville Y, Baez E, Visser GH, Hecher K. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol* 2001; **18**: 564–570.
- 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.
- Ribbert LS, Visser GH, Mulder EJ, Zonneveld MF, Morssink LP. Changes with time in fetal heart rate variation, movement incidences and haemodynamics in intrauterine growth retarded fetuses: a longitudinal approach to the assessment of fetal well being. *Early Hum Dev* 1993; **31**: 195–208.
- Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, Rodis JF. Relationship between fetal biophysical activities and umbilical cord blood gas values. *Am J Obstet Gynecol* 1991; **165**: 707–713.
- Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relationship of fetal biophysical profile and blood gas values at cordocentesis in severely growth-retarded fetuses. *Am J Obstet Gynecol* 1990; **163**: 569–571.
- 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.
- 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.
- Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. *Br J Obstet Gynaecol* 1986; **93**: 471–475.
- Manning FA. Fetal biophysical profile. *Obstet Gynecol Clin North Am* 1999; **26**: 557–577.
- 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.
- Baschat AA. Fetal responses to placental insufficiency – an update. *BJOG* 2004; **111**: 1031–1041.
- Arbeille P, Maulik D, Fignon A, Stale H, Berson M, Bodard S, Locatelli A. Assessment of the fetal pO<sub>2</sub> changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. *Ultrasound Med Biol* 1995; **21**: 861–870.
- Reed KL, Anderson CF, Shenker L. Changes in intracardiac Doppler flow velocities in fetuses with absent umbilical artery diastolic flow. *Am J Obstet Gynecol* 1987; **157**: 774–779.
- Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. *Obstet Gynecol* 1992; **79**: 416–420.
- Rizzo G, Arduini D. Fetal cardiac function in intrauterine growth retardation. *Am J Obstet Gynecol* 1991; **165**: 876–882.
- Akalin-Sel T, Nicolaides KH, Peacock J, Campbell S. Doppler dynamics and their complex interrelation with fetal oxygen pressure, carbon dioxide pressure, and pH in growth-retarded fetuses. *Obstet Gynecol* 1994; **84**: 439–444.
- Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and uteroplacental circulations: relationship with umbilical venous blood gases measured at cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 115–120.
- Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. *Am J Obstet Gynecol* 1995; **173**: 10–15.
- Rizzo G, Capponi A, Talone PE, Arduini D, Romanini C. Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. *Ultrasound Obstet Gynecol* 1996; **7**: 401–410.
- Ribbert LS, Nicolaides KH, Visser GH. Prediction of fetal acidemia in intrauterine growth retardation: comparison of quantified fetal activity with biophysical profile score. *Br J Obstet Gynaecol* 1993; **100**: 653–656.
- Arabin B, Becker R, Mohnhaupt A, Entezami M, Weitzel HK. Prediction of fetal distress and poor outcome in intrauterine growth retardation – a comparison of fetal heart rate monitoring combined with stress tests and Doppler ultrasound. *Fetal Diagn Ther* 1993; **8**: 234–240.
- Ott WJ, Mora G, Arias F, Sunderji S, Sheldon G. Comparison of the modified biophysical profile to a “new” biophysical profile incorporating the middle cerebral artery to umbilical artery velocity flow systolic/diastolic ratio. *Am J Obstet Gynecol* 1998; **178**: 1346–1353.
- Divon MY, Girz BA, Lieblich R, Langer O. Clinical management of the fetus with markedly diminished umbilical artery end-diastolic flow. *Am J Obstet Gynecol* 1989; **161**: 1523–1527.
- Pillai M, James D. Continuation of normal neurobehavioural development in fetuses with absent umbilical arterial end-diastolic velocities. *Br J Obstet Gynaecol* 1991; **98**: 277–281.