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Monitoring of fetuses with intrauterine growth restriction: a longitudinal study

K. HECHER, C. M. BILARDO*, R. H. STIGTER†, Y. VILLE‡, B. J. HACKELÖER, H. J. KOK*, M. V. SENAT‡ and G. H. A. VISSER†

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

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ABSTRACT

Objective *To describe the time sequence of changes in fetal monitoring variables in intrauterine growth restriction and to correlate these findings with fetal outcome at delivery.*

Methods *This was a prospective longitudinal observational multicenter study on 110 singleton pregnancies with growth-restricted fetuses after 24 weeks of gestation. Short-term variation of fetal heart rate, pulsatility indices of fetal arterial and venous Doppler waveforms and amniotic fluid index were assessed at each monitoring session. The study population was divided into two groups: Group 1 comprised pregnancies with severely premature fetuses, which were delivered ≤ 32 weeks and Group 2 included pregnancies delivered after 32 completed weeks. Logistic regression was used for modeling the probability for abnormality of a variable in relation to the time interval before delivery. Trends over time were analyzed for all variables by multilevel analysis.*

Results *Ninety-three (60 in Group 1 and 33 in Group 2) fetuses had at least three data sets (median, 4; range, 3–27) and had the last measurements taken within 24 h of delivery or intrauterine death. The percentage of abnormal test results and the degree of abnormality were higher in Group 1 compared to Group 2. Amniotic fluid index and umbilical artery pulsatility index were the first variables to become abnormal, followed by the middle cerebral artery, aorta, short-term variation, ductus venosus and inferior vena cava. In Group 1, short-term variation and ductus venosus pulsatility index showed mirror images of each other in their trend over time. Perinatal mortality was significantly higher if both variables were abnormal compared to only one or neither being abnormal (13/33 (39%) vs. 4/60 (7%);* P = *0.0002; Fisher's exact test).*

Conclusion *Ductus venosus pulsatility index and short-term variation of fetal heart rate are important indicators for the optimal timing of delivery before 32 weeks of gestation. Delivery should be considered if one of these parameters becomes persistently abnormal.*

INTRODUCTION

The optimal timing of delivery in pregnancies complicated by intrauterine growth restriction is still an issue to be resolved. Clinicians have to balance the risks of prematurity against the risks of prolonged fetal exposure to hypoxemia and acidemia, possibly resulting in fetal damage or death. In a cross-sectional Doppler study of the fetal circulation, the appearance of significant changes in venous Doppler waveforms from the ductus venosus, inferior vena cava and hepatic veins was observed after fetal arterial blood flow redistribution from the descending thoracic aorta to the middle cerebral artery was established[1]. Furthermore, the changes in the venous circulation seemed to be closely related to the onset of abnormal fetal heart rate (FHR) patterns. Reduced FHR variation and the occurrence of FHR decelerations have been associated with fetal hypoxemia[2–6] whereas extremely low values of short-term variation (STV) were found to be a reliable predictor of metabolic acidemia at delivery or intrauterine death[7–9].

The aim of this multicenter study was to investigate the time sequence of alterations of fetal monitoring variables in a large group of growth-restricted fetuses and to correlate these findings with fetal outcome at delivery. The results of this study may be helpful in the design of management protocols for future intervention studies and may assist clinicians in decision making and optimizing the timing of delivery in pregnancies with fetal growth restriction.

METHODS

This was a prospective longitudinal multicenter study on 110 singleton pregnancies with small-for-gestational-age fetuses,

Correspondence: Dr K. Hecher, Department of Prenatal Diagnosis and Therapy, AK Barmbek, Rübenkamp 148, D-22291 Hamburg, Germany (e-mail: khecher@compuserve.com)

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defined as a fetal abdominal circumference < 5th centile for gestational age[10] with or without pregnancy-induced hypertension. The study was approved by the local medical ethics committees and all women gave their informed consent. Patients were recruited between 24 and 34 weeks of gestation. Multiple pregnancies and cases with morphological or chromosomal abnormalities or preterm rupture of the membranes were excluded. Biometry was assessed every 2 weeks and the following variables were assessed at each fetal monitoring session: (i) FHR recordings for a minimum of 40 min were analyzed by a computerized system (Oxford Sonicaid System 8002, Oxford Instruments, Abingdon, UK), which fits a baseline to the FHR trace and calculates STV (in ms) as fetal pulse interval differences averaged over successive periods of 3.75 s, after exclusion of decelerations[7,11]; (ii) assessment of the fetal circulation by an experienced operator using color and pulsed wave Doppler ultrasound and calculation of pulsatility indices (PI) from blood flow velocity waveforms of the umbilical artery, descending thoracic aorta, middle cerebral artery, ductus venosus and inferior vena cava[12,13]; (iii) amniotic fluid index (AFI) calculated as the sum of the deepest vertical pools without fetal parts or cord, measured sonographically in each quadrant of the uterus[14].

The time intervals between monitoring sessions were dependent on the findings of Doppler investigations and FHR recordings. If only the PI in the umbilical artery was > 95th centile for gestational age, fetal monitoring was performed weekly. In the presence of fetal blood flow redistribution, defined as a PI in the middle cerebral artery < 5th centile, monitoring sessions were scheduled at least twice weekly. If there were abnormal venous flow velocity waveforms with a PI > 95th centile for gestational age or a suspicious or abnormal FHR recording with a STV < 5 ms, monitoring was scheduled daily. Cases were included for longitudinal analysis if a minimum of three monitoring sessions had been performed. For correlation with fetal outcome at delivery, the last assessment had to be within 24 h before delivery.

There was no management protocol, as this study was not designed as a management study, but as an observational one. The indication for elective delivery or the decision to abstain from intervention was left to the discretion of the attending obstetrician and included considerations such as gestational age, estimated fetal weight and weight gain, coexisting maternal disease and parental preference. FHR analysis was the standard parameter for clinical decisions and a STV of < 3 ms or the presence of a decelerative heart rate pattern was regarded as indicating a high risk for metabolic acidemia or intrauterine death[7,8]. To discriminate between early and late fetal compromise, the study population was divided into two groups for statistical analysis. Group 1 comprised all fetuses delivered ≤ 32 weeks of gestation and Group 2 included all fetuses delivered after 32 completed weeks.

To study the time sequence of changes in fetal monitoring variables, two approaches were chosen. First, the variables were analyzed in a discrete fashion according to normality or abnormality[11–14]. Logistic regression was used to model the probability for the quality of a variable in correlation to the time interval before delivery. This method can be used to predict probabilities for the presence of abnormality of a variable as a percentage during the course of pregnancy. Second, the variables were analyzed in a continuous fashion according to their trend over time. For each individual, variables were expressed in standard deviation (SD) from the normal mean for gestational age[11–14] and multilevel analysis was carried out using the software program Mln (Multilevel Model Project, London, UK)[15]. This model can be used if repeated measurements have been made at different points in time. The course over time was modeled with a polynomial curve. To determine the shape of the curves during modeling, it was tested whether it was linear or a polynomial of the second degree. Repeated measurements at different gestational ages in the same individual comprised Level 1 and those in different fetuses comprised Level 2 and the stepwise method was used as a model-building strategy, as described previously[11]. For each individual, the parameters of the curve were assumed to be randomly drawn from a normal distribution. Individual regression lines for each variable were calculated for each fetus and from these the regression lines for the whole group were derived. Thereby, for each variable, the degree of deviation from the normal mean could be expressed. Days before delivery was used as a time variable by introducing this linearly as well as quadratically. Both groups of pregnancies were compared to investigate whether they differed in the fitted model.

Special attention was paid to the relationship between ductus venosus PI, STV and perinatal mortality. Non-parametric descriptive statistics (medians and ranges) were used in the tables, the Mann–Whitney test was used for the comparison of continuous variables and two-sided Fisher's exact test was used for comparison of categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

Ninety-six patients had at least three observations (median, 4; range, 3–27), resulting in a total of 547 observations, which were used for Mln analysis. In 93 patients, the last measurements were taken within 24 h of delivery or intrauterine death and these were analyzed in relation to perinatal mortality. The first measurements were taken at a median of 15 (range, 2–83) days before delivery and 75% of all measurements were taken within 15 days before delivery. Sixty patients belonged to Group 1 and 33 patients to Group 2. Birth characteristics are shown in Table 1.

Figures 1 and 2 show the probability of an abnormal finding for each variable in relation to time before delivery for Groups 1 and 2. Overall, the trend and rank order were identical, both before and after 32 weeks, although the percentage of abnormal findings was much higher in fetuses delivered before 32 weeks. Amniotic fluid index and umbilical artery PI were the first variables to become abnormal and they were followed by the middle cerebral artery, aorta, STV, ductus venosus and inferior vena cava. All variables showed a trend towards an increase in abnormal findings close to delivery, apart from the PI in the aorta.

The results of the multilevel analysis and regression lines indicating the trend over time before delivery for each variable in comparison to the reference ranges (±2 SDs) are

Table 1 Comparison of clinical characteristics for Groups 1 and 2

	Group 1 (n = *60*) *Delivery ≤ 32 weeks*	*Group 2* (n = *33*) *Delivery > 32 weeks*	P
Monitoring sessions (median (range))	4 (3–27)	4 (3–14)	0.515
GA at delivery (weeks, median (range))	29.7 (24.4–31.9)	35.1 (32.0–40.4)	< 0.001
Birth weight (g, median (range))	780 (250–1350)	1490 (875–2900)	< 0.001
Cesarean section (*n* (%))	53 (88)	20 (61)	0.003
Perinatal deaths (*n*)	16 (6 IUD, 10 NND)	1 (NND)	0.004
Arterial cord pH (median (range))	7.23 (6.97–7.39) (*n* = 39)	7.25 (7.10–7.36) (*n* = 30)	0.103

GA, gestational age; IUD, intrauterine death; NND, neonatal death.

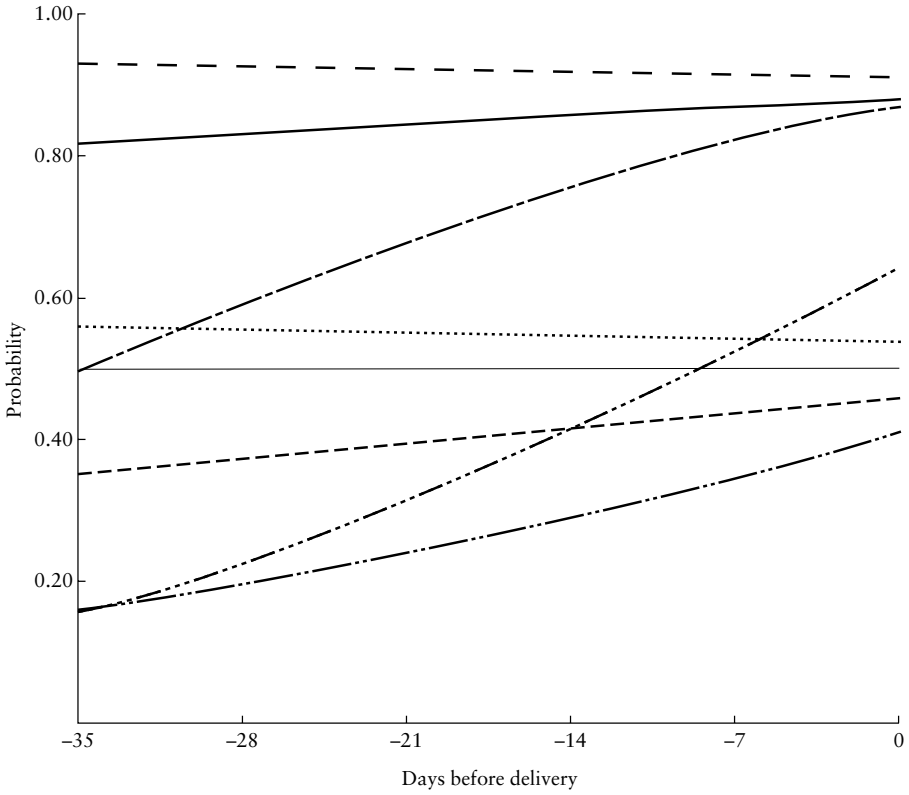

Figure 1 Probabilities for abnormal findings of variables in relation to time before delivery for Group 1 (fetuses delivered before or at 32 weeks of gestation). A probability of 50% (0.50) is indicated by a thin solid line. – –, amniotic fluid index; ——, umbilical artery; –·–, middle cerebral artery; —·—·—, short-term variation; ····· , aorta; – – –, ductus venosus; —··—, inferior vena cava.

shown in Figures 3 and 4. There were significant differences between both groups for all variables except for the PI in the inferior vena cava. In Group 1 (Figure 3), umbilical artery and thoracic aorta PI were > +2 SD and middle cerebral artery PI and AFI < –2 SD from the beginning of the observational period. Regression lines for ductus venosus PI and STV showed trends as a mirror image of each other. Ductus venosus PI increased and STV decreased from 21 days before delivery onwards and the regression lines crossed the respective limits of +2 SD and –2 SD at almost the same point in time, namely approximately 7 days before delivery. In Group 2 (Figure 4), amniotic fluid index and middle cerebral artery PI were < –2 SD from the beginning of the observational period, but umbilical artery PI crossed the limit of +2 SD only 3 weeks before delivery. Middle cerebral artery PI showed a trend towards normalization close to delivery.

When STV and ductus venosus PI were related to perinatal mortality, it appeared that the poorest outcome occurred if both parameters were abnormal (Table 2). Overall, there were 13/33 (39%) perinatal deaths, including all intrauterine deaths, if both were abnormal, in contrast to 4/60 (7%) if only one or neither was abnormal ($P = 0.0002$). This difference also remained significant if analysis was confined to Group 1, where 16 of the 17 deaths occurred: perinatal mortality was 12/30 (40%) if both parameters were abnormal and 4/30 (13%) if only one or neither was abnormal ($P = 0.04$). Birth weight was also significantly lower if both parameters were abnormal. In Group 1, STV was the first variable to become

persistently abnormal in 29 fetuses and 4 (14%) of them died perinatally, whereas ductus venosus PI was the first to become persistently abnormal in 23 fetuses and 10 (43%) of them died perinatally ($P = 0.03$). Only eight (28%) of the former also developed an abnormal ductus venosus PI later during the observational period, whereas 19 (83%) of the latter also developed an abnormal STV later ($P = 0.0001$). The median time interval between the occurrence of the first persistently abnormal finding and delivery was 3 days (range, 0–19 days) if STV was abnormal first and 7 days (range, 0–43 days), if ductus venosus PI was the first variable to become abnormal ($P = 0.035$).

DISCUSSION

This large longitudinal observational study describes the sequence of events in fetal deterioration comparing fetal Doppler ultrasound and FHR analysis.

This study shows that changes in umbilical artery PI, middle cerebral artery PI and amniotic fluid index are the first to occur. In the majority of fetuses with early onset growth restriction, there is increased placental vascular resistance and preferential blood flow to vital organs, such as the brain, must be considered as a compensatory mechanism for hypoxemia and malnutrition. Therefore, once these pregnancies

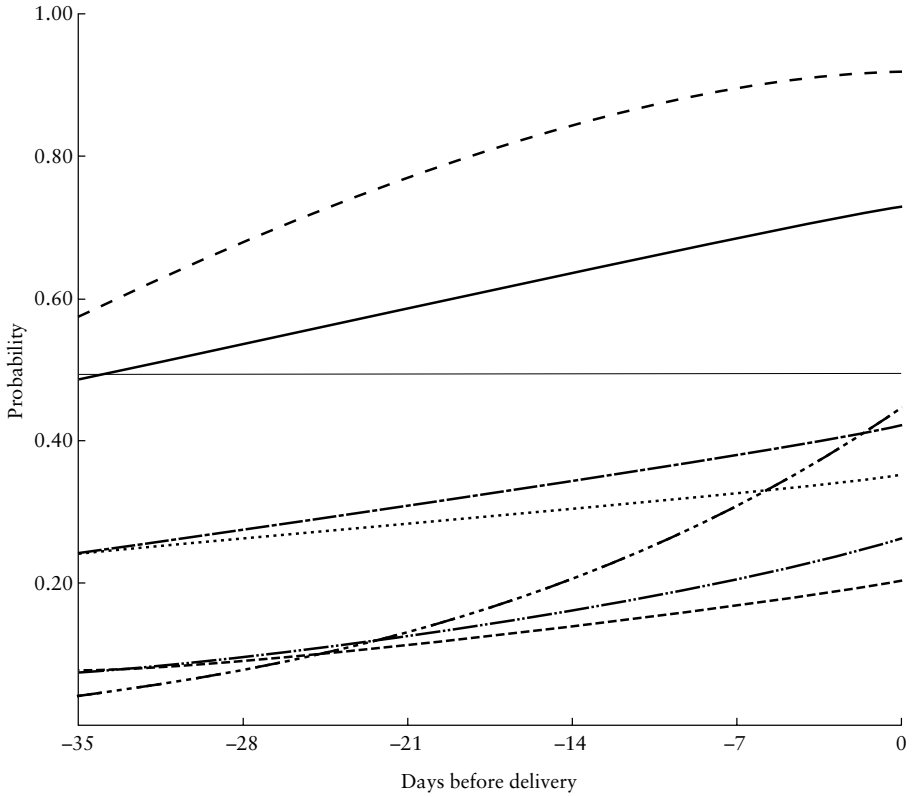

Figure 2 Probabilities for abnormal findings of variables in relation to time before delivery for Group 2 (fetuses delivered after 32 weeks of gestation). A probability of 50% (0.50) is indicated by a thin solid line. – –, amniotic fluid index; ——, umbilical artery; —·—·—, short-term variation; —··—, middle cerebral artery; ····, aorta; —···—, inferior vena cava; – – –, ductus venosus.

Table 2 Short-term variation and ductus venosus pulsatility index at last measurement before delivery and perinatal outcome

	STV/PI	n	*Alive* (n)	*IUD* (n)	*NND* (n)	*GA (weeks) (median (range))*	*Birth weight (g) (median (range))*
Group 1							
	Both normal	5	4	0	1	29.8 (28.4–31.0)	780 (460–970)[b]
	One abnormal	25	22	0	3	29.9 (26.6–31.9)	850 (540–1350)[b]
	Both abnormal[a]	30	18	6	6	29.3 (24.4–31.6)	625 (250–1170)[b]
Group 2							
	Both normal	16	16	0	0	36.3 (32.0–40.4)	1850 (960–2900)[c]
	One abnormal	14	14	0	0	35.0 (32.0–38.4)	1520 (935–2370)[c]
	Both abnormal[a]	3	2	0	1	33.6 (32.0–35.3)	940 (875–1250)[c]

[a]In four fetuses (three in Group 1 and one in Group 2), both parameters became persistently abnormal at the same time; [b]$P = 0.039$; [c]$P = 0.025$; STV, short-term variation; PI, pulsatility index; GA, gestational age; IUD, intrauterine death; NND, neonatal death.

have been referred to a high-risk prenatal unit, owing to their smallness detected by fetal biometry, abnormal PI values in these vessels are likely to be found from the very beginning of the observational period. The explanation for the early occurrence of a low amniotic fluid index may be the smallness of the uterus itself, which may still be in proportion to the smallness of the growth-restricted fetus with a deepest vertical pool of amniotic fluid measuring more than 2 cm.

The decrease in PI of the middle cerebral artery follows the changes in the umbilical artery (Figures 1 and 2) which is in agreement with other studies[16]. In fetuses delivered before 32 weeks of gestation, middle cerebral artery PI became progressively abnormal until delivery (Figure 3), which is in contrast to the findings of Arduini *et al.*[17] who found that the PI of cerebral vessels did not change in the last weeks preceding FHR abnormalities, and Weiner *et al.*[18] who even found a normalization of middle cerebral artery PI before the occurrence of an abnormal FHR. However, in fetuses delivered after 32 weeks of gestation, we found a trend towards normalization of middle cerebral artery PI (Figure 4). This seems to be due to the physiological decrease of the vascular resistance in the brain with advancing gestational age, reflected by a marked decrease of the normal range for the PI, rather than the loss of the adaptive mechanism of blood flow redistribution. We could not demonstrate a trend in thoracic aorta PI, which suggests that there is no role for this vessel in the timing of delivery. Measurements of the actual aortic blood flow velocities might be more valuable, but they are more difficult to perform[19]. The inferior vena cava PI was also rather stable, with a trend towards +2 SD at the time of delivery, most probably due to increased right cardiac afterload.

Before 32 weeks, the increase in ductus venosus PI and the decrease in STV were steeper than those of the other parameters and they became abnormal on average only a few days before delivery (Figure 3), suggesting that these parameters reflect the more acute changes in the fetal condition. Data from a preliminary study, focusing on the transverse cerebral sinus, have already shown a negative correlation between pulsatility of venous flow and FHR variation[20]. FHR abnormalities are known to follow the occurrence of an abnormal PI in the umbilical artery by many weeks at an early gestational age[21]. If a probability of 50% for an abnormal finding is taken as a reference point, an abnormally low STV can be expected approximately 3 weeks after the occurrence of abnormal waveforms in the middle cerebral artery (Figure 1). Reduced heart rate variation indicates a decrease in the physiological fluctuations of the autonomic nervous system and a diminished modulation of vagal activity[22]. Before 32 weeks of gestation, this seems to coincide with the development of cardiac failure, since the trend for abnormality of ductus venosus flow patterns shows a mirror image of the trend for abnormality of STV (Figure 3). However, this does not necessarily reflect the trend in each individual fetus, as shown by the comparative analysis of the first occurrence of an abnormal finding in ductus venosus PI and STV, respectively. Increased venous pulsatility seems to reflect myocardial

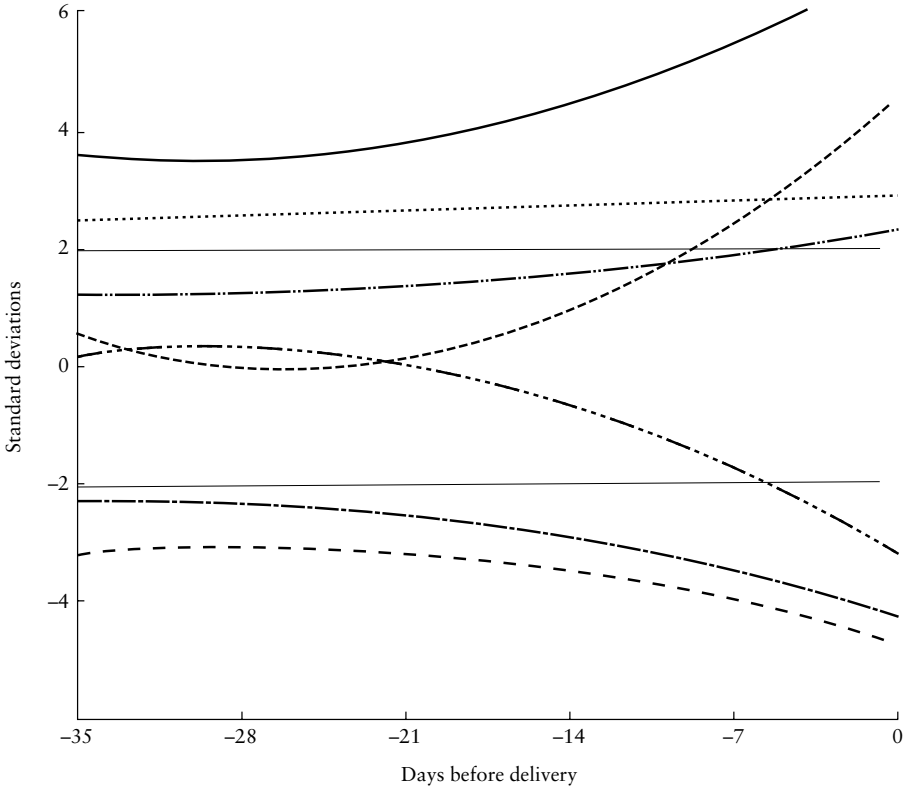

Figure 3 Trends over time of variables in relation to time before delivery and reference ranges (±2 SD) for Group 1 (fetuses delivered before or at 32 weeks of gestation). ——, umbilical artery; – – –, ductus venosus; ····· , aorta; —·—, inferior vena cava; —··—, short-term variation; —·—, middle cerebral artery; – –, amniotic fluid index.

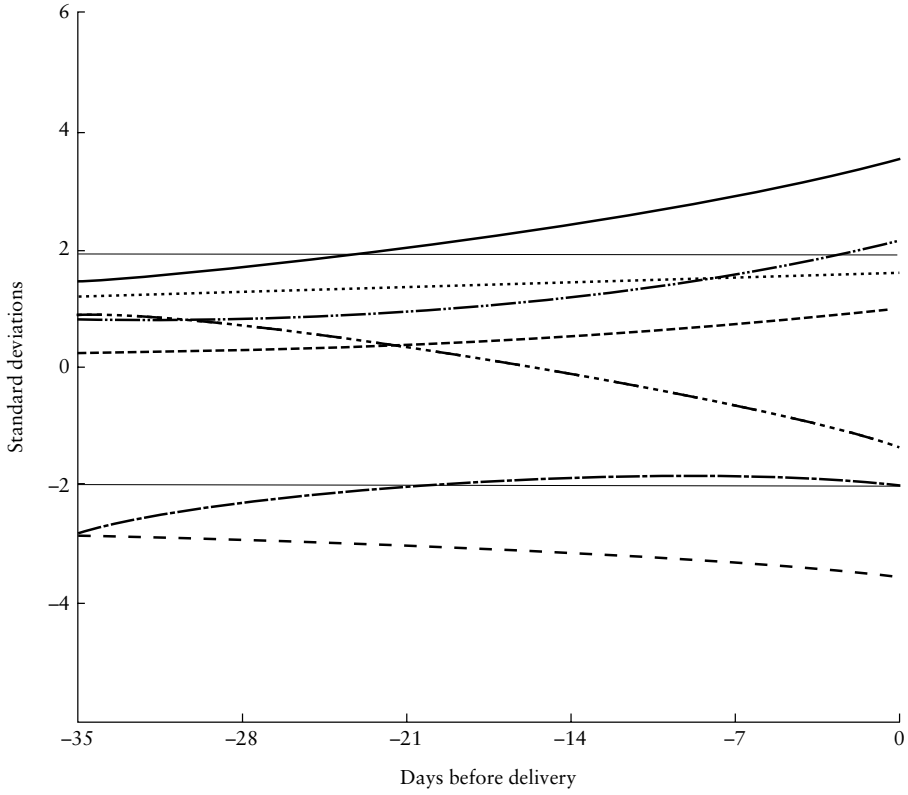

Figure 4 Trends over time of variables in relation to time before delivery and reference ranges (±2 SD) for Group 2 (fetuses delivered after 32 weeks of gestation). ——, umbilical artery; —·—, inferior vena cava; ····, aorta; – – –, ductus venosus; —··—, short-term variation; —·—, middle cerebral artery; – –, amniotic fluid index.

decompensation resulting in increased end-diastolic ventricular pressure and a decrease of flow velocities during atrial contraction. This mechanism was confirmed in a recent study showing that neonatal troponin T concentrations were significantly increased in the presence of pulsations in the intra-abdominal umbilical vein, suggesting myocardial cell destruction[23]. There is also an increasing risk of fetal acidemia with increasing pulsatility in the ductus venosus[24].

In the group delivered after 32 weeks of gestation, the probability of finding abnormal test results was much lower and the degree of changes in Doppler variables and STV was much less pronounced than in fetuses delivered before 32 weeks of gestation. This may partly be due to earlier delivery of these fetuses, before signs of severe fetal compromise occurred, as prematurity was no longer regarded as a serious problem. At a more advanced gestational age, we found a shorter time interval between the first abnormal Doppler measurement in the umbilical artery and the occurrence of FHR abnormalities compared to those delivered before 32 weeks of gestation, confirming findings by others[25,26]. In our study, there was no difference between the middle cerebral artery PI and STV in the probability for an abnormal test result just before delivery (Figure 2).

Analysis of the sequence of abnormal results in ductus venosus flow and STV shows that the majority of fetuses developing an abnormal ductus venosus flow first belonged to the group delivered before 32 weeks of gestation, and that STV became abnormal later in most of them. This is in contrast to fetuses showing an abnormal STV first, where a significantly lower proportion of fetuses also subsequently developed abnormal ductus venosus flow. This may reflect a more aggressive approach by the clinician in the presence of abnormal FHR variation, in contrast to a more expectant management if only ductus venosus flow was abnormal. This is also supported by the longer time interval between the first occurrence of an abnormal test result and delivery, if the PI in the ductus venosus was the first test to become abnormal. Perinatal mortality was higher in fetuses showing an abnormal ductus venosus flow first and in those where both variables were abnormal. These data suggest that these fetuses may have been delivered too late and delivery should be considered if one of the two variables becomes persistently abnormal, or at least immediately after the second one becomes abnormal as well. The significantly lower birth weight of fetuses with both variables abnormal, although gestational age at delivery was not different, also indicates that they suffered from a more severe degree of placental insufficiency (Table 2).

It is important to stress that only analysis of trends of monitoring variables in each individual fetus will give reliable information as to the optimal timing of delivery and that each fetus should serve as its own control. Gestational age not only has considerable impact on neonatal mortality and morbidity rates, but also requires consideration when interpreting test

results with a view to decide on elective delivery. The currently performed Growth Restriction Intervention Trial will give valuable information on early vs. delayed delivery, if the obstetrician is uncertain about the timing of delivery[27]. However, there is an urgent need to design management protocols based on fetal monitoring findings and to test whether management guided by fetal Doppler ultrasound and computerized FHR analysis improves outcome of these fetuses. We hope that the results of this study will provide a sound basis for such a management protocol.

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