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Progression of Doppler abnormalities in intrauterine growth restriction

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KEYWORDS: ductus venosus; intrauterine growth restriction; longitudinal analysis; middle cerebral artery; umbilical artery

ABSTRACT

Objective *To identify the sequence of progression of arterial and venous Doppler abnormalities from the onset of placental insufficiency in intrauterine growth restriction (IUGR).*

Methods *Prospective observational study of singletons with IUGR (abdominal circumference $< 5^{th}$ percentile) who underwent serial standardized umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV) and umbilical vein (UV) Doppler surveillance. Time intervals between progressive Doppler abnormalities and patterns of deterioration were related to UA Doppler status and gestational age.*

Results *Six hundred and sixty-eight longitudinal examinations were performed in 104 fetuses, identifying three patterns of progression: (1) Mild placental dysfunction (*n = *34) that remained confined to the UA/MCA. The UA became abnormal at a median of 32 weeks' gestation but the pulsatility index never exceeded 3 SD above normal. Progression took a median of 33 days, requiring delivery at a median of 35 weeks. (2) Progressive placental dysfunction (*n = *49). Initially normal UA Doppler PI at 29 weeks' gestation increased beyond 3 SD, progressing to abnormal MCA, absent/reversed UA diastolic flow, abnormal DV, UV pulsations in 9-day intervals requiring delivery by 33 weeks. (3) Severe early-onset placental dysfunction (*n = *21). Markedly elevated UA PI established by 27 weeks' gestation was associated with rapid (7-day intervals) progression to abnormal venous Doppler with median delivery at 30.6 weeks. Gestational age at onset, time to delivery and progression intervals were different between patterns (all* $P < 0.05$*).*

Conclusion *The characteristics of cardiovascular manifestations in IUGR are determined by the gestational age at onset and the severity of placental disease. Recognition of these factors is critical for planning fetal surveillance in IUGR. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Placenta-based intrauterine growth restriction (IUGR) is predominantly a vascular disorder. It starts with abnormal tertiary villous vessels and ends with characteristic fetal multi-vessel cardiovascular manifestations[1]. These effects can be documented with Doppler ultrasound examination of a number of vessels: maternal uterine arteries and the fetal umbilical arteries for the placenta; middle cerebral artery (MCA) for preferential brain perfusion; and precordial veins for the cardiac effects of placental dysfunction. As IUGR worsens, Doppler abnormalities in these vascular territories also deteriorate[2], suggesting a sequential pattern of disease progression. This presumed sequence and the anticipation of fetal deterioration form the basis for Doppler surveillance in IUGR. Deterioration in Doppler findings typically leads to several changes in clinical IUGR management: increased monitoring frequency, administration of antenatal steroids and delivery[3].

Relationships between fetal Doppler findings and perinatal risks have been defined in numerous cross-sectional studies[4]. While these studies are useful for suggesting outcome relationships, a sequence of Doppler changes is inferred, rather than proven, from cross-sectional data. Cross-sectional studies define an anticipated range of observations for individual members of a cohort. With

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large sample sizes such studies may provide reasonably reliable estimates of group behavior. However, the inherent variability of each individual and the true longitudinal progression from a specific entry point cannot be determined. In contrast, appropriately constructed longitudinal studies can evaluate the progression in individual fetuses from a predefined entry point and therefore provide narrower confidence limits and a more accurate description of biological behavior[5]. Only a handful of longitudinal studies specific to IUGR have evaluated the arterial and venous circulations[6–10]. Our understanding of the progression of fetal cardiovascular responses to placental dysfunction is therefore largely based on weaker scientific evidence from cross-sectional observations[4]. This evidence is weakened further because neither the Doppler techniques nor the characteristics of fetuses studied were consistent between studies. Moreover, in focusing on referred cases of end-stage IUGR, investigators may not have fully evaluated the progression of mild or moderate placental disease. Placenta-based IUGR often first becomes apparent at a less developed stage, when customizing surveillance is key and moving towards delivery is not yet appropriate[3].

The aim of this study was to evaluate the longitudinal progression of arterial and venous Doppler parameters from the clinical onset of IUGR in individual pregnancies. It was our hypothesis that arterial and venous Doppler parameters progress in a predictable sequence in these fetuses.

PATIENTS AND METHODS

This prospective multicenter study of singleton pregnancies complicated by IUGR was conducted from January 2000 to March 2006. Fetuses at an early stage of placenta-based growth restriction were defined by the following inclusion criteria: (1) gestational age determined by sure date of last menstrual period confirmed by ultrasound examination at < 20 weeks' gestation; (2) abdominal circumference (AC) < 5th percentile; and (3) early placental insufficiency as defined by umbilical artery (UA) pulsatility index (PI) elevation more than 2 SD above the mean and/or cerebroplacental ratio (CPR) more than 2 SD below the mean[11]. To be eligible for longitudinal analysis, it was necessary for patients to have had at least three Doppler examinations prior to delivery, including a complete set of study variables at both the first and last examination. Exclusion criteria were: (1) fetuses with chromosomal abnormalities or structural anomalies; and (2) fetuses with advanced fetal vascular disease at recruitment (brain sparing, absent or reversed flow in UA, elevated ductus venosus (DV) PI, absent or reversed a-wave in DV and umbilical vein (UV) pulsation).

Patients gave informed written consent, and the study protocol was approved by the Institutional Review Board at each participating center.

Doppler parameters were obtained from the UA, MCA, DV and UV according to uniform standards provided by the originating institution[3]. UA end-diastolic velocity was classified as present, absent (AEDV) or reversed (REDV). The CPR was calculated as previously described[11]. DV velocity during atrial systole was characterized as forward or absent/reversed (DV-RAV). Pulsations in the UV were noted. The pulsatility index for each vessel was converted to its *Z*-score to exclude the effect of gestational age. For the UA and DV, a two-SD elevation of the Doppler index was considered abnormal. Redistribution was defined as a two-SD decrease in the CPR[11], and brain sparing was defined as a two-SD decline in MCA-PI[12].

Determination of monitoring intervals and delivery timing were at the discretion of the attending obstetrician. Perinatal characteristics and delivery details such as indication, route, gestational age, birth weight, Apgar scores, and UA blood gases were ascertained. Neonatal mortality and the presence of major neonatal morbidity were noted.

Longitudinal progression of Doppler abnormalities was evaluated in several ways. The day of delivery was used as the primary reference point for describing Doppler changes (Figure 1). Three time intervals were defined to assess progression: (1) enrollment-to-delivery interval; (2) progression interval, defined as the time between two successive Doppler abnormalities; and (3) duration of each individual Doppler abnormality, calculated as the interval from its first appearance to delivery.

Doppler index *Z*-scores were related to duration of abnormality for each vessel to give a mathematical description of longitudinal progression for each fetus. This analysis defined the sequence of categorical Doppler abnormalities. Patterns were categorized by their consistent sequence of Doppler abnormalities. For this analysis the sequence of categorical Doppler abnormalities was noted for each fetus. This sequence of categorical Doppler abnormalities was independently reviewed by five authors (O.M.T., S.T., S.G., C.R.H. and A.A.B.) and defined the pattern of progression. Patterns were compared for their gestational age at onset, difference in intervals between Doppler changes and severity of placental disease.

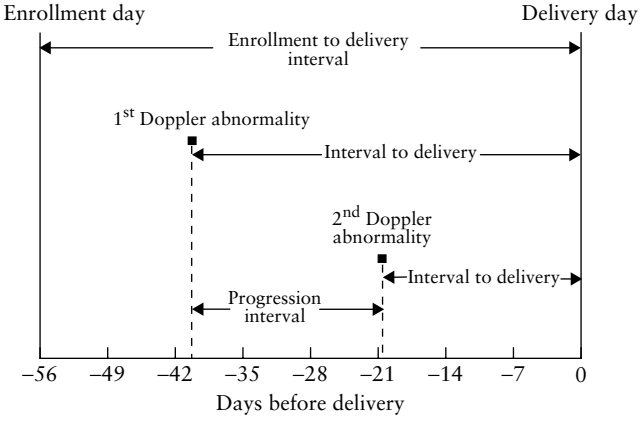

Figure 1 Time intervals (days) that were used to analyze the longitudinal progression of Doppler abnormalities. The time interval between the appearance of two consecutive Doppler abnormalities was termed the progression interval, and for each individual Doppler abnormality the interval to delivery was calculated.

Continuous variables were analyzed with the Mann–Whitney *U*-test after evaluation for normal distribution by the Kolmogorov–Smirnov test. Logarithmic transformation of PI *Z*-scores was performed where appropriate. Categorical variables were analyzed with Chi-square or Fisher's exact test depending on cell size. Regression analysis was performed to describe the determinants of clinical progression, and variances of the intervals in the Doppler abnormalities were analyzed by ANOVA. SPSS 13.0 (SPSS Co., Chicago, IL, USA) was used for these analyses. Finally, differences in the slopes of regression lines for various Doppler indices were analyzed using Statgraphics Centurion software (Statpoint, Herndon, VA, USA). $P < 0.05$ was considered as statistically significant.

RESULTS

In the study period a total of 177 pregnant women were recruited for longitudinal evaluation. Of these, 104 pregnancies met the specific inclusion criteria of early-onset placental dysfunction. The maternal characteristics and delivery details are displayed in Tables 1 and 2. In these patients 668 Doppler examinations were performed with a median of 8 (range, 3–26) examinations per patient. The distribution of Doppler abnormalities at enrollment and delivery are displayed in Table 3. By the time of delivery almost all patients had elevated UA blood flow resistance ($n = 97$, 93.3%), the majority had brain sparing ($n = 61$, 58.7%) and approximately one third had an elevated DV Doppler index ($n = 30$, 28.8%).

Individual Doppler abnormalities had successively shorter duration (ANOVA $P < 0.0001$). The duration of each individual Doppler abnormality is displayed in order in Figure 2. The rate of progression for Doppler abnormalities was significantly related to gestational age. When the abnormality presented early in gestation, it progressed more rapidly; when an abnormality emerged later, progression was slower. This was true for the UA, MCA and DV (Figure 3).

When the sequence of Doppler abnormalities was categorized, three principal patterns of deterioration were identified (Figure 4). In the first pattern Doppler abnormalities were confined to the umbilical/cerebral circulation. In the other two patterns, Doppler abnormalities progressed to the venous system, following very different time courses. These three patterns were characterized as mild, progressive or severe early-onset placental dysfunction according to the following criteria:

Table 1 Maternal demographics ($n = 104$)

Parameter	*Value*
Maternal age (years, mean (range))	28 (14–45)
Parity (*n* (%))	
0	77 (74)
1	19 (18.3)
2	7 (6.7)
3	1 (1)
Ethnicity (*n* (%))	
Caucasian	70 (67.3)
African American/Afro-Caribbean	32 (30.8)
Asian	2 (1.9)
Gestational age at enrollment (weeks, median (range))	27 (23–33.6)

Table 2 Delivery and postpartum characteristics ($n = 104$)

Parameter	*Value*
Indication for delivery (*n* (%))	
Non-reassuring fetal status	61 (59.8)
Pre-eclampsia	11 (10.8)
Abruption	2 (2)
Oligohydramnios	2 (2)
Spontaneous vaginal delivery	18 (17.6)
Elective (breech presentation)	8 (7.8)
Mode of delivery (*n* (%))	
Vaginal	26 (25)
Cesarean section	78 (75)
Gestational age at delivery (weeks, median (range))	33.4 (26.4–40.3)
Birth weight (g, median (range))	1235 (420–2790)
5-min Apgar score < 7 (*n* (%))	5 (4.9)
Umbilical artery pH < 7.20 (*n* (%))	29 (27.9)
Antepartum death (*n* (%))	2 (1.9)
Major morbidity (*n* (%))*	12 (11.5)
Intact survival (*n* (%))†	90 (86.5)

*Major morbidity defined as neonatal bronchopulmonary dysplasia, necrotizing enterocolitis or Grade III–IV intraventricular hemorrhage. †No major morbidity and neonatal death.

Table 3 Distribution of ultrasound and Doppler abnormalities at enrollment and delivery

Parameter	*Value*
Gestational age at enrollment (weeks, median (range))	27 (23–33.6)
Doppler examination	
Total number of scans (*n*)	668
Number of scans per patient (median (range))	8 (3–26)
Interval of Doppler examination (days, median (range))	5 (1–56)
Ultrasound findings at enrollment (*n* (%))	
AC < 5th percentile without Doppler abnormality	49 (47.1)
AC < 5th percentile + elevated umbilical artery PI	32 (30.8)
AC < 5th percentile + elevated umbilical artery PI + reduced CPR	23 (22.1)
Frequency of Doppler abnormalities at delivery (*n* (%))	
Elevated umbilical artery PI	97 (93.3)
Reduced CPR	82 (78.8)
Brain sparing	61 (58.7)
Elevated ductus venosus PI	30 (28.8)
Umbilical artery AEDV	24 (23.1)
Umbilical artery REDV	18 (17.3)
Umbilical vein pulsation	19 (18.3)
Ductus venosus absent/reversed a-wave	5 (4.8)

AC, abdominal circumference; PI, pulsatility index; CPR, cerebroplacental ratio; AEDV, absent end-diastolic velocity; REDV, reversed end-diastolic velocity.

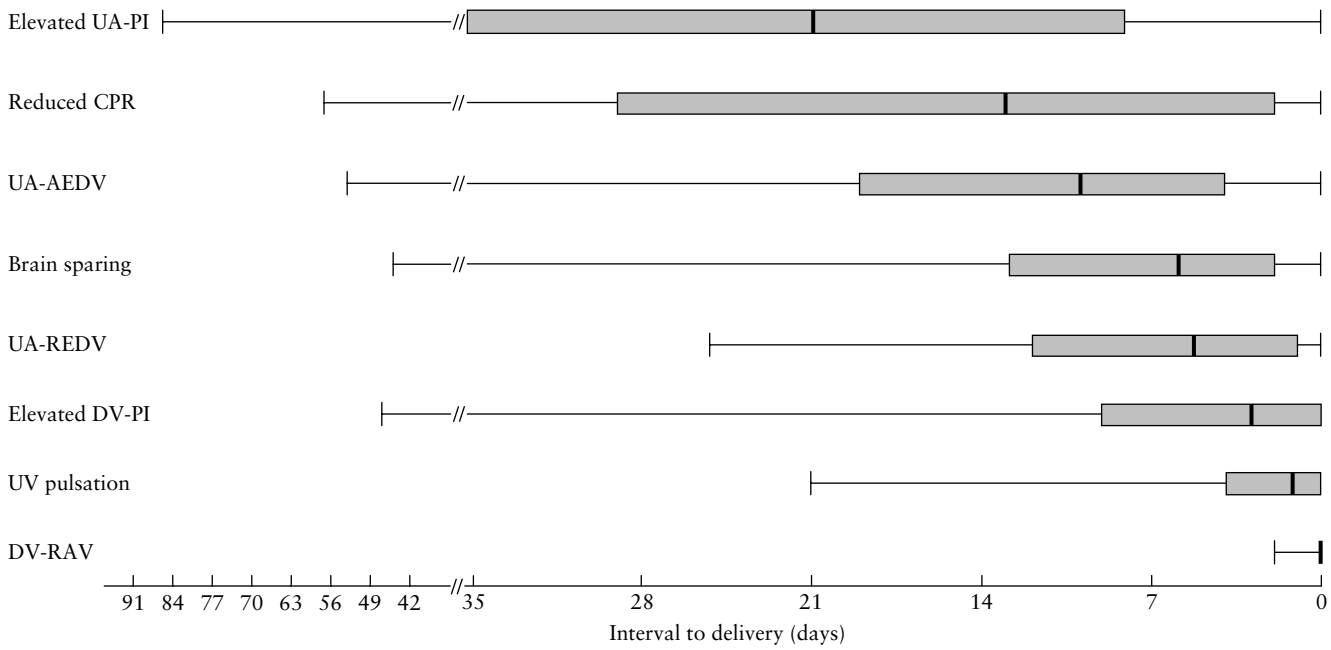

Figure 2 Sequence of Doppler abnormalities determined by the interval to delivery in the whole study population. The minimum and maximum values with interquartile range and median are displayed. The median intervals from the occurrence of an elevated umbilical artery (UA) pulsatility index (PI), reduced cerebroplacental ratio (CPR), UA absent end-diastolic velocity (AEDV), brain sparing, UA reversed end-diastolic velocity (REDV), elevated ductus venosus (DV)-PI, umbilical vein (UV) pulsation and DV reversed a-wave (RAV) were 21, 13, 10, 6, 5, 3, 1 and 0 days, respectively, with a statistically significant difference overall (ANOVA $P < 0.0001$).

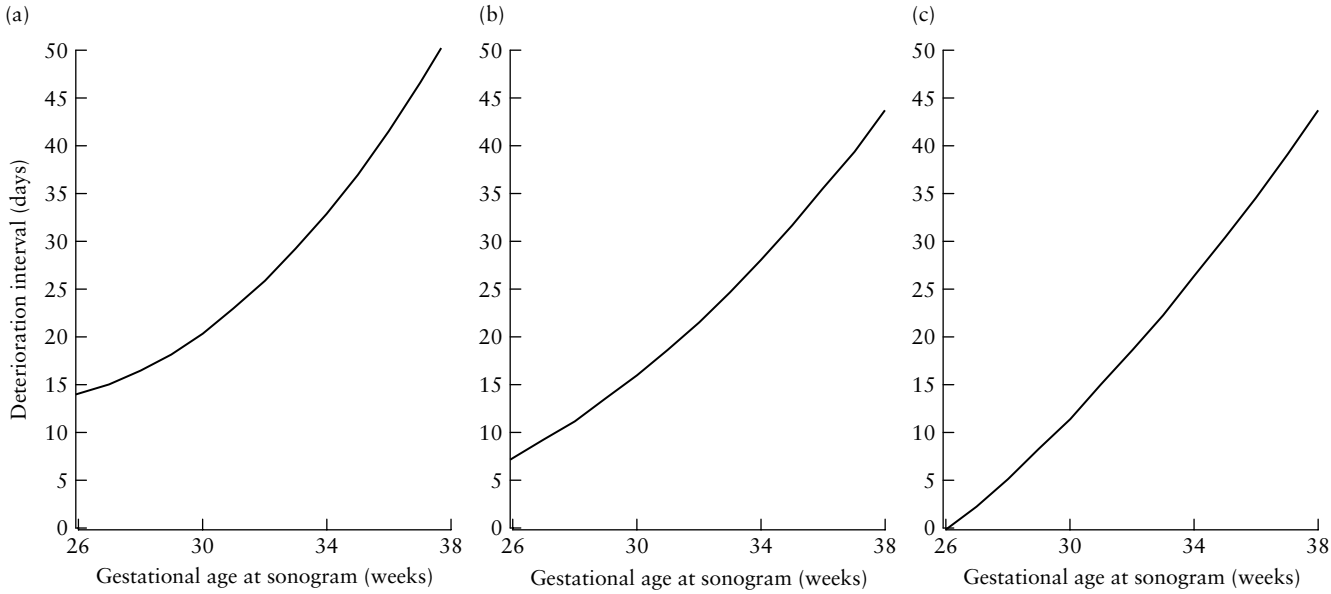

Figure 3 Relationship between deterioration interval and gestational age in the umbilical artery (a), middle cerebral artery (b) and ductus venosus (c). The graphs illustrate that the deterioration interval for the progression of Doppler abnormalities is shorter at early gestational ages and increases with advancing gestation. The relationships between deterioration interval (DI) and gestational age (GA) are:
(a) $DI = 0.2 \times GA^2 - 9.6 \times GA + 129.9$; $R^2 = 0.35$, $P < 0.0001$.
(b) $DI = 0.1 \times GA^2 - 3.4 \times GA + 28.8$; $R^2 = 0.36$, $P < 0.0001$.
(c) $DI = 0.1 \times GA^2 - 2.5 \times GA$; $R^2 = 0.48$, $P < 0.0001$.

- Mild placental dysfunction: Mild onset and non-progressive abnormalities characterize this pattern. Of the 34 fetuses in this category, 11 (32.4%) presented with an elevated UA-PI, two (5.9%) with reduced CPR and four (11.8%) with isolated brain sparing. The patients were enrolled at a median gestational age of 27.4 (range, 23.0–33.4) weeks, and the initial Doppler abnormality was detected at 31.5 (range, 23.3–40.2) weeks' gestation. The median gestational age at delivery was 35.3 (range, 28.0–40.3) weeks. The UA-PI *Z*-score was typically normal at initial presentation and never rose above three SD elevations.

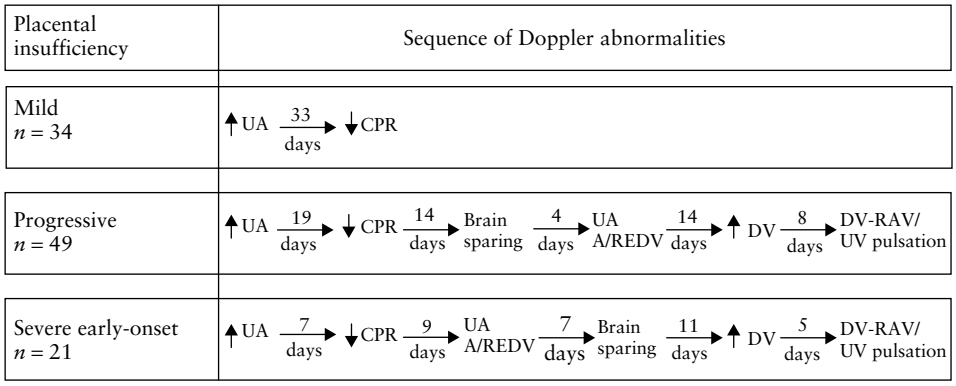

Figure 4 Categorization of placental insufficiency according to the sequence of Doppler abnormalities. The progression interval is expressed as median (days). UA, umbilical artery; CPR, cerebroplacental ratio; A/REDV, absent or reversed end-diastolic velocity; DV, ductus venosus; RAV, absent/reversed a-wave; UV, umbilical vein.

This group had the longest enrollment-to-delivery interval (median 46 days, range 7–97). No antepartum death was observed. Two patients (5.9%) developed pre-eclampsia and 15 (44.1%) were delivered for fetal indications. Progression from an elevated UA-PI to a reduced CPR took a median of 33 (range, 4–96) days, significantly longer than in the progressive and severe early-onset groups ($P = 0.02$ and $P < 0.0001$, respectively).

- Progressive placental dysfunction: Mild onset but progressive cardiovascular compromise were the main characteristics of this pattern, observed in 49 fetuses. The sequence of abnormal Doppler findings was elevated UA-PI, reduced CPR, brain sparing, UA-AEDV, UA-REDV, elevated DV-PI, and DV-RAV/UV pulsation. The patients were diagnosed at a median gestational age of 27.0 (range, 24.0–33.6) weeks and the initial Doppler abnormality was diagnosed at a gestational age of 29.1 (range, 24.0–38.0) weeks. The median gestational age at delivery was 33.4 (range, 26.4–39.5) weeks. The UA-PI *Z*-score was typically normal at enrollment but progressively increased beyond 3 SD. The enrollment-to-delivery interval was 38 (range, 7–90) days and the median progression interval was 9 (range, 0–75) days. Two antepartum deaths were observed, seven patients (14.3%) developed pre-eclampsia and 29 (59.2%) were delivered for fetal indications. Progression from an elevated UA-PI to reduced CPR took a median of 19 (range, 2–75) days, significantly slower than in severe early-onset placental dysfunction ($P = 0.005$).
- Severe early-onset placental dysfunction: This pattern was typified by severe cardiovascular compromise, presenting early in gestation and progressing rapidly, and was observed in 21 fetuses. Although most fetuses showed a typical progression pattern (elevated UA-PI, reduced CPR, UA-AEDV, UA-REDV, brain sparing, elevated DV, DV-RAV/UV pulsation), an elevated DV was the initial finding in five of them. Patients were diagnosed at a median gestational age of 26.3 (range, 24.0–33.4) weeks, and the initial Doppler abnormality presented at 27.1 (range, 24.1–36.3) weeks' gestation. The median gestational age at delivery was 30.6 (range, 27.1–36.3) weeks. The UA-PI *Z*-score always showed a greater elevation than 3 SD and increased progressively. The enrollment-to-delivery interval was 23 (range, 8–86) days and the median progression interval between successive Doppler abnormalities was 7 (range, 1–48) days. No antepartum death was observed in this group. Two patients (9.5%) developed pre-eclampsia and 17 (81.0%) were delivered for fetal indications ($P < 0.05$ compared to patients with mild placental dysfunction). The progression interval from elevated UA-PI to reduced CPR was a median of 7 days (range, 2–30).

Once the patterns had been defined their characteristics were compared. The primary differentiating factor between the patterns was the way UA Doppler abnormality progressed (Figure 5). The terminology for the three patterns was chosen because it emphasizes the impact of placental dysfunction on the progression of Doppler

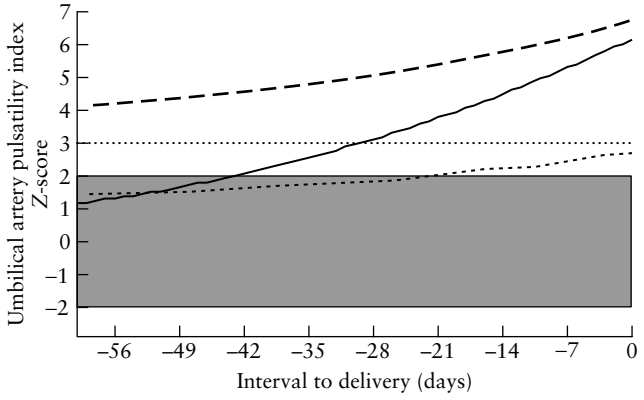

Figure 5 Regression lines for the umbilical artery (UA) Doppler pulsatility index (PI) *Z*-score in the three different progression patterns. Regression lines were created using the interval to delivery in days as the independent variable and the UA-PI *Z*-score as the dependent variable. The slopes of these regression lines were significantly different from each other ($P < 0.0001$ for all comparisons). The shaded area indicates the normal range. ····· , 3 SD elevations; - - - -, mild insufficiency; ——, progressive insufficiency; — —, severe early-onset insufficiency.

Table 4 Characteristics of placental insufficiency patterns

Characteristic	*Degree of placental insufficiency*		
	Mild	*Progressive*	*Severe early-onset*
Gestational age at enrollment (weeks)	27.4 (23.0–33.4)	27.0 (24.0–33.6)	26.3 (24.0–33.4)
Gestational age at detection of first Doppler abnormality (weeks)	31.5 (23.3–40.2)*	29.1 (24.0–38.0)§	27.1 (24.1–36.3)†
Gestational age at delivery (weeks)	35.3 (28.0–40.3)*	33.4 (26.4–39.5)§	30.6 (27.1–36.3)‡
Time from enrollment to delivery (days)	46 (7–97)	38 (7–90)§	23 (8–86)†
Progression interval (days)	—	9 (0–75)§	7 (1–48)

Data are given as median (range). *Mild vs. progressive, $P < 0.05$. †Mild vs. severe, $P < 0.05$. ‡Mild vs. severe, $P < 0.001$. §Progressive vs. severe early-onset, $P < 0.05$.

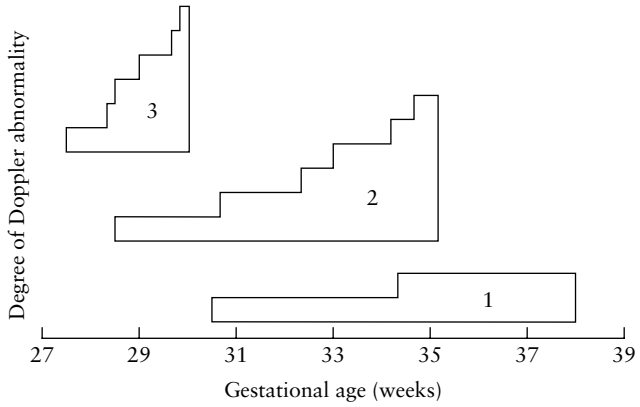

Figure 6 Relationship between gestational age, degree and rate of Doppler escalation. Each step in the cluster graph indicates progression to a new Doppler abnormality. The graph illustrates that severe progressive placental dysfunction (3) has an earlier onset and a more extensive and rapid deterioration than do progressive (2) and mild non-progressive (1) placental dysfunction.

abnormalities. Significant differences in enrollment-to-delivery interval, progression interval and gestational age at delivery were observed between the three patterns (Table 4). The relationships between gestational age and rate and degree of Doppler escalation are displayed in Figure 6.

DISCUSSION

Numerous cross-sectional studies have shown associations between abnormal Doppler findings and adverse outcomes in IUGR that help frame delivery decisions[2,4,7–9]. At the end of IUGR progression, arterial and venous Doppler ultrasonography can provide an estimate of imminent fetal risk, thereby indicating immediate management. However, most of these associations are derived from studies of end-stage IUGR – they do not describe the pathway of deterioration. Therefore, cross-sectional observations do not specify how to monitor individual fetuses that are not yet compromised. In this context, longitudinal assessment may provide key information, if patterns can be discerned that predict progression from the onset of clinical disease. The goal of antenatal surveillance, of course, is not to prove that the associations are true by allowing adverse outcomes, but to avoid them by anticipating changes. By examining early factors and allowing that anticipation, our longitudinal observations clarify crucial monitoring decisions in IUGR.

Choices for monitoring intervals, determinants of accelerating disease and expected patterns of progression have been extrapolated from cross-sectional studies, most recently in both arterial and venous systems. Several longitudinal studies have utilized various approaches for analyzing these Doppler abnormalities in IUGR. For example, Rigano *et al.* found that a persistent reduction in umbilical venous volume flow precedes the development of growth delay[13]. Similarly, Harrington *et al.* showed that the degree of growth delay mirrors the increase in UA pulsatility[14]. Several studies have shown that cerebral blood flow abnormalities become more prevalent as growth restriction progresses[15]. Worsening arterial Doppler results do parallel worsening fetal status, but only the addition of venous Doppler has allowed a comprehensive understanding of cardiovascular deterioration[16,17]. Our study is another step in understanding IUGR, as the first longitudinal study of arterial and venous Doppler parameters documenting progression from its early onset. Based on the defined entry point of first clinical diagnosis, our observations illustrate the sequence and character of progression, before the phase of fetal compromise.

How IUGR progresses is determined by when it starts and how it starts, i.e. gestational age and degree of UA abnormality at onset. In patients presenting much before 30 weeks, a pattern of worsening UA Doppler established in the first 7–10 days reliably predicts progression to venous Doppler abnormalities and very early intervention (severe early-onset placental dysfunction). In those presenting closer to 30 weeks with decreased (but still present) UA end-diastolic velocity, Doppler progression is also typically forecast within the first 2 weeks of monitoring and falls into one of two patterns. If initial Doppler abnormalities have not worsened in that first interval, they are unlikely to do so. Abnormalities remain confined to umbilical and mild cerebral changes. These fetuses do not develop venous Doppler abnormalities and are likely to deliver near term (mild placental dysfunction). If the first few weeks of monitoring show progressive elevation of UA Doppler indices, progression to abnormal venous Doppler findings and preterm delivery become more likely (progressive placental dysfunction).

Previous studies that focused on associations with outcome analyzed steps in final deterioration by examining events backward from the time of delivery. Senat *et al.* correlated arterial and venous Doppler waveforms in 75 IUGR singleton pregnancies[10]. They documented parallel progression of cerebral and precordial venous Doppler abnormalities. Ferrazzi *et al.* analyzed the percentage of Doppler abnormalities and longitudinal cumulative onset time of Doppler abnormalities in 26 fetuses with severe early-onset growth restriction[6]. Early Doppler changes of brain sparing and UA end-diastolic velocity were present in 50% of fetuses up to 16 days prior to delivery. Late Doppler changes including an elevated DV Doppler index and reversed UA end-diastolic velocity were observed in the week prior to delivery in up to 40% of fetuses. The daily incidence of these Doppler abnormalities was 0.052 and 0.046. Bilardo *et al.*[7] and Hecher *et al.*[8] also studied trends in IUGR Doppler leading to a delivery decision[7,8]. Both studies confirmed the proposed sequence of Doppler abnormalities, but also noted a higher probability of escalation at earlier gestational ages and a cumulative impact on perinatal outcome. However, our group, and later Cosmi and colleagues[18] have shown that many growth-restricted fetuses do not follow the classical Doppler progression.

These studies documented components of IUGR deterioration in already established disease. By starting earlier, and analyzing behavior prospectively, we have illustrated differing patterns of progression. In fact, many fetuses progress slowly or not at all from the onset of IUGR. Further, these patterns of progression determine the structure of antenatal surveillance. First, primary consideration is given to gestational age at onset and the trends observed in short-term serial evaluation of UA Doppler. Early-onset IUGR carries a risk for rapid parallel progression of umbilical and venous Doppler abnormalities. Late-onset disease is less likely to progress in such a way. At identical gestational ages progression from isolated UA Doppler abnormality to brain sparing doubles the rate of progression, and DV Doppler abnormalities are associated with a tenfold acceleration of deterioration. The progression of UA Doppler abnormalities is the primary tool for distinguishing between these patterns of anticipated progression. This role of the progression of UA Doppler abnormality has not been accounted for in previous studies. Therefore, differences in the prevalence of venous Doppler abnormalities and in the patterns of progression have remained unexplained. Our observations clarify that the prevalence of venous Doppler abnormalities and their rate of progression is highest in preterm IUGR and very rare among fetuses presenting with growth restriction beyond 30 weeks' gestation.

Our observations suggest a schedule for IUGR surveillance. Once IUGR has been diagnosed weekly UA Doppler examination is suggested to determine the pattern of progression. After the initial 14 days, rapidly progressive severe disease will be revealed by definitive deterioration of UA Doppler and the emergence of additional vessel abnormalities. For the remainder, a less fulminant course is expected. If there is still no change over the next 2 weeks then venous Doppler monitoring is unlikely to yield abnormal results. Of interest, this nonprogressive subset may show isolated increased cerebral diastolic blood flow near term. The significance of this isolated Doppler finding in near-term IUGR has been emphasized previously[19] and merits further study. Those fetuses that do progress in subsequent intervals require frequent, serial, arterial and venous testing, but often may gain many weeks of valuable maturation time before delivery. Further study needs to address whether there are additional factors such as UA Doppler status or the development of pregnancy-induced hypertensive disorders that impact on this anticipated progression.

In conclusion, the characteristics of cardiovascular manifestations in IUGR are determined by the gestational age at onset and the severity of placental disease, identified by UA Doppler alone. The precise mechanisms mediating these differences require further study. These associations are not recognized when extrapolated from cross-sectional studies. Recognition of these factors is critical for planning fetal surveillance in IUGR. Serial observations of UA Doppler status remain a cornerstone for determining monitoring intervals in IUGR. At early gestation escalation of UA Doppler parameters and elevation of the DV Doppler index are relevant modifiers of testing. Near-term progression beyond an abnormal MCA Doppler is not observed.

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