

# The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens

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**KEYWORDS:** Antenatal surveillance, Biophysical profile score, Doppler, Fetal compromise, Fetal growth restriction

## ABSTRACT

**Objective** To test the hypothesis that hemodynamic changes depicted by Doppler precede deteriorating biophysical profile score in severe intrauterine growth restriction.

**Methods** Intrauterine growth-restricted fetuses with elevated umbilical artery Doppler pulsatility index (PI) > 2 standard deviations above mean for gestational age and birth weight < 10th centile for gestational age were examined longitudinally. Fetal well-being was assessed serially with five-component biophysical profile scoring (tone, movement, breathing, amniotic fluid volume and non-stress test) and concurrent Doppler examination of the umbilical artery, middle cerebral artery and ductus venosus, inferior vena cava and free umbilical vein. For fetuses with a final biophysical profile score < 6/10, progression of biophysical profile scoring, arterial PI and venous peak velocity indices were analyzed longitudinally. Gestational age effect was removed by converting indices to Z-scores (deviation from gestational age mean, in standard deviations).

**Results** Forty-four of 236 intrauterine growth-restricted fetuses (18.6%) required delivery for abnormal biophysical profile scoring. The median gestational age at entry was 25 weeks and 1 day and at delivery was 29 weeks and 6 days. The median interval between examinations was 1.5 days and the majority had daily testing in the week prior to delivery. Between first examination and delivery, significant deterioration was observed for Doppler criteria (*chi-square*,  $P < 0.001$ ) and biophysical parameters (*Fisher's exact*,  $P = 0.02$ ) predominantly confined to the week prior to delivery/still-birth. Doppler variables changed first. In 42 fetuses (95.5%), one or more vascular beds deteriorated, accelerating especially in the umbilical artery and ductus venosus at a median of 4 days before biophysical profile scoring deteriorated. Two to 3 days before delivery, fetal breathing movement began to decline. The next day, amniotic fluid volume began to drop. Composite biophysical profile score dropped

abruptly on the day of delivery, with loss of fetal movement and tone. Three principal patterns of Doppler deterioration were observed: (i) worsening umbilical artery PI, advent of brain sparing and venous deterioration ( $n = 32$ , 72.7%); (ii) abnormal precordial venous flows, advent of brain sparing ( $n = 6$ , 13.6%); and (iii) abnormal ductus venosus only ( $n = 4$ , 9.1%). In the majority (31, 70.5%), Doppler deterioration was complete 24 h before biophysical profile score decline. In the remainder (11, 25%), Doppler deterioration and biophysical profile score < 6/10 were simultaneous.

**Conclusion** In the majority of severely intrauterine growth-restricted fetuses, sequential deterioration of arterial and venous flows precedes biophysical profile score deterioration. Adding serial Doppler evaluation of the umbilical artery, middle cerebral artery and ductus venosus to intrauterine growth restriction surveillance will enhance the performance of the biophysical score in the detection of fetal compromise and therefore optimizing the timing of intervention.

## INTRODUCTION

Biophysical profile scoring and Doppler surveillance are the primary methods for fetal assessment in intrauterine growth restriction (IUGR). As placental insufficiency worsens, the fetus adapts by progressive compensation. Initial mechanisms, such as increasing red cell mass and oxygen extraction, give way to deliberate shunting of blood away from non-essential vascular beds. As this second hemodynamic mechanism is maximized, the final resort (reduction in oxygen expenditure) is invoked. At this point, adaptation is exhausted and demise is threatened. Biophysical profile scoring and fetal multivessel Doppler surveillance provide insight into different facets of these fetal responses.

The biophysical profile score (BPS) incorporates dynamic fetal variables (tone, movement, breathing), amniotic fluid volume and the non-stress test (NST) into a composite scoring system<sup>1</sup>. While individual components show correlation

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with fetal status, a composite score of all variables is the best predictor. The depiction of fetal status by this composite score has been validated by fetal and neonatal outcome data<sup>1-5</sup>. Application of these principles to the management of high-risk pregnancies produces significant improvement of short- and long-term outcomes<sup>1</sup>.

Doppler ultrasound in IUGR fetuses describes downstream vascular resistance (umbilical arteries), preferential organ blood flow (middle cerebral artery) and the filling capacity of the fetal heart (precordial veins). While individual components show correlation with fetal status, the composite evaluation using multivessel Doppler is the best predictor<sup>6,7</sup>. Delineation of fetal status by this multivessel Doppler evaluation also has strong correlation with outcome variables<sup>6-10</sup>. While there have been some studies demonstrating the beneficial application of umbilical artery Doppler surveillance, long-term results using multivessel Doppler have not been assessed.

It has been suggested that the sequential changes in arterial and venous flows occur before some biophysical parameters decline<sup>6,11-14</sup>. However, these relationships have not been examined in detail. Studies comparing individual Doppler variables with various expressions of biophysical behavior have focused on isolated outcome measures. Yet, the five component BPS provides the best evidence that assessment utilizing multiple components has superior performance. The relationship between all five biophysical components and arterial and venous Doppler variables has never been studied.

We sought to determine the relationship between biophysical fetal parameters and arterial and venous Doppler parameters in fetuses with severe IUGR. It was our hypothesis that sequential deterioration of arterial and venous Doppler precedes an abnormal BPS.

## PATIENTS AND METHODS

### Patients

Between 1997 and 2001, patients referred for suspected IUGR were examined serially if they met the following criteria:

(i) normal fetal anatomy; (ii) fetal abdominal circumference < 5th percentile for gestational age by local reference values; (iii) umbilical artery Doppler pulsatility index<sup>15</sup> (PI) more than 2 standard deviations (SDs) above the gestational mean by local reference values; (iv) absent maternal/fetal indication for immediate delivery at the time of initial referral (i.e. available for continued antenatal surveillance); (v) deterioration of biophysical profile score below 6 prior to delivery; (vi) birth weight below the 10th percentile for gestational age.

Gestational age was determined by last menstrual period and/or sonographic examination prior to 20 weeks of gestation. Karyotyping, performed either antepartum or postpartum, was normal in all patients.

### Ultrasound examination

For all ultrasound examinations, 4 or 5-MHz sector ultrasound transducers (Acuson 128 XP/10ob, Sequoia 512, Mountain View, CA, USA; HDI 5000 ATL, Bothell, WA, USA) were used, with spatial peak temporal average intensities below 100 mW/cm<sup>2</sup> and the high pass filter at 100 Hz. During each examination, a five-component BPS was assigned in a 30-min interval<sup>1</sup>. A maximal vertical fluid pocket below 2 cm was considered as oligohydramnios and fetal heart rate reactivity was graded for gestational age (Table 1). Concurrently, Doppler measurements were obtained from the umbilical artery (UA), middle cerebral artery (MCA), inferior vena cava (IVC), ductus venosus (DV) and the mid-portion of the free umbilical vein (UV) by previously described methods<sup>6,7,9</sup>.

During examinations, each Doppler result was verified by at least three measurements and the best result was included for final analysis. The arterial PI and peak velocity index for the veins (PVIV)<sup>16</sup> were plotted against local reference values for gestational age. Since the normal distribution of Doppler indices changes with gestational age, individual measurements were normalized for statistical analysis by converting measurements into Z-scores (SD from the gestational age mean).

**Table 1** Biophysical profile score after Manning<sup>1</sup>

| <i>Biophysical variable*</i> | <i>Normal score (score = 2)</i>  | <i>Abnormal score (score = 0)</i>   |
|------------------------------|--|---|
| Fetal breathing movement     | At least one episode of fetal breathing of at least 30 s duration  | Absent fetal breathing, or no episode of more than 30 s   |
| Gross fetal body movement    | At least three discrete body/limb movements  | Two or fewer body/limb movements  |
| Fetal tone                   | At least one episode of active extension with return to flexion of fetal limbs or trunk. Includes opening or closing of the hand   | Slow extension with return to partial flexion or limb movement without flexion or absent fetal movement |
| Fetal heart rate             | Below 26 weeks gestation: at least two accelerations of $\geq 10$ beat accelerations of $\geq 10$ s duration<br>26–36 weeks gestation: at least two episodes of $\geq 10$ beat accelerations of $\geq 15$ s duration<br>Beyond 36 weeks gestation: at least two episodes of $\geq 20$ beat accelerations of $\geq 20$ s duration | Less than two episodes of accelerations and durations as specified                                      |
| Amniotic fluid volume        | At least one amniotic fluid pocket of $2 \times 2$ cm in perpendicular planes  | No amniotic fluid pocket of $2 \times 2$ cm in perpendicular planes                                     |

\*All parameters are examined in a 30-min monitoring interval.

For the UA, IVC and DV, elevation of the respective index > 2 SD above the mean and pulsatile flow in the free umbilical vein were considered abnormal. An MCA PI more than 2 SD below the gestational age mean was considered as evidence of 'brain sparing'<sup>17</sup>. If a low middle cerebral artery PI rose into the normal range on two subsequent examinations, the definition of 'normalization of PI' was met<sup>18</sup>. In the final analysis, these fetuses were categorized as having 'brain sparing'. The assessment of non-reassuring fetal status and indications for delivery were based on a combination of BPS and Doppler.

### Outcome

Neonatal evaluation included Apgar scores assigned by the attending pediatric team, birth weight and birth weight percentile as charted against local reference values for gestational age and gender. Umbilical cord arterial pH and blood gases were obtained from a cord segment clamped immediately at delivery.

Statistical analysis was performed with SPSS 10.0 (SPSS Co, Chicago, IL, USA). After tests of normality and homogeneity of variance, the Mann-Whitney *U*-test was used for continuous variables according to their distribution. Fisher's exact and chi-square tests were used for the analysis of categorical variables. *P* < 0.05 was considered statistically significant.

## RESULTS

Two hundred and thirty-six patients had Doppler and biophysical profile scoring performed during the study period. Forty-four of these (18.6%) had deterioration of the BPS below 6 prior to delivery. The median gestational age at the initial referral was 25 + 1 weeks' gestation (Table 2). Delivery was at a median of 29 + 6 weeks (Table 3). The testing interval ranged from 6 to 69 days (median, 21 days). While the median interval between examination was 1.5 days over the entire study period, the majority of fetuses had daily testing in the last week prior to delivery. All live birth babies had their last ultrasound examination on the day of delivery.

There were 10 stillbirths (22.7%). In stillborn fetuses, the parents opted for non-intervention due to the expected poor prognosis based on non-viable size and extreme prematurity (< 400 g and < 27 weeks' gestation in all cases) (Table 3). These families received non-directive counseling by a perina-

tologist and neonatologist. As such, there were no unexpected stillbirths.

Most babies were delivered by Cesarean section for non-reassuring fetal status. The median birth weight was 725 g (range, 420–2260 g) including 15 neonates (44.1%) below the 3rd percentile. A low 1-min Apgar score was persistent at 5 min in three cases (8.8%) and cord artery blood gas values were abnormal in all cases. Amongst 34 live births, there was one iatrogenic neonatal death (2.9%). He was a recovering 32-week IUGR neonate who received a lethal intravenous injection. The total perinatal mortality rate was 25%.

While all fetuses had abnormal UA indices (entry criterion), 22 (50%) had absent or reversed UA end-diastolic velocity at the first examination; 'brain sparing' was present in 10 (22.7%). Thirteen (29.5%) had elevated initial venous Doppler indices (DV and/or IVC) including four with UV pulsation (9.1%) (Figure 1). At the same time, all fetuses had a BPS above 6. When individual components were analyzed, fetal tone (100%), movement (100%) and amniotic fluid volume (42, 95.5%) were usually normal. In contrast, fetal breathing was observed in 33 (75%) and NST was only reactive in six fetuses 6 (13.6%) (Figure 1).

Between the first examination and delivery, significant deterioration was observed for Doppler criteria (chi-square, *P* < 0.001) and biophysical parameters (Fisher's exact test,

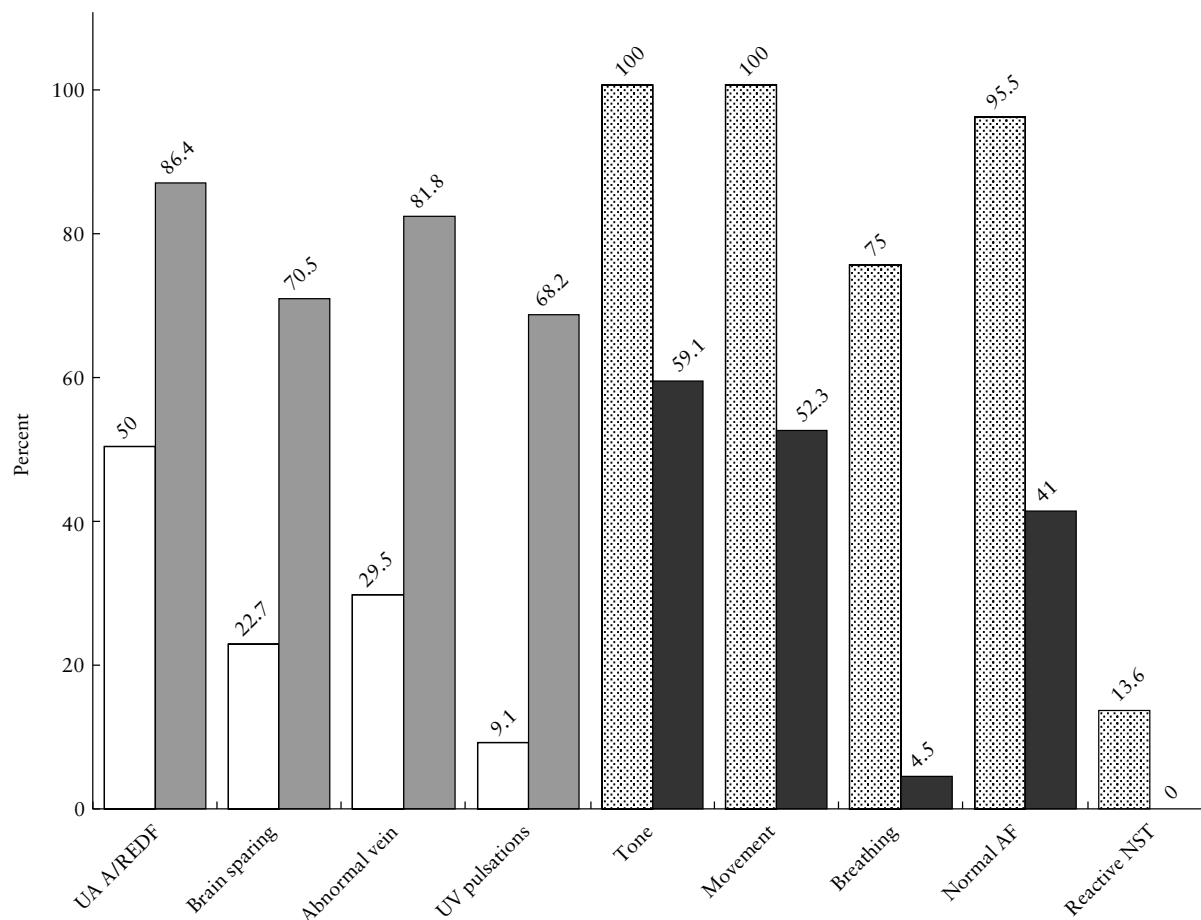
Table 3 Delivery outcomes

| Delivery outcome  | Median/n | Range/%          |
|---|----------|------------------|
| Gestational age at delivery, live birth only (weeks + days) | 29 + 6   | 26 + 4 to 37 + 6 |
| Gestational age at delivery, stillbirths (weeks + days)     | 26 + 6   | 25 + 1 to 28     |
| Mode of delivery (live birth only)                          |          |                  |
| Vaginal   | 1        | 2.9%             |
| Cesarean section  | 33       | 97.1%            |
| Diagnoses at Cesarean section*                              |          |                  |
| Fetal intolerance to labor/distress                         | 7        | 21.2%            |
| Non-reassuring fetal status                                 |          |                  |
| Low BPS   | 9        | 27.3%            |
| Low BPS and late decelerations                              | 9        | 27.3%            |
| Positive OCT  | 3        | 9.1%             |
| Severe pre-eclampsia/HELLP                                  | 5        | 15.1%            |
| Birth weight (g)  | 725      | 420 to 2260      |
| Birth weight percentiles                                    |          |                  |
| ≤ 3   | 15       | 44.1%            |
| ≤ 5   | 10       | 29.4%            |
| ≤ 10  | 9        | 26.5%            |
| Apgar score < 7   |          |                  |
| At 1 min  | 18       | 52.9%            |
| At 5 min  | 3        | 8.8%             |
| Cord gases (median/range)                                   |          |                  |
| Arterial pH   | 7.23     | 6.95 to 7.29     |
| Arterial pO <sub>2</sub> (mmHg)                             | 11.5     | 6 to 36          |
| Arterial pCO <sub>2</sub> (mmHg)                            | 52       | 38.8 to 72       |
| Arterial HCO <sub>3</sub> (mmol/L)                          | 22.5     | 12.4 to 28.8     |
| Arterial base excess (mmol/L)                               | -4.6     | -14.5 to 0.9     |

Data are presented as median and range or numbers and percentages as indicated. Unless otherwise indicated, data represent live births only. BPS, biophysical profile scoring; OCT, oxytocin challenge test; HELLP, syndrome of hemolysis, elevated liver enzymes and low platelets. \*Percentages are calculated for patients with Cesarean section only.

Table 2 Examination details of study group

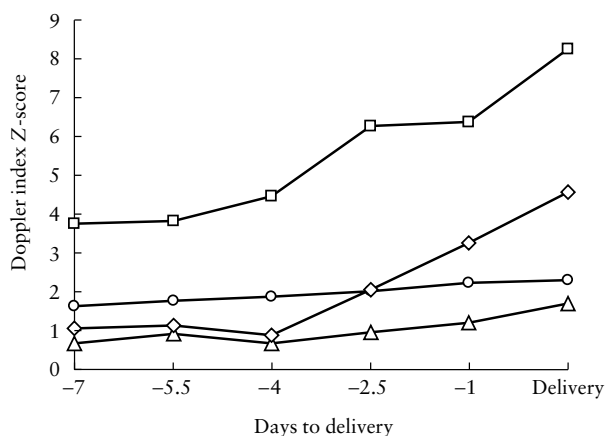
| Variable   | Median | Range            |
|--|--------|------------------|
| Gestational age at study entry (weeks + days)      | 25 + 1 | 16 + 4 to 31 + 6 |
| Gestational age at last examination (weeks + days) | 28 + 4 | 24 + 2 to 37 + 1 |
| Monitoring period (days)                           | 21     | 6–69             |
| Interval between examinations (days)               | 1.5    | 1–14             |
| Number of examinations                             | 8      | 4–17             |



**Figure 1** Percentages of individual Doppler and biophysical findings at study entry (□, Doppler; ▨, biophysical) and the last examination prior to delivery (▤, Doppler; ■, biophysical). UA, umbilical artery; A/REDF, absent or reversed end-diastolic flow; UV, umbilical vein; AF, amniotic fluid; NST, non-stress test. Fetuses which developed middle cerebral artery pulsatility index 'normalization' are categorized as having 'brain sparing'.

$P = 0.02$ ). Significant deterioration of Doppler indices was predominantly confined to the week before delivery/still-birth. The deterioration of Doppler indices between day 1 and day 7 of the last week was most marked for the umbilical artery and ductus venosus (median PI Z-score, 3.8 vs. 8.2; median PVIV Z-score 1.1 vs. 4.6; Mann-Whitney  $U$ -test,  $P < 0.001$ , respectively). The deterioration was less pronounced for the IVC (median PVIV Z-score, 0.6 vs. 1.7; Mann-Whitney  $U$ -test,  $P < 0.01$ ) and least pronounced for the MCA (median PI Z-score, -1.6 vs. -2.3, Mann-Whitney  $U$ -test,  $P < 0.05$ ). Doppler variables changed first. In 42 fetuses (95.5%) one or more vascular beds deteriorated. At a median of 4 days before BPS fell, the parallel increases in UA and DV indices accelerated; 1–2 days later, IVC PVIV began to rise more gradually. MCA PI showed little change over this interval (Figure 2).

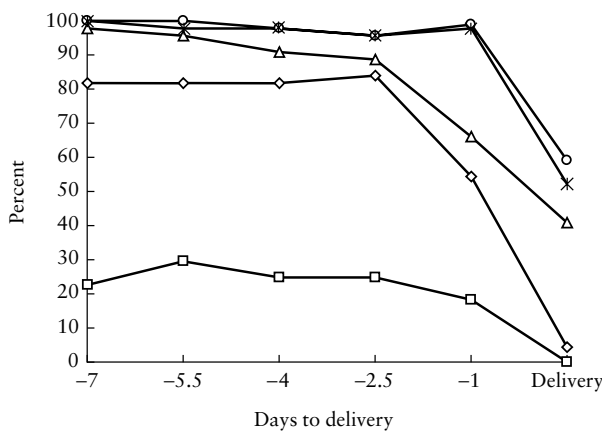
By study definition, all fetuses demonstrated decline in BPS significant for every parameter. The exception was heart rate reactivity. Reactive NST increased from the initial 13% to 22.3% of fetuses 1 week before delivery, but declined to 0% by day of delivery (not statistically significant). Decline in other BPS parameters tended to follow Doppler changes. Just 2–3 days before delivery, fetal breathing movement began to



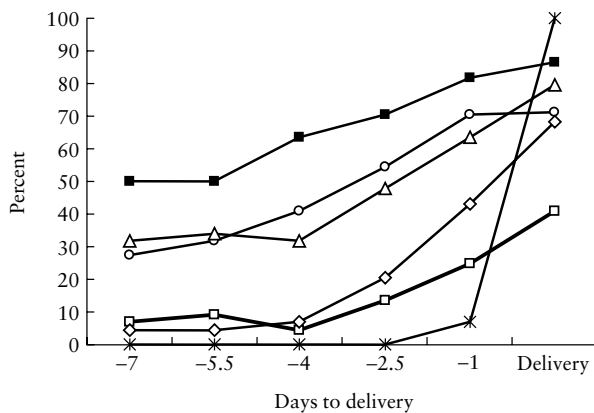
**Figure 2** The median delta Doppler indices in the week prior to delivery: umbilical artery pulsatility index (□), middle cerebral artery pulsatility index (○), inferior vena cava peak velocity index for veins (△) and ductus venosus peak velocity index for veins (◇). Umbilical artery and ductus venosus indices show a steady parallel elevation, while middle cerebral artery changes are not as marked and those in the inferior vena cava are variable.

decline. The next day, amniotic fluid volume began to drop. Composite BPS dropped abruptly on day of delivery, with loss of fetal movement and tone (Figure 3).

Three principal patterns of Doppler deterioration were observed. The most common sequence was worsening umbilical artery PI, advent of brain sparing, followed by venous deterioration. Among the 32 (72.7%) fetuses who followed this sequence, 28 completed all three steps, four progressed only to brain sparing. Six fetuses (13.6%) demonstrated the second pattern: precordial venous flows were abnormal for a median of 2 weeks (range, 7–60 days) before brain sparing developed. The third pattern was unusual: four fetuses (9.1%) showed DV abnormality without ever altering cerebral blood flow. In the majority (31, 70.5%) Doppler deterioration was complete 24 h before BPS decline. In the remainder (11, 25%)



**Figure 3** Presence of individual biophysical components during the last week prior to delivery: normal tone (O), normal movement (X), breathing (◇), normal amniotic fluid (△) and reactive non-stress test (□). All fetuses had a non-reactive non-stress test. Fetal breathing, amniotic fluid volume, tone and movement were sequentially lost prior to delivery.



**Figure 4** The percentage of abnormal Doppler findings in individual vessels and the incidence of a biophysical profile score below 6 (X) in the week prior to delivery. ■, umbilical artery absent or reversed end-diastolic flow; O, abnormal middle cerebral artery flow; □, abnormal inferior vena cava flow; △, abnormal ductus venosus flow; ◇, umbilical vein pulsations. Deterioration of Doppler findings precedes decline in biophysical profile score.

Doppler deterioration and BPS < 6/10 were simultaneous (Figure 4).

**DISCUSSION**

The goal of fetal surveillance in IUGR is to balance fetal and neonatal risks to optimize the timing of intervention. As placental function worsens, the fetus may demonstrate, by a variety of indicators, progressive extremes of adaptation. This study is unique in relating circulatory changes and changes in fetal behavior longitudinally in one IUGR population. For the first time, we have documented concomitant changes in hemodynamic and behavioral manifestations of this adaptation. We are able to define the relationship of multivessel Doppler changes and the development of an abnormal biophysical profile.

First, we assessed changes in individual components of the biophysical profile score (Figure 3). The majority of fetuses did not show heart rate reactivity throughout the study period despite the application of graded criteria to account for gestational age. Fetal breathing movements were the next variable to be lost, followed by decline in amniotic fluid volume and, finally, loss of movement and tone. Vintzileos suggested that this ‘sequential loss of variables’ correlates with worsening acidemia, hypoxemia and hypercapnia<sup>19</sup>. Although there were fluctuations in individual components, the composite BPS deteriorated abruptly just before delivery. That this was a useful trigger for delivery may be supported by the outcome of this study where there were no neonatal deaths due to the condition of babies at birth.

Experience with biophysical profile scoring suggests limitations. Observer variability in the interpretation of the NST is a long recognized problem<sup>20</sup>. Coupling of fetal activity and heart rate accelerations, variation in the cyclicity of periods of quiescence and breathing and altered maturation of organized behaviors, can result in a wider range of biophysical profile scores<sup>2,21,22</sup>. Substituting computerized heart rate analysis for the traditional NST, and enhancing amniotic fluid assessment by criteria for subjective reduction, may address some of these issues<sup>13,14,20,23</sup>. James *et al.*, however, suggested that when fetal breathing is absent, the other ultrasound variables change too late and only heart rate analysis should be used<sup>12</sup>. In our population, this approach would have been of limited utility, since the majority of fetuses had a non-reactive NST. Intrauterine growth restriction is a disease which offers other (i.e. hemodynamic) evidence of fetal compromise, and biophysical profile scoring may not completely represent all the stages of fetal adaptation.

Most IUGR fetuses demonstrated a significant progression in deteriorating placental circulation (UA), deliberate redistribution of blood flow (brain sparing) and direct cardiac compromise (abnormal venous Doppler) before an abnormal BPS. Abnormality of umbilical arterial resistance was a prerequisite for study entry: the umbilical artery PI worsened progressively in almost all fetuses. Arterial redistribution with preferential perfusion of vital organs (brain sparing) was already established in 23%, and accumulated steadily over the study, reaching over 80%. In contrast, the precordial veins

were relatively stable in the majority, until deterioration, approximately 4 days prior to delivery (Figure 2). Thus, the majority of these IUGR fetuses demonstrated a progression in deteriorating placental circulation, deliberate redistribution of blood flow and direct cardiac compromise. This fits with published models of hemodynamic compromise in IUGR, which are first related to fetal hypoxemia and then correlate with serious acidemia in the final stages<sup>6-9,24,25</sup>.

The sequential timing of circulatory changes in IUGR has not been fully delineated. Based on previous studies, it is reasonable to assume that deterioration of uteroplacental function is initially reflected by abnormal blood flow in the umbilical circulation, descending aorta and middle cerebral artery<sup>24,26</sup> and that ongoing compromise is manifested by abnormal venous Doppler<sup>6,7,14</sup>. For the purpose of clinical management, it is important to realize that there are exceptions. Not all fetuses in this study followed the expected sequence. Only 70% demonstrated severe abnormalities of all vascular beds by the time they were delivered. While over 90% showed significant deterioration in at least one Doppler parameter, the remaining 10% showed no significant circulatory change. Some fetuses were unable to maintain brain sparing and 'normalization' occurred, potentially altering statistical analysis; we corrected for this by analyzing normalized fetuses as having brain sparing. Individual Doppler measurements also demonstrated variability. For example, many fetuses had established brain sparing long before other changes occurred and MCA Doppler does not appear to change very much as compromise progresses (Figures 1 and 2). Also, changes in inferior vena cava pulsatility are indeterminate. Finally, it has been our observation, and that of others<sup>6,13,25</sup>, that this full Doppler progression is uncommon beyond 32–34 weeks of gestation. Our data suggest that multivessel Doppler analysis is not absolute and that additional information is necessary to adequately assess the fetal status.

This study is unique in relating circulatory changes and changes in fetal behavior longitudinally in one IUGR population. Previous studies have compared individual Doppler variables (mainly umbilical artery) with individual biophysical behaviors (mostly fetal heart rate analysis)<sup>12-14,26-28</sup>. While Senat *et al.* did examine venous Doppler, the comparison was limited to computerized fetal heart rate variation<sup>14</sup>. Hecher *et al.* examined multiple vascular beds but, in this cross-sectional study, only six fetuses had abnormal BPS<sup>6</sup>. In addressing the concurrent changes in Doppler and biophysical behavior, our observations have important implications for antenatal surveillance.

Doppler analysis presages biophysical deterioration. At least one-third of fetuses had early signs of circulatory deregulation 1 week prior to delivery, when the BPS was still normal. As arterial and venous flows continue to deteriorate gradually, they provide early warning of a rapid fall in BPS, often over 1 day. On the other hand, the normal biophysical profile score illustrated by all fetuses at the beginning of the study validated delaying delivery by up to 20 days. It would seem that combining Doppler and BPS will maximize the precision of fetal assessment. A confounding factor in IUGR is that multiple patterns of cyclicity interact with underlying fetal status to produce very variable behavior and even more

variable compensatory responses. A combination of multiple timeframes of BPS components and multivessel Doppler (umbilical artery, middle cerebral artery, ductus venosus, inferior vena cava and free umbilical vein) addresses these concerns. Doppler deterioration would call for increased frequency of testing. In the face of severe Doppler deterioration, maintenance of normal biophysical behavior, 'BPS = 10/10', would allow for preparation for delivery (antenatal steroids, neonatology consultation, appropriate transport). When both systems fail, the need for urgent delivery is certain.

If the goal of fetal surveillance is met, perinatal outcome and long-term quality of life will be optimized. According to different viewpoints, the decision for delivery may be based on different gold standards. The question has been raised: which gold standard is best, Doppler or BPS? Our data and the suggestions of others indicate that it is time for the development of a new gold standard incorporating both testing modalities<sup>29</sup>. Combining multivessel Doppler and composite biophysical profile scoring will provide significant early warning and a definitive indication for action in the management of severe intrauterine growth restriction. This new gold standard can be validated by a prospective, randomized trial examining short-term and long-term outcomes.

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